Highly Efficient Synthesis of Thieno[2,3-*b*]indole Derivatives

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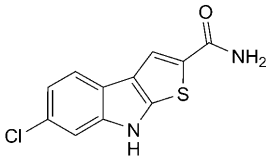
Thieno[2,3-*b*]indole derivatives were efficiently prepared *via* the reaction of 1,3-dihydro-2*H*-indole-2-thiones with α-bromo-substituted ketones or aldehydes and in the presence of Et_3N (*Scheme 2* and *Table*). The reaction took place under very mild conditions and in short times with good to excellent yields.

Introduction. – Thienoindole derivatives are important target compounds because they have potential biological activities with applications in agricultural chemistry and pharmaceutical industries. So design and synthesis of thienoindoles have attracted more and more attention over the years. For instance, thienodolin (=6-chloro-8*H*-thieno[2,3-*b*]indole-2-carboxamide), which was extracted from the fermentation mixture of a streptomycete strain, specified as *Streptomyces albogriseolus*, has shown both growth-promoting and -inhibiting activities in rice seedlings [1]. Thienoindoles are also widely used in medicinal chemistry with applications in drug discovery and development [2], and in organic electronics as novel electroluminescence materials for designing light-emitting devices [3]. Therefore, development of an efficient procedure for the synthesis of substituted thienoindoles is still an urgent need.



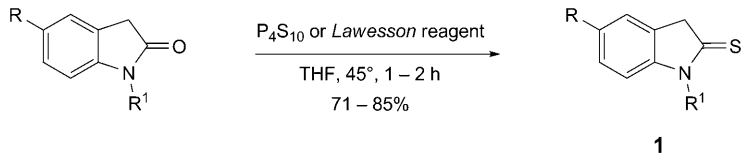
Thienodolin

Results and Discussion. – One approach to thienoindole derivatives benefits from triflic anhydride ($(CF_3SO_2)_2O$) promoted cyclization of sulfides [4]. This route is restricted to the synthesis of dihydro thienoindole derivatives. The most convenient method for preparing thienoindoles is the reaction of oxindole derivatives having a C=O group in position 3 with P_4S_{10} in a suitable solvent [5]. Although this reaction takes place with fair to good yields, some drawbacks are associated with the method, which are a long reaction time (several hours) and the sluggishness of the transformation. Recently, a *Pauson–Khand*-type reaction of 2-(alkynyl)phenyl isothiocyanates with stoichiometric amounts of $[Co_2(CO)_8]$ has been developed for the synthesis of 2*H*-thieno[2,3-*b*]indol-2-ones [6].

Thioamides have been used as useful synthons in the synthesis of heterocycles [7]. Others and we have shown the versatility of these compounds for the synthesis of S-containing heterocycles [8]. For example, thioacetomorpholides (=1-(morpholin-4-yl)ethanethione) have been successfully used for the construction of fully substituted thiophenes. In continuation of our work on the synthesis of S-heterocycles from thioamides, we now report a rapid, versatile, and mild method for the preparation of substituted thienoindoles *via* the reaction of 1,3-dihydro-2*H*-indole-2-thiones **1** with α-bromo-substituted ketones or aldehydes **2**[1]) in the presence of Et_3N.

The starting 1,3-dihydro-2*H*-indole-2-thiones **1** could easily be prepared by reaction of the corresponding 1,3-dihydro-2*H*-indol-2-ones with P_4S_{10} (or *Lawesson* reagent) in a suitable solvent (*Scheme 1*).

Scheme 1[a])



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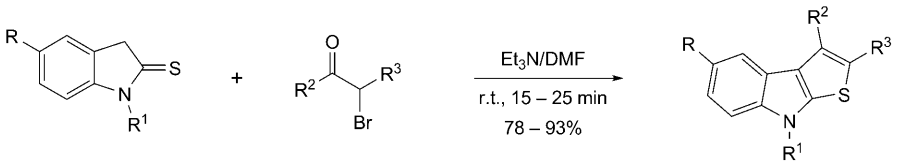
[a]) For R and R^1, see *Table*.

