Section B  Synthesis of C₃-Aroylated 3,5-Dichloro-2-(1H)-pyrazinones using NHC as Catalyst
2.1. Introduction

2.1.1. Pyrazinones: Natural Occurrence and Biological Importance

Pyrazinones are heterocyclic compounds and a derivative of pyrazines, with one carbonyl at C2-position (Figure 1). Over the past two decades, 2(1H)-pyrazinones have emerged as a useful starting material for the synthesis of various biologically interesting compounds. Thus, these heterocyclic systems are of interest to many organic as well as medicinal chemists.

![Figure 1](image1.png)

The 2(1H)-pyrazinone core is present in a number of natural products for example, Hamacanthin A (1) and Hamacanthin B (2) containing pyrazinone nucleus were isolated from sponge Spongosorites sp. (Order Halichondrida, Family Halichondriidae), are known to be inhibitors of tryptase and sortase A (gram positive inhibitor) (Figure 2).

![Figure 2](image2.png)

A family of compounds isolated from Dragmacidon sp. (*i.e.* the dragmacidins), from more complex pyrazinone-containing family members, of which dragmacidins D (3), E (4), and F (5) are important compounds in terms of biological perspective, and are
attractive targets for total synthesis\textsuperscript{4}. In particular, dragmacidins D (3) and F (5) have been extensively studied. In addition to displaying anti-inflammatory activity, cytotoxicity and phosphatase inhibition,\textsuperscript{3a,3b} compound 3 has shown selectivity as an inhibitor of neural nitric oxide synthase.\textsuperscript{5} Also, compound 5 is reported to exhibit in vitro antiviral activity against herpes simplex virus (HSV) and human immunodeficiency virus (HIV-I).\textsuperscript{3c}

The 2(1\textit{H})-pyrazinones easily undergo different reactions like cycloaddition-elimination with acetylenes forming pyridines/pyridones\textsuperscript{6} and bicyclic compounds which are valuable building blocks for the synthesis of \(\beta\)-turn mimics.\textsuperscript{7} The substituted 2(1\textit{H})-pyrazinones and compounds derived from them have shown important biological activity which include non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs),\textsuperscript{8} allosteric modulators for \(\gamma\)-aminobutyric acid A receptors\textsuperscript{9} and selective tissue factor VIIa inhibitors.\textsuperscript{10} The 2(1\textit{H})-pyrazine scaffold allows the easy introduction of a wide range of pharmacologically active groups with the ability to address the diverse set of biological targets. Fused pyridine pyrazinones (6)\textsuperscript{11} and 3-indolylpyrazinones (7)\textsuperscript{12} can function as corticotropin releasing factor (CRF) receptor antagonists and can be useful for the treatment of various neurological disorders. Moreover, pyrazinones of type 8 are reported as potential caspase-3-reversible inhibitors after cleavage from the resin (Figure 3).\textsuperscript{13}

A number of pyrazinones with an alkyl group at N1-position and phenyl group at C3-position show inhibitory action on platelet aggregation, vasodilating activity, and inhibitory action on liperoxide generation.\textsuperscript{14,15} Pyrazinones bearing an alkyl amino substituent at C3-position in 9 and 10 are known to be a potential tissue factor VIIa and thrombin inhibitor\textsuperscript{10,16} and also often preferred over the analogues 2-pyridinones 7 in view of air-sensitivity of the latter and their oxidizability in neutral and alkaline media.\textsuperscript{17} Recently, it has been shown that the compound 9 frameworks can effectively replace a dipeptide segment in a peptide lead that attributed to the correct alignment of the CO- and NH- groups coupled with the rigidity of the pyrazinone ring.\textsuperscript{18} Pyrazinones with (orthochloro) phenyl group 11 at C6-position are good ligands that bind to a new site of GABA\textsubscript{A}/chloride ionophore complex.\textsuperscript{19} Pyrazinones substituted with anilines (12) at C3-position and phenols at C5-position can be useful in
inhibiting HIV replication. Some 1,2,4-triazolo[4,5-b]pyrazinones (13) and 3-thiopyrazinones (14) can act as antibacterial and antifungal agents (Figure 3).

Further constraint using a more rigid bicyclic pyrazinone can create more potent compounds and recent report describes 2-amino substituted pyrido[3,2-b]pyrazinone (15) class of compounds as potent and selective PDE5 (phosphodiesterase) inhibitors. Another class of serine protease as prolyloligopeptide (POP) is also known to be inhibited by pyrazinone analogues 16.

2.1.2. General Methods for the Synthesis of 2-(1\(H\))-Pyrazinones

There are only a few methods reported in literature for the synthesis of N1- and C6-disubstituted 2(1\(H\))-pyrazinones. A versatile synthesis of the 2(1\(H\))-pyrazinone scaffold was developed by Hoornaert et al. in 1983 starting from a suitable amine (17), an aldehyde (18) and cyanide (19) to give an \(\alpha\)-aminonitrile (20) which on treatment with oxalyl chloride afforded the desired 2(1\(H\))-pyrazinone (21) in moderate to good yield (Scheme 1).
A wide variation in the substitution pattern at the N1- and C6-positions can be determined by an appropriate choice of the amine (19) and aldehyde (18). Various substituents can easily be introduced at the C3-position via addition/elimination reactions on the sensitive imidoyl chloride moiety.\(^{25}\)

**Scheme 1.** Two-step synthesis of N1- and C6-disubstituted 3,5-dichloro-2(1\(H\))-pyrazinones

In 2005, Van der Eycken and his co-workers\(^ {26}\) demonstrated the first solid-phase synthesis of 2(1\(H\))-pyrazinones based on the Strecker reaction of Wang amide resin (22) with an appropriate aldehyde and trimethylsilyl cyanide (TMSCN). The resultant solid-supported \(\alpha\)-aminonitriles (23) were then cyclized in presence of oxalyl chloride generating the pyrazinone skeleton (24) with a wide array of diverse groups at the C6-position (Scheme 2). Compound 24 underwent addition elimination reaction with \textit{in situ} generated sodium methoxide to give compound 25, this provides an additional diversity point. The authors also demonstrated the smooth cleavage of the pyrazinones 25 from the solid-support under microwave irradiation using a mixture of TFA:DCM (1:2), affording compounds 26 in moderate 14-67 % yield (Scheme 2).

Recently, the first report of a rapid and versatile one-pot, microwave-assisted protocol for the synthesis of N1- and C6-substituted 3,5-dichloro-2(1\(H\))-pyrazinones was
reported by Larhed and his co-workers.\textsuperscript{27} The α-aminonitrile (27) was first generated in a Strecker reaction using trimethylsilyl cyanide (TMSCN) under microwave irradiation and thereafter cyclized with oxalyl chloride under microwave heating to afford desired 2(1H)-pyrazinone (21b) in good yields (Scheme 3).

![Scheme 3. Microwave-assisted one-pot synthesis of the 3,5-dichloro-2(1H)-pyrazinone scaffold](image)

2.1.3. Decoration of the Pyrazinone Scaffold

Apart from the fact that the 3,5-dihalo-2(1H)-pyrazinones (21) already contain two variable substituents \( R_1 \) and \( R_2 \), they still contain reactive functionality at C3- and C5-positions. There is a difference in the reactivity of the two chlorine atoms at C3- and C5-position in the dichloropyrazinone scaffold (Figure 4).

![Figure 4](image)

The chlorine atom at C3-position is part of an imidoyl chloride system, whereas the chlorine at C5-position is a vinylic chloride system. Inherently, the C3-position is more prone to selective functionalisation. Many reactions have been reported at C3-as well as C5-position viz. Suzuki coupling, Sonagashira coupling, Heck coupling, Leibensgic Schrogel coupling, Chan-Lam coupling, Stille coupling, Click reactions, Buchwald-Hartwig coupling, Ullmaan type coupling and many more. Some of the recent examples demonstrating functionalization on pyrazinone scaffold are discussed in this section.
2.1.3.1. Functionalization at C3-position of Pyrazinone

Kaval et al.\textsuperscript{28} investigated the introduction of an acetylene moiety at the C3-position of the 2(1\textit{H})-pyrazinone scaffold. Therefore, the 2(1\textit{H})-pyrazinone (21) was reacted with propargyl alcohol to afford C3-substituted pyrazinones 28 (Scheme 4). Alternatively, the pyrazinone (21) was subjected to a microwave-enhanced Sonogashira reaction with (trimethylsilyl)acetylene, according to previously reported procedure,\textsuperscript{29} followed by desilylation upon treatment with tetrabutylammonium fluoride (TBAF) affording pyrazinones (29).

![Scheme 4. Introduction of an Acetylene Unit at the C3-Position](image)

The robust Stille reaction is another option to substitute the C3-chlorine atom of the dichloropyrazinones. Treatment of dichloropyrazinone (21) with tetraalkyltin or tetraaryltin and Pd(PPh\textsubscript{3})\textsubscript{4} in toluene at 110 °C affords the corresponding C3-substituted 2(1\textit{H})-pyrazinones (31) in good yields (Scheme 5).\textsuperscript{30,31}

![Scheme 5](image)
Contrary to the case of the boronic ester, it is possible to convert the pyrazinones into the corresponding 3-tributyltin derivatives (30) which can in turn be used in subsequent coupling reactions. The reaction time for the Stille coupling at the C3- and C5-positions of the pyrazinone scaffold 21, could be reduced to mere minutes with good to excellent yields under microwave-assisted conditions, in comparison with the order of hours needed for the corresponding reactions under conventional heating conditions (Scheme 6). 29

![Scheme 6](image_url)

Scheme 6. Stille reactions under microwave irradiation

The Suzuki coupling at the C3-position of pyrazinones (21) has been studied. Aryl, heteroaryl and alkenyl groups were introduced using the boronic acids. The best results were obtained with Pd(PPh3)4 as the catalyst and aqueous sodium carbonate as the base in toluene or DME as solvent (Scheme 7). 30,31 It is well documented that under microwave irradiation, the rate of palladium catalyzed cross-coupling reactions are enhanced remarkably.

![Scheme 7](image_url)

Scheme 7

Suzuki reaction on the 2(1H)-pyrazinone system 21 upon microwave irradiation, result not only in a substution in the C3-position, but also to the unreactive C5-position, when switching the base to Cs2CO3 and solvent to DME as described in Scheme 8. 32
Chapter I
Section B: Synthesis of C3-Aroylated 3,5-Dichloro-2-(1H)-pyrazinones using NHC as Catalyst

Another interesting reaction, which further broadens the substituent diversity achievable on the pyrazinone scaffold, is the Heck reaction. Applying the Heck reaction to 3,5-dichloro-2(1H)-pyrazinones (36) provides a direct method for preparing 3-alkenyl-5-chloro-2(1H)-pyrazinones (38). Thus reaction of pyrazinone (36) with various alkenes (37) using Pd(OAc)$_2$/P(ortho-tolyl)$_3$/NEt$_3$ in DMF at 100 °C afforded the corresponding C3-alkenyl substituted products 38 in good yields (Scheme 9).

