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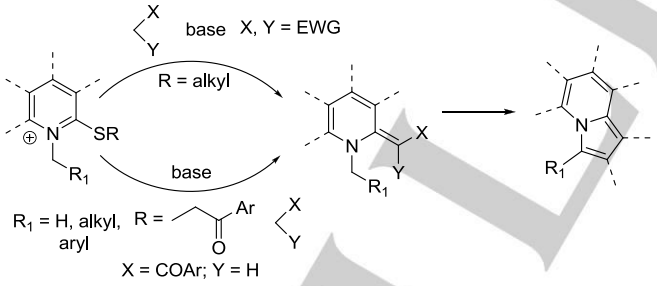
# An Unusual Route to Synthesize Indolizines *via* a Domino $S_N2$/Michael Addition Reaction Between 2-Mercaptopyridine and Nitroallylic Acetates

Suparna Roy*[a]

**Abstract:** We have demonstrated a straightforward synthesis of indolizines from the reaction of 2-mercaptopyridine and nitroallylic acetates in the presence of a base. The products were obtained in good isolated yield in a relatively mild reaction condition. The mechanistic insight of the reaction has been revealed by performing some control experiments demonstrating the reaction initiates *via* a sequential $S_N2$/Michael addition reaction followed by removal of S-moiety. The unconventional application of nitroallylic acetate has been realized.

## Introduction

Development of new synthetic routes for the generation of indolizines continues to be a striking area of research in organic chemistry. The fact is evidenced by persistent flow of numerous research publications over the years.[1-4] In this regard one of the widely used methods involves 1,3-dipolar cycloaddition reaction between pyridinium salt and a suitable dipolarophile.[1a,e,2] A large variety of 2-substituted pyridines have been used as powerful synthetic precursors to access various indolizine frameworks but often required a transition metal-catalyst to trigger the reaction.[1a,f,g,l,2a-c] 2-Mercaptopyridine derivatives are brought into the scope of such transformation but with limited access which requires removal of sulfur moiety




**Scheme 1.** Previous concept for the formation of indolizine from 2-mercaptopyridine derivatives.

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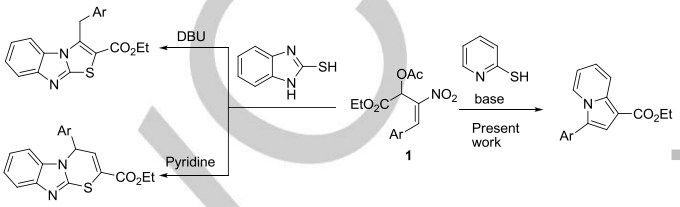



**Scheme 2.** Nitroallylic acetate in relevant reactions.

during the course of the reaction.[2b,3] Step wise cyclization of the derivatives of 2-mercaptopyridinium salts towards indolizines has been documented in a few discrete cases.[3] The sequence commenced with a C–C bond forming reaction when 2-mercaptopyridine derivatives reacted with active methylene compounds in the presence of a base (Scheme 1). Moreover, generation of indolizines has been proposed from a S-containing intermediate *via* extrusion of sulfur moiety.[4a]

On the other hand, nitroallylic acetates are basically the Baylis-Hillman adducts generated from ethyl glyoxalate and β-nitrostyrenes.[5,6] The allylic acetates substituted with adjacent electron withdrawing groups are said to have "all electophilic position."[6i] They have been subjected to react with various dinucleophilic components for the synthesis of a number of heterocycles.[6] In a previous report nitroallylic acetates delivered indolizines when reacted with ethyl 2-pyridylacetate and 2-pyridylacetonitrile.[6i] Again, 2-mercaptobenzimidazole delivered S-containing heterocycles when reacted with nitroallylic acetates *via* an $S_N2$ reaction followed by ring closure process (Scheme 2);[6k] thus manifesting the systematic dinucleophilic and dielectrophilic behaviours of mercapto-substituted N-heterocycle

