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Facile three-component domino reactions in the regioselective synthesis and antimycobacterial evaluation of novel indolizines and pyrrolo[2,1-*a*]isoquinolines

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ABSTRACT

The domino reactions of pyridine/isoquinoline, bromoacetonitrile/ethyl bromoacetate and a series of β-nitrostyrenes in the presence of triethylamine afforded novel tri-/disubstituted indolizines and pyrrolo[2,1-*a*]isoquinolines regioselectively, presumably via substitution-dipole generation-1,3-dipolar cycloaddition-elimination and/or aromatisation sequence. In vitro screening of all the seventeen compounds synthesized against *Mycobacterium tuberculosis* H37Rv discloses that ethyl 2-(4-fluorophenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate displays maximum potency with minimum inhibitory concentration (MIC) of 1.0 μM, being 7.6 and 4.7 times more potent than the standard first line TB drugs, ethambutol and ciprofloxacin, respectively.

Indolizine, being isomeric to indole, constitutes the core structure of many naturally occurring alkaloids, viz. (−)-slaframine,[1] (−)-dendroprimine,[2] indolizidine 167B[3] and coniceine.[4] They are important as potential central nervous system depressants,[5] calcium entry blockers,[6] cardiovascular[7] and antimycobacterial agents,[8] spectral sensitizers[9] and novel dyes.[10] They are also used for the treatment of angina pectoris[11] and as testosterone 5*R*-reductase inhibitors,[12] besides serving as key intermediates for the synthesis of cycloazines.[13] Consequently, the synthesis of indolizines, especially the biologically active ones,[14] continues to attract the attention[15] of organic chemists. Typical syntheses of indolizine have been well documented in the literature[16] among which, the 1,3-dipolar cycloaddition reaction of pyridinium N-ylide generated in situ from a pyridinium salt in the presence of a base with an electron-deficient alkene/alkyne is one versatile methodology.[17]

The biological importance of indolizines prompted the synthesis of the hitherto unreported substituted indolizines and pyrrolo[2,1-*a*]isoquinolines **5–8** (Scheme 1) employing domino reactions, to screen them for antimycobacterial activities and to report the results in this Letter. Incidentally, domino reactions[18] being convergent enable a rapid and elegant access to molecules of high levels of diversity and complexity in high yields relative to multi-step reactions and hence are increasingly preferred. This study stems as a part of our research programme embarked on the construction of novel heterocycles employing tandem/domino multi-component reactions[19] and/or to screen them for antimycobacterial activities.[20]

In the present investigation, the domino reactions of a mixture of pyridine **3** or isoquinoline **4**, bromoacetonitrile **2a** or ethyl bromoacetate **2b** and β-nitrostyrenes **1** (Scheme 1) in a 1:1.2:1 molar ratio in the presence of triethylamine were performed in acetonitrile at room temperature for 3–5 h.[21] The reaction afforded 1-nitro-2-aryl-3-indolizine carbonitriles **5**, ethyl 2-aryl-1-nitroindolizine-3-carboxylates **6**, 1-nitro-2-arylpyrrolo[2,1-*a*]isoquinoline-3-carbonitrile **7** and ethyl 2-arylpyrrolo[2,1-*a*]isoquinoline-3-carboxylates **8** (Scheme 1) from the respective reactants in moderate to good yields (44–80%) of the product (Table 1). All these reactions are regioselective affording only **5–8**, whilst their regioisomers **5′–8′** were not obtained even in traces (Scheme 2).

The reaction performed in the presence of different bases, viz. Et_3N, DBU, DMAP, piperidine and K_2CO_3 (Table 2) clearly shows that Et_3N is the most efficient base for these domino reactions and that the reaction affords a maximum yield of the product when a molar equivalent of Et_3N was employed.

