Chapter-IV

TBAF - A versatile promoter for one pot hydrocyanation of chalcones

4.1 Introduction (TBAF)

Tetra-n-butylammonium fluoride (TBAF) is a quaternary ammonium salt with the chemical formula (CH₃CH₂CH₂CH₂)₄N⁺F⁻. It is available in market as both forms of trihydrate and as molar solution in THF (trihydrate m.p. 58-60 °C, CAS-No, 87749-50-6 and 429-41-4 for molar solution). The trihydrate complex is very stable and decompose upon heating to 77 °C under vacuum forming the hydrogen difluoride salt.¹ It can be used as a phase transfer catalyst and as a mild base.² The tetrabutylammonium fluoride (TBAF) is highly soluble in organic solvents, and weakly nucleophilic. Despite the considerable basicity of "naked" fluoride ion, in the absence of water, solutions of the salt in acetonitrile and dimethyl sulfoxide are surprisingly stable towards elimination.³ Over the past years, tetrabutylammonium fluoride (TBAF) has been widely used for most fluoride-assisted reactions,⁴a desilylation,⁴b deprotection of silyl groups,⁴e trifluoromethylation and fluorination.⁵ TBAF has been widely renowned as a convenient, organic soluble source of naked fluoride ion. It has also been widely used for a variety of base-catalyzed reactions such as elimination, alkylation, Michael addition, and aldol condensation.⁶ Although it was envisaged that TBAF could be used as the preferred base or oxidant, it can also act as a nucleophilic fluorinating reagent.⁷ It has been reported that, it can acts as an excellent catalytic system for a wide range of synthetic transformation like synthesis of 4-aryl-1H-1,2,3-triazoles, Sonogashira cross-coupling, [3+2] cycloaddition reaction, alkynes from bromo alkane, etc.⁸ All these properties of the trihydrate and
molar solution of tetrabutylammonium fluoride, allow us to carry out some synthetic transformations, which were previously carried out using expensive catalysts.

![Tetrabutylammonium fluoride](image)

Fig. 4.1. Tetrabutylammonium fluoride

4.2 Review of literature for the TBAF applications in organic transformation

John et al., have reported that tetrabutylammonium fluoride was a very efficient catalyst for the addition of trialkylsilylalkynes to aldehyde, ketones, and trifluoromethyl ketones in THF solvent at room temperature. The reaction conditions were mild and operationally simple, and a variety of aryl functional groups, such as chloro, trifluoromethyl, bromo, and fluoro groups were well tolerated.\(^9\)

![Scheme 4.1. TBAF catalyzed trialkylsilylalkynes addition to aldehyde](image)

Scheme 4.1. TBAF catalyzed trialkylsilylalkynes addition to aldehyde

Vaccaro et al., have reported the TBAF-catalyzed [3+2] cycloadditions of 2-aryl-1-cyano- or 2-aryl-1-carbethoxy-1-nitroethenes with TMSN\(_3\) under solvent-free conditions allow the preparation of 4-aryl-5-cyano- or 4-aryl-5-carbethoxy-1H-1,2,3-triazoles under mild reaction conditions with good to excellent yield.\(^10\)

![Scheme 4.2. Synthesis of tetrazole in presence of TBAF](image)

Scheme 4.2. Synthesis of tetrazole in presence of TBAF
Liang et al., reported the modified palladium-catalyzed Sonogashira cross-coupling reactions using TBAF under copper, amine, and solvent-free conditions affording the coupled products in moderate to excellent yields.\textsuperscript{11}

\[
\begin{array}{c}
\text{Ar–X} + \mathbf{\equiv \mathbf{R}} \xrightarrow{3 \text{mof}\% \text{PdCl}_2(\text{PPh}_3)} \text{Ar–} \mathbf{\equiv \mathbf{R}} \\
\text{X: I, Br}
\end{array}
\]