When doing Heck reactions on dichloropyrazinones at more elevated temperatures (150 °C), there can be a problem of competitive Diels-Alder reaction between the azadiene of the pyrazinone and the alkenes. This problem was encountered in the study of the microwave-assisted version of the above mentioned reaction. Appropriate choice of the catalyst system, however solved this problem, even at elevated temperature (Scheme 10).
Chapter I
Section B: Synthesis of C3-Aroylated 3,5-Dichloro-2-(1H)-pyrazinones using NHC as Catalyst

Scheme 10. Heck vs. Diels-Alder under microwave irradiation

It has been well described that the C3-position of the 2(1H)-pyrazinones can be selectively dechlorinated (42) in the presence of the C5-chlorine upon Pd(PPh₃)₄ catalyzed reaction in DMF at 100 °C with sodium formate (Scheme 11) in 2-3 hours.³³

Scheme 11

However, this dechlorination process at C3-position can be achieved in few minutes by performing reaction under MW irradiation. Upon prolonging the reaction time to 55 min and switching the solvent from DMF to n-butanol, the bis-reduction of the C3- and C5-positions could also be performed in satisfactorily yields whereas the
corresponding reactions applying conventional heating conditions required longer
time (Scheme 11).

Another interesting methodology for the efficient C3-substitution of the 2(1H)-pyrazinone scaffold 27 was elaborated by De Borggraeve and co-workers\textsuperscript{34} using an Arbuzov-type reaction (Scheme 12).\textsuperscript{35} The authors reported a simple and catalyst-free method for the synthesis of phosphonated 2(1H)-pyrazinones (45) starting from 3,5-dichloropyrazinones under conventional and microwave irradiation conditions. Although, only a slight improvement of the yields was observed, the reaction times were tremendously decreased from 12 h under conventional heating to mere 20 min under microwave irradiation.

![Scheme 12. Microwave-assisted Arbuzov-type reaction of 3,5-dichloro-2(1H)-pyrazinones](image)

2.1.3.2. Functionalisation at C5-position of Pyrazinone

The functionalization of the C5-position of 3,5-dihalo-2(1H)-pyrazinones (21) is much more difficult compared to the functionalization of the more reactive C3-position. It is obvious that substitution of the C3-position has to be performed before attempting any substitution at the C5-position of the systems. A limited number of nucleophilic substitution reactions, including Ullmann-type couplings and Pd catalyzed reactions could give rise to substitution at this difficult C5-position. Problems of poor reactivity of 5-chloropyrazinones were partially alleviated by using 5-bromopyrazinones or 5-iodopyrazinones.

2.1.3.2.1. Synthesis of 5-Bromo- and 5-Iodo-pyrazinones from 5-Chloropyrazinones

5-Bromopyrazinones (47) or 5-iodopyrazinones (48) could be synthesized starting from pyrazinones (46) which are prepared by hydrogenolysis of the 5-chloro derivatives 33 using 10 % Pd/C as a catalyst in methanol. Bromination and iodination
of pyrazinones (46) was achieved by using NBS and NIS as halogenating agents in DMF (Scheme 13).\textsuperscript{30,31}

\[
\begin{align*}
\text{H}_2, \text{Pd/C} & \quad \text{MeOH} \\
\text{46} & \quad \text{NBS or NIS} \\
\text{DMF} & \quad 66-82\% \\
\text{47: } X = \text{Br} & \quad \text{48: } X = \text{I}
\end{align*}
\]

Scheme 13

Another interesting method to synthesize 5-substituted pyrazinones is the Ullmann-type reaction using a copper catalyst. The reaction of 5-halo-3-arylamo-2(1H)-pyrazinones (47 and 48) and phenol (49) or thiophenol (50) derivatives with CuCl and Cs\(_2\)CO\(_3\) in toluene afforded the 5-substituted pyrazinones 51 and 52 (Scheme 14).\textsuperscript{36}

\[
\begin{align*}
\text{R} & \quad \text{CuCl} \\
\text{X} & \quad \text{Z} \quad \text{N} \\
\text{47: } X = \text{Br} & \quad \text{51: } Z = \text{O} \\
\text{48: } X = \text{I} & \quad \text{52: } Z = \text{S}
\end{align*}
\]

Scheme 14

Suzuki cross-coupling of C5-halopyrazinones (47 and 48) with aryl-, heteroaryl- and 1-alkenylboronic acids in all cases goes well to produce the corresponding 5-aryl- and 5-alkenyl-2(1H)-pyrazinones (53) (Scheme 15).\textsuperscript{30,31} The Heck reaction of 5-bromo-
2(1H)-pyrazinones (47) with alkenes was studied by using the same reaction conditions as described above for 3-chloro-2(1H)-pyrazinones (36) and afford compound 54.

2.1.3.2.2. O-Alkylation and N1-Alkylation/Arylation of the 2(1H)-Pyrazinone Scaffold

Recently, an efficient microwave assisted strategy for the selective O-alkylation of the 2(1H)-pyrazinone system 55 in the C2-position has been reported.37 When the alkylation was performed using AgCO3 with different alkyl halides in dry hexane under microwave irradiation the corresponding O-alkylated products 56 were formed in excellent yield of 75-89 % as shown in Scheme 16.

Scheme 16. Microwave-assisted Ag(I)-mediated selective O-alkylation of 2(1H)-pyrazinones

Alkylation of the lactam nitrogen atom of pyrazinone (57) is possible but suffers from a potential undesired O-alkylation. If there is a hydrogen atom at the C6-position of the pyrazinone, Cs2CO3 as a base in dioxane exclusively gives N-alkylated product 58 (Scheme 17) and O-alkylation product 59 was greatly reduced.38,39 Whereas when a substituent is present at the C6-position of pyrazinone, O-alkylation is a side reaction under these optimized conditions.

Scheme 17

Van der Eycken and co-workers40 have demonstrated a Cu(II)-mediated Chan-Lam cross-coupling procedure for imparting diversity at the N1-position of the 2(1H)-
pyrazinone scaffold 55 (Scheme 18). During attempts to improve the sluggish couplings under classical conditions performed at room temperature, the authors found that the reaction could greatly be improved when performed under microwave irradiation in combination with simultaneous cooling.

Scheme 18. MW assisted Chan-Lam cross-coupling for N1-substitution of the 2(1H)-pyrazinone scaffold

2.1.4. N-Heterocyclic Carbenes

A carbene is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons and having general formula :CRR'. Carbenes are classified as either singlets or triplets depending upon their electronic structure. Triplet carbenes have two unpaired electrons, one in each of a sp² and a p-orbital, while singlet carbenes have a pair of electrons in a nonbonding sp² orbital and have an empty p orbital (Figure 5).

Figure 5

Most carbenes are very short lived species, although persistent carbenes are known. Persistent carbenes can exist in the singlet or the triplet state, with the singlet state carbenes being more stable. The relative stability of these compounds is only partly due to steric hindrance by bulky groups. Stable carbenes had been proposed to exist by R. Breslow in 1957. Breslow proposed that a relatively stable nucleophilic carbene, a thiazol-2-ylidene derivative, was involved in the catalytic cycle of vitamin B1 (thiamine) that yields furin from furfural. In this cycle, the vitamin's thiazolium ring exchanges a hydrogen atom (attached to C2-position of the ring) for a furfural
residue. Through a deuterium exchange experiment, Breslow demonstrated that C2-proton was readily removed and the exchange occurred through the generation of a stable thiazol-2-ylidene intermediate **61** (Scheme 19).  

\[
\begin{align*}
\text{Br} & \quad \text{S} & \quad \text{N} & \quad \text{N} \\
\text{Br} & \quad \text{S} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

**Scheme 19**

N-heterocyclic carbenes (NHCs), are singlet carbenes with the carbene being incorporated in a nitrogen-containing heterocycle. The concept of NHC was first investigated by Wanzlick in the early 1960 and shortly thereafter, the first application of NHC as a ligand for metal complexes was independently described by Wanzlick45 and Öfele46 in 1968. Surprisingly, the field of of NHCs as ligands in transition metal chemistry remained dormant for more than 20 years. In 1991, a stable, isolated and crystalline dicarbene, which can be represented as a carbene or a nitrogen carbon ylide, was obtained by A. Arduengo and co-workers47 by deprotonation of an imidazolium chloride with a strong base (Scheme 20).

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{N} & \quad \text{N} & \quad \text{Cl} \\
\text{H} & \quad \text{N} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

**Scheme 20**. Preparation of \(N,N'\)-diadamantyl-imidazol-2-ylidene

NHCs are electronically and sterically stabilized. First of all, steric shielding of the carbene carbon by means of the sterically demanding adamantyl groups is an important factor. Second and most importantly, the singlet carbene is stabilized by the orbital interaction of its empty p-orbital with the electron lonepairs of the two neighboring nitrogen atoms. Whereas “traditional” carbenes are generally considered to be electron-deficient, NHCs are electron rich, nucleophilic compounds, which is indicated by the resonance forms 62a and 62b (Figure 6).
The most common way to prepare N-heterocyclic carbenes is the deprotonation of the corresponding azolium salts like imidazolium, triazolium, tetrazolium, pyrazolium, benzimidazolium, oxazolium or thiazolium salts or their partly saturated pendants with the help of suitable bases. Arguably, imidazolium-based carbenes have proven to be especially versatile and useful.

For the synthesis of imidazolium salts, two different routes can be distinguished. On one hand, existing imidazoles can be alkylated using suitable electrophiles, resulting in the formation of symmetrical or unsymmetrical N-alkyl-substituted imidazolium salts and on the other hand, the imidazolium ring can be built up condensation reactions (Schemes 21).

This later route has become the method of choice for many sterically demanding imidazolium salts, e.g. symmetrically N,N-disubstituted imidazolium salts (63) which
can be formed with the reaction of glyoxal with formaldehyde and a primary amine in the presence of a strong acid, resulting in the formation of imidazolium salts. Alternatively, alklylation of monosubstituted imidazoles afford unsymmetrically \(N,N\)-disubstituted imidazolium salts \((64)^{48}\).

Initially, NHCs were studied to promote the benzoin condensation\(^{49}\) and thereafter tremendous increase of the scope of NHCs has been reported. Scope of NHCs has been utilized in various reactions such as, Stetter reaction\(^{50,51}\), hydroacylation reactions\(^{52}\), homoenolate generation\(^{53}\), 1,2-additions\(^{54}\), polymerizations\(^{55}\), hydrosilylation, transesterification\(^{56}\), and Diels–Alder reactions\(^{57}\).