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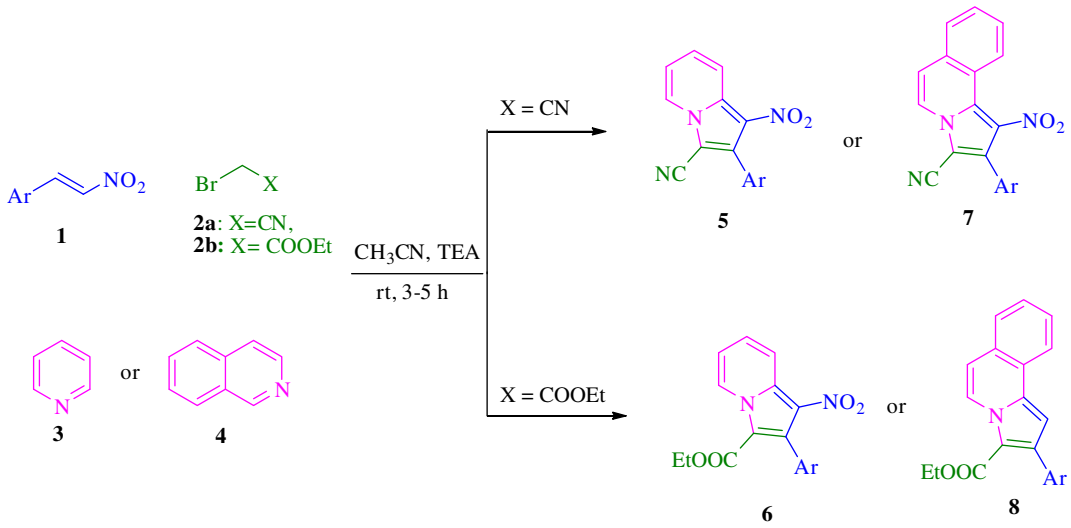


Scheme 1. Synthesis of indolizines and pyrrolo[2,1-*a*]isoquinolines **5**–**8**.

Table 1
Synthesis and antimycobacterial activities of indolizines and pyrrolo[2,1-*a*]-isoquinolines **5**–**8** against MTB

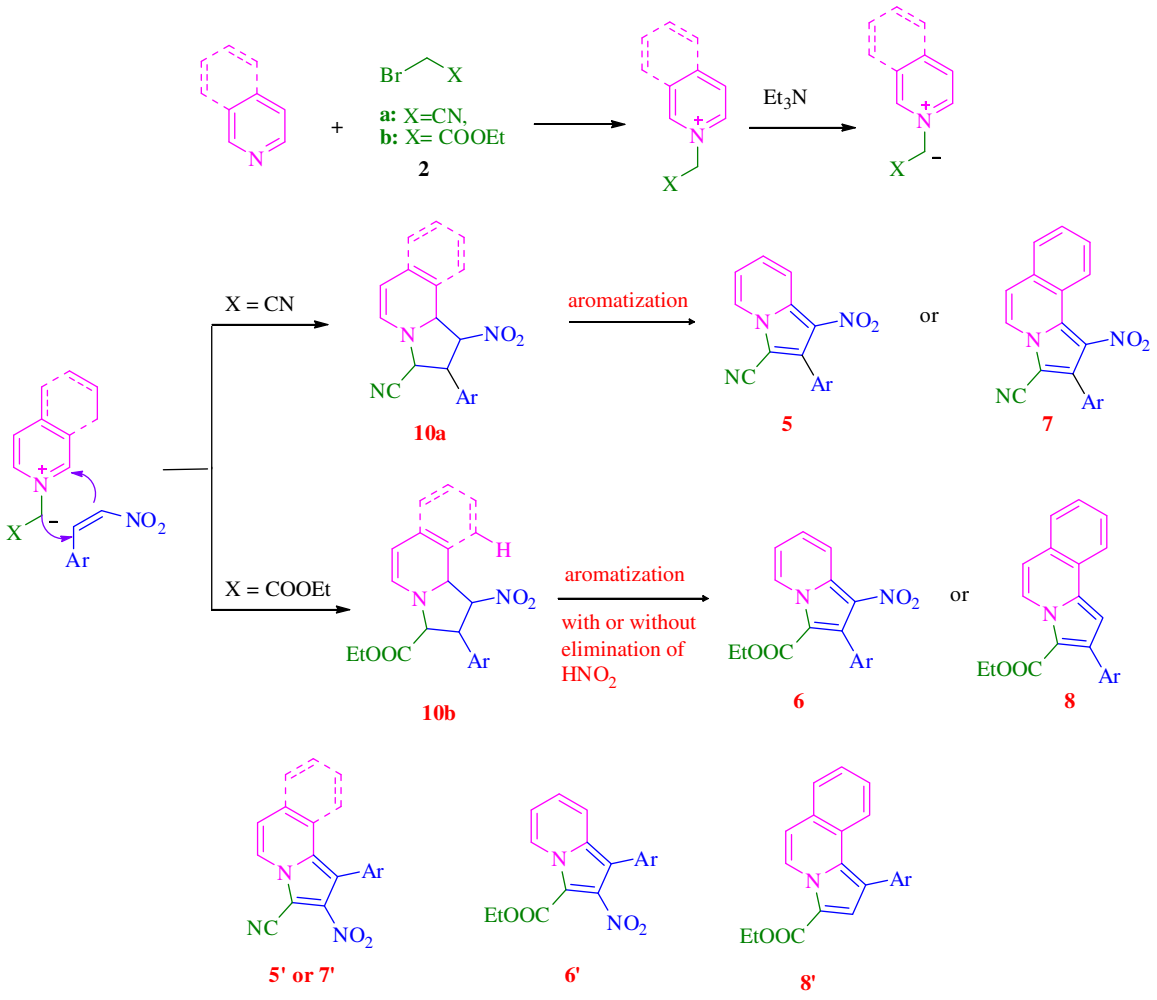
Entry	Compd.	Ar	X	Reaction time (h)	Yield (%)[a]	MIC (μM)
1	**5a**	2,4,6-$(MeO)_3C_6H_2$	CN	3	44	>85
2	**5b**	4-$MeOC_6H_4$	CN	5	52	85
3	**5c**	4-MeC_6H_4	CN	3	54	45.1
4	**5d**	4-$Pr^iC_6H_4$	CN	5	51	40.9
5	**5e**	4-ClC_6H_4	CN	4	57	21.0
6	**5f**	4-FC_6H_4	CN	4	53	5.5
7	**6a**	4-ClC_6H_4	COOEt	3	58	9.1
8	**6b**	2,4-$Cl_2C_6H_3$	COOEt	3	54	NT[b]
9	**7a**	4-$MeOC_6H_4$	CN	5	53	36.4
10	**7b**	4-MeC_6H_4	CN	3	60	9.6
11	**7c**	4-ClC_6H_4	CN	4	71	9.0
12	**7d**	4-FC_6H_4	CN	4	58	2.3
13	**8a**	4-$MeOC_6H_4$	COOEt	3	62	16.0
14	**8b**	4-MeC_6H_4	COOEt	4	68	16.7
15	**8c**	C_6H_5	COOEt	3	65	17.3
16	**8d**	4-$Pr^iC_6H_4$	COOEt	3	80	7.8
17	**8e**	4-ClC_6H_4	COOEt	4	62	3.9
18	**8f**	4-FC_6H_4	COOEt	3	77	1.0
Rifampicin						0.1
Isoniazid						0.4
Ciprofloxazin						4.7
Ethambutol						7.6