Scheme 4.3. TBAF catalyzed modified Sonagashira reaction

Larock et al., have disclosed the [3+2] cycloaddition of a variety of diazo compounds with o-(trimethylsilyl)aryl triflates in the presence of CsF or TBAF at room temperature providing a wide range of biologically and pharmaceutically interesting substituted indazoles in good to excellent yields under mild reaction conditions. Synthesis of indazoles has been achieved by the [3+2] cycloaddition of diazo compounds with arynes and subsequent acyl migration.\textsuperscript{12}

\[
\begin{array}{c}
\text{R} \quad \text{SiMe}_3 \quad \text{OTf} + \mathbf{\equiv \mathbf{R}} \quad \text{N}_2 \quad \text{CO}_2 \mathbf{R^1} \xrightarrow{1.2 \text{eq. TBAF}} \text{R} \quad \text{N} \quad \text{H} \\
\text{THF} \quad -78^\circ \text{C} \quad \text{rt}, 20 \text{h}
\end{array}
\]

Scheme 4.4. TBAF catalyzed cycloaddition reaction with diazo compounds

Mori et al., have reported the tetra-n-butylammonium fluoride as a mild and efficient base for the elimination of bromoalkenes. Treatment of 1,1-dibromoalkenes, (Z)-1-bromoalkenes, and internal bromoalkenes with 5 equiv of TBAF•3H$_2$O in DMF yielded terminal and internal alkynes in high yields without problems regarding the presence of water.\textsuperscript{13}

\[
\begin{array}{c}
\text{R} \quad \text{Br} \quad \text{Y} \xrightarrow{5 \text{ eq. TBAF}, 3 \text{ H}_2\text{O}} \text{R} \quad \text{equiv} \quad \text{Y} \\
\text{DMF, 60}^\circ \text{C, 0.5-22h}
\end{array}
\]

Scheme 4.5. Synthesis of alkynes in the presence of TBAF
Joege et al., have disclosed the hydrosilylation of alkynes using the ruthenium catalyst \([\text{Cp}^*\text{Ru(MeCN)}_3]\text{PF}_6\) providing only the (Z)-trans addition products. Subsequent protodesilylation of the crude vinylsilane products by the action of cuprous iodide and TBAF provided a general trans-alkyne reduction, which is compatible with many sensitive functional groups.\(^{14}\)

![Scheme 4.6. TBAF catalyzed synthesis of alkene from alkyne](image)

Coudert et al., have reported a mild and selective deprotection of carbamates with TBAF.\(^{15}\)

![Scheme 4.7. Amino carbamate cleavage with TBAF](image)

Ramon et al., have described the use of tetrabutylammonium fluoride for the intramolecular carbon-carbon bond formation to convert inexpensive, enantiomerically-pure carbohydrates directly to highly functionalized, enantiomerically-pure carbocycles.\(^{16}\)

![Scheme 4.8. TBAF catalyzed the intramolecular C-C bond formation reaction](image)
Toshimichi, and Michinori., have reported the use of TBAF as a nucleophilic reagent for intramolecular hydride transfer reaction in presence of silane as protected group.\textsuperscript{17}

![Scheme 4.9. Piperidine syntheses from pyridinium salt with TBAF catalyst](image1)

Vaccaro et al., have disclosed tertabutylammonium fluoride as an efficient catalyst in the (3+2) cycloaddition reaction of organic nitriles with trimethyl silylazide (TMSN\textsubscript{3}) in solvent conditions to provide the corresponding 5-substituted 1H-tetrazoles.\textsuperscript{18}

![Scheme 4.10. TBAF catalyzed tetrazole synthesis](image2)

4.3 Results and Discussion

In this Chapter, we describe the TBAF promoted 1,4-addition of TMSCN to chalcones in CH\textsubscript{2}Cl\textsubscript{2} which provides a new and practical synthetic approach to β-cyano ketones.

![Scheme 4.11. TBAF-promoted 1,4-addition of TMSCN with chalcones](image3)
In order to determine the most appropriate reaction conditions and to evaluate the efficiency of TBAF as promoter; initially a model study was carried out on the synthesis of 4-oxo-2,4-diphenylbutanenitrile (Entry 10, Table 4.3).  

