A Versatile Approach for the Synthesis of 8H-Thieno [2,3-b]indoles and *N*-[2-(2-*N*-(R_1,R_2)-2-Thioxoacetyl)-phenyl]acetamides from 1-Acetyl-1,2-dihydro-3H-indol-3-one (Acetylindoxyl) and Its Derivatives: A Novel Synthesis of Intermediate (1-Acetyl-1H-indol-3-yl)malononitrile/cyanoacetates

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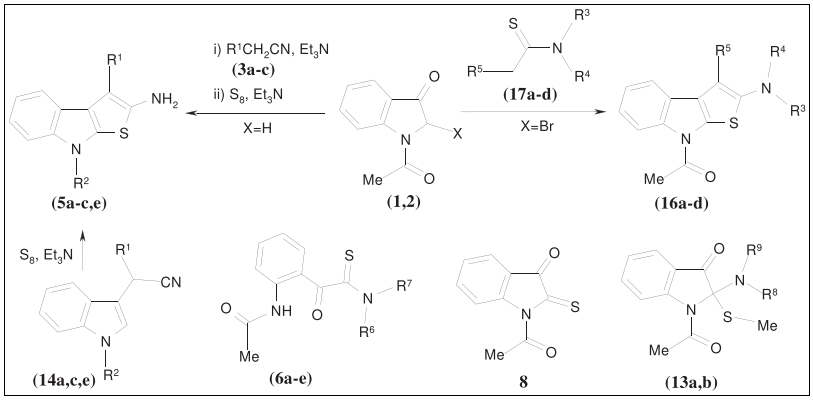

We report on two approaches for the synthesis of new 2-amino-3-cyano/alkoxycarbonyl-8H-thieno [2,3-b]indoles **5** and another one for the synthesis of 2-*N*,*N*-dialkylamino-3-cyano/aryl-8H-thieno[2,3-b] indoles **16**, based either on acetylindoxyl **1** and (1-acetyl-1H-indol-3-yl)malononitrile/cyanoacetates **14** or 2-bromoacetylindoxyl **2** transformations. A new, simple, rapid, and efficient method for the synthesis of valuable key intermediate malononitrile/cyanoacetates **14** based on acetylindoxyl **1** condensation with malononitrile or cyanoacetates in the presence of triethylamine has been developed. A number of synthetic procedures for the preparation of thioacetamides **6**, 1-acetylthioisatin **8**, and 2,2-disubstituted indoxyls **13** have been elaborated during the synthesis of thieno[2,3-b]indoles. Thioacetamides **6** have been shown as novel agents active against *Mycobacterium tuberculosis* $H_{37}Rv$, the cause of tuberculosis, with minimal inhibitory concentration values ranging between 5 and 21 μg/mL.

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INTRODUCTION

In the course of our ongoing studies of the chemical and biological properties of linear hetero[b]fused indoles [1–4], we have developed effective and simple methods for the synthesis of pharmacologically interesting pyridazino[4,3-b]indoles [5], pyrano[3,2-b]indoles [6], pyrrolo[3,2-b] indoles [7], imidazo[4,5-b]indoles, thiazolo[5,4-b]indoles [8], and some of their analogs [9,10]. A number of representatives of these series displayed antituberculosis, monoamine oxidase inhibiting, antiviral, antihypoxic, and hepatoprotective activities some of which may be attributable to monoamine oxidase inhibition. In the syntheses of such fused indoles, available starting materials, 1-acetyl-1,2-dihydro-3H-indol-3-one (**1**) (acetylindoxyl) and some of its derivatives, such as 2-bromoacetylindoxyl **2**, 2-aminoacetylindoxyl, as well as 2-arylidene-1,2-dihydro-3H-indol-3-ones, were used [8,5]. It is noteworthy that acetylindoxyl derivatives were also used for the synthesis of such hetero[b]fused indoles as alkaloids ellipticine [11] and quindoline [12] and other fused indoles [13–15]. Thus, they demonstrated the capability of serving as key intermediates for annulations of nitrogen, oxygen, and sulfur–nitrogen rings onto the existing indole or indoline cores.