Scope of NHCs in metal catalyzed cross coupling reactions are known and discussed in this section\(^{58,59}\). Many reactions have been reported in this context but only few of them are demonstrated here. Since, NHCs have a wide scope in organic synthesis, it can be utilized in cross coupling reactions of 3,5-dichloropyrazinones. Chen has disclosed the use of chelating κ2-NHC–Pd complex \((65)\) in Hiyama cross-coupling that leads to unsymmetrical biphenyl ring formation (Scheme 22)\(^{60}\). Coupling reaction was found to be successful with aryl bromides and activated aryl chlorides in the presence of TBAF and Cs\(_2\)CO\(_3\). Unfortunately, unactivated aryl chlorides resulted in poor yields.

![Scheme 22](image)

Rovis and co-workers\(^{61}\) had designed a new chiral NHC catalyst that renders the desired asymmetric product \((71)\) via intermolecular Stetter reaction of nitroalkenes \((70)\) and heteroarylaldehydes \((69)\) in highly efficient and enantioselective manner through manipulation of stereoelectronic as well as steric effects (Scheme 23).
Suzuki et al.\textsuperscript{62} have demonstrated that the NHC derived from 1,3,4,5-tetramethylimidazolium iodide is a powerful catalyst for the nucleophilic aroylation. The catalyst loading can be reduced to 1 mol % without a significant drop in the product yield of the reaction between reactant 72 and 73 (Scheme 24).
2.2. Present Work
Growing interest in 2(1H)-pyrazinones nucleus for many chemists and biologists has made this nucleus an interesting scaffold for the elaboration of different types of skeletons of biological interesting compounds. A wide range of biologically active groups can be easily introduced to this nucleus. Recently, it has been reported by our group, that 2(1H)-pyrazinones can be decorated with different alkyl and aryl groups at the most active C3-position and further on the C5-position using microwave assisted cross-coupling reactions.\(^{63}\)

In view of this, we became interested in exploring the possible bioactivity of pyrazinone scaffold with the introduction of aroyl group at C3-position. This was inspired by the fact that related 3-aryloquinoxalin-2(1H)-ones (75) have been described as late sodium channel inhibitors\(^{64}\) and 3-benzoyl-2-piperazinyl-quinoxalines (76) have been reported as potential antitumor agents\(^{65}\) (Figure 7). Since, the selective aroylation of the C3-position of the 2(1H)-pyrazinone system has not known in the literature. We herein report the synthesis of C3-arylated 2(1H)-pyrazinone using NHC as catalyst.

![Figure 7](image)

2.2.1. Synthesis of C3-Aroylated 2(1H)-Pyrazinones
The synthesis of C3-arylated 2(1H)-pyrazinone was started with the optimization of reaction on the model substrate 3,5-dichloro-1-(4-methoxybenzyl)-6-methylpyrazin-2(1H)-one (77a) with the 4-methoxybenzaldehyde (78a). Initially, the literature reported\(^{66}\) procedure was followed for the aroylation of model substrate 77a with the aldehyde 78a using NHC catalyst A and NaH as a base in DMF as solvent and the desired 5-chloro-3-(4-methoxybenzoyl)-1-(4-methoxybenzyl)-6-methylpyrazin-2(1H)-one (79a) was obtained in 62 % yield (Scheme 25).
To improve the yield of reaction various organic and inorganic bases were screened which resulted in either no reaction or traces of desired compound 79a was observed by GC/MS or TLC analysis. However, switching to solvent from DMF to DMSO afford the desired product 79a in much improved yield of 83 %.

With improved results by changing the solvent, we also applied less polar solvents but no improvement in the yield of desired compound 79a was observed. Different NHC catalysts (B, C and D) were also investigated for the aroylation of pyrazinone 77a and did not result in any promising results. Further, with lowering the loading of catalyst to 30 mol% to 5 mol% did not affect the yield and 84 % of the desired product 79a was observed. Hence, the best condition for the aroylation of pyrazinone 77a was obtained using catalyst A (5 mol%)/ NaH (2.0 eq.) and DMSO as a solvent at room temperature in 0.5-3 hours to achieve the desired C3-aroylated pyrazinones 79a. The optimized results are described in Table 1.

With the optimized conditions, we have synthesized a small library of C3-aroylated pyrazinones 79a-y using different substituted 3,5-dichloropyrazinones 77a-l and aldehydes 78a-m as shown in Scheme 26. The coupling reaction of pyrazinones 77a-k with aldehyde 78a afforded 3-aroyl-2-(1H)-pyrazinone 79a-l in good to excellent yield. It was assumed that the nature of substituent at C6-position did not seem to play a major role in the product formation. However, when substrate 77k (with C6-benzyl substituted pyrazinone) was treated with aldehyde 78a, there was significant drop in the yield (52 %) of 79k was observed (Scheme 26).
Table 1. Optimisation for the reaction of \( p \)-methoxy benzaldehyde \( 78a \) with pyrazinone (\( 77a \))

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Base</th>
<th>Solvent</th>
<th>Yields( ^a ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A (30 mol%) /DBU (1.2 eq.)</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>A (30 mol%) /DIEA (1.2 eq.)</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>A (30 mol%) /Cs(_2)CO(_3) (1.2 eq.)</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>A (30 mol%) /Et(_3)N (1.2 eq.)</td>
<td>DMF</td>
<td>traces(^b)</td>
</tr>
<tr>
<td>5</td>
<td>A (30 mol%) /NaH (2.0 eq.)</td>
<td>DMF</td>
<td>83(^a)</td>
</tr>
<tr>
<td>6</td>
<td>A (30 mol%) /((\text{Me}_3\text{Si})_2)NLi (1.2 eq.)</td>
<td>DMF</td>
<td>36(^a)</td>
</tr>
<tr>
<td>8</td>
<td>A (30 mol%) /NaH (2.0 eq.)</td>
<td>DMSO</td>
<td>84(^a)</td>
</tr>
<tr>
<td>9</td>
<td>A (30 mol%) /NaH (2.0 eq.)</td>
<td>THF</td>
<td>65(^b)</td>
</tr>
<tr>
<td>10</td>
<td>A (30 mol%) /NaH (2.0 eq.)</td>
<td>Dioxane</td>
<td>70(^b)</td>
</tr>
<tr>
<td>11</td>
<td>A (30 mol%) /NaH (2.0 eq.)</td>
<td>CH(_3)CN</td>
<td>68(^b)</td>
</tr>
<tr>
<td>12</td>
<td>B (30 mol%) /NaH (2.0 eq.)</td>
<td>DMSO</td>
<td>NR</td>
</tr>
<tr>
<td>13</td>
<td>C (30 mol%) /NaH (2.0 eq.)</td>
<td>DMSO</td>
<td>traces(^b)</td>
</tr>
<tr>
<td>14</td>
<td>D (30 mol%) /NaH (2.0 eq.)</td>
<td>DMSO</td>
<td>NR</td>
</tr>
<tr>
<td>15</td>
<td>A (5 mol%) /NaH (2.0 eq.)</td>
<td>DMSO</td>
<td>84(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yields; \(^b\)Conversion of reaction after 2 h and determined by GC–MS analysis

Further, the scope of both aromatic as well as few aliphatic aldehydes were evaluated, and the desired aroylated product \( 79l\text{-}w \) was obtained in good yields. However, use of aliphatic aldehydes \( 79o \) and \( 79p \) did not result in the formation of product \( 79x \) and \( 79y \), and the corresponding starting materials were decomposed. Remarkably, good yields were observed with the \textit{ortho}-substituted benzaldehydes. However, when furfural was employed as heteroaromatic aldehyde, the corresponding aroylated product \( 79w \) was obtained in poor yield (36 %) as shown in \textbf{Scheme 26}. 
Chapter I
Section B: Synthesis of C3-Aroylated 3,5-Dichloro-2-<sup>1H</sup>-pyrazinones using NHC as Catalyst

![Scheme 26](image)

### Table 26

<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMB</td>
<td>Me</td>
<td>FMP</td>
<td>84</td>
</tr>
<tr>
<td>PMB</td>
<td>isobutyl</td>
<td>PMB</td>
<td>78</td>
</tr>
<tr>
<td>PMB</td>
<td>H</td>
<td>PMB</td>
<td>70</td>
</tr>
<tr>
<td>PMB</td>
<td>2-naphthyl</td>
<td>PMB</td>
<td>67</td>
</tr>
<tr>
<td>PMB</td>
<td>4-F-Ph</td>
<td>PMB</td>
<td>81</td>
</tr>
<tr>
<td>Ph</td>
<td>PMP</td>
<td>Ph</td>
<td>66</td>
</tr>
<tr>
<td>Ph</td>
<td>2-Br-5-ChPh</td>
<td>Ph</td>
<td>84</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>79</td>
</tr>
<tr>
<td>Ph</td>
<td>2-OMe-Ph</td>
<td>Ph</td>
<td>82</td>
</tr>
<tr>
<td>2-OMe-Ph</td>
<td>Ph</td>
<td>2-OMe-Ph</td>
<td>52</td>
</tr>
<tr>
<td>2-OMe-Ph</td>
<td>[1,4]dioxole&lt;sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;&lt;/sub&gt;</td>
<td>PMB</td>
<td>72</td>
</tr>
<tr>
<td>Furan</td>
<td>PMB</td>
<td>isobutyl</td>
<td>85</td>
</tr>
<tr>
<td>PMB</td>
<td>isobutyl</td>
<td>2-naphthyl</td>
<td>82</td>
</tr>
<tr>
<td>PMB</td>
<td>isobutyl</td>
<td>4-F-Ph</td>
<td>83</td>
</tr>
<tr>
<td>PMB</td>
<td>isobutyl</td>
<td>[1,3]dioxole&lt;sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;&lt;/sub&gt;</td>
<td>83</td>
</tr>
<tr>
<td>PMB</td>
<td>2-Br-5-ChPh</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>PMB</td>
<td>3,4,5-OMe-Ph</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>PMB</td>
<td>2-Ch6-F-Ph</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>PMB</td>
<td>2,4,5-Me-Ph</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>PMB</td>
<td>[1,4]dioxole&lt;sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;&lt;/sub&gt;</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Furan</td>
<td>PMB</td>
<td>isobutyl</td>
<td>36</td>
</tr>
<tr>
<td>PMB</td>
<td>isobutyl</td>
<td>n-decyl</td>
<td>0</td>
</tr>
<tr>
<td>PMB</td>
<td>isobutyl</td>
<td>isopropyl</td>
<td>0</td>
</tr>
</tbody>
</table>

**Scheme 26**

2.2.2. Proposed Mechanism for C3-acylation of Pyrazinone using NHC Catalyst

The proposed mechanism for the formation of the C3-acylated pyrazinones 79 has been described in Scheme 27. N,N-dimethyl imidazolium carbene I acts as a nucleophile and activates the aldehyde 78 forming in situ Breslow intermediate III through II with the subsequent proton migration. In the next step, nucleophilic attack of Breslow intermediate III takes place on the more electrophilic C3-position of pyrazinone 77 leading to the intermediate IV followed by the removal of chloride to afford intermediate V. In the final step, base regenerates the catalyst I with the formation of desired C3-acylated pyrazinone 79.
Chapter I
Section B: Synthesis of C3-Aroylated 3,5-Dichloro-2-(1H)-pyrazinones using NHC as Catalyst

Scheme 27
2.3. Results and Discussion

Compounds 79a-w are new and being reported for the first time. The structure of all the compounds 79a-w were unambiguously established on the basis of spectral data (\(^1\)H NMR, \(^{13}\)C NMR and HRMS). The structural characterization of a few representative examples is discussed in this section.

