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A microwave-assisted facile regioselective Fischer indole synthesis and antitubercular evaluation of novel 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles

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ABSTRACT

A series of novel 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles has been synthesised regioselectively in good yields from the reaction of 5-aryldihydro-3(2*H*)-thiophenones and arylhydrazine hydrochloride. This reaction is found to be assisted by microwaves. The thieno[3,2-*b*]indoles were evaluated for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). Among 22 compounds screened, [2-(2,4-dichlorophenyl)-7-fluoro-3,4-dihydro-2*H*-thieno[3,2-*b*]indole] (**6t**) was found to the most active compound with MIC of 0.4 μg/mL against MTB and MDR-TB.

For well over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed.[1] Among the synthetic methodologies reported so far for the preparation of the indole analogs, the Fischer indole synthesis still maintains its prominent role for the large scale production of biologically active compounds.[2] Indoles are of great significance in view of their (i) occurrence in nature as a prominent sub-structure of a large number of alkaloids,[3] and (ii) wide-ranging biological activities.[4] Some indole derivatives function as dopamine agonists and/or selective serotonin reuptake inhibitors (SSRIs), the latter being a class of anti-depressants.[5] Acemetacin[6] and indometacin[7] are clinically used as anti-inflammatory drugs and fluvastatin sodium[8] is a well-known HMG-CoA reductase inhibitor.

Thiophene fused nitrogen heterocycles also display important biological activities. For instance, thienoquinolones display antitumour activities,[9] while thienopyrimidinones possess analgesic and anti-inflammatory activities.[10] Thienocarbolines and heteroarylaminobenzothiophenes exhibit antimicrobial[11] and anti-oxidant activities[12] respectively. The biological importance of indoles and thiophene fused nitrogen heterocycles prompted the Fischer indole synthesis of the hitherto unreported 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles **6** in excellent yields (Scheme 1) and their screening for antimycobacterial activities. This study forms part of our research programme embarked on to evolve new methodologies for the construction of novel heterocycles[13] and to discover new lead molecules with antimycobacterial activities.[14]

This study assumes importance as tuberculosis has become one of the most prevalent diseases that is responsible for the death of about one billion people during the last two centuries.[15] TB remains a serious public health problem in India, accounting for nearly one-third of the global burden, and it has been estimated that 3.5 million of the population are infected with TB.[15,16] Currently, the recommended standard chemotherapeutic regimen for TB treatment prescribed under DOTS comprises an initial 2-month phase of treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol followed by a continuation phase of treatment lasting 4 months with isoniazid and rifampicin.[17,18] Poor patient compliance can promote the emergence of drug resistance, and this is particularly true in TB chemotherapy.[17,18] The emergence of strains resistant to either of these drugs causes major concern, as it leaves only drugs that are far less effective, have more toxic side effects, and result in higher death rates, especially among HIV-infected persons. Serial selection of drug resistance, thus, is the predominant mechanism for the development of MDR strains; the patients with MDR strains constitute a pool of chronic infections,

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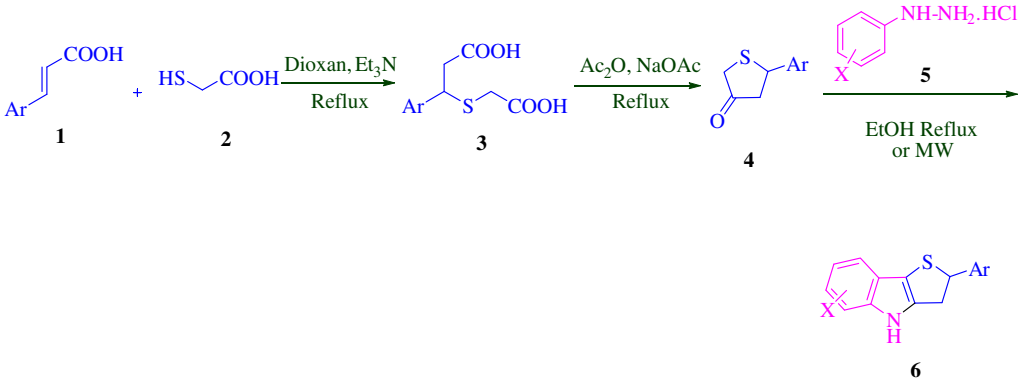


Scheme 1.

which propagate primary MDR resistance. In addition to accumulation of mutations in the individual drug target genes, the permeability barrier imposed by the MTB cell wall can also contribute to the development of low-level drug resistance.[19,20] In the last 50 years, only a few drugs have been approved by the Food and Drug Administration (FDA) to treat TB, which reflects the inherent difficulties in the discovery and clinical testing of new agents and the lack of pharmaceutical industry research in this area.[21] Hence, the discovery of fast-acting effective newer drugs to effectively cure TB, including multidrug resistant tuberculosis, is imperative.