Among the products resulting from the annulation of sulfur heterocycles to [b]indole or indoline cores, thienoindoles being analogs of biologically important naturally occurring pyrroloindoles offer a prospective class of compounds for drug discovery. The heterocyclic systems of pyrrolo[2,3-b]indoles as well as their O- and S-isoelectronic analogs, furo[2,3-b]indoles and thieno[2,3-b]indoles, do represent structural cores of bioactive molecules, alkaloids

physostigmine, physovenine, madindoline, and thiophysovenin [16]. In particular, a series of thienoindoles have been investigated as potential depressants of central nervous system activities [17], inhibitors of acetylcholine esterase and butyrylcholine esterase [18], as well as anti-inflammatory [1] and antituberculosis agents [2]. In particular, thienodolin (6-chlorothieno[2,3-b]indole-2-carboxamide) isolated from the culture broth of *Streptomyces albogriseolus* [3] and characterized by Japanese researches has proved to have plant-growth-regulation activity. The parent thieno [2,3-b]indole also demonstrated antifungal activity [4]. Several syntheses of thieno[2,3-b]indoles have been reported, some in recent years [19–24]. However, the number of publications is less than those describing the preparation of fused indoles with five-membered nitrogen and oxygen rings reflecting the relative difficulty in obtaining the starting compounds. Thieno[2,3-b]indoles with alkyl- or aryl-substituents in the thiophene ring were obtained by the Paal-Knorr reaction between 3-(2-oxoalkyl)-oxoindoles and phosphorus pentasulfide [25]. Thieno[2,3-b]indoles were also synthesized by cyclization of 3-indolylthioalcanoic acid [26] and by the interaction of 2-chloroindole-3-carbaldehyde with methyl thioglycolate [27]. The first examples of C═S-induced Pauson–Khand-type reactions were described involving conversion of 2-alkynylphenyl isothiocyanates to 3-substituted-2H-thieno[2,3-b]indol-2-ones in the presence of a stoichiometric amount of Mo $(CO)_6$ or $Co2(CO)_8$, or a catalytic amount of Rh catalyst [28]. A simple and effective method was also elaborated for the synthesis of the thieno[2,3-b]indole ring system based on the electrophilic recyclization of 2-alkyl-5-(2-isothiocyanoaryl)furans in the presence of anhydrous AlCl3 [29]. A number of thieno[3,2-b]indoles have been regioselectively synthesized in 85–90% yield by the tandem cyclization of 1-acetyl-3-(4′-aryloxybut-2′-ynylthio) indoles on treatment with 1 equiv of *m*-CPBA in CH_2Cl_2 at room temperature (RT) for 1 h. The latter were in turn prepared from indole *via* the formation of thiuronium salt and subsequent reaction with 1-aryloxy-4-chlorobut-2-yne and acetylation by acetyl chloride [30]. The synthesis of 4,5,6,7- tetrahydro-8H-thieno[2,3-b]indoles was performed by the Fisher reaction from corresponding thienylhydrazines and cyclohexanone [31].

RESULTS AND DISCUSSION

As further examples of the application of acetylindoxyl **1** and its derivatives for fused indole synthesis, we report on the straightforward preparation of 2-amino- and 2-*N*,*N*-dialkylamino-3-cyano/alkoxycarbonyl/aryl-8H-thieno[2,3-b]indoles. The presence of the vicinal amino, nitrile, or alkoxycarbonyl groups, in particular, provides the background for further functionalization of the molecules.

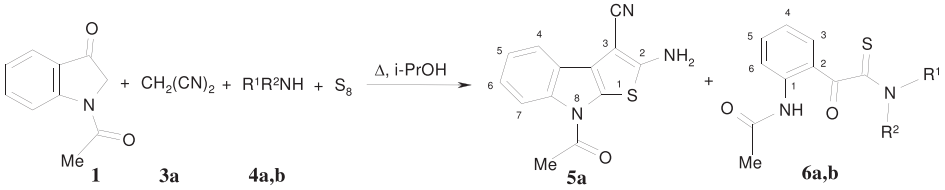
We first decided on the synthesis of some thienoindoles that could be obtained in a single step by a simple reaction earlier offered by Gewald [32]. The method was successfully used for the preparation of 2-amino-3-cyano/carbalkoxythiophenes. Acetylindoxyl **1** and malononitrile **3a** were taken as the ketone and the active-hydrogen nitrile, respectively. When these compounds were refluxed in alcohol solution in the presence of elemental sulfur and a secondary amine **4a** or **4b** as a base, the reaction occurring was supposed to furnish 2-amino-8-acetyl-3-cyano-8H-thieno[2,3-b]indole (**5a**). However, although **5a** may arise from the Gewald reaction, it has not been described so far.