Table 4.1. One-pot synthesis of 4-oxo-2,4-diphenylbutanenitrile derivatives in presence of various solvents.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>TBAF</td>
<td>12</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>TBAF</td>
<td>24</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>EDC</td>
<td>TBAF</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>TBAF</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>TBAF</td>
<td>12</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>TBAF</td>
<td>12</td>
<td>Nil</td>
</tr>
<tr>
<td>7</td>
<td>1,4-Dioxane</td>
<td>TBAF</td>
<td>12</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>DCM</td>
<td>TBAF</td>
<td>6-12</td>
<td>80-95</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were conducted with 1mmol of TBAF, 1mmol of chalcones and 1.2 mmol of TMSCN in 10 vol of solvent.

Among the tested solvents, hydrocyanation of (E)-chalcone (1 equiv) and TMSCN (1.2 equiv) was more facile and proceeded to give the highest yield, in DCM (Table 4.1, Entry 8). The use of polar solvents like DMF, DMSO, etc., did not yield the expected product which may be due to the fact that they can interact with TBAF and reduce its activity.<sup>19</sup> Hydrocarbons as solvent afforded moderate yields but unsuitable because of forming heterogenous reaction mixtures.

To study the role and effectiveness of the TBAF, the 1,4-addition of chalcone with TMSCN was carried out using different halides. No addition occurred in most of the cases when inorganic fluorides such as SiF, KF and CsF were used (Table 4.2, Entries 1-3). When AgF was used, the desired product was obtained in 60% yield (Table 4.2, Entry 4). However, AgF worked well only with chalcones.
having nitro and phenoxy substituents, but with other chalcones it failed to afford the desired products.

Table 4.2. One-pot synthesis of 4-oxo-2,4-diphenylbutanenitrile derivatives in presence of various additives

<table>
<thead>
<tr>
<th>Entry*</th>
<th>Additive</th>
<th>Temp</th>
<th>Temp (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SiF</td>
<td>rt</td>
<td>24</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>KF</td>
<td>rt</td>
<td>24</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>CsF</td>
<td>rt</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>AgF</td>
<td>100 °C</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>TBAF</td>
<td>rt</td>
<td>6-12</td>
<td>80-95</td>
</tr>
<tr>
<td>6</td>
<td>TBACl</td>
<td>rt</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>TBABr</td>
<td>rt</td>
<td>24</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>TBAI</td>
<td>rt</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>TMSOTf</td>
<td>rt</td>
<td>24</td>
<td>Nil</td>
</tr>
</tbody>
</table>

* all reactions were conducted with 1mmol of promoter, 1 mmol of chalcone and 1.2 mmol of TMSCN in 10 vol of dry DCM.

We tried to explore an effective system for the 1,4-addition reactions by screening other tetra-n-butylammonium halides under the same conditions and it has been observed that the fluoride ion from TBAF was the most reactive one than any other halides (Table 4.2, Entries 6-9). Interestingly, TBACl and TBAI were also able to promote the reaction to some extent, but no product formation was observed when TBABr was used as the catalyst. These observations indicate that the bond strength in the hypervalent silicate intermediate formed during the course of the reaction plays an important role for the success of the reaction.

In order to extend the scope of the fluoride ion promoted hydrocyanation reaction, various chalcones were subjected to the reaction (Table 4.3). Interestingly, no substituent effects on the yields were noted. Thus, the chalcones with either
electron withdrawing or electron donating groups at any positions, gave the 1,4-adducts in good to moderate yields (Table 4.3, Entries 1-15). In any event, no 1,2-adduct was obtained. In order to further explore the scope and limitation of the present method, some enones other than chalcones were used under the same reaction conditions. Unfortunately, α, β-unsaturated esters such as methyl cinnamate and cyclohexenone did not undergo 1,4-addition at all, and the starting materials were recovered as such.