2.3.1. 5-Chloro-3-(4'''-methoxybenzoyl)-1-(4'''-methoxybenzyl)-6-(4''''-methoxyphenyl)pyrazin-2(1\(H\))-one (79e)

![Chemical Structure of 79e](image)

Compound 79e was obtained as yellow solid in 87 % yield. Its HRMS showed peak at \(m/z\) 490.1318, which is in close agreement with the molecular formula C\(_{27}\)H\(_{23}\)ClN\(_2\)O\(_3\) (calcd. 490.1295). In the \(^1\)H NMR spectrum, the characteristic peak of benzylic protons appeared as a singlet at \(\delta\) 5.08 integrating for two protons; and protons of three methoxy groups appeared as two singlets at \(\delta\) 3.77 (3H) and 3.89 (6H) as shown in Figure 8. Similarly, in its \(^{13}\)C NMR spectrum the characteristic peaks for two carbonyl carbons of ketonic and amide groups appeared at \(\delta\) 188.98 and 154.13 respectively. The peak for C-3 carbon appeared in downfield region of spectrum at \(\delta\) 151.09, due to carbonyl groups in vicinity which indicate the carbon-carbon coupling (Figure 8). Carbon bearing three methoxy groups, *i.e.* C-4', C-4''' and C-4'' appeared at \(\delta\) 159.38, 161.05 and 164.47, respectively. The peaks of carbon for three methoxy groups appeared at \(\delta\) 55.26, 55.47 and 55.55 whereas, the benzylic carbon appeared at \(\delta\) 49.57.

The peaks of all other protons and carbons of the molecule were present in \(^1\)H and \(^{13}\)C NMR spectra of the molecule. Based on the above spectral data analysis, the structure of the compound 79e was unambiguously established as 5-chloro-3-(4'''-methoxybenzoyl)-1-(4'''-methoxybenzyl)-6-(4''''-methoxyphenyl)pyrazin-2(1\(H\))-one.
Figure 8. $^1$H and $^{13}$C NMR spectra of compound 79e (400, 100 MHz, CDCl$_3$)
2.3.1. 5-Chloro-3-(4''-fluorobenzoyl)-6-isobutyl-1-(4''-methoxybenzyl)pyrazin-2(1H)-one (79o)

Compound 79o was obtained as a yellow semi-solid in 83 % yield. Its HRMS showed peak at \( m/z \) 428.1303, which is in close agreement with the molecular formula \( \text{C}_{23}\text{H}_{22}\text{ClFNO}_3 \) (calcd. 428.1303). In the \( ^1\text{H} \) NMR spectrum, the characteristic peaks of methylene protons, \( i.e. \) C-1'''H appeared as a doublet with \( J = 7.32 \) Hz at \( \delta \) 2.81 and methine proton, \( i.e. \) C-2'''H appeared as a multiplet in the range of \( \delta \) 2.14-2.21, due to its coupling with the neighboring six methyl protons and methylene protons. The protons of methyl groups \( (2 \times \text{C-3''}''\text{H}) \) appeared as a doublet with the \( J = 6.52 \) Hz at \( \delta \) 1.09 integrating for six protons. N-CH\(_2\) and OCH\(_3\) protons appeared as a singlet at \( \delta \) 5.34 and 3.79, respectively. In its \( ^{13}\text{C} \) NMR spectrum, the characteristic peaks for two carbonyl carbons appeared at \( \delta \) 188.58 (ketonic) and 154.24 (amidic). The peak for C-3 carbon appeared in downfield region at \( \delta \) 147.56 indicating the carbon-carbon coupling (Figure 9). Carbon bearing methoxy group, \( i.e. \) C-4' appeared at \( \delta \) 159.57. A doublet was observed for carbon bearing flourine, \( i.e. \) C-4'' at \( \delta \) 166.25 \( (J_{\text{CF}} = 254.46 \text{ Hz}) \), whereas carbon bearing chlorine appeared at \( \delta \) 143.10 and carbons N-CH\(_2\) and OCH\(_3\) appeared at \( \delta \) 48.34 and 55.34. Carbons C-1'''', C-2'''' and C-3'''' appeared at \( \delta \) 29.01, 38.48, and 22.59, respectively.

The peaks of all other protons and carbons of the molecule were present in \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectra of the molecule. On the basis of above spectral data, the structure of the compound 79o was unambiguously established as 5-chloro-3-(4''-fluorobenzoyl)-6-isobutyl-1-(4''-methoxybenzyl)pyrazin-2(1H)-one.
Figure 9. $^1$H and $^{13}$C NMR spectra of compound 79o (400, 100 MHz, CDCl$_3$)
2.3.2. 3-(Benzo[d][1''',3''']dioxole-5'''-carbonyl)-5-chloro-6-isobutyl-1-(4'-methoxy benzyl)pyrazin-2(1H)-one (79p)

Compound 79p was obtained as yellow semi-solid in 83%. Its HRMS showed peak at \( m/z \) 454.1301, which is in close agreement with the molecular formula \( \text{C}_{24}\text{H}_{23}\text{ClN}_{2}\text{O}_{5} \) (calcd. 454.1295). In the \(^1\text{H} \) NMR spectrum, the characteristic peaks of methylene protons, \( i.e. \) C-1''H appered as a doublet with \( J = 7.35 \) Hz at \( \delta 2.79 \) and methine proton, \( i.e. \) C-2''H appeared as a multiplet in the range of \( \delta 2.09-2.23 \) due to its coupling with the neighboring six methyl protons and methylene protons. The protons of methyl groups (2 x C-3''H) appeared as a doublet with the \( J = 6.6 \) Hz at \( \delta 1.09 \) integrating for six protons as shown in Figure 10. N-CH\(_2\) and O-CH\(_3\) protons appeared as a singlet at \( \delta 5.32 \) and 3.79, respectively. The protons at carbon, C-2'' of dioxole ring appeared as a singlet at \( \delta 6.06 \) integrating for two protons. In its \(^{13}\text{C} \) NMR spectrum, the characteristic peaks for two carbonyl carbons appeared at \( \delta 188.47 \) (ketonic) and 152.79 (amidic). The peak for carbon, C-3 appeared downfield at \( \delta 148.23 \) indicating the carbon-carbon coupling (Figure 10), and carbon C-2'' appeared at \( \delta 102.04 \). Carbon bearing methoxy group \( i.e. \) C-4' appeared at \( \delta 159.49 \) and carbon bearing chlorine appeared at \( \delta 142.21 \). The bridgehead carbons, \( i.e. \) C-9'' and C-8'' appeared downfield at \( \delta 148.66 \) and 154.30, respectively. Carbons N-CH\(_2\) and OCH\(_3\) appeared at \( \delta 48.21 \) and 55.34 respectively and carbons C-1''', C-2''' and C-3''' appeared at \( \delta 29.00, 38.37 \) and 22.60, respectively.

The peaks of all other protons and carbons of the molecule were present in \(^1\text{H} \) and \(^{13}\text{C} \) NMR spectra of the molecule. Based on the above spectral data analysis, the structure of the compound 79p was unambiguously established as 3-(Benzo[d][1''',3''']dioxole-5'''-carbonyl)-5-chloro-6-isobutyl-1-(4'-methoxy benzyl)pyrazin-2(1H)-one.
Figure 10. $^1$H and $^{13}$C NMR spectra of compound 79p (300, 75 MHz, CDCl$_3$)
2.3.4. \( \text{5-Chloro-1-(4'-methoxybenzyl)-3-(3''\text{,}4''\text{,}5''\text{-trimethoxybenzoyl})pyrazin-2(1H)-one} \) (79s)

Compound 79s was obtained as a colourless solid in 70 % yield. Its HRMS showed peak at \( m/z \) 444.1084, which is in close accordance with the molecular formula \( \text{C}_{33}\text{H}_{38}\text{ON}_{2} \) (calcd. 444.1084). In the \( ^1\text{H} \) NMR spectrum, the characteristic peak of benzylic protons appeared as a singlet at \( \delta \) 5.06 integrating for two protons; peaks for protons of four methoxy groups appeared as three singlets at \( \delta \) 3.83 (3H), 3.86 (6H) and 3.93 (3H) as shown in Figure 11. In its \( ^{13}\text{C} \) NMR spectrum, the characteristic peaks for two carbonyl carbons appeared at \( \delta \) 188.87 (ketonic) and 151.86 (amidic). The peak for C-3 carbon appeared in downfield region due to carbonyl in vicinity at \( \delta \) 143.85 indicating the carbon-carbon coupling (Figure 11). Carbon bearing methoxy groups, i.e. C-4', C-3'' & C-5'' and C-4'' appeared at \( \delta \) 160.33, 153.09 and 129.71, respectively. The peaks for four methoxy carbons and benzylic carbon appeared at \( \delta \) 61.00, 56.36 and 55.39 (4 x O-CH\text{3}) and 52.55 (N-CH\text{2}).