Contrary to our expectations, thienoindole **5a** was isolated only in low yield (8–9%). Both in the presence and the absence of malononitrile, acetylindoxyl **1** underwent ring opening to afford the corresponding thioamides **6a,b** as the main products when secondary amines were used. Thus, acetylindoxyl **1,** when refluxed with malononitrile, elemental sulfur, and morpholine **4a** or piperidine **4b** in isopropanol for 3 h, gave thioamides **6a,b** in yields of 61 and 55%, respectively (Scheme 1). Without malononitrile the yields of thioamides **6a,b** turned out to be even higher (76 and 67%).

Under the same conditions, a primary amine, butylamine **4c**, also induces acetylindoxyl ring opening to give the Schiff base 7 but in 35% yield only (Scheme 2).

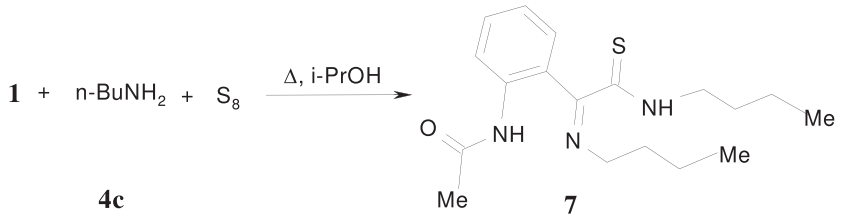
It is worth noting that thioamides **6a**,**b** were obtained in the above yields when the reactions were carried out in air, while under argon they were formed in such small amounts that their presence in the reaction mixture could be revealed by TLC only. Since the yields of compounds **6a**, **b** turned out to be less when malononitrile was present and compound **5a** was among the products, a question to be considered was whether **5a** could be formed from **6a**

Scheme 1



4, **6**: R^1+R^2=$CH_2CH_2OCH_2CH_2$ (**a**); $CH_2(CH_2)_3CH_2$ (**b**).

Scheme 2



under the action of malononitrile. However, no transformation of thioamide **6a** into thienoindole **5a** occurred when the former was treated with malononitrile under the reaction conditions. Again, **5a** should not be an intermediate that malononitrile converts into **6a** since the latter is formed without malononitrile, and moreover, **5a** did not furnish **6a** when specially treated with malononitrile and morpholine.

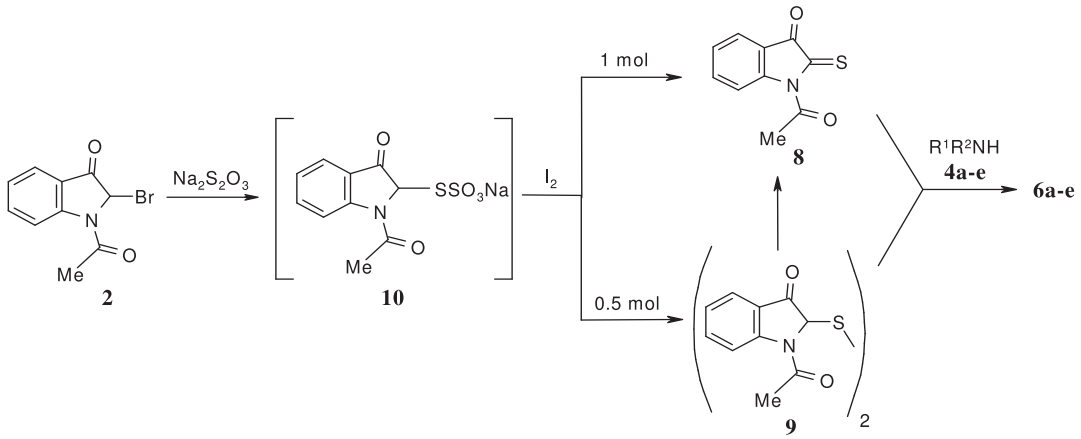
On the contrary, the ring opening of isatin under the action of various nucleophiles was reported to be facile [33]. The same should obviously be characteristic of 2-thioisatin derivative **8**. It means that a reaction pathway involving compound **8** or its hydrodimer **9** as an intermediate seems plausible.