![Chemical diagram](image)

Scheme 4.12. A plausible mechanism for the 1,4-addition of TMSCN with chalcones

It is well documented in the literature\(^{20}\) that the hypervalent silicate form may be obtained from the addition of TBAF to trimethylsilyl cyanide and this adduct then reacts with chalcones to form the second trigonal bipyramidal\(^{21}\) silicate intermediate, which under quenching conditions with water can give rise to the enol form of the product.\(^{22}\) This enol can tautomerize to give the final product (Scheme 4.12).
Table 4.3. One-pot synthesis of 4-oxo-2,4-diphenylbutanenitrile derivatives

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Chalcone</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Chalcone" /></td>
<td>12</td>
<td><img src="image2" alt="Product" /></td>
<td>87&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Chalcone" /></td>
<td>12</td>
<td><img src="image4" alt="Product" /></td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Chalcone" /></td>
<td>11</td>
<td><img src="image6" alt="Product" /></td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Chalcone" /></td>
<td>7</td>
<td><img src="image8" alt="Product" /></td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Chalcone" /></td>
<td>6</td>
<td><img src="image10" alt="Product" /></td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Chalcone" /></td>
<td>6</td>
<td><img src="image12" alt="Product" /></td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Chalcone" /></td>
<td>6</td>
<td><img src="image14" alt="Product" /></td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Chalcone" /></td>
<td>11</td>
<td><img src="image16" alt="Product" /></td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17" alt="Chalcone" /></td>
<td>10</td>
<td><img src="image18" alt="Product" /></td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19" alt="Chalcone" /></td>
<td>12</td>
<td><img src="image20" alt="Product" /></td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td><img src="image21" alt="Chalcone" /></td>
<td>12</td>
<td><img src="image22" alt="Product" /></td>
<td>80</td>
</tr>
</tbody>
</table>
4.4 Conclusion

In conclusion, we reported a highly efficient one pot 1,4-addition of cyano group to chalcones with TMSCN as cyanide source in presence of TBAF as a promoter, without liberation of HCN gas. The reaction proceeded rapidly, and selectively giving 1,4-adduct in good yields. The experimental procedures described are simple, mild, and efficient. The use of TBAF as a base has the advantages of being economically viable and more efficient for activating Si-C≡N bond.

4.5 Experimental Section

4.5.1 General procedure for hydrocyanation of chalcones

To a mixture of chalcones (1 mmol) and TMSCN (1.2 mmol), TBAF solution (1 mmol) in DCM (10 vol.) was added and the mixture was stirred for appropriate time under N₂ atmosphere. The mixture was quenched with 5 mL water and extracted with ether (3X10 mL). The combined organic layer was dried (MgSO₄), concentrated, and purified by column chromatography (hexane/ethyl
acetate 8:2) to give the product. All of the products were characterized by LCMS, \(^1\)H NMR, and \(^{13}\)C NMR, melting point, and elemental analysis. TMSCN was purchased from Alfa aesar, (purity > 97%), and TBAF was purchased from Aldrich (purity>98%, molar soln in THF)

4.5.2 Spectral data

4-Oxo-4-phenyl-2-(2-(trifluoromethyl)phenyl)butanenitrile (Entry 1, Table 4.3): Yellow Colour Oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 3.42\) (dd, \(J = 3.6, 18.0\) Hz, 1H), 3.72 (dd, \(J = 10.4, 18.0\) Hz, 1H), 4.89 (dd, \(J = 3.6, 10.4\) Hz, 1H), 7.48–7.54 (m, 3H, ArH), 7.62–7.65 (t, 1H, ArH), 7.67–7.71 (t, 1H, ArH), 7.74–7.76 (d, 1H, ArH), 7.84–7.86 (d, 1H, ArH), 7.95–7.97 (d, 1H, ArH) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 28.81, 44.70, 120.01, 123.79\) (q, \(J = 273.82\)Hz, \(\text{CF}_3\)), 126.84 (q, \(J = 6.03\) Hz, ortho carbon to \(\text{CF}_3\)), 127.61, 127.92, 128.12, 128.75, 128.87, 129.88, 132.95, 133.96, 135.43, 193.91 ppm. \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta = -59.22\) ppm. MS: m/z = 303.29 (M\(^+\)). Anal. Calcd. for C\(_{17}\)H\(_{13}\)F\(_3\)NO: C: 67.33; H: 3.99; N: 4.62%; Found: C: 67.30; H: 3.93, N: 4.64%.