The peaks of all other protons and carbons of the molecule were present in \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectra of the molecule. Based on the spectral data analysis, the structure of the compound 79s was unambiguously established as 5-Chloro-1-(4'-methoxybenzyl)-3-(3''\text{,}4''\text{,}5''\text{-trimethoxybenzoyl})pyrazin-2(1H)-one.
Chapter I

Section B: Synthesis of C3-Aroylated 3,5-Dichloro-2-(1H)-pyrazinones using NHC as Catalyst

Figure 11. $^1$H and $^{13}$C NMR spectra of compound 79s (300 Hz, 75 MHz, CDCl$_3$)
On the similar basis we have characterized the 5-chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)-6-methyl-pyrazin-2(1H)-one (79a), 5-chloro-6-isobutyl-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79b), 5-chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79c), 6-benzyl-5-chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79d), 5-chloro-3-(4''-methoxybenzoyl)-6-(4''-methoxyphenyl)-1-phenylpyrazin-2(1H)-one (79f), 5-chloro-3-(4''-methoxybenzoyl)-1-methyl-6-phenylpyrazin-2(1H)-one (79g), 5-chloro-3-(4''-methoxybenzoyl)-6-methyl-1-phenylpyrazin-2(1H)-one (79h), 5-chloro-3-(4'-methoxybenzoyl)-1,6-dimethylpyrazin-2(1H)-one (79i), 5-chloro-3-(4''-methoxybenzoyl)-6-(2''-methoxyphenyl)-1-phenylpyrazin-2(1H)-one (79j), 6-benzyl-5-chloro-3-(4''-methoxybenzoyl)-1-(2'-methoxybenzyl)pyrazin-2(1H)-one (79k), 5-chloro-6-isobutyl-1-(4''-methoxybenzyl)-3-(4''-methylbenzoyl)pyrazin-2(1H)-one (79l), 3-[4''-(benzyloxy)benzoyl]-5-chloro-6-isobutyl-1-(4''-methoxybenzoyl)pyrazin-2(1H)-one (79m), 3-(2''-naphthoyl)-5-chloro-6-isobutyl-1-(4''-methoxybenzoyl)pyrazin-2(1H)-one (79n), 3-(2''-bromo-5''-chlorobenzoyl)-5-chloro-6-isobutyl-1-(4''-methoxybenzoyl)pyrazin-2(1H)-one (79q), 3-(2''-bromo-5''-methoxybenzoyl)-5-chloro-1-(4''-methoxybenzyl)pyrazin-2(1H)-one (79r), 5-chloro-3-(2''-chloro-6''-fluorobenzoyl)-1-(4''-methoxybenzyl)pyrazin-2(1H)-one (79t), 5-chloro-1-(4''-methoxybenzyl)-3-(2''-4''-6''-trimethylbenzoyl)pyrazin-2(1H)-one (79u), 5-chloro-3-(2''-3''-dihydrobenzo[b][1,4]dioxine-6''-carbonyl)-1-(4''-methoxybenzoyl)pyrazin-2(1H)-one (79v) and 5-Chloro-3-(furan-2''-carbonyl)-1-benzylpyrazin-2(1H)-one (79w).
2.4. Conclusions

- An efficient and mild one-pot methodology regarding the coupling of a Breslow intermediate with the imidoylchloride system of a 3,5-dichloro-2(1H)-pyrazinones was developed for the synthesis of C3-aroylated 3,5-dichloro-2-(1H)-pyrazinones 79a-w.
- The compounds 79a-w are novel and have not been reported in literature earlier.
- The structure of all the compounds 79a-w were unambiguously established on the basis of spectral data (\(^1\)H NMR, \(^{13}\)C NMR spectra and HRMS analysis).
2.5. Experimental

2.5.1. General

Analytical TLCs were performed on Merck silica gel 60 F_{254} plates. All flash chromatographic separations were performed on 100-200 mesh silica gel. The $^1$H NMR and $^{13}$C NMR spectra (in CDCl$_3$) were recorded on Bruker Avance 300 (300 and 75 MHz) and Bruker AMX-400 (400 and 100 MHz) spectrometers at Katholieke Universiteit Leuven, Belgium. TMS was used as an internal standard. The chemical shifts values were quoted on δ scale, i.e. in ppm and the coupling constant (J) were quoted in Hertz (Hz). Low-resolution mass spectra were recorded on a HEWLETT-PACKARD instrument (CI and EI) and LCQ Advantage instrument (ESI). High-resolution mass spectra (EI) were recorded on a KRATOS MS50TC instrument. Melting Points were determined using Reichert-Jung Thermovar apparatus and are uncorrected.

2.5.2. Materials

Chemicals were obtained from commercial suppliers and were used without further purification unless otherwise noted. All used solvents, i.e. tetrahydrofuran, hexane, dimethylsulphoxide, dioxane, acetonitrile, $N,N$-dimethyl formamide, ethyl acetate and acetone were distilled prior to use.

2.5.3. General procedure for the preparation of compounds (77a-l)

General procedure for the preparation of pyrazinones 77a-l is the same as previously described by our group.\textsuperscript{67} Data for the compounds 77a, 77c, 77e,\textsuperscript{67} 77f,\textsuperscript{29} 77h,\textsuperscript{68} 77j, 77k\textsuperscript{69} and 77l\textsuperscript{24} are in accordance with the previously published work.

2.5.3.1. 1-(4'-Methoxybenzyl)-3,5-dichloro-6-isobutylpyrazin-2(1H)-one (77b)

It was obtained as a yellow solid in 44 % yield.
Melting Point (M.P.): 118-120 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 1.05 (6H, d, J = 6.57 \text{ Hz}, 2 \times \text{C-3'H}), 2.03-2.14 (1H, m, \text{C-2''H}), 2.70 (2H, d, J = 7.35 \text{ Hz}, \text{C-1''H}), 3.78 (3H, s, OCH\(_3\)), 5.30 (2H, s, N-CH\(_2\)), 6.86 (2H, d, J = 8.67 \text{ Hz}, \text{C-3'H and C-5'H}), 7.10 (2H, d, J = 8.49 \text{ Hz}, \text{C-2'H and C-6'H}).

\(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta 22.43 (2 \times \text{C-3''}), 28.88 (\text{C-2''}), 37.87 (\text{C-1''}), 49.30 (\text{N-CH}_2), 55.31 (\text{OCH}_3), 114.46 (\text{C-3' and C-5'}), 124.74 (\text{C-1'}), 126.25 (\text{C-6}), 128.31 (\text{C-2' and C-6'}), 138.97 (\text{C-5}), 143.88 (\text{C-3}), 153.15 (\text{C-2}), 159.49 (\text{C-4'}).

HRMS (EI) \textit{m/z}: C\(_{16}\)H\(_{18}\)Cl\(_2\)N\(_2\)O calcd. 340.0745, found 340.0753.

2.5.3.2. 3,5-Dichloro-1-methyl-6-phenylpyrazin-2(1\(H\))-one (77g)

It was obtained as a yellow solid in 39 % yield.

Melting Point (M.P.): 177-179 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 3.32 (3H, s, \text{N-CH}_3), 7.30-7.33 (2H, m, \text{Ar-H}), 7.56-7.58 (3H, m, \text{Ar-H}).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 36.16 (\text{N-CH}_3), 123.74 (\text{C-5}), 128.75 (\text{C-2' and C-6'}), 129.55 (\text{C-3' and C-5'}), 130.51 and 130.61 (\text{C-4' and C-6}), 138.72 (\text{C-1'}), 145.11 (\text{C-3}), 152.72 (\text{C-2}).

HRMS (EI) \textit{m/z}: C\(_{17}\)H\(_{18}\)Cl\(_2\)N\(_2\)O calcd. 254.0014, found 254.0033.

2.5.3.3. 3,5-Dichloro-1,6-dimethylpyrazin-2(1\(H\))-one (77i)

It was obtained as a yellow solid in 51 % yield.
Melting Point (M.P.): 93-95 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.49 (3H, s, CH$_3$), 3.64 (3H, s, N-CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 17.09 (CH$_3$), 33.84 (N-CH$_3$), 123.35 (C-6), 136.20 (C-5), 142.83 (C-3), 152.87 (C-2).

HRMS (EI) $m/z$: calcd. C$_6$H$_6$Cl$_2$N$_2$O 191.9857, found 191.9869.

2.5.4. General procedure for C3-aroylated 3,5-dichloro-2(1H)-pyrazinone (79a-w)
To an oven-dried two-necked flask equipped with rubber septum and stir bar were added 3,5-dichloro-2(1H)-pyrazinone (77a-l, 0.33 mmol), NHC catalyst A (5 mol%), corresponding aldehyde (78a-o, 0.4 mmol), and DMSO (4 mL) as solvent. The resulting solution was flushed with argon (3 times), stirred for 10 min and then cooled to 0 °C. Then NaH (2.0 eq., 60 % in mineral oil) was added all at once, and the reaction mixture was allowed to warm to room temperature and was further stirred for 0.5-3 h. The reaction was monitored by GC/MS and TLC analysis. After the reaction was complete, H$_2$O (20 mL) was added and the mixture was extracted by CH$_2$Cl$_2$ (3 X 50 mL). The combined organic layers were washed with brine (25 mL) and subsequently H$_2$O (20 mL) and then dried over Na$_2$SO$_4$, filtered, and concentrated under vaccum by rota-vapour. The resulting crude product was purified by silica gel column chromatography using (hexane/EtOAc 9:1 to 7:3) to afford corresponding C3-aroylated products 79a-w in moderate to good yields.

2.5.4.1. 5-Chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)-6-methyl-pyrazin-2(1H)-one (79a)

![Chemical structure of 5-Chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)-6-methyl-pyrazin-2(1H)-one (79a)](image)

It was obtained as a yellow solid in 83 % yield.

Melting Point (M.P.): 172-174 °C.
**Section B: Synthesis of C3-Aroylated 3,5-Dichloro-2-(1H)-pyrazinones using NHC as Catalyst**

\[ \delta 2.53 (3H, s, CH_3), 3.79 \text{ and } 3.88 (6H, 2 \times s, 2 \times OCH_3), 5.31 (2H, s N-CH_2), 6.87 (2H, d, J = 8.67 Hz, C-3'\text{H and C-5''H}), 6.94 (2H, d, J = 8.85 Hz, C-3''\text{H and C-5'H}), 7.21 (2H, d, J = 8.46 Hz, C-2'\text{H and C-6'H}), 7.94 (2H, d, J = 8.85Hz, C-2''\text{H and C-6''H}). \]

\[ \delta 17.38 (CH_3), 48.59 (N-CH_2), 55.35 \text{ and } 55.57 (2 \times O-CH_3), 113.93 \text{ and } 114.51 (C-3' \text{ & C-5'} \text{ & C-3''} \text{ & C-5''}), 125.81, 126.19 \text{ and } 128.12 (C-1', C-1'' \text{ and C-6}), 128.89 (C-2' \text{ & C-6'}), 132.58 (C-2'' \text{ and C-6''}), 139.23 (C-5), 148.69 (C-3), 154.30 (C-2), 159.56 (C-4'), 164.36 (C-4''), 188.83 (CO). \]

HRMS (EI) \( m/z \): \( C_{23}H_{19}ClN_2O_4 \) calcd. 398.1033, found 398.1044.

2.5.4.2. 5-Chloro-6-isobutyl-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)-pyrazin-2(1H)-one (79b)

It was obtained as brown viscous liquid in 78 % yield.

\[ \delta 1.08 (6H, d, J = 6.57 Hz, 2 \times C-3'''H), 2.11-2.20 (1H, m, C-2''''H), 2.79 (2H, d, J = 7.32 Hz, C-1''''H), 3.78 \text{ and } 3.87 (6H, 2 \times s, 2 \times OCH_3), 5.33 (2H, s, N-CH_2), 6.87 (2H, d, J = 8.67 Hz, C-3'''H and C-5''''H), 6.94 (2H, d, J = 8.85 Hz, C-3''''H and C-5'H), 7.15 (2H, d, J = 8.46 Hz, C-2'H and C-6'H), 7.92 (2H, d, J = 8.85 Hz, C-2''''H and C-6''''H). \]

\[ \delta 22.58 (2 \times C-3''), 28.98 (C-2''), 38.35 (C-1''), 48.13 (N-CH_2), 55.33 \text{ and } 55.55 (2 \times O-CH_3), 113.90 \text{ and } 114.47 (C-3' \text{ & C-5' \text{ & C-3''' \& C-5'''}), 126.61, 126.63 \text{ and } 128.07 (C-1', C-1'' \text{ and C-6}), 128.52 (C-2' \text{ & C-6'}), 132.56 (C-2'' \text{ and C-6''}), 142.05 (C-5), 148.91 (C-3), 154.31 (C-2), 159.46 (C-4'), 164.33 (C-4''), 188.82 (CO). \]

HRMS (EI) \( m/z \): \( C_{24}H_{25}ClN_2O_4 \) calcd. 440.1503, found 440.1497.
2.5.4.3. 5-Chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79c)

It was obtained as yellow solid in 70 % yield.