Unlike 2-thioisatin and indoxyl disulfide lacking substituents at the ring nitrogen, their 1-acetyl derivatives **8** and **9** have not been described so far. So, we purposefully prepared indoxyl disulfide **9** and thioisatin **8** in 45 and 72% yields, respectively, by interaction of bromoacetylindoxyl **2** with sodium thiosulfate. The reaction proceeded *via* Bunte salt **10** that further reacted with iodine at RT in the molar ratio of 0.5/1. The conversion of disulfide **9** into thioisatin **8** was spontaneous in these media (Scheme 3).

Taking into account the above facts, we suggest the following scheme for the transformation of acetylindoxyl **1** into thioamides **6** (Scheme 3). The first step, α-thiolation of acetylindoxyl **1** to thiol **11,** seems rather obvious since ketones are known to react in such a manner in the presence of bases [34]. For comparison, acetylindoxyl **1** is readily brominated at position 2; bromoacetylindoxyl **2** was obtained by us previously in quantitative yield by heating **1** with bromine in methylene chloride for several minutes [7]. The presence of a base (amine) is essential for the formation of thiol **11** as shown by the lack of the latter when acetylindoxyl **1** and sulfur were reacted without amine producing unidentified polymeric materials instead.

Thiol **11** can undergo the second thiolation to furnish dithiol **12** since the ketone bisthiolation was shown to occur in the Gewald reaction with malononitrile, *e.g.*, bis (5-amino-3-methyl-4-cyanoethyl)sulfide is formed from acetone [35]. Dithiol **12** should be unstable producing thioisatin **8** after elimination of hydrogen sulfide [36]. However, there is a possibility for **8** to be formed *via* oxidation of thiol **11** in light of the well-known fact that indoxyl and its 2-substituted derivatives are prone to oxidation by air oxygen [37] and is in line with the finding mentioned above that the reaction studied proceeds smoothly and with good yields only in air. Moreover, the oxidation may proceed *via* disulfide **9** since the latter was shown to undergo the transformation into thioisatin **8** when

Scheme 3



4, **6**: R^1+R^2=$CH_2CH_2OCH_2CH_2$ (**a**); $CH_2(CH_2)_3CH_2$ (**b**); R^1=H, R^2=n-Bu (**c**);

R^1+R^2 =$CH_2CH_2N(CH_3)CH_2CH_2$ (**d**); R^1=H, R^2=i-Pr (**e**).

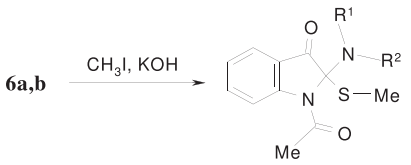
standing in air in the presence of small amounts of a base (Scheme 4). The ring opening occurs by means of an amine attack on the resulting C=S bond of **8**.

In fact, thioamides **6a–e** were shown to be formed by the interaction of either 1-acetyl-2-thioisatin **8** or acetylindoxyl disulfide **9** with amines **4a–e**, morpholine, piperidine, *N*-methylpiperazine, butylamine, and isopropylamine, respectively (Schemes 3 and 4). The reactions occurred in dioxane, isopropanol, or acetone at RT. The nature of the solvent did not markedly affect the yields of thioamides **6a–e**. The highest yields of thioamides **6a–e** (91–87%) were achieved when thioisatin **8** was used as the starting compound, whereas **6a,b** were obtained from disulfide **9** in somewhat lower yields (78 and 70%, respectively). As in the case of the reactions of acetylindoxyl **1** with sulfur and amines (*vide supra*), the yields of thioamides **6a,b** were less in the presence of malononitrile. Under the reaction conditions, thioisatin **8** and disulfide **9** were shown not to react with malononitrile and, thus, are not precursors of thienoindole **5a**.