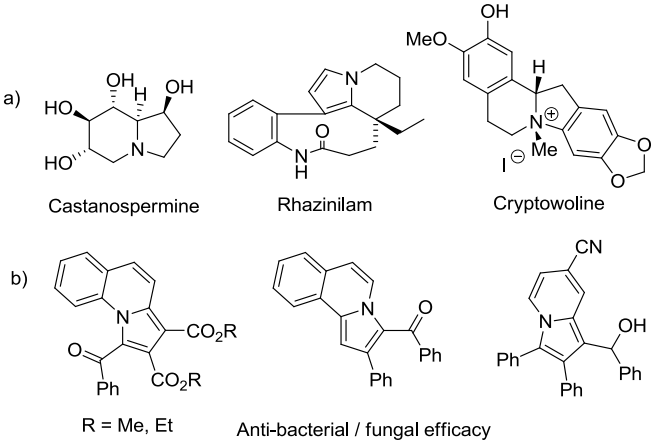



**Fig. 1** Selected examples of natural products and biologically active compounds containing indolizine skeleton.

and nitroallylic acetates respectively. We herein, present a one-pot unconventional route to indolizines from the reaction between 2-mercaptopyridine and nitroallylic acetates in the presence of a base *via* an $S_N2$/Michael addition reaction sequence followed by removal of S-moiety (Scheme 2).

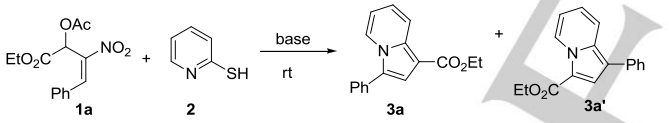
Indolizines are integral part of a number of naturally occurring alkaloids such as swainsonine, camptothecin, cryptowoline, castanospermine, lamellarin, rhazinilam etc and synthetic drugs having pharmacological activities (Fig. 1a).[7] It has been found simply functionalized indolizines can have interesting biological activities (Fig. 1b).[8] In addition, these compounds are known to have fluorescent properties and can be used as dyestuffs.[9]

## Results and Discussion

In our very first attempt we carried out reaction between nitroallylic acetate **1a** and 2-mercaptopyridine (**2**, 1 equiv.) in the presence of quinidine (20 mol%) in DCM for 24 h (Table 1, entry 1). Indolizine **3a** was obtained in 28% isolated yield as a product. The initial result prompted us to find out the suitable base for the reaction. We carried out the reaction in the presence of various nucleophilic bases e. g DABCO, $Et_3N$, DIPA, DBU, DMAP and pyridine (entries 2-7). But in all the cases reaction rendered either decomposition of reactants or complex mixture except pyridine which afforded trace amount of the product. When 2,6-lutidine (1 equiv.) was employed the yield of the reaction was slightly improved to 38% (Table 1, entry 8). Again use of $K_2CO_3$ resulted in decomposition of starting materials(Table 1, entry 9). NaOMe afforded the product only in 18% isolated yield (Table 1, entry 10). The reaction even worked in the presence of ammonium acetate (1 equiv.) though with inferior yield (26%) (entry 11). The reaction worked in absence of any base in MeOH but with low yield (30%) (entry 12). Then various solvents (IPA, 1,4-dioxan, DMF, $CF_3CH_2OH$) were screened without any base but failed to obtain optimum yield (see SI). 2,6-lutidine was employed as a base to optimize the reaction conditions. After several attempts we understood that excessive nitroallylic acetate is needed for completion of the reaction. The fact can be rationalized by partial decomposition of acetate in the presence of a base. So after extensive investigation when we carried out the reaction between 2-mercaptopyridine and nitroallylic acetate (**1a**, 2 equiv.) in the presence of 2,6-lutidine (1 equiv.) in $CS_2$ for 2 days the product **3a** was obtained in 75% isolated yield along with minor regioisomer **3a'** in <5% isolated yield (entry 14). We found that equivalent amount of base was optimal for the reaction as catalytic amount of the same afforded the product in 64% yield in longer reaction time (entry 15). Again nitroallylic acetate was decomposed on using excess base (entry 16).