Then, a 1,3-dihydro-2*H*-indole-2-thione **1** was treated with an equimolar amount of a suitable α-bromo-substituted ketone or aldehyde **2** at room temperature in the presence of Et_3N in DMF as solvent to obtain the thienoindole **3** within a short time and in good to excellent yield (*Scheme 2* and *Table*).

Thus, a wide variety of substituted thienoindoles were obtained by this method; *e.g.*, 2,5-dimethyl-8*H*-thieno[2,3-*b*]indole (**3g**) was isolated from the reaction of 2-bromopropanal and 1,3-dihydro-5-methyl-2*H*-indole-2-thione in very good yield (88%) after only 15 min.

Other types of heterocyclic thioamides could also be subjected to the described procedure. Thus, when 1*H*-benzimidazole-2-thiol was treated with chloroacetone for 3 h, compound **3h** could easily be isolated by pouring the reaction mixture in aqueous MeOH (*Scheme 3*).

Scheme 2[a])



1 **2** **3a – 3g**

[a]) For R, R^1, R^2, and R^3, see *Table*.

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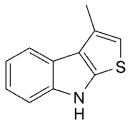
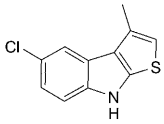
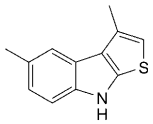
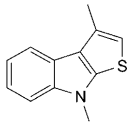
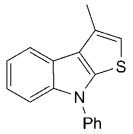
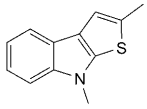
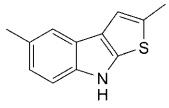
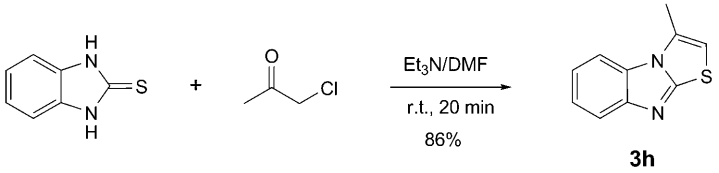
[1]) The reaction also works properly with α-chloro-substituted ketones or aldehydes.

Table. *One-step Synthesis of Thieno[2,3-*b*]indoles*

Thioamide **1**		Ketone or aldehyde **2**		Time [min]	Product **3**[a])	Yield [%][b])
R	R^1	R^2	R^3			
H	H	Me	H	15	**3a** 	85
Cl	H	Me	H	20	**3b** 	93
Me	H	Me	H	20	**3c** 	80
H	Me	Me	H	15	**3d** 	87
H	Ph	Me	H	25	**3e** 	78
H	Me	H	Me	15	**3f** 	83
Me	H	H	Me	15	**3g** 	88

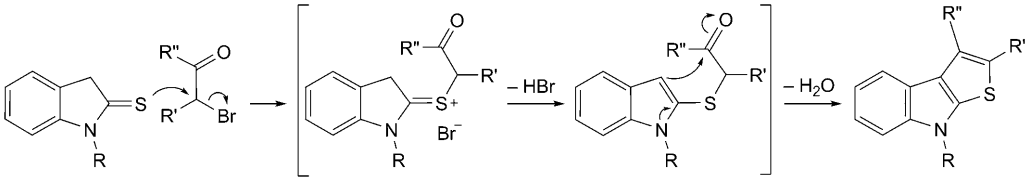
[a]) All compounds were characterized with ^{1}H- and ^{13}C-NMR, IR, and elemental analysis. [b]) The yields refer to isolated pure compounds.

Scheme 3



A mechanism is proposed for the reaction course (*Scheme 4*). The cyclic thioamide undergoes first an *S*-alkylation with the α-halocarbonyl compound, and the subsequent treatment with the base leads to ring closure to the thienoindole by elimination of H_2O.