In a typical reaction, the synthesis of 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles **6**[22] was effected by refluxing a mixture of 5-aryldihydro-3(2*H*)-thiophenones **4**[13e,h] and arylhydrazine hydrochloride **5** (Scheme 1) in a 1:1.3 molar ratio in ethanol for 30–70 min. The reaction mixture reached a temperature of 80 °C during reflux as measured by inserting a thermometer inside the reaction mixture. Work up of the reaction mixture after completion of the reaction (TLC) followed by crystallization afforded the product **6** in a pure state in good yields (80–95%).

This reaction was further investigated under microwave irradiation with a view to exploring whether, (i) the reaction could be expedited and, (ii) the yield of **6** could be enhanced. A mixture of 5-aryldihydro-3(2*H*)-thiophenones **4** and arylhydrazine hydrochloride **5** in the molar ratio of 1:1.3 in ethanol taken in a sealed tube (10 mL) was subjected to microwave irradiation[22] at 90 °C and 2 bar pressure for 3–6 min. The reaction progress was monitored after every 1 min of irradiation by TLC. This reaction also furnished pure product in excellent yields (85–98%; Table 1). The temperature of 90 °C was chosen to obtain the optimum reaction

Table 1
Synthesis and antimycobacterial activities of 2-aryl-3,4-dihydro-2*H*-thieno [3,2-*b*]indoles **6**

Compound	Ar	X	Reaction time (min)		Yield of **6** (%)		MIC (μg/mL)	
			Reflux[a] (80 °C)	MW[b] (90 °C)	Reflux[c]	MW[c]	MTB	MDR-TB
6a	C_6H_5	H	50	3	95	97	25.00	—[d]
6b	4-ClC_6H_4	H	50	5	90	95	12.50	—[d]
6c	4-MeC_6H_4	H	50	3	92	95	6.25	12.50
6d	2,4-$Cl_2C_6H_3$	H	70	6	88	90	1.76	0.78
6e	3-$O_2NC_6H_4$	H	70	5	85	93	1.76	0.78
6f	2-BrC_6H_4	H	60	6	80	92	3.13	3.13
6g	2-ClC_6H_4	H	60	6	83	90	6.25	—[d]
6h	3-FC_6H_4	H	65	5	85	88	3.13	—[d]
6i	4-$Pr^iC_6H_4$	H	40	5	80	85	0.78	0.40
6j	C_6H_5	7-Cl	40	5	83	90	12.50	—[d]
6k	4-ClC_6H_4	7-Cl	30	4	85	90	12.50	—[d]
6l	4-MeC_6H_4	7-Cl	40	5	85	95	6.25	6.25
6m	2,4-$Cl_2C_6H_3$	7-Cl	30	4	90	98	0.78	0.40
6n	2-ClC_6H_4	7-Cl	30	4	83	90	3.13	1.56
6o	4-$PriC_6H_4$	7-Cl	40	6	80	88	0.78	0.78
6p	4-FC_6H_4	7-Cl	40	5	85	90	3.13	0.78
6q	C_6H_5	7-F	40	5	80	95	6.25	12.50
6r	4-ClC_6H_4	7-F	40	5	80	95	1.56	1.56
6s	4-MeC_6H_4	7-F	40	5	85	90	3.13	1.56
6t	2,4-$Cl_2C_6H_3$	7-F	30	4	95	97	0.40	0.40
6u	2-ClC_6H_4	7-F	30	4	85	95	1.76	1.56
6v	4-$Pr^iC_6H_4$	7-F	50	6	80	85	0.78	0.40
Isoniazid							0.05	1.56
Rifampicin							0.10	3.13
Ethambutol							1.56	12.50
Pyrazinamide							6.25	50.00

[a] Refluxed in ethanol.
[b] Irradiated with ethanol.
[c] Yield after crystallization from chloroform.
[d] Not tested.

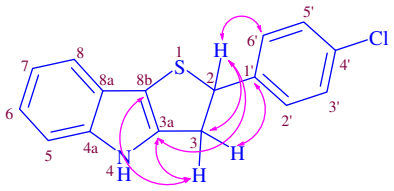


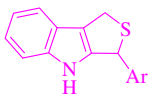
Figure 1. HMBC correlations in **6b**.

time. Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 90 °C did slow down the reaction.