[a] Isolated yield after purification by column chromatography.
[b] Not tested.

The structure of the indolizines and arylpyrrolo[2,1-*a*]isoquinolines **5–8** was established from ^1H, ^{13}C and 2D NMR spectroscopic data. The chemical shifts of **5c**, a representative example, were assigned on the basis of straightforward considerations including HMBCs and H,H-COSY correlations, substituent induced chemical shifts and signal multiplicities of ^1H NMR signals (Fig. 1). A comparison of the chemical shifts of **5c** with those of a model compound, ethyl 2-iodo-1-nitroindolizine-3-carboxylate,[22] shows that the chemical shifts and vicinal *J* values of H-6, H-7 and H-8 of both the compounds differ little supporting the position of the nitro function in **5c** and hence the regiochemistry of the reaction. The chemical shift of H-5 of **5c** and that of model compound alone differ significantly ascribable to the van der Waals deshielding of H-5 by the ester function in the latter.[23] The IR spectrum of **5c** had the frequencies expected for the nitrile and nitro groups at 2214 cm^{-1} (CN) and 1500 and 1367 cm^{-1} (NO_2). The structures deduced from NMR spectra were further confirmed by the X-ray crystallographic studies of single crystals of two representative cases, **5b** and **8d** (vide Supplementary data).[24]

A plausible mechanism for the formation of **5–8** is depicted in Scheme 2. Presumably, a domino sequence of reactions involving substitution, generation of 1,3-dipole and cycloaddition of pyridinium ylides to β-nitrostyrenes **1** afford **10**, which undergo spontaneous elimination and/or aromatisation to furnish **5–8** (Scheme 2). The regioselectivity observed in the formation of **5–8** is ascribable to the preference of the anionic centre of the dipole to react with the electron-deficient α-carbon of the β-nitrostyrenes during the cycloaddition reaction. Probably, the enhanced steric interaction in the intermediate **10b** with the isoquinoline sub-structure triggers the elimination of HNO_2 and the concomitant aromatisation affording **8** (Scheme 2).

In previous synthetic methods, indolizines and pyrrolo[2,1-*a*] isoquinolines were obtained by multi-step protocols from the reactions of pyridinium/isoquinolinium yide, prepared in a separate



Scheme 2. Plausible mechanism for the formation of indolizines and pyrrolo-[2,1-*a*]isoquinolines **5**–**8**.