Next, the generality of the methodology has been established with the optimized reaction condition. A wide variety of nitroallylic acetates has been brought into the substrate scope to obtain indolizine derivatives in good to moderate yields (Table 2). It has been found that nitroallylic acetates substituted with electron releasing groups on aryl ring worked well to afford the

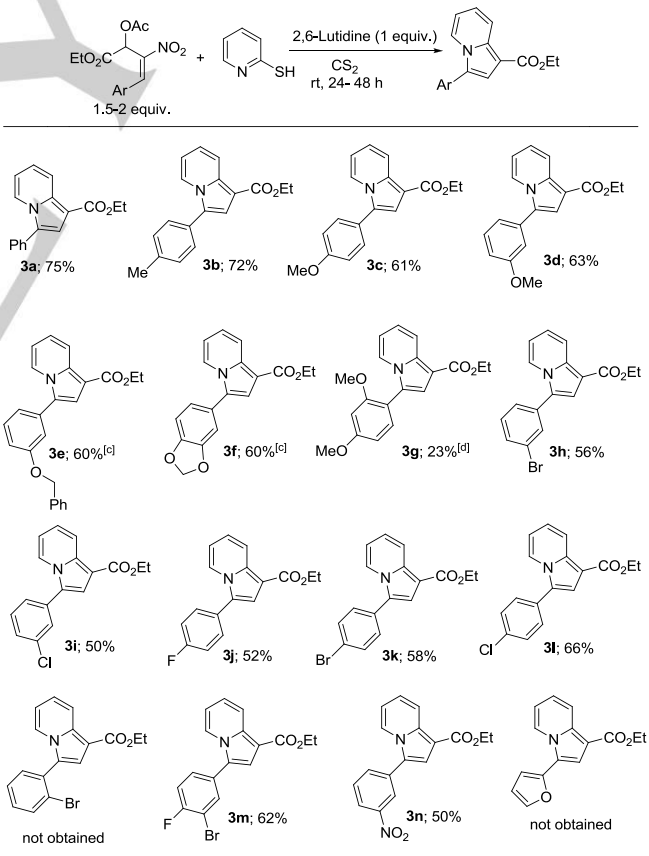
**Table 1.** Optimization of reaction condition.[a]




| Entry | Solvent | Base | Time (h) | Yield 3a (%)[b] |
|---|---|---|---|---|
| 1[c] | DCM | Quinidine | 24 | 28 |
| 2 | DCM | DABCO | 24 | ND |
| 3 | DCM | $Et_3N$ | 8 | ND |
| 4 | DCM | DIPA | 10 | ND |
| 5 | DCM | DBU | 0.5 | Decomp. |
| 6 | DCM | DMAP | 8 | ND |
| 7 | DCM | Pyridine | 24 | trace |
| 8 | DCM | 2,6-Lutidine | 24 | 38 |
| 9 | MeOH | $K_2CO_3$ | 10 | Decomp. |
| 10 | DCM | NaOMe | 24 | 18 |
| 11 | DCM | $NH_4OAc$ | 24 | 26 |
| 12 | MeOH | - | 24 | 30 |
| 13 | $CCl_4$ | 2,6-Lutidine | 24 | 49 |
| 14[d] | **$CS_2$** | **2,6-Lutidine** | **48** | **75** |
| 15[e] | $CS_2$ | 2,6-Lutidine | 88 | 64 |
| 16[f] | $CS_2$ | 2,6-Lutidine | 24 | Decomp. |

[a] Al the reactions were carried out in 0.2 mmol scale of reactants at room temperature. [b] Isolated yield of the product after column chromatography. [c] 20 mol% of quinidine was used. [d] Nitroallylic acetate (2 equiv.) was used. [e] Nitroallylic acetate (2 equiv.) and base (20 mol%) was used. [f] Base (2 equiv.) was used. ND = not detected.