Scheme 4



Conclusions. – A new, general, efficient, and simple procedure for the preparation of substituted thieno[2,3-*b*]indoles was developed. The reaction proceeds under very mild conditions and within a rather short time. The isolation of the products is also very simple. Moreover, the starting materials are cheap and readily available. The new materials (and their variants) have potential to be used as antiviral drugs and in agricultural chemistry.

Providing of facilities for this work from the University of Isfahan is gratefully acknowledged.

Experimental Part

General. All solvents used were dried and distilled before use according to standard procedures. M.p.: in sealed capillaries; uncorrected. Anal. TLC: silica gel (SiO_2; *Merck 60 F_{254}*) coated on aluminium plates; visualizing by UV and by aq. $KMnO_4$ soln. IR Spectra: *UR-20* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Bruker AMX-500* spectrometer; $CDCl_3$ solns; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz.

*1,3-Dihydro-2*H*-indole-2-thiones* **1**: *General Procedure.* A soln. of 1,3-dihydro-2*H*-indol-2-ones (10 mmol) in dry THF (20 ml) and P_2S_5 (11 mmol, 2.44 g) were stirred at 45° for 1–2 h. Then, the mixture was filtered, the filtrate treated with 5% aq. $NaHCO_3$ soln. (20 ml) and extracted with AcOEt (30 ml), the extract concentrated, and the residue purified by flash column chromatography (SiO_2, AcOEt/hexane 1:4) to give the cyclic thioamides as light yellow solids.

Compounds **3a**–**3g**: *General Procedure.* The 1,3-dihydro-2*H*-indole-2-thione (2 mmol) and the α-bromo-substituted carbonyl compound (2.2 mmol) were dissolved in DMF (2 ml) at r.t. and stirred for the times noted in the *Table.* At the end of reaction, Et_3N (2.5 mmol, 0.35 ml) was added and the mixture stirred and poured in MeOH/H_2O 80:20 (20 ml). The precipitated compound was filtered and recrystallized in a suitable solvent to afford the target compounds as colorless solids.

*3-Methyl-8*H*-thieno[2,3-*b*]indole* (**3a**): IR: 3392, 2916, 2493, 2123, 1647, 1613. ^{1}H-NMR: 8.18 (*s*, 1 H); 7.88 (*d*, *J* = 7.6, 1 H); 7.42 (*d*, *J* = 7.9, 1 H); 7.20–7.27 (*m*, 2 H); 6.49 (*s*, 1 H); 2.66 (*s*, 3 H). ^{13}C-NMR:

142.5; 141.2; 129.9; 125.7; 123.3; 122.3; 120.2; 119.1; 112.7; 111.6; 15.5. Anal. calc. for $C_{11}H_9NS$ (187.26): C 70.55, H 4.84, N 7.48; found: C 70.86, H 4.71, N 7.40.

*5-Chloro-3-methyl-8*H-*thieno[2,3-*b*]indole* (**3b**): IR: 3390, 2910, 2499, 2120, 1648, 1615. ^{1}H-NMR: 7.98 (*d*, *J* = 1.3, 1 H); 7.33 (*dd*, *J* = 8.6, 1.8, 1 H); 6.80 (*d*, *J* = 8.6, 1 H); 6.46 (*s*, 1 H); 2.24 (*s*, 1 H). ^{13}C-NMR: 142.4; 140.5; 129.7; 125.8; 124.9; 123.9; 122.3; 118.6; 112.3; 15.2. Anal. calc. for $C_{11}H_8ClNS$ (221.71): C 59.59, H 3.64, Cl 15.99, N 6.32; found: C 60.11, H 3.50, Cl 15.75, N 6.36.