2-(5-Chloro-2-(trifluoromethyl)phenyl)-4-oxo-4-phenylbutanenitrile (Entry 2, Table 4.3): Yellow pasty mass. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 3.43\) (dd, \(J = 4, 18\) Hz, 1H), 3.77 (dd, \(J = 10.4, 18\) Hz, 1H), 4.89 (dd, \(J = 3.6, 10.4\) Hz, 1H), 7.46–7.49 (t, 3H, ArH), 7.61–7.64 (m, 1H, ArH) 7.68–7.73 (d, 1H, ArH), 7.83 (s, 1H, ArH), 7.95–7.99 (d, 2H, ArH) ppm. \(^{13}\)C NMR (100.66 MHz, CDCl\(_3\)) \(\delta = 28.74, 44.41, 119.46, 123.51\) (q, \(J = 273.79\)Hz, \(\text{CF}_3\)), 126.24 (q, \(J = 31.2\) Hz, \(\text{C}–\text{CF}_3\)), 128.28 (q, \(J = 5\)Hz, Ortho carbon to \(\text{CF}_3\)) 128.62, 128.91, 129.07, 130.18, 134.15, 135.25, 135.90, 136.53, 139.40, 193.50 ppm. MS: m/z = 337.04 (M\(^+\)). Anal. Calcd. for C\(_{17}\)H\(_{11}\)ClF\(_3\)NO: C: 60.46; H: 3.28; N: 4.15%; Found: C: 60.43; H: 3.26; N: 4.18%.
2-(4-Bromo-2-fluorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 3, Table 4.3):
White solid; mp = 118.2–119.7 °C, $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.56 (dd, J = 5.73, 18 Hz, 1H), 3.72 (dd, J = 8, 18 Hz, 1H), 4.70 (dd, J = 5.7, 7.8 Hz, 1H), 7.26–7.34 (m, 2H, ArH), 7.43–7.51 (m, 3H, ArH), 7.59–7.64 (m, 1H, ArH), 7.91–7.94 (d, 2H, ArH) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 26.35, 42.05, 118.92, 119.59, 119.91, 121.32, 123.04, 128.02, 128.82, 130.73, 134.00, 135.32, 159.64 (broad d, J = 251.25 Hz, F attached Carbon), 194.07 ppm. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = −114.04 ppm. MS: m/z = 332.17 (M$^+$). Anal Calcd. for C$_{16}$H$_{11}$BrFNO: C: 57.85; H: 3.34; N: 4.22%; Found: C: 57.82; H: 3.31, N: 4.25%.

2-(4-Fluorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 4, Table 4.3): White Solid; mp = 100.7–101.6 °C (mp 101.9-102.5 °C); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.51 (dd, J = 6.3, 18 Hz, 1H), 3.71 (dd, J = 7.5, 18 Hz, 1H), 4.55–4.59 (t, 1H), 7.05–7.10 (m, 2H, ArH), 7.38–7.58 (m, 5H, ArH), 7.60–7.61 (dd, 2H, ArH) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ = 31.19, 44.44, 116.26, 120.46, 128.08, 128.87, 129.28, 131.05, 133.99, 135.62, 162.53 (broad d, J = 246.75 Hz, F attached Carbon), 194.41 ppm. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = −112.04 ppm. MS: m/z = 253.27 (M$^+$). Anal Calcd. for C$_{16}$H$_{12}$FNO: C: 75.88; H: 4.78; N: 5.53%; Found: C: 75.86; H: 4.76, N: 5.51%.

2-(3-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 5, Table 4.3): Yellow Solid; mp = 101–102.8 °C, $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 3.50 (dd, J = 6.4, 18 Hz, 1H), 3.71 (dd, J = 7.2, 18 Hz, 1H), 4.58 (dd, J = 7.2, 14 Hz, 1H), 7.35–7.44 (m, 3H, ArH), 7.45–7.49 (m, 1H, ArH), 7.56–7.67 (m, 2H, ArH), 7.90–7.92 (m, 1H, ArH), 7.99–8.04 (m, 1H, ArH), 8.01–8.10 (m, 1H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 31.32, 44.31, 119.7, 127.75, 128.23, 128.84, 129.43, 129.90, 130.04,
132.41, 133.8, 135.61, 194.42 ppm. MS: m/z = 269.32 (M)^+.
Anal. Calcd. for C_{16}H_{12}ClNO: C: 71.25; H: 4.48; N: 5.19%; Found: C: 71.28; H: 4.45; N: 5.16%.