**Melting Point (M.P.):** 124-125 °C

**$^1$H NMR (300 MHz, CDCl$_3$):** δ 3.83 and 3.88 (6H, 2 x s, 2 x OCH$_3$), 5.04 (2H, s, N-CH$_2$), 6.92-6.96 (4H, m, C-3''H & C-5''H and C-3'H & C-5'H), 7.29-7.33 (3H, m, C-2'H & C-6'H and C-6H), 7.91 (2H, d, $J = 8.67$ Hz, C-2''H and C-6''H).

**$^{13}$C NMR (75 MHz, CDCl$_3$):** δ 52.35 (N-CH$_2$), 55.39 and 55.59 (2 x OCH$_3$), 113.73, 114.01 and 114.81 (C-3' & C-5', C-3'' & C-5'' and C-6), 125.37, 125.82, 127.71, 128.15, 130.80, 132.31 and 132.62 (Ar-C), 152.51 and 153.20 (C-2 and C-3), 160.30 (C-4'), 164.57 (C-4''), 188.66 (CO).

**HRMS (EI) m/z:** C$_{20}$H$_{17}$ClN$_2$O$_4$ calcd. 384.0877, found 384.0884.

2.5.4.4. 6-Benzyl-5-chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79d)

It was obtained as yellow solid in 67 % yield.

**Melting Point (M.P.):** 107-108 °C.

**$^1$H NMR (300 MHz, CDCl$_3$):** δ 3.80 and 3.89 (6H, 2 x s, 2 x OCH$_3$), 4.23 (2H, s, CH$_2$-Ph), 5.13 (2H, s, N-CH$_2$), 6.88 (2H, d, $J = 8.56$ Hz, C-3' and C-5'), 6.97 (2H, d, $J$
= 8.80 Hz, C-3''H and C-5''H), 7.13-7.17 (4H, m, Ar-H), 7.34-7.41 (3H, m, Ar-H), 7.97 (2H, d, J = 8.80 Hz, C-2''H and C-6''H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 35.64 (CH$_2$-Ph), 48.05 (N-CH$_2$), 55.37 and 55.59 (2 x OCH$_3$), 114.02 and 114.62 (C-3'' & C-5'' and C-3' & C-5'), 126.54, 127.16, 127.58, 127.83, 128.03, 129.55 and 132.60 (Ar-C), 133.86 (C-5), 140.17 (C-1''), 150.30 (C-3), 154.44 (C-2), 159.57 (C-4'), 164.49 (C-4''), 188.74 (CO).

HRMS (EI) m/z: C$_{27}$H$_{23}$ClN$_2$O$_4$ calcd. 474.1346, found 474.1360.

2.5.4.5. 5-Chloro-3-(4''-methoxybenzoyl)-1-(4'-methoxybenzyl)-6-(4'''-methoxyphenyl) pyrazin-2(1H)-one (79e)

![Chemical Structure](image)

It was obtained as yellow solid in 87 % yield.

Melting Point (M.P.): 147-148 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 3.77 and 3.89 (9H, 2 x s, 3 x OCH$_3$), 5.08 (2H, s, N-CH$_2$), 6.72 (2H, d, J = 8.80 Hz, C-3'H and C-5'H), 6.83 (2H, d, J = 8.56 Hz, C-3''H and C-5''H), 6.96-7.01 (4H, m, C-3''H & C-5''H and C-2'H & C-6'H), 7.09 (2H, d, J = 8.80 Hz, C-2''H and C-6''H), 7.99 (2H, d, J = 9.04 Hz, C-2''H and C-6''H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 49.57 (N-CH$_2$), 55.26, 55.47 and 55.58 (3 x OCH$_3$), 113.88, 113.99, 114.45, 122.63, 126.60, 127.22, 128.05, 129.56, 130.76, 132.62 and 141.05 (Ar-C), 151.09 (C-3), 154.13 (C-2), 159.38 (C-4'), 161.05 (C-4''), 164.47 (C-4''), 188.98 (CO).

HRMS (EI) m/z: C$_{27}$H$_{23}$ClN$_2$O$_4$ calcd. 490.1295, found 490.1318.
2.5.4.6. 5-Chloro-3-(4''-methoxybenzoyl)-6-(4'''-methoxyphenyl)-1-phenylpyrazin-2(1H)-one (79f)

It was obtained as yellow solid in 66 % yield.

**Melting Point (M.P.):** 101-102 °C.

**1H NMR (300 MHz, CDCl₃):** δ 3.76 and 3.89 (6H, 2 x s 2 x OCH₃), 6.77 (2H, d, J = 8.85 Hz, C-3''H and C-5''H), 6.98 (2H, d, J = 8.85 Hz, 3''H and C-5''H), 7.03 and 7.10 (4H, m, Ar-H), 7.23 and 7.30 (3H, m, Ar-H), 8.03 (2H, d, J = 8.85 Hz, C-2''H and C-6''H).

**13C NMR (100 MHz, CDCl₃):** δ 55.23 and 55.57 (2 x OCH₃), 113.81 (C-3'' & C-5'' and C-3'' & C-5''), 113.99 (C-5), 122.89, 125.90, 128.04, 128.10, 128.96, 129.14, 131.26 and 132.67 (Ar-C), 136.70 (C-1'), 140.64 (C-6), 151.72 (C-3), 153.64 (C-2), 160.27 (C-4''), 164.47 (C-4''), 188.72 (CO).

**HRMS (EI) m/z:** C₂₉H₁₉ClN₂O₄ calcd. 446.1033, found 446.1048.

2.5.4.7. 5-Chloro-3-(4''-methoxybenzoyl)-1-methyl-6-phenylpyrazin-2(1H)-one (79g)

It was obtained as yellow viscous oil in 84 % yield.

**1H NMR (300 MHz, CDCl₃):** δ 3.34 (3H, s, N-CH₃), 3.90 (3H, s, OCH₃), 6.98 (2H, d, J = 8.85 Hz, C-3''H and C-5''H), 7.35, 7.38, 7.59 and 7.61 (5H, m, Ar-H), 8.01 (2H, d, J = 8.85 Hz, C-2''H and C-6''H).
\[ ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3\text{):} \delta 35.20 (\text{N-CH}_3), 55.60 (\text{OCH}_3), 113.99 (\text{C-3}'' \text{ and C-5}'''), 125.52, 127.93, 128.53, 129.57, 130.65, 130.80 \text{ and 132.72 (Ar-C)}, 141.24 (\text{C-1}'), 150.19 (\text{C-3}), 153.99 (\text{C-2}), 164.51 (\text{C-4}''), 188.86 (\text{CO}). \]

HRMS (EI) \( m/z \): \( \text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_3 \) calcd. 354.0771, found 354.0768.

**2.5.4.8. 5-Chloro-3-(4''-methoxybenzoyl)-6-methyl-1-phenylpyrazin-2(1H)-one (79h)**

It was obtained as brown solid in 79 % yield.

Melting Point (M.P.): 105-106\(^\circ\)C.

\[ ^1\text{H} \text{NMR (300 MHz, CDCl}_3\text{):} \delta 2.19 (3\text{H, s, CH}_3), 3.88 (3\text{H, s, OCH}_3), 6.95 (2\text{H, d, } J = 8.85 \text{ Hz, C-3}'' \text{ and C-5}''\text{H}), 7.21, 7.24, 7.48 \text{ and 7.60 (5H, m, Ar-H)}, 7.97 (2\text{H, d, } J = 8.85 \text{ Hz, C-2}''\text{H and C-6}''\text{H}). \]

\[ ^{13}\text{C} \text{NMR (75 MHz, CDCl}_3\text{):} \delta 18.74 (\text{CH}_3), 55.57 (\text{OCH}_3), 113.91 (\text{C-3}'' \text{ and C-5}'''), 125.26 (\text{C-1}'), 127.04 (\text{C-5}), 128.08 (\text{C-2}'' \text{ and C-6}'''), 129.99 (\text{C-4}''), 130.29 (\text{C-3}'' \text{ and C-5}'''), 132.63 (\text{C-2}'' \text{ and C-6}''), 136.62 (\text{C-6}), 139.08 (\text{C-1}'), 149.68 (\text{C-3}), 153.91 (\text{C-2}), 164.35 (\text{C-4}''), 188.56 (\text{CO}). \]

HRMS (EI) \( m/z \): \( \text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_3 \) calcd. 354.0771, found 354.0774.

**2.5.4.9. 5-Chloro-3-(4''-methoxybenzoyl)-1,6-dimethylpyrazin-2(1H)-one (79i)**

It was obtained as yellow solid in 75 % yield.

Melting Point (M.P.): 151-152 \(^\circ\)C.
2.5.4.10. 5-Chloro-3-(4''-methoxybenzoyl)-6-(2'''-methoxyphenyl)-1-phenylpyrazine-2(1H)-one (79j)

**1H NMR (400 MHz, CDCl3):** δ 2.58 (3H, s, CH₃), 3.64 (3H, s, N-CH₃), 3.87 (3H, s, OCH₃), 6.94 (2H, d, J = 8.80 Hz, C-3'H and C-5'H), 7.92 (2H, d, J = 8.56 Hz, C-2'H and C-6'H).

**13C NMR (100 MHz, CDCl3):** δ 17.59 (CH₃), 32.71 (N-CH₃), 55.56 (OCH₃), 113.90 (C-3' and C-5'), 125.32 (C-6), 128.13 (C-1'), 132.56 (C-2' and C-6'), 139.27 (C-5), 147.88 (C-3), 154.07 (C-2), 164.34 (C-4'), 188.83 (CO).

**HRMS (EI) m/z:** C₁₄H₁₃ClN₂O₃ calc'd. 292.0615, found 292.0597.

**2.5.4.10. 5-Chloro-3-(4''-methoxybenzoyl)-6-(2'''-methoxyphenyl)-1-phenylpyrazine-2(1H)-one (79j)**

![Chemical Structure](image)

It was obtained as yellow solid in 82 % yield.

**Melting Point (M.P.):** 177-178 °C.

**1H NMR (400 MHz, CDCl3):** δ 3.74 and 3.89 (6H, 2 x s, 2 x OCH₃), 6.72 (1H, d, J = 8.28 Hz, (C-3"H), 6.88 (1H, t, J = 7.52 Hz, C-5"H), 6.97 and 6.99 (3H, m, C-3"H & C-5"H and C-4"H), 7.11 (1H, dd, J = 1.24, 7.56 Hz, C-6"H ), 7.19- 7.29 (5H, m, Ar-H), 8.05 (2H, d, J = 8.80 Hz, C-2"H and C-6"H).