**Table 2.** Scope of substrates.[a, b]




[a] Al the reactions were carried out between 2-mercaptopyridine (0.2 mmol, 22.2 mg), and nitroallylic acetates (4 mmol) in the presence of 2,6-lutidine (0.2 mmol, 24 µl) in $CS_2$ (2 mL) at room temperature for 24-48 h. [b] Isolated yield of the products after column chromatography. [c] Nitroallylic acetate (1.5 equiv.) was used and the reaction was kept stirring for 3 days. [d] Product was isolated with slight minor isomer.

corresponding products in good yields irrespective of their position (**3b**-**g**). Whereas, 2,4-dimethoxy substituted one afforded the product in low isolated yield. Various halo substituted nitroallylic acetates were well-tolerated in the present methodology and provided the products in good to moderate yields (**3h**-**m**). The reaction did not work in case of 2-bromophenyl substituted nitroallyl acetate which can be rationalized by proximal steric bulk. Electron withdrawing group substituted nitroallylic acetate was also susceptible for the reaction to afford the corresponding indolizine in 50% isolated yield (**3n**). Again, 2-fural substituted indolizine was not obtained in our current protocol.

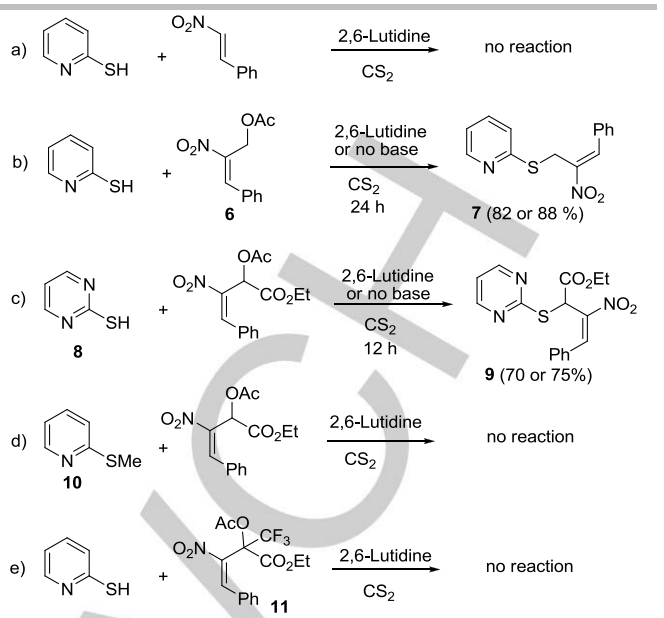
We have intended to include 2-mercaptopyridines with various substitution profiles in this methodology (Fig. 2). Unfortunately, 5-trifluoromethyl 2-mercaptopyridine (**4**) and 6-methyl 2-mercaptopyridine (**5**) did not fit in the optimized reaction conditions and failed to deliver the corresponding products. The probable reason could be based on electronic and steric grounds respectively.


**4** **5**

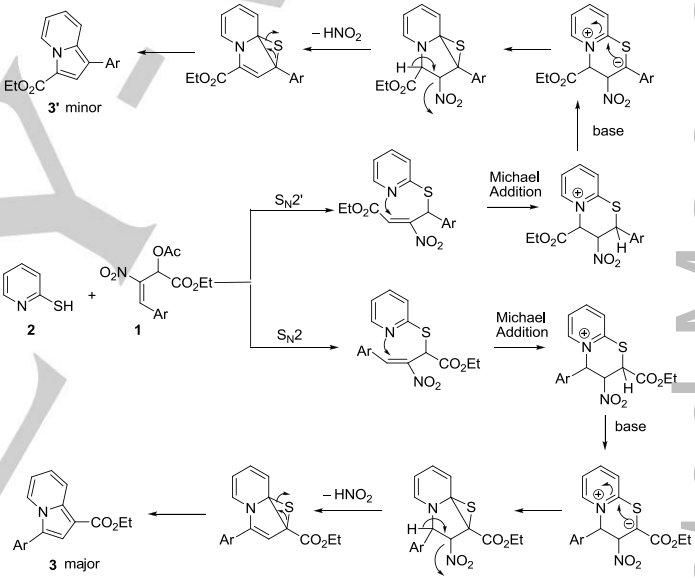
**Fig. 2** Limitation of the reaction methodology.