2-(4-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 6, Table 4.3): White Solid; mp = 111.2–111.9 °C, (mp 112-113 °C);^1 H NMR (400 MHz, CDCl₃): δ = 3.50 (dd, J = 6.4 19.6 Hz, 1H), 3.71 (dd, J = 7.2, 14.4 Hz, 1H), 4.57 (dd, J = 6.58, 13.6 Hz, 1H), 7.35–7.44 (m, 3H, ArH), 7.59–7.62 (m, 1H, ArH), 7.90–7.93 (m, 2H, ArH), 7.99–8.01 (m, 2H, ArH), 8.01–8.10(dd,1H, ArH) ppm. ^13CNMR (100MHz, CDCl₃) δ = 31.32, 44.33, 120.96, 126.82, 128.50, 128.56, 128.61, 128.67, 128.97, 133.77, 134.06, 134.48, 135.55, 194.43 ppm. MS: m/z = 269.32 (M)+.
Anal. Calcd. for C_{16}H_{12}ClNO: C: 71.25; H: 4.48; N: 5.19%; Found: C: 71.28; H: 4.45; N: 5.16%.

4-(3-Bromophenyl)-4-oxo-2-phenylbutanenitrile (Entry 7, Table 4.3): Yellow Solid; mp = 85.7–86.4 °C (mp 86–87 °C); ^1 H NMR (400 MHz, CDCl₃): δ = 3.45 (dd, J = 6, 18 Hz, 1H), 3.69 (dd, J = 8, 19.6 Hz,1H), 4.52 (dd, J = 5.97, 18 Hz, 1H), 7.36–7.45 (m, 5H, ArH), 7.70–7.72 (m, 2H, ArH), 7.80–7.84 (m, 2H, ArH) ppm.^13C NMR(100 MHz, CDCl₃) δ = 31.28, 44.50, 120.30, 127.45, 128.0, 128.46, 129.01, 129.35, 129.56, 132.22, 134.23, 135.05, 194.28 ppm. MS: m/z = 314.18 (M)^+.

4-(4-Bromophenyl)-4-oxo-2-phenylbutanenitrile (Entry 8, Table 4.3): Yellow Solid; mp = 119.4–121.5 °C, (mp 122-124 °C); ^1 H NMR (400 MHz, CDCl₃): δ = 3.45 (dd, J = 6, 18 Hz,1H), 3.68 (dd, J = 8, 19.6 Hz,1H), 4.54 (dd, J = 7.2, 8 Hz, 1H), 7.34–7.43 (m, 5H, ArH), 7.60–7.62 (m, 2H, ArH), 7.77–7.79 (m, 2H, ArH) ppm.^13C NMR (100 MHz, CDCl₃) δ = 31.28, 44.50, 120.30, 127.48, 128.0, 128.49, 129.04, 129.35, 129.56, 132.22, 134.20, 135.05, 194.28 ppm. MS: m/z = 314.18 (M)^+.
Anal Calcd. for C_{16}H_{12}BrNO: C: 61.17; H: 3.85; N: 4.46 %; Found: C: 61.15; H: 3.88; N: 4.49%.

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4-Oxo-4-phenyl-2-p-tolylbutanenitrile (Entry 9, Table 4.3): White Solid; mp = 129.3–131.7 °C, (mp 129-131 °C); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.42$ (s, 3H), 3.41 (dd, $J = 5.2$, 17.2 Hz, 1H), 3.74 (dd, $J = 9.2$ 18 Hz, 1H), 4.71 (dd, $J = 5$, 8.8 Hz,1H), 7.20–7.27 (m, 2H, ArH),7.28–7.29(m, 1H, ArH), 7.46–7.51(m, 3H, ArH),7.61–7.93 (m, 1H, ArH),7.94–7.96 (m, 2H, ArH) ppm.$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 19.27$, 28.75, 43.10, 120.72, 127.04, 127.50, 128.13, 128.48, 128.87, 131.27, 133.40, 133.94, 135.68, 194.77 ppm. MS: m/z = 249.32 (M)$^+$. Anal Calcd. for C$_{17}$H$_{15}$NO: C: 81.90; H: 6.06; N: 5.62%; Found: C: 81.87; H: 6.00; N: 5.59%.