Table 2
Influence of base on the formation of **5c**

Entry	Base	Mol %	Reaction time (h)	Yield of **5c** (%)[a]
1	Et_3N	25	14	10
2	Et_3N	50	14	45
3	Et_3N	75	14	51
4	Et_3N	100	3	72
5	DMAP	100	5	65
6	DBU	100	5	55
7	Piperidine	100	15	—[b]
8	K_2CO_3	100	10	—[b]

[a] Isolated yield after purification by column chromatography.
[b] Product not obtained.

step, with electron-deficient alkenes which proceed via cycloaddition-elimination/oxidation sequence.[22,25–30] Only one three-component domino approach has been reported in the literature, viz. for the synthesis of indolizines by the reaction of pyridine, α-haloketone and alkyne under microwave irradiation.[31] Hence, the present work constitutes the first report on the synthesis of novel tri-/disubstituted indolizines and pyrrolo[2,1-*a*]isoquinolines in high yields of 44–80% (Table 1) by the three component domino reaction of pyridinium/isoquinolinium ylide, generated in situ from pyridine/isoquinoline with bromoacetonitrile or ethyl bromoacetate, with β-nitrostyrenes at ambient temperature.

The indolizines and pyrrolo[2,1-*a*]isoquinolines synthesized in the present work were screened for their in vitro antimycobacterial activity against *M. tuberculosis* H37Rv (MTB) by agar dilution method[32] for the determination of minimum inhibitory concentration (MIC) in triplicate and these MIC values along with those of the standard drugs are presented in Table 1. Among all the compounds screened, three compounds, viz. **7d**, **8e** and **8f** with MIC values of 2.3, 3.9 and 1.0 μM, respectively, emerged more potent than the standard drug ethambutol (MIC: 7.6 μM). Ethyl 2-(4-fluorophenyl)pyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**8f**) displayed maximum activity, being 7.6 and 4.7 times more potent than ethambutol and ciprofloxacin, respectively. However, all the compounds are less active against MTB than the drugs, isoniazid (MIC: 0.4 μM) and rifampicin (MIC: 0.1 μM), It is to be noted that, in general, both indolizine series **6** bearing ester and nitro groups and pyrrolo[2,1-*a*]isoquinoline series **8**, respectively, with ester function in the pyrrole sub-structure led to enhanced activity than series **5** and **7** with nitrile and nitro functions (Table 1).

In conclusion, a facile, regioselective synthesis of novel indolizines and pyrrolo[2,1-*a*]isoquinolines has been achieved via a domino sequence of reactions from simple, readily available starting materials in a one-pot operation. These compounds also display significant antimycobacterial activities.

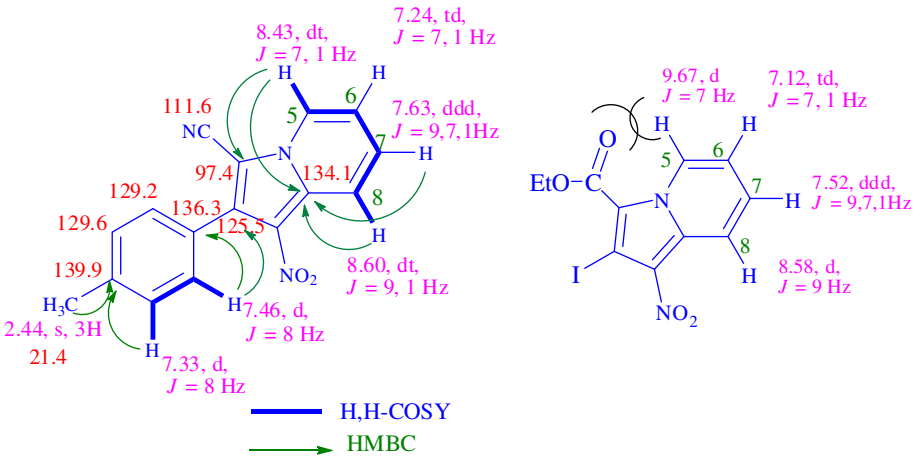


Figure 1. Selected 2D-correlations and chemical shifts for **5c** and for model compound, ethyl 2-iodo-1-nitroindolizine-3-carboxylate.[22]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.128.