It is interesting to note that thioamides **6a,b** undergo cyclization to 2,2-disubstituted indoxyls **13a,b** in 52 and 45% yields upon alkylation with methyl iodide in the presence of potassium hydroxide (Scheme 5). This cyclocondensation of thioamides **6a,b** and their analogs opens a simple way to 2,2-disubstituted indoxyls with different substituents in position 2, which are difficult to obtain by other methods.

The spectral data (IR, NMR, mass spectrometry) were used to prove the structures of thioamides **6a–e**. In the IR spectra of **6a–e**, the groups $NCOCH_3$, CO, and NH are observed at 1640–1660, 1675–1700, and 3000–3300 cm^{-1}, respectively. For indoxyls **13a,b**, the bands associated with the NCOMe and CO groups have the frequencies of 1675, 1680, and 1720 cm^{-1}, respectively. The ^{1}H- and ^{13}C-NMR data are in accord with the structures of compounds **6a** (Table 1). The ^{1}H-NMR spectra of these compounds indicate nonequivalence of the edges of the cyclic amine residue, which manifests itself in different chemical shifts for

Scheme 5



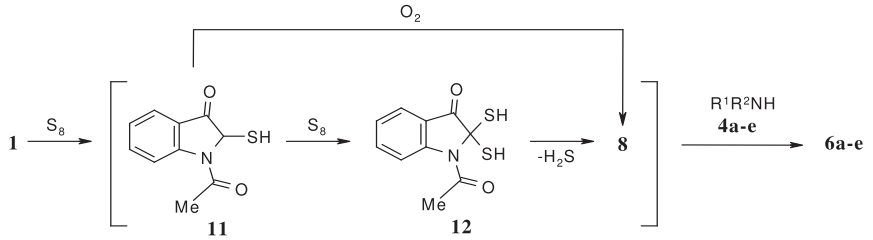
13a,b

13: $R^1+R^2 = CH_2CH_2OCH_2CH_2$ (**a**); $CH_2(CH_2)_3CH_2$ (**b**).

the protons of the CH_2 groups in equal positions but on different sides relative to the nitrogen. These differences achieve 0.6 and 0.7 ppm for the CH_2 groups in the α-position relative to the nitrogen atom of morpholine and piperidine residues, respectively, and are probably associated with the hindered rotation of the ring around the thioamide bond. The ^{13}C-NMR spectra confirm the presence of the thioamide and amide bonds and the conjugated carbonyl in compounds **6a**, the carbon atoms of which have the signals at 192.4, 169.1, and 190.1 ppm. As well as in the ^{1}H-NMR spectra, the ^{13}C-NMR spectra differ markedly by the chemical shifts for the α-carbons of the amine moiety, which occupy opposite positions relative to the nitrogen atom: $\Delta\delta_c$ = 4.9 ppm. The structures of **13a** and **13b** are confirmed by the ^{1}H-NMR spectra and by the ^{13}C-NMR spectrum for **13a**, in which there are the signals for the conjugated ketone and amide carbonyls at δ 195.6 and 171.1, respectively, the signal at δ 89.1 corresponding to the quaternary sp^3-hybridized carbon atom C2.

The thioamides **6a–e** were evaluated for their *in vitro* activity against *Mycobacterium tuberculosis* H_{37}Rv according to protocols developed at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (courtesy of Dr. Anne Lenaerts), Colorado State University (http://www.mrl.coloradostate.edu), with minimal inhibitory concentration (MIC) values ranging between 5 and 21 μg/mL.

Scheme 4



11 **12**

4, **6**: $R^1+R^2=CH_2CH_2OCH_2CH_2$ (**a**); $CH_2(CH_2)_3CH_2$ (**b**); R^1=H, R^2=n-Bu (**c**);

$R^1+R^2 = CH_2CH_2N(CH_3)CH_2CH_2$ (**d**); R_1=H, R_2=i-Pr (**e**).

Table 1

N-[2-(2-*N*-(R^1R^2)-Thioxoacetyl)-phenyl]acetamides (**6a–e**).

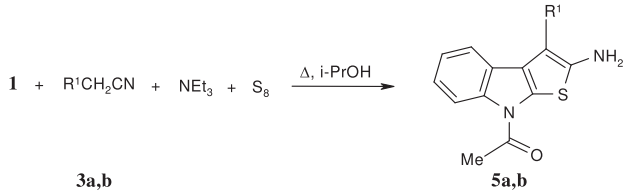
Comp.	3-H	4-H	5-H	6-H	N-Ac	NH	R^1, R^2
6a	7.68 (d)	7.06 (t)	7.56 (t)	8.75 (d)	2.22 (s)	11.28 (s)	3.57 (m, 2H, CH_2), 3.67 (m, 2H, CH_2), 3.88 (m, 2H, CH_2), 4.29 (m, 2H, CH_2)
6b	7.70 (d)	7.19 (t)	7.66 (t)	8.53 (d)	2.18 (s)	11.02 (s)	1.52 (m, 2H, CH_2), 1.70 (m, 4H, CH_2), 3.59 (t, 2H, CH_2), 4.18 (t, 2H, CH_2)
6c	7.70 (d)	7.20 (t)	7.65 (t)	8.36 (d)	2.16 (s)	10.92 (s)	0.92 (t, 3H, CH_3), 1.37 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 3.65 (br, 2H, CH_2),11.05 (br d, 1H, NH)
6d	7.72 (d)	7.21 (t)	7.68 (t)	8.52 (d)	2.19[a](s)	11.00 (s)	2.23[a](s, 3H, CH_3), 2.35 (br, 2H, CH_2), 2.51[b](2H, CH_2), 3.62 (br, 2H, CH_2), 4.21 (br, 2H, CH_2)
6e	7.69 (d)	7.20 (t)	7.65 (t)	8.40 (d)	2.17 (s)	10.95 (s)	1.26 (d, 6H, $2CH_3$), 4.58 (m, 1H, CH), 10.99 (br d, 1H, NH)

[a]An alternative assignment of the signals is possible.
[b]The signal merges with that of the solvent (DMSO-d_6).

Thus, acetylindoxyl **1** has been successfully used for the convenient preparation of thioamides **6**; this was possible since the competitive Gewald reaction leading to thienoindoles apparently proceeds slower under the described conditions. Nevertheless, the latter reaction afforded thienoindole **5a** in low yield in the presence of a secondary amine (*vide supra*). That is why we decided to use a tertiary amine as a base in this process instead of a secondary one believing that it would provide more favorable conditions for the formation of both thienoindole **5a** and its analog **5b** containing a COOEt group at position 3. In fact, when triethylamine was used instead of morpholine or piperidine, thienoindole **5a** was obtained in 52% yield compared to only 10% yield for **5b** (Scheme 6).

The reactions were carried out by refluxing a mixture of acetylindoxyl **1**, malononitrile **3a**, or ethyl cyanoacetate **3b**, elemental sulfur, and excess of triethylamine in isopropanol or acetonitrile. Resinification of the reaction mixture was observed, which was especially noticeable in the case of **5b**. The use of cyanoacetamide as the less active-hydrogen component under the same conditions did not give the corresponding thienoindole at all. Such relatively low reactivity of acetylindoxyl **1** in the Gewald reaction is akin to that of cyclopentanone [32]. We assumed that desired thienoindole should readily be formed only in the case

Scheme 6



3a,b **5a,b**

3, 5: R^1=CN (**a**); R^1=COOEt (**b**).

when the condensation of acetylindoxyl **1** with active-hydrogen nitrile would occur before the interaction with sulfur. So, we decided to use 1-acetyl-3-indolylmalononitrile **14a** and 3-indolylcyanoacetates **14c–e** with the COMe/COOEt/H moiety at the ring nitrogen (N-1), respectively, instead of acetylindoxyl **1** and the corresponding active-hydrogen nitriles. The first can be considered as one of synthetic equivalents of the Knoevenagel reaction products between acetylindoxyl **1** and activated nitriles. Among malononitrile derivatives only ylidenemalononitriles are known to be successfully used in the Gewald reaction instead of ketones [32], whereas, as far as we know, such type of fully heteroaromatic nitriles as **14** has not been tested in the reaction. We already reported the synthesis of 3-indolylmalononitrile **14a** that was obtained by condensation of acetylindoxyl **1** with malononitrile in DMSO in the presence of sodium hydride [38]. In this work, we showed that the condensation proceeded more readily in acetonitrile or isopropanol in the presence of triethylamine. By application of this protocol, we prepared 1-acetyl-3-indolylmalononitrile **14a** in 88% yield. In the series of 3-indolylcyanoacetates, their 1-carbalkoxy derivatives are the most available. 3-Indolylcyanoacetates bearing a substituent at the position 1 are formed in yields from 30 to 92% upon the interaction of 3-indolylacetonitriles with dialkylcarbonates in the presence of sodium hydride, yields depending on the nature of the substituent at positions 1 or 5 [39]. In some cases, 3-indolylcyanoacetates with the unsubstituted ring nitrogen atom were isolated as a byproduct in low (8–12%) yields. It is not surprising since this species as well as its benzene-substituted derivatives, as a rule, are not easily available even *via* the Fischer reaction because of side processes [40]. It should also be noted that Nenitzescu and Raileanu attempted to obtain 1-acetyl-3-indolylcyanoacetic acid by condensation of acetylindoxyl **1** with cyanoacetic acid but failed; they also did not observe the formation of

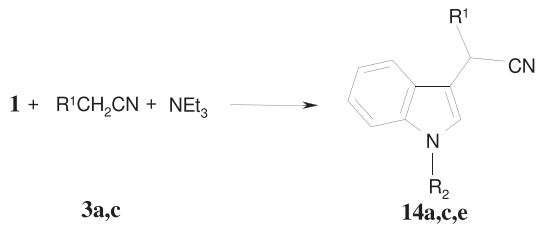
3-indolylcyanoacetic acid [41]. 1-Acetyl-3-indolylacetonitrile was obtained instead probably due to the fact that the reaction was carried out under severe conditions and was therefore accompanied by decarboxylation. We managed to implement the condensation between acetylindoxyl **1** and methyl cyanoacetate **3c** in the presence of triethylamine that furnished methyl 1-acetyl-3-indolylcyanoacetate **14c** in 72% yield using acetonitrile or isopropanol as solvents (Scheme 7). The same reaction, when allowed to proceed in methanol, resulted **14e** in 62% yield (Scheme 7). To all appearance, lacking of the acetyl group in the primarily formed **14c** occurs by its methanolysis under these conditions. In reality, **14c** gradually transforms into NH-cyanoester **14e** at 20°C in methanol in the presence of an equivalent of triethylamine, the transformation being complete in 24 h. TLC of the reaction mixture showed that only partial splitting out of the acetyl group occurred if the reaction was carried out in ethanol for 24 h as well. The method is distinguished by its preparative potentialities and apparent generality that it can be used for the preparations of the corresponding 3-indolylmalononitriles and 3-indolylcyanoesters bearing various substituents at the benzene ring. The latter are known to be applied in the syntheses of biologically active compounds [40]. Ethyl cyanoacetate **14d** bearing 1-NCOOEt substituent was obtained from 3-indolylacetonitrile and diethylcarbonate by the method given in ref. 39.

The structures of **14a,c,e** were assigned on the basis of elemental analysis, mass, ^{1}H, ^{13}C, and 1D and 2D (COSY, HSQC, and HMBC) NMR spectral data (Table 2). The ^{1}H spectrum of **14a** showed both the CH_3 and CH aliphatic signals at 2.70 and 6.76 ppm, respectively, and the chemical shifts (δ C 24.3 and 20.10) correspond with the carbons at methyl and methine groups, respectively. HMBC experiments showed methine CH proton correlations to the ring C-3 and C-2 carbons as well as CN groups.

We used 3-indolylmalononitrile **14a** and 3-indolylcyanoesters **14c,d** for the synthesis of thienoindoles **5a,c,d** with various substituents in positions 3 and 8 of the ring system (Scheme 8). The yields of thienoindoles **5a,c,d** were in the range from high for **5a** (80%) to low for **5c** (25%) and **5d** (33%) and depended mainly on the nature of the substituent in position 3 of the ring system. Thienoindole **5e** lacking the substituent at the ring nitrogen was