4-Oxo-2,4-diphenylbutanenitrile (Entry 10, Table 4.3): White Solid; mp = 121–123.4 °C, (mp 122-125 °C);$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 3.49$ (dd, $J = 6$, 18.0 Hz,1H), 3.70 (dd, $J = 8$, 18.0 Hz, 1H), 4.56 (dd, $J = 6.0$, 8.0 Hz,1H), 7.34–7.49 (m, 7H, ArH), 7.57–7.60 (m, 1H, ArH), 7.89–7.92 (m, 2H, ArH)pm. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 31.38$, 44.31,120.9, 127.5, 128.09, 128.88, 128.95, 129.45, 134.03, 135.3, 135.8, 194.6 ppm. MS: m/z = 235.29 (M)$^+$. Anal. Calcd. for C$_{16}$H$_{13}$NO: C: 81.68; H: 5.57; N: 5.95%; Found: C: 81.64; H: 5.53; N: 5.98%.

2-(4-Nitrophenyl)-4-oxo-4-phenylbutanenitrile (Entry 11, Table 4.3): Yellow Solid; mp = 127.8–130.5 °C, $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 3.63$ (dd, $J = 8.8$, 18 Hz, 1H), 3.76 (dd, $J = 3.2$, 17.6 Hz, 1H) 4.77 (dd, $J = 6.4$, 8.8 Hz, 1H), 7.46–7.50 (m, 2H, ArH), 7.59–7.63 (m, 3H, ArH), 7.93–7.96 (m, 2H, ArH), 8.22–8.25 (m, 2H, ArH) ppm.$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 46.96$, 110.27, 120.14, 123.82, 126.56, 128.15, 128.84, 134.03, 136.20, 147.42, 150.17, 199.52ppm. MS: m/z = 280.29 (M)$^+$. Anal Calcd. for C$_{16}$H$_{12}$N$_2$O$_3$: C: 68.57; H: 4.32; N: 9.99; O: 17.22%; Found: C: 68.55; H: 4.30; N: 9.96%.
4-oxo-2-(3-phenoxyphenyl)-4-phenylbutanenitrile (Entry 12, Table 4.3): Yellow solid. $^1$H NMR (400 MHz, CDCl$_3$): δ 3.390-3.444 (d, 1H), 3.690 3.761 (d, J = 5.2, Hz, 1H), 4.874–4.909 (q, 1H), 7.465–7.527 (q, 3H), 7.595–7.632 (q, J = 9.6, Hz 1H), 7.654–7.692 (t, 1H), 7.728–7.748 (d, 1H), 7.823-7.934(t,1H), 7.938-9.957(t,2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 28.918, 44.680, 128.869, 128.108, 128.726, 128.856, 129.874, 132.961, 193.869, ppm; MS: m/z = 327.39 (M$^+$. Anal. Calcd. for C$_{22}$H$_{17}$NO$_2$: C: 80.71; H: 5.23; N: 4.28%; Found: C: 80.73; H: 5.20; N: 4.30%.

2-(2,4-Dichlorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 13, Table 4.3): White Solid; mp = 89.2–90.1 °C,(reported mp = 90–91 °C, $^1$H NMR (400 MHz, CDCl$_3$): δ = 3.53 (dd, J = 4.6, 18 Hz, 1H), 3.69 (dd, J = 9.2, 18.0 Hz, 1H), 4.88 (dd, J = 5.2, 12.0 Hz, 1H), 7.34–7.37 (m, 1H, ArH), 7.40–7.48 (m, 3H, ArH), 7.65–7.69 (m, 2H, ArH), 7.72–7.74 (m, 1H, ArH), 7.93–7.95 (m, 1H, ArH) ppm.$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 28.91, 44.68, 118.9, 126.86, 128.10, 128.72, 128.85, 129.87, 132.92, 133.96, 135.2, 135.5, 193.86, ppm. MS: m/z = 303.39 (M$^+$. Anal. Calcd. for C$_{18}$H$_{11}$Cl$_2$ NO: C: 64.18; H: 3.65; N: 4.28; O: 9.77%; Found: C: 64.08; H: 3.71; N: 4.30%.

