Summary

Nitroketene N,S-acetal route to functionalized 4H-chromenes and further transformation into hybrid amino acids and DOPA isomers

For the present research work we have explored the chemistry of the two-carbon synthon, N-methyl-N-[(E)-1-(methylsulfanyl)-2-nitro-1-ethenyl]amine (1N-methyl-1S-methyl-2-nitroethylene, NMSM) 1a (Figure 1), a nitroketene N,S-acetal, for the synthesis of 2-alkylamino-3-nitro-4H-chromenes, 2-alkylamino-4-aryl-3-nitro-4H-chromenes and some amino acids. NMSM is embodied with three functional groups present on the ethylene motif, viz., alkyamine, methylsulfanyl and nitro, each one of which is amenable for synthetic exploitation and functional group manipulation. With an excellent electron-withdrawing nitro group in place, the nitroethylene substructure in 1a is a good Michael acceptor. The methylsulfanyl group is an electron donor and is also a good leaving group. Utilizing well established methods the methylsulfanyl group in 1a can be replaced with a variety of nucleophiles by substitution nucleophilic vinyl (SNV) mechanism. The ethylene moiety in NMSM 1a is a polarized push-pull alkene with electron flow emanating from methylamino / methylsulfanyl to nitro group. Due to polarization, the C1 in NMSM 1a exhibits electrophilic characteristics and the C2 exhibits nucleophilic characteristics. We reasoned that since nitroketene dithioacetals have electrophilic and nucleophilic carbons at adjacent (C1 and C2) positions they can be condensed with bifunctional molecules having nucleophilic and electrophilic centers in 1,4-position so that six-member rings can be generated. The NMSM analogs 1a-g were prepared by SNV substitution of SMe group in 1,1-bis(methylsulfanyl)-2-nitroethylene.

\[ \text{Figure 1} \]
We treated readily available nitroketene \( N,S \)-acetals 1a with substituted 2-hydroxybenzaldehydes (salicylaldehydes) 2a-k in the presence of catalytic amount of DBU in MeOH at rt to furnish a combinatorial library of 3-nitro-4H-chromenes 3a-k (Scheme 1).

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\begin{array}{c}
\text{R1} \text{SMe} \\
\text{MeOH} \quad \text{DBu (10 mol%)} \\
\text{R2} @ \text{NO2} \\
\text{MeOH} \quad \text{rt, 12-19 h} \\
75-93\% \\
\text{R1} \text{NHMe} \\
\text{R3} + \text{MeS8NHMe} \\
\text{R4} \\
\text{R2} = \text{R3} \text{=} \text{R4} = \text{H} \\
\end{array}
\]

2a, 3a: R1 = R2 = R3 = R4 = H
2b, 3b: R1 = OMe, R2 = R3 = R4 = H
2c, 3c: R1 = R3 = R4 = H, R2 = OMe
2d, 3d: R1 = R3 = R4 = H, R2 = Me
2e, 3e: R1 = R3 = R4 = H, R2 = Et
2f, 3f: R1 = R3 = R4 = H, R2 = t-Bu
2g, 3g: R1 = R3 = R4 = H, R2 = Br
2h, 3h: R1 = R3 = R4 = H, R2 = Cl
2i, 3i: R1 = Me, R2 = Cl, R3 = R4 = H
2j, 3j: R1 = R2 = R4 = H, R3 = OCH2Ph
2k, 3k: R1 = R2 = R3 = H, R4 = Ome

Scheme 1

Possible mechanism for the formation of 3-nitro-4H-chromene 3a from 2-hydroxybenzaldehyde 2a and NMSM 1a is given in Scheme 2. The conversion of NMSM 1a and 2-hydroxybenzaldehyde 2a into 4H-chromene 3a follows four major steps namely i. Michael addition, where the anion generated from 2-hydroxybenzaldehyde 2a adds to NMSM 1a in conjugate manner (rate determining step, rds). ii. nitroaldol condensation to provide the pyran ring (steps 1 and 2: click; rds in the case of 2-hydroxybenzaldehydes with C4-OMe). iii. dehydration and dethiomethylation (split) to generate intermediate benzpyrilium cation. iv. thiomethyl anion present in the solution adds on to the benzpyrilium cation forming 3-nitro-4H-chromene 3a (add). Thus the mechanism of the reaction follows click, split and add (CSA) route.
Similarly, condensation of NMSM analogs 1b-e with 2-hydroxybenzaldehyde under optimized conditions furnished 4H-chromenes 4a-f (Figure 2).

Figure 2

We prepared nitroketene N,S-acetals 5a-g from nitroketene S,S-acetal with amino acid methyl esters in acetonitrile reflux (Figure 3). Enantiomeric excess in 5b-5e, 5g and diastereomeric excess in 5f were determined by chiral HPLC analysis which showed that there was some amount or raceimization at the stereogenic center during SNV substitution.
The nitroketene N,S-acetals possessing amino acid residues of alanine 5b, phenylalanine 5c, valine 5d, leucine 5e, isoleucine 5f and tryptophan 5g, on treatment with 2-hydroxybenzaldehyde 2a under optimized conditions yielded the CSA products 6a-g as inseparable mixture of diasteromers (Scheme 3). The glycine substituted nitroketene N,S-acetal 5a, however, failed to undergo this condensation reaction, possibly, because of the acidic nature of the active methylene proton in the glycine unit.