**13C NMR (100 MHz, CDCl3):** δ 55.34 and 55.57 (2 x OCH₃), 110.94 (C-5), 113.98 (C-3" and C-5"), 120.04, 120.49, 126.20, 127.22, 127.78, 128.09, 128.51, 128.58, 129.07, 130.71 and 131.89 (Ar-C), 132.70 (C-2" and C-6"), 136.59 (C-1'), 138.77 (C-6), 151.81 (C-3), 153.76 (C-2), 156.06 (C-2"'), 164.46 (C-4"'), 188.93 (CO).

**HRMS (EI) m/z:** C₂₅H₁₉ClN₂O₄ calc'd. 446.1033, found 446.1033.
2.5.4.11. 6-Benzyl-5-chloro-3-(4''-methoxybenzoyl)-1-(2''-methoxybenzyl)pyrazin-2(1H)-one (79k)

![Chemical Structure]

It was obtained as yellow solid in 52 % yield.

**Melting Point (M.P.):** 90-91°C.

**¹H NMR (400 MHz, CDCl₃):** δ 3.85 and 3.88 (6H, 2 x s, 2 x OCH₃), 4.19 (2H, s, (CH₂-Ph), 5.26 (2H, s, N-CH₂), 6.88 and 6.97 (5H, m, Ar-H), 7.13 (2H, d, J = 7.28 Hz, Ar-H), 7.28 and 7.37 (4H, m, Ar-H), 7.96 (2H, d, J = 8.56 Hz, C-2''H and C-6''H).

**¹³C NMR (100 MHz, CDCl₃):** δ 35.76 (CH₂-Ph), 48.86 (N-CH₂), 55.38 and 55.56 (2 x OCH₃), 110.64 (C-3'), 113.97 (C-3'' and C-5''), 121.15 (C-5'), 122.48 (C-6'), 127.00, 127.41, 127.60, 127.73, 128.12, 129.20 and 129.31 (Ar-C), 132.59 (C-2'' and C-6''), 134.16 (C-5), 140.67 (C-1'''), 150.03 (C-3), 154.52 (C-2), 156.49 (C-2'), 164.42 (C-4'), 188.81 (CO).

**HRMS (EI) m/z:** C₂₄H₂₃ClN₂O₄ calcld. 474.1346, found 474.1360.

2.5.4.12. 5-Chloro-6-isobutyl-1-(4''-methoxybenzyl)-3-(4''-methylbenzoyl)pyrazin-2(1H)-one (79l)

![Chemical Structure]

It was obtained as yellow oil in 72 % yield.

**¹H NMR (400 MHz, CDCl₃):** δ 1.09 (6H, d, J = 6.80 Hz, 2 x C-3''H), 2.14 and 2.20 (1H, m, C-2''H), 2.42 (3H, s, CH₃-Ph), 2.79 (2H, d, J = 7.28 Hz, C-1''H), 3.79 (3H, s, O-CH₃), 5.30 (2H, s, N-CH₂), 6.87 (2H, d, J = 8.56 Hz, C-3'H and C-5'H), 7.15 (2H,
2.5.4.13. 3-[(4''-(Benzyloxy)benzoyl)-5-chloro-6-isobutyl-1-(4'-methoxybenzyl)pyrazin-2(1\textit{H})-one (79m)

\[
\text{\textit{C}} \text{ NMR (100 MHz, CDCl}_3\text{): } \delta \text{ 21.83 (CH}_3\text{-Ph), 22.58 (2 x C-3'''), 28.98 (C-1''), 38.40 (C-2''), 48.17 (N-CH}_2\text{), 55.34 (OCH}_3\text{), 114.52 (C-3' and C-5'), 126.62 and 126.72 (C-1' and C-6'), 128.51 (C-3'' and C-5''), 129.29 (C-2'' and C-6''), 130.22 (C-2' and C-6'), 132.67 (C-1''), 142.31 (C-5), 145.03 (C-4''), 148.66 (C-3), 154.32 (C-2), 159.52 (C-4'), 189.98 (CO).
\]

\textbf{HRMS (EI) }m/z: C\textsubscript{24}H\textsubscript{25}ClN\textsubscript{2}O\textsubscript{3} calcd. 424.1554, found 424.1538.

It was obtained as a yellow solid in 85 % yield.

\textbf{Melting Point (M.P.):} 158-159 °C.

\textbf{\textit{H} NMR (400 MHz, CDCl}_3\text{): } \delta \text{ 1.09 (6H, d, } J = 6.80 \text{ Hz, 2 x C-3''H), 2.11 and 2.21 (1H, m, C-2''H), 2.78 (2H, d, } J = 7.28 \text{ Hz, C-1''H), 3.79 (3H, s, OCH}_3\text{), 5.14 (2H, s, N-CH}_2\text{), 5.32 (2H, s, OCH}_2\text{), 6.86 (2H, d, } J = 8.80 \text{ Hz, C-3'H and C-5'H), 7.01 (2H, d, } J = 9.08 \text{ Hz, C-3''H and C-5''H), 7.15 (2H, d, } J = 8.56 \text{ Hz, C-2'H and C-6'H), 7.34 and 7.43 (5H, m, Ar-H), 7.92 (2H, d, } J = 8.84 \text{ Hz, C-2''H and C-6''H).
\]

\textbf{\textit{C} NMR (75 MHz, CDCl}_3\text{): } \delta \text{ 22.60 (2 x C-3''), 28.98 (C-1''), 38.38 (C-2''), 48.18 (N-CH}_2\text{), 55.35 (OCH}_3\text{), 70.23 (OCH}_2\text{), 114.53 and 114.79 (C-3' & C-5' and C-3'' & C-5''), 126.67, 127.48, 128.27, 128.32, 128.53 and 128.72 (Ar-C), 132.58 (C-6), 136.09 (C-5), 142.11 (C-1''), 148.93 (C-3), 154.33 (C-2), 159.51 (C-4'), 163.52 (C-4''), 188.82 (CO).
\]

\textbf{HRMS (EI) }m/z: C\textsubscript{30}H\textsubscript{29}ClN\textsubscript{2}O\textsubscript{4} calcd. 516.1816, found 516.1829.
2.5.4.14. 3-(2''-Naphthoyl)-5-chloro-6-isobutyl-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79n)

It was obtained as yellow viscous oil in 82 % yield.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.09 (6H, d, \(J = 6.60\) Hz, 2 x C-3''H), 2.14 - 2.23 (1H, m, C-2''H), 2.80 (2H, d, \(J = 7.35\) Hz, C-1''H), 3.80 (3H, s, OCH\(_3\)), 5.33 (2H, s, N-CH\(_2\)), 6.87 (2H, d, \(J = 8.46\) Hz, C-3'H and C-5'H), 7.13 (2H, d, \(J = 8.64\) Hz, C-2'H and C-6'H ), 7.48 (1H, t, \(J = 7.71\) Hz, Ar-H), 7.55 (1H, t, \(J = 6.96\) Hz, Ar-H), 7.62 (1H, t, \(J = 6.94\) Hz, Ar-H), 7.77 (1H, d, \(J = 6.60\) Hz, Ar-H), 7.90 (1H, d, \(J = 7.92\) Hz, Ar-H), 8.05 (1H, d, \(J = 8.28\) Hz, Ar-H), 8.85 (1H, d, \(J = 8.49\) Hz, C-1''H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 22.61 (C-3''), 29.00 (C-1''), 38.47 (C-2''), 48.16 (N-CH\(_2\)), 55.35 (OCH\(_3\)), 114.52 (C-3' and C-5'), 124.24, 125.91, 126.54 and 126.64 (Ar-C), 126.89 (C-2' & C-6' and C-6), 127.84, 128.46, 128.54, 131.09, 131.79, 132.57, 133.98 and 134.16 (Ar-C), 142.90 (C-1''), 149.24 (C-3), 154.33 (C-2), 159.51 (C-4'), 192.62 (CO).

HRMS (EI) m/z: C\(_{27}\)H\(_{25}\)ClN\(_2\)O\(_3\) calcd. 460.1554, found 460.1552.

2.5.4.15. 5-Chloro-3-(4''-fluorobenzoyl)-6-isobutyl-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79o)

It was obtained as yellow semi-solid in 83 % yield.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.09 (6H, d, $J = 6.62$ Hz, 2 x C-3"H), 2.14-2.21 (1H, m, C-2"H), 2.81 (2H, d, $J = 7.32$ Hz, C-1"H), 3.79 (3H, s, OCH$_3$), 5.34 (2H, s, N-CH$_2$), 6.87 (2H, d, $J = 8.56$ Hz, C-3'H and C-5'H), 7.12-7.16 (4H, m, C-2'H & C-6'H and C-3'H & C-5'H), 7.96-7.99 (2H, m, C-2"H and C-6"H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 22.59 (C-3"), 29.01 (C-1"), 38.48 (C-2"), 48.34 (N-CH$_2$), 55.34 (OCH$_3$), 114.54 (C-3' and C-5'), 115.79 (d, $^2J_{CF} = 21.88$ Hz, C-3" and C-5"), 126.44 and 126.64 (C-6 and C-1'), 128.53 (C-2' and C-6'), 131.63 (d, $^4J_{CF} = 2.91$ Hz, C-1"), 132.89 (d, $^3J_{CF} = 9.48$ Hz, C-2" and C-6"), 143.10 (C-5), 147.56 (C-3), 154.24 (C-2), 159.57 (C-4'), 166.25 (d, $^1J_{CF} = 254.46$ Hz, C-4"), 188.58 (CO).

HRMS (EI) $m/z$: C$_{23}$H$_{22}$ClF$_2$N$_2$O$_5$ calcd. 428.1303, found 428.1303.

2.5.4.16. 3-(Benzo[d][1''3''5'']dioxole-5'-carbonyl)-5-chloro-6-isobutyl-1-(4'-methoxy benzyl)pyrazin-2(1H)-one (79p)

It was obtained as yellow semi-solid in 83 % yield.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.09 (6H, d, $J = 6.78$ Hz, 2 x C-3"H), 2.09-2.23 (1H, m, C-2"H), 2.79 (2H, d, $J = 7.35$ Hz, C-1"H), 3.79 (3H, s, OCH$_3$), 5.32 (2H, s, N-CH$_2$), 6.06 (2H, s, C-2"H), 6.84-6.89 (3H, m, C-3'H & C-5'H and C-7"H), 7.15 (2H, d, $J = 8.67$ Hz, C-2'H and C-6'H), 7.46-7.49 (2H, m, C-4"H and C-6"H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 22.60 (C-3"), 29.00 (C-1"), 38.37 (C-2"), 48.21 (N-CH$_2$), 55.34 (OCH$_3$), 102.04 (C-2"), 108.07 and 109.19 (C-4" and C-7"), 114.50 (C-3" and C-5"), 126.52, 126.67 and 127.60 (C-6", C-1' and C-6), 128.52 (C-2' and C-6'), 129.79 (C-5"), 142.21 (C-5), 148.23 and 148.66 (C-3 and C-9"), 152.79 (C-2), 154.30 (C-8), 159.49 (C-4'), 188.47 (CO).