To enable a comparison of the efficacies of the thermal and microwave reactions, the reaction under microwave irradiation was also performed in one representative case, viz. **6a** at the temperature of the reaction mixture at reflux under thermal conditions, viz. 80 °C. At 80 °C, the reaction under microwave irradiation was completed in 5 min, viz. ten times faster than the thermal reaction (50 min) in the same solvent showing that the reaction is assisted by microwaves.

5-Aryldihydro-3(2*H*)-thiophenones **4** were prepared by a literature method[23] with slight modifications described below. Addition of triethyl amine in dioxan to a mixture of mercaptoacetic acid **2** and cinnamic acid **1** in dioxan yielded the 3-[(carboxymethyl)sulfanyl]-3-arylpropanoic acids **3**, which upon heating on an oil-bath at 120 °C with acetic anhydride and sodium acetate (in place of lithium acetate[23] employed in the previous study) to afford **4**. The solid product obtained in both the steps were filtered and washed well with water to obtain pure product instead of extraction with ether in the previous study. These modifications resulted in an enhancement in yield of the product (~10%) in the present investigation.

The structure of the 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles **6** was established from ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for **6b**. In the ^{1}H NMR spectrum of **6b**, H-2 appeared as a 1H triplet at 5.46 ppm (J = 8.3 Hz) which showed HMBC correlations (Fig. 1) with the *ipso* carbon (C-3a) at 140.9 ppm, C-3 at 37.2 ppm and C-2' and C-6′ at 128.6 ppm. The diastereotopic 3-CH_2 protons appeared as a doublet of doublets at 3.30 and 3.56 ppm (J = 15.5, 7.7 Hz and 15.5, 8.6 Hz). These protons showed HMBC correlations with *ipso* carbons C-3a, C-8b and C-1', respectively at 140.9, 112.3 and 134.2 ppm. The NH proton gave a broad singlet at 7.98 ppm.



12
(not formed)

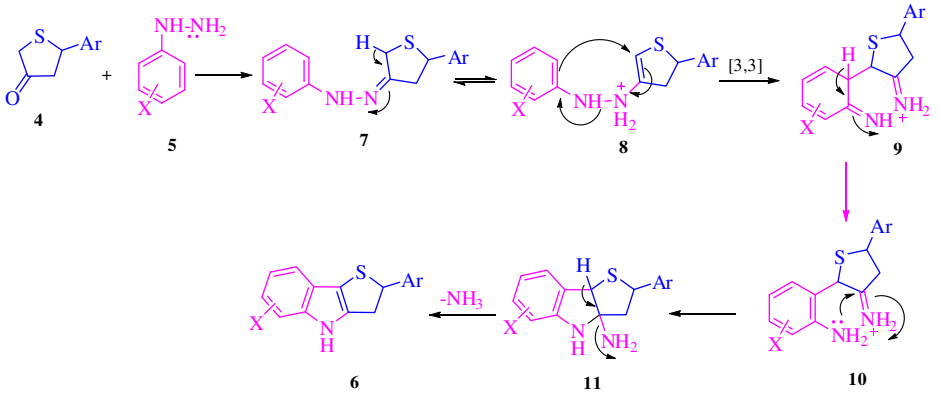
Figure 2. Regioisomer of **6**.

Although the Fischer indole synthesis is the most widely used method for the preparation of indoles, it suffers from (i) low yields, 2a,b,24,25 (ii) formation of numerous by-products, and (iii) low regioselectivity in the case of unsymmetrical ketones.[2a,b,26–29] In contrast, the reaction in the present work led to the exclusive formation of one regioisomer of thienoindoles **6** in very good yield under mild reaction conditions. The other regioisomer **12** (Fig. 2) is not obtained even in traces in this reaction. The structure of **6** is readily assigned from the AMX spin system arising from the H-2 and 3-CH_2 hydrogens in its ^{1}H NMR spectrum, which distinguishes from the regioisomer **12**.

During the preparation of this manuscript, we came across a literature report on the synthesis of unsubstituted dihydrothieno[3,2-*b*]indole lacking the aryl ring at 2-position in 60% yield from the reaction of dihydrothiophen-3(2*H*)-one and phenylhydrazine hydrochloride in ethanol, in contrast to the excellent yields (88–97%) of **6** obtained in the present work.[30] This prompted us to reexamine the reaction between dihydrothiophen-3(2*H*)-one and phenylhydrazine hydrochloride in ethanol, which led to an enhanced yield (90%) of the product. It is pertinent to note that there are only a few reports on the synthesis of dihydrothieno[3,2-b]indoles[30,31] and thieno[3,2-b]indoles.[32]

A plausible mechanism for the formation of **6** involving a [3,3]-sigmatropic rearrangement of the enehydrazine tautomer **8** to **9** with concomitant cyclization and aromatization with the loss of ammonia is depicted in Scheme 2. The regioselectivity of this reaction is presumably ascribable to the influence of sulfur in favouring the formation of the tautomer **8** with the double bond involving the carbon bearing sulfur which ultimately leads to the regioisomeric thienoindole **6**.