Next, some control experiments were performed to enlighten the mechanistic insight of the reaction methodology towards indolizines (Scheme 3). At first we carried out reaction between 2-mercaptopyridine and β-nitrostyrene (Scheme 3a). But there was no reaction at all as both the starting materials were intact. Next when we employed primary nitroallylic acetate (**6**) for the same reaction; the product **7** obtained only after nucleophilic substitution reaction (Scheme 3b). The results implied that the reaction initiates *via* an $S_N2$ reaction and a suitably positioned ester group is required for further cyclization *via* Michael addition. Again, similar reaction with 2-mercaptopyrimidine (**8**) resulted in product (**9**) after $S_N2$ reaction (Scheme 3c). Less nucleophilic pyrimidine moiety perhaps restricted further cyclization. It was also observed that synthesis of **7** and **9** could be achieved in absence of a base in comparable isolated yields. Reaction did not work when methylated 2-mercaptopyridine (**10**) and quaternary allylic acetate (**11**) were used in two discrete cases (Scheme 3d and e). This again emphasized that the reaction initiates *via* an $S_N2$ reaction.

On the basis of the above mentioned experiments done we predict that the reaction proceeds through an $S_N2$/Michael addition sequence (Scheme 4). The subsequent ring contraction towards indolizine can be rationalized via the formation of episulfide intermediate (Eschenmoser sulfide contraction). The first step involves an $S_N2$ reaction between 2-mercaptopyridine and nitroallylic acetate at a tertiary carbon centre. The resulting intermediate then undergoes intramolecular Michael addition reaction to generate a cyclic pyridinium ion which gets deprotonated in the presence of a base at active methylenic site and forms an episulfide intermediate. Subsequent aromatization *via* elimination of nitrous acid and removal of S-moiety delivers the product as indolizine.[4a] The formation of minor regioisomer can be realised as a side reaction initiates *via* an $S_N2'$ reaction.




**Scheme 3** Control experiments.




**Scheme 4** Plausible reaction mechanism.

## Conclusions

We have demonstrated a base-mediated reaction between 2-mercaptopyridine and nitroallylic acetates to deliver substituted indolizines. A number of nitroallylic acetates were susceptible for the methodology to obtain the product in high to moderate yields. The mechanism of the reaction has been understood as a sequential $S_N2$ reaction at less likely tertiary centre followed by Michael addition and aromatization process. The result definitely discloses the versatility of nitroallylic acetate as an efficient precursor for the synthesis of indolizine moiety in a rather unusual manner.

## Experimental Section

Supporting Information: Experimental procedures and compound characterization data (IR, $^{1}H$, $^{13}C$ NMR and HRMS). This material is available free of charge in the Supporting Information.

## Acknowledgement

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**Keywords:** Domino reaction • Indolizine • Michael addition • Nitroallylic acetate • $S_N2$ reaction

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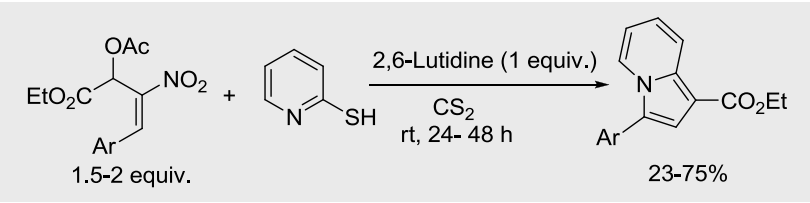
# COMMUNICATION




An unusual reaction between 2-mercaptopyridine and nitroallylic acetates has been demonstrated. The reaction initiates by a domino sequence including an $S_N2$ reaction at tertiary centre followed by Michael addition and removal of S-moiety to deliver substituted indolizines as products.

**Synthetic method**

*Suparna Roy**

**An Unusual Route to Synthesize Indolizines *via* a Domino $S_N2$/Michael Addition Reaction Between 2-Mercaptopyridine and Nitroallylic Acetates**