2-(4-Methylnaphthalen-1-yl)-4-oxo-4-phenylbutanenitrile (Entry 14, Table 4.3): Yellow Solid Mp = 132.4–134.7 °C, $^1$H NMR (400 MHz, CDCl$_3$): δ = 2.71 (s, 3H), 3.56 (dd, J = 4, 18 Hz,1H), 3.86 (dd, J = 9.6, 18 Hz ,1H), 5.31 (dd, J = 3.8, 10 Hz,1H), 7.35–7.37 (m, 1H, ArH), 7.44–7.46 (m, 2H, ArH), 7.48–7.61 (m, 3H, ArH), 7.67–7.69 (m, 1H ArH),7.93–7.96 (m, 3H, ArH), 7.97–8.07 (m, 1H, ArH) ppm. $^{13}$CNR(100MHz,CDCl$_3$) δ = 19.517, 28.971, 43.836, 12.79, 122.51, 125.54, 125.61, 126.13, 126.86, 128.15, 128.83, 129.73, 133.29, 133.90, 135.70, 194.98 ppm. MS: m/z
= 299.38 (M)⁺. Anal. Calcd. for C₂₁H₁₇NO: C: 84.25; H: 5.72; N: 4.68; O: 5.34%;
Found: C: 84.28; H: 5.69; N: 4.68%.
4-(1-Cyano-3-oxo-3-phenylpropyl)benzonitrile (Entry 15, Table 4.3): Yellow Solid;
mp = 134.7–135.2 °C, ¹H NMR(400 MHz, CDCl₃): δ = 3.55 (dd, J = 6.8, 18 Hz ,1H),
3.75 (dd, J = 6.8, 18 Hz, 1H), 4.67 (dd, J = 6.8, 13.8 Hz, 1H), 7.46–7.50 (m, 2H,
ArH), 7.58–7.61 (m, 3H, ArH), 7.69–7.71 (m, 2H, ArH), 7.90–7.92 (m, 2H, ArH) ppm.
¹³C NMR(100 MHz, CDCl₃) δ = 10.58, 11.74, 28.97, 43.82, 128.11, 128.44, 129.61,
129.85, 129.50, 133.03 ppm. MS: m/z = 260.30(M)⁺. Anal. Calcd. for C₁₇H₁₂N₂O: C:
78.44; H: 4.65; N: 10.76; O: 6.15%; Found: C: 78.40; H: 4.63; N: 10.64%.
4.5.3 Spectra for selected compounds

Fig. 4.2. $^1$H and $^{13}$C-NMR spectra of 2-(2-chlorophenyl)-4-oxo-4-phenylbutanenitrile
(Entry 5, Table 4.3)
Fig. 4.3. $^1$H and $^{13}$C-NMR spectra of 4-(4-bromophenyl)-4-oxo-2-phenylbutanenitrile
(Entry 8, Table 4.3)
Fig. 4.4. $^1$H and $^{13}$C-NMR spectra of 4-oxo-4-phenyl-2-p-tolylbutanenitrile (Entry 9, Table 4.3)
Fig. 4.5. $^1$H and $^{13}$C-NMR spectra of 2-(4-nitrophenyl)-4-oxo-4-phenylbutanenitrile
(Entry 11, Table 4.3)
Fig. 4.6. $^1$H and $^{13}$C-NMR spectra of 4-oxo-2-(3-phenoxyphenyl)-4-phenylbutanenitrile
(Entry 12, Table 4.3)
Fig. 4.7. $^1$H-NMR spectra of 2-(4-methylnaphthalen-1-yl)-4-oxo-4-phenylbutanenitrile
(Entry 14, Table 4.3)
Fig. 4.8. $^1$H and $^{13}$C-NMR spectra of 4-(1-cyano-3-oxo-3-phenylpropyl)benzonitrile
(Entry 15, Table 4.3)
4.6 References