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21. *General procedure for the synthesis of indolizines and pyrrolo[2,1-a]isoquinolines*: A mixture of β-nitrostyrene **1** (1 mmol), pyridine **3** (1 mmol), bromoacetonitrile **2** (1.2 mmol) and triethylamine (1 mmol) in acetonitrile (8 ml) was stirred at room temperature for 3 h. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the solvent was removed and the product was purified by column chromatography using petroleum ether–ethyl acetate mixture (4:1 v/v) as eluent to afford indolizines and pyrrolo[2,1-*a*]isoquinolines. Spectroscopic data for representative indolizines and pyrrolo[2,1-*a*]isoquinolines are given below.
2-(4-methylphenyl)-1-nitro-3-indolizinecarbonitrile **5c**: Isolated as white solid. Yield 54%. Mp 234–238 °C; IR (KBr) 2214 cm^{-1} (C≡N), 1367, 1500 cm^{-1} (NO_2); ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.44 (s, 3H), 7.24, td (1H, *J* = 7,1 Hz), 7.33 (d, 2H, *J* = 8 Hz), 7.46 (d, 2H, *J* = 8 Hz) 7.63 (ddd, 1H, *J* = 9, 7, 1 Hz), 8.43 (dt, 1H, *J* = 7, 1 Hz), 8.60 (dt, 1H, *J* = 9, 1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.4, 97.4, 111.6, 116.7, 120.2, 125.5, 125.7, 129.2, 129.6, 130.0, 134.1, 136.3, 139.9. Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.35; H, 3.97; N, 15.12.
Ethyl 2-(4-chlorophenyl)-1-nitroindolizine-3-carboxylate **6a**: Isolated as white solid. Yield 58%. Mp 175–178 °C; IR (KBr) 1750, 1622 cm^{-1} (COOEt); ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.91 (t, 3H, *J* = 7 Hz), 4.09 (q, 2H, *J* = 7 Hz), 7.17–7.22 (m, 1H), 7.30 (d, 2H, *J* = 7 Hz), 7.42 (d, 2H, *J* = 7 Hz), 7.60–7.70 (m, 1H) 8.62 (dd, 1H, *J* = 8, 1 Hz), 9.75 (d, 1H, *J* = 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.4, 60.7, 113.3, 116.3, 119.2, 127.8, 128.3, 129.6, 130.4, 131.5, 133.03, 133.8, 134.1, 161.1. Anal. Calcd. for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; N, 8.13. Found C, 59.35; H, 3.88; N, 8.05.
2-(4-Chlorophenyl)-1-nitropyrrolo[2,1-a]isoquinoline-3-carbonitrile **7c**: Isolated pale yellow solid. Yield 71%. Mp 270–274 °C; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.09 (d, 1H, *J* = 7 Hz), 7.45–7.48 (m, 2H), 7.53–7.64 (m, 2H), 7.69–7.72 (m, 1H), 7.77–7.81 (m, 2H), 8.08 (d, 1H, *J* = 7 Hz), 8.14 (dd, 1H, *J* = 8, 2 Hz); ^3C NMR (75 MHz, $CDCl_3$) δ_C 94.6, 99.9, 113.7, 114.2, 122.4, 123.0, 124.6, 127.4, 127.9, 128.1, 128.4, 129.2, 130.8, 134.2, 134.3, 135.4. Anal. Calcd. for $C_{19}H_{10}ClN_3O_2$: C, 65.62; H, 2.90; N, 12.08. Found C, 65.55; H, 3.01; N, 12.15.
Ethyl 2-phenylpyrrolo[2,1-a]isoquinoline-3-carboxylate **8c**: Isolated as white solid. Yield 65%. Mp 140–144 °C; IR (KBr) 1675, 1606 cm^{-1} (COOEt); ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.10 (t, 3H, *J* = 7 Hz), 4.21 (q, 2H, *J* = 7 Hz), 7.02 (d, 2H, *J* = 7 Hz), 7.34–7.39 (m, 3H), 7.48–7.56 (m, 4H), 7.66–7.69 (m, 1H), 8.12 (d, 1H, *J* = 8 Hz), 9.30 (d, 1H, *J* = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 59.8, 103.7,

112.5, 113.1, 123.1, 124.7, 125.2, 126.8, 127.0, 127.4, 127.5, 128.0, 129.9, 134.1, 136.7, 136.8, 162.0. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found C, 79.90; H, 5.51; N, 4.40.

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23. It appears that the long range couplings ($^4J_{H,H}$ = 1 Hz) of both H-5 and H-8 for the model compound. ethyl 2-iodo-1-nitroindolizine-3-carboxylate[22] have not been reported in the earlier work probably because of poor resolution but are essential to explain the observed multiplicities of H-6 and H-8 as found for **5c**.
24. Crystallographic data (excluding structure factors) for ethyl 2-(4-isopropylphenyl)pyrrolo(2,1-*a*)isoquinoline-3-carboxylate **8d** and 2-(4-methoxyphenyl)-1-nitro-3-indolizinecarbonitrile **5b** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 775513 and 775514. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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