HRMS (EI) $m/z$: C$_{24}$H$_{23}$ClN$_2$O$_5$ calcd. 454.1295, found 454.1301.
2.5.4.17. 3-(2''-Bromo-5''-chlorobenzoyl)-5-chloro-6-isobutyl-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79q)

It was obtained as yellow viscous oil in 78 % yield.

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.07 (6H, d, \(J = 6.57\) Hz, 2 x C-3''H), 2.13-2.23 (1H, m, C-2''H), 2.81 (2H, d, \(J = 7.35\) Hz, C-1''H), 3.79 (3H, s, OCH\(_3\)), 5.34 (2H, s, N-CH\(_2\)), 6.86 (2H, d, \(J = 8.64\) Hz, C-3'H and C-5'H), 7.11 (2H, d, \(J = 8.49\) Hz, C-2'H and C-6'H), 7.31 (1H, dd, \(J = 2.64, 8.49\) Hz, C-4'H), 7.49 (1H, d, \(J = 8.67\) Hz, C-6''H), 7.58 (1H, d, \(J = 2.46\) Hz, C-3''H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 22.53 (C-3'''), 29.00 (C-1''''), 38.74 (C-2''''), 48.28 (N-CH\(_2\)), 55.34 (OCH\(_3\)), 114.53 (C-3' and C-5'), 118.16 (C-2''), 126.17 and 127.30 (C-1' and C-6), 128.43 (C-2' and C-6'), 130.66 (C-5), 132.38 (C-6'), 134.03 and 134.17 (C-3' and C-5''), 140.91 (C-4''), 144.32 (C-1''), 145.87 (C-3), 154.04 (C-2), 159.55 (C-4''), 189.93 (CO).

HRMS (EI) \(m/z\): C\(_{23}\)H\(_{21}\)BrCl\(_2\)N\(_2\)O\(_3\) calcd. 522.0113, found 522.0114.

2.5.4.18. 3-(2''-Bromo-5''-methoxybenzoyl)-5-chloro-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79r)

It was obtained as yellow solid in 80 % yield.

Melting Point (M.P.): 147-148 °C.
1H NMR (400 MHz, CDCl3): δ 3.83 and 3.84 (6H, 2 x s, 2 x OCH₃), 5.05 (2H, s, N-CH₂), 6.92-6.96 (3H, m, Ar-H), 7.24 (1H, d, J = 2.46 Hz, Ar-H), 7.28-7.32 (3H, m, Ar-H), 7.44 (1H, d, J = 8.80 Hz, Ar-H).

13C NMR (75 MHz, CDCl3): δ 52.19 (N-CH₂), 55.37 and 55.69 (2 x OCH₃), 111.31 (C-2"), 114.74 (C-3' and C-5'), 115.84 (C-6), 119.97 (C-6"), 125.49 and 126.05 (C-4" and C-1'), 130.31 and 130.62 (C-5 and C-2' & C-6'), 134.11 (C-3"), 139.16 (C-1''), 149.64 (C-3), 153.08 (C-2), 159.04 (C-4), 160.22 (C-5"), 190.88 (CO).

HRMS (EI) m/z: C₂₀H₁₆BrClN₂O₄ calcd. 461.9982, found 461.9992.

2.5.4.19. 5-Chloro-1-(4'-methoxybenzyl)-3-(3''',4''',5'''-trimethoxybenzoyl)pyrazin-2(1H)-one (79s)

It was obtained as yellow solid in 70 % yield.

Melting Point (M.P.): 161-162 °C.

1H NMR (300 MHz, CDCl₃): δ 3.83, 3.86 and 3.93 (12H, 3 x s, 4 x OCH₃), 5.06 (2H, s, N-CH₂), 6.93 (2H, d, J = 8.46 Hz, C-3'H and C-5'H), 7.19 (2H, s, C-2"H and C-6"H), 7.32-7.35 (3H, m, C-2'& & C-6'H and C-6H).

13C NMR (75 MHz, CDCl₃): δ 52.55 (N-CH₂), 55.39, 56.36 and 61.00 (4 x OCH₃), 107.78 (C-2" and C-6"), 114.78 (C-3' & C-5' and C-6), 125.38 and 125.67 (C-1' and C-5), 128.67 (C-1''), 129.71 (C-4"), 130.79 (C-2' and C-6'), 143.85 (C-3), 151.86 (C-2), 153.09 (C-3" and C-5''), 160.33 (C-4''), 188.87 (CO).

HRMS (EI) m/z: C₂₂H₂₁ClN₂O₆ calcd. 444.1088, found 444.1084.
2.5.4.20. 5-Chloro-3-(2''-chboro-6''-fluorobenzoyl)-1-(4'-methoxybenzyl)pyrazin-2(1H)-one (79t)

It was obtained as yellow solid in 81 % yield.

Melting Point (M.P.): 111-112 °C.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.83 (3H, s, OCH$_3$), 5.09 (2H, s, N-CH$_2$), 6.94 (2H, d, $J = 8.46$ Hz, C-3'H and C-5'H), 7.05 (1H, t, $J = 8.67$ Hz, Ar-H), 7.22 (1H, d, $J = 8.10$ Hz, Ar-H), 7.31 (2H, d, $J = 8.67$ Hz, Ar-H), 7.37 (1H, dd, $J = 2.25$, 8.10 Hz, Ar-H), 7.41 (1H, s, C-6H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 52.57 (N-CH$_2$), 55.40 (OCH$_3$), 114.36 (d, $^2$J$_{CF} = 21.54$ Hz, C-5''), 114.87 (C-3' and C-5''), 125.11 (C-1''), 125.56 (d, $^4$J$_{CF} = 3.54$ Hz, C-3''), 125.66 (C-6), 127.11 ((d, $^2$J$_{CF} = 19.91$ Hz, C-1''), 130.85 (C-2' and C-6''), 131.77 (d, $^3$J$_{CF} = 9.27$ Hz, C-2''), 132.31 (d, $^3$J$_{CF} = 5.45$ Hz, C-4''), 132.67 (C-5), 145.34 (C-3), 152.50 (C-2), 160.06 (d, $^1$J$_{CF} = 250.37$ Hz, C-6''), 160.37 (C-4''), 186.32 (CO).

HRMS (EI) m/z: C$_{19}$H$_{13}$Cl$_2$FN$_2$O$_3$ calcd. 406.0287, found 406.0305.

2.5.4.21. 5-Chloro-1-(4'-methoxybenzyl)-3-(2'',4'',6''-trimethylbenzoyl)pyrazin-2(1H)-one (79u)

It was obtained as yellow viscous liquid in 82 % yield.
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.19 and 2.29 (6H, 2 x s, 3 x CH\(_3\)), 3.82 (3H, s, OCH\(_3\)), 5.06 (2H, s, N-CH\(_2\)), 6.84 (2H, s, C-3'H and C-5'H), 6.93 (2H, d, \(J = 8.46\) Hz, C-3''H and C-5''H), 7.28-7.32 (3H, m, C-2'H & C-6'H and C-6H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 19.94 and 21.26 (3 x CH\(_3\)), 52.31 (N-CH\(_2\)), 55.39 (OCH\(_3\)), 114.86 (C-3' & C-5' and C-6), 125.31 and 125.58 (C-1' and C-5), 128.67 (C-3'' and C-5''), 130.58 and 130.78 (C-2' & C-6' and C-1''), 135.19 (C-2'' and C-6''), 136.26 (C-4''), 139.52 (C-3), 149.02 (C-2), 160.34 (C-4), 196.25 (CO).

HRMS (EI) \(m/z\): C\(_{19}\)H\(_{12}\)Cl\(_2\)N\(_2\)O\(_3\) calcd. 396.1241, found 396.1289.

\[\text{2.5.4.22. 5-Chloro-3-(2''},3''\text{-dihydrobenzo[b][1''},4''\text{-dioxine-6''-carbonyl]-1-(4'\text{-methoxybenzyl})pyrazin-2(1H)-one (79v)}\]

It was obtained as yellow solid in 78 \% yield.

Melting Point (M.P.): 151-152 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.83 (3H, s, OCH\(_3\)), 4.26-4.34 (4H, m, C-2''H and C-3''H), 5.04 (2H, s, N-CH\(_2\)), 6.91-6.94 (3H, m, Ar-H), 7.26 (1H, brs, Ar-H), 7.31 (2H, d, \(J = 8.56\) Hz, Ar-H), 7.45-7.47 (2H, m, Ar-H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 52.29 (N-CH\(_2\)), 55.39 (OCH\(_3\)), 64.04 and 64.80 (C-2'' and C-3''), 114.80 (C-3' and C-5'), 117.54, 119.51, 124.53, 125.43, 125.78, 128.20 and 128.40 (Ar-C), 130.77 (C-2' and C-6'), 143.43 (C-3), 149.28 (C-10''), 152.50 and 153.11 (C-2 and C-9''), 160.28 (C-4'), 188.66 (CO).

HRMS (EI) \(m/z\): C\(_{21}\)H\(_{17}\)ClN\(_2\)O\(_5\) calcd. 412.0826, found 412.0812.
2.5.4.23. 5-Chloro-3-(furan-2''-carbonyl)-1-benzylpyrazin-2(1\textit{H})-one (79w)

It was obtained as brown viscous liquid in 36 % yield.

\textbf{\textsuperscript{\textit{1}}H NMR (400 MHz, CDCl\textsubscript{3})}: $\delta$ 5.13 (2H, s, N-CH\textsubscript{2}), 6.59 (1H, q, $J = 1.52$ Hz, Ar-H), 7.36-7.43 (7H, m, Ar-H), 7.69 (1H, s, C-6H).

\textbf{\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3})}: $\delta$ 52.92 (N-CH\textsubscript{2}), 112.79 (C-4''), 122.44 (C-6), 125.41 (C-3''), 129.11, 129.22 and 129.40 (Ar-C), 130.19 (C-5), 133.61 (C-1'), 148.42 (C-3), 149.36 (C-5''), 150.85 (C-2'), 152.74 (C-2''), 176.60 (CO).

\textbf{HRMS (EI) m/z}: C\textsubscript{16}H\textsubscript{11}ClN\textsubscript{2}O\textsubscript{3} calcd. 314.0458, found 314.0472.
2.6. References


42. (a) Breslow, R. Chemistry and Industry 1957, 26 893; (b) Breslow, R. J. Am. Chem. Soc. 1958, 80, 3719.
46. Öfele, K. J. Organomet. Chem. 1968, 12, P42.