*3,5-Dimethyl-8*H-*thieno[2,3-*b*]indole* (**3c**): IR: 3399, 2920, 2501, 2129, 1652, 1621. ^{1}H-NMR: 7.49 (*m*, 1 H); 7.06 (*m*, 2 H); 6.47 (*s*, 1 H); 5.61 (*s*, 1 H); 2.57 (*s*, 3 H); 2.20 (*s*, 3 H). ^{13}C-NMR: 142.6; 142.0; 129.8; 125.1; 123.2; 122.6; 121.9; 112.9; 112.7; 109.4; 23.6; 19.2. Anal. calc. for $C_{12}H_{11}NS$ (201.29): C 71.60, H 5.51, N 6.96; found: C 71.81, H 5.46, N 7.05.

*3,8-Dimethyl-8*H-*thieno[2,3-*b*]indole* (**3d**): IR: 3387, 2911, 2496, 2125, 1645, 1612. ^{1}H-NMR: 7.62 (*d*, *J* = 7.8, 1 H); 7.35 – 7.37 (*m*, 2 H); 7.15 (*t*, *J* = 7.1, 1 H); 6.84 (*s*, 1 H); 3.92 (*s*, 3 H); 1.97 (*s*, 3 H). Anal. calc. for $C_{12}H_{11}NS$ (201.29): C 71.60, H 5.51, N 6.96; found: C 72.0, H 5.43, N 6.81.

*3-Methyl-8-phenyl-8*H-*thieno[2,3-*b*]indole* (**3e**): IR: 3385, 2918, 2489, 2127, 1641, 1613. ^{1}H-NMR: 7.58 – 7.62 (*m*, 3 H); 7.48 – 7.54 (*m*, 3 H); 7.15 – 7.19 (*m*, 3 H); 6.83 (*s*, 1 H); 2.17 (*s*, 3 H). Anal. calc. for $C_{17}H_{13}NS$ (263.36): C 77.53, H 4.98, N 5.32; found: C 77.70, H 5.22, N 5.50.

*2,8-Dimethyl-8*H-*thieno[2,3-*b*]indole* (**3f**): IR: 3391, 2910, 2492, 2128, 1646, 1616. ^{1}H-NMR: 7.71 (*d*, *J* = 7.9, 1 H); 7.33 (*d*, *J* = 8.7, 1 H); 7.25 (*t*, *J* = 7.9, 1 H); 7.14 (*t*, *J* = 7.7, 1 H); 7.04 (*s*, 1 H); 3.92 (*s*, 3 H); 2.65 (*s*, 3 H). Anal. calc. for $C_{12}H_{11}NS$ (201.29): C 71.60, H 5.51, N 6.96; found: C 71.81, H 5.39, N 6.91.

*2,5-Dimethyl-8*H-*thieno[2,3-*b*]indole* (**3g**): IR: 3398, 2913, 2489, 2123, 1641, 1615. ^{1}H-NMR: 8.17 (*s*, 1 H); 7.22 (*d*, *J* = 7.9, 1 H); 7.15 (*d*, *J* = 7.9, 1 H); 6.99 (*s*, 1 H); 6.51 (*s*, 1 H); 2.90 (*s*, 3 H); 2.73 (*s*, 3 H). Anal. calc. for $C_{12}H_{11}NS$ (201.29): C 71.60, H 5.51, N 6.96; found: C 71.66, H 5.35, N 7.12.

*3-Methylthiazolo[3,2-*a*]benzimidazole* (**3h**): IR: 3410, 2970, 2539, 2162, 1655, 1625. ^{1}H-NMR: 7.81 (*d*, *J* = 7.9, 1 H); 7.79 (*d*, *J* = 7.9, 1 H); 7.37 (*t*, *J* = 7.6, 1 H); 7.25 (*t*, *J* = 7.7, 1 H); 6.35 (*s*, 1 H); 2.75 (*s*, 3 H). ^{13}C-NMR: 157.2; 149.8; 131.1; 129.7; 123.4; 120.5; 120.1; 110.8; 104.1; 13.7. Anal. calc. for $C_{10}H_8N_2S$ (196.31): C 63.80, H 4.28, N 14.88; found: C 64.01, H 4.21, N 14.75.

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