Scheme 3
When we conducted the CSA reaction of 2-hydroxybenzaldehyde 2a with NMSM 1a-f in NaH-THF reflux, we isolated a minor amount (4-24%) of the adducts 7a-f along with the major products 3a, 4a-e. (Figure 4).

![Figure 4](image)

We treated the benzpyrilium cation intermediate readily generated from 4H-chromene 3a with different nucleophiles like thiols or phenols to provide substitution products like 9. For example, 3-nitro-4H-chromene 3a was reacted with three-equivalents of high boiling aromatic thiols like thiophenol 8a, 4-methylthiophenol 8b, 4-chlorothiophenol 8c and aliphatic thiols like butanethiol 8d and octanethiol 8e in ethanol reflux to provide C4-substituted 4H-chromenes 9a-e in excellent yield (Scheme 4)
In contrast to the reaction of 3-nitro-4H-chromene 3a with thiophenol 8a, which yielded substitution product 9a, the reaction with phenol 10a yielded the regioselective electrophilic ring substitution product 10a (Scheme 5).

To ascertain generality of the electrophilic ring substitution with phenols, we prepared a library of 4-aryl-3-nitro-4H-chromenes 11a-n (Figure 5) by taking three different phenols, namely, phenol, para-cresol, para-chlorophenol and four different NH-substituted 3-nitro-4H-chromenes 3a, 4a-c to furnish twelve 4-aryl-3-nitro-4H-chromenes 11a-c and 11f-n in good yields. In each case, the substitution was exclusive to C2 position of phenol. Other than above three phenols, we carried out reactions using ortho-cresol, meta-cresol with the parent 3-nitro-4H-chromene 3a to yield two isomeric 4-aryl-3-nitro-4H-chromenes 11d, 11e.
Some of the phenol substituted 4-aryl-4H-chromenes exhibit atropisomerism due to restricted rotation around C-C single bond possibly due to strong hydrogen bonding stabilization between the hydroxyl and the nitro group of the chromene moiety. We found that two consecutive reactions namely, CSA condensation and aryl substitution could be conducted in one-pot operation, by taking one equivalent of 2-hydroxybenzaldehyde 2a, one equivalent of NMSM 1a and 1.1 equivalent of phenol 10a in the presence of 0.1 equivalent of NaOAc in water. This reaction furnished 4-aryl-4H-chromene 11a in 81% yield.

Reaction of 1,3-dihydroxybenzene, 1,4-dihydroxybenzene in presence or absence of NaOAc provided only a monosubstitution product 12 and 13 respectively (Scheme 6). However, the reaction of 4H-chromene 3a (2.0 equiv), 1,2-dihydroxybenzene (1.0 equiv) provided two products 14 and 15 (Scheme 6). The major product is the monosubstitution product 14 and the minor being bis-chromene 15.
In continuation of the above, substitution of SMe in parent 4\(\text{H}\)-chromene 3a with 1-naphthol, 2-naphthol or 8-hydroxyquinoline in ethanol reflux proceeds smoothly and regioselectively to furnish 4-aryl-3-nitro-4\(\text{H}\)-chromenes 16a-c respectively in quantitative yields (Figure 6).

3-Nitro-4\(\text{H}\)-chromene 3a underwent ready substitution with electron rich aromatic compounds like \(N,N\)-dimethylaniline, indole, pyrrole to provide 4-aryl-3-nitro-4\(\text{H}\)-chromenes 17a-c respectively (Scheme 7).
It was our next task to reductively remove SMe group in 3 in the first step in the process of transformation into amino acids. Reductive desulfurization reaction 3a with Raney nickel with ethanol reflux and at rt led to the formation of minor amounts of 18 and 19 (Scheme 8).

Treatment of 3-nitro-4H-chromenes 3a-c, 3j, 3k with Hantzsch ester was most facile among several reagents we have tried and the reaction furnished dethiomethylation products 20a-e (Figure 7).
The Zn- Ac₂O / AcOH reduction of 4H-chromene 20a at 110 °C provided 68% of N-acetyl ortho-tyrosine lactone 21a, a natural non-essential amino acid (Figure 8). Applying this methodology we were able to prepare and characterize lactones of DOPA isomers 21b-e (Figure 8).

Novel non-natural hybrid amino acids 22 and 24 were synthesized from indole or phenol substituted 3-nitro-4H-chromenes 17b and 10a on Zn-AcOH / Ac₂O reduction (Scheme 9 and 10). On the other hand, treatment of 17b and 10a with Zn, AcOH led to the formation of enamines 23 and 25 (Scheme 9 and 10).
The hybrid amino acid 22 having both tryptophan and tyrosine units was found to possess trans stereochemistry. On the other hand 24 was a mixture of cis and trans isomers. Fractional crystallization resulted in pure cis-isomer of 24.

Thus in the present study we have shown versatility of NMSM in the synthesis of wide variety of 4H-chromenes, 4-aryl-4H-chromenes, ortho-tyrosine, DOPA isomers and few hybrid amino acids.