All the newly synthesized compounds were screened for their in vitro antimycobacterial activity against MTB and MDR-TB by an agar dilution method and MICs of the synthesized compounds along with the standard drugs for comparison are reported (Table 1). In the first phase of screening against MTB, all the compounds showed good in vitro activity against MTB with MIC of ⩽25 μg/mL. Five compounds (**6i**, **6m**, **6o**, **6t** and **6v**) inhibited MTB with MIC of <1 μg/mL and were more potent than standard ethambutol (MIC: 1.56 μg/mL) and pyrazinamide (MIC: 6.25 μg/mL). The compound, [2-(2,4-dichlorophenyl)-7-fluoro-3,4-dihydro-2*H*-thieno[3,2-*b*]indole] (**6t**) was found to be the most active in vitro with MIC of 0.4 μg/mL against MTB and was 4 and 16 times more



Scheme 2. Proposed mechanism for the formation **6**.

potent than ethambutol and pyrazinamide respectively. Subsequently, sixteen compounds were evaluated against MDR-TB and all these compounds inhibited MDR-TB with MIC ranging from 0.4 to 12.5 μg/mL. Eight compounds (**6d**, **6e**, **6i**, **6m**, **6o**, **6p**, **6t** and **6v**) inhibited MDR-TB with MIC of <1 μg/mL and were more potent than the currently available anti-TB drugs such as isoniazid (MIC: 1.56 μg/mL), rifampicin (MIC: 3.13 μg/mL), ethambutol (MIC: 12.5 μg/mL) and pyrazinamide (MIC: 50.0 μg/mL). Compounds **6i**, **6m**, **6t** and **6v** were found to display maximum activity in vitro with MIC of 0.4 μg/mL against MDR-TB, being 4 and 8 times more potent than isoniazid and rifampicin respectively.

With respect to structure–MTB activity relationship, the results demonstrated that the presence of halogens in the thienoindole moiety enhances the activity. Among the halogens, fluoro derivatives exhibit greater activity than chloro derivatives. With respect 2-aryl group, aryl ring with halogen or propyl group enhances the activity. Similarly disubstitution in the aryl ring also amplifies the activity.

The present work describes a microwave-assisted facile, efficient and rapid regioselective Fischer indole synthesis of new 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles in excellent yields under mild reaction conditions. These thienoindoles displayed good in vitro antimycobacterial activity against MTB and MDR-TB.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.04.029.

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22. *General procedure for the synthesis of 2-aryl-3,4-dihydro-2H-thieno[3,2-b]indoles* **6**: Conventional method: A mixture of 5-aryldihydro-3(2*H*)-thiophenone (4.7 mmol) and arylhydrazine hydrochloride (6.1 mmol) was refluxed in ethanol for 50–70 min. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was poured onto crushed ice, the resulting solid filtered and crystallized from chloroform to afford **6**.*Under microwave irradiation*: 5-Aryldihydro-3(2*H*)-thiophenone (0.52 mmol) and arylhydrazine hydrochloride (0.68 mmol) was dissolved in ethanol (5 mL) and subjected to MW irradiation (Biotage microwave oven, 90 °C, 2 bar pressure) for 3–6 min. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was poured onto crushed ice, the resulting solid filtered and crystallized from chloroform to afford **6**.Spectroscopic data for representative dihydrothienoindole is given below.*2-(4-Chlorophenyl)-3,4-dihydro-2H-thieno[3,2-b]indole,* **6b**: (Table 1, entry 2): Pale yellow solid; mp = 165–166 °C; ^{1}H NMR (300 MHz, CDCl3) δ_H 3.30 (dd, 1H, *J* = 15.5, 7.7 Hz), 3.56 (dd, 1H, *J* = 15.5, 8.6 Hz), 5.46 (t, 1H, *J* = 8.3 Hz), 7.10–7.19 (m, 2H), 7.27–7.34 (m, 3H), 7.38–7.43 (m, 3H), 7.98 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 37.2, 57.9, 111.7, 112.3, 118.7, 120.1, 121.6, 122.9, 128.6, 128.8, 133.4, 134.2, 140.2, 140.9. Anal. Calcd for $C_{16}H_{12}ClNS$: C, 67.24; H, 4.23; N, 4.90. Found: C, 67.30; H, 4.30; N, 4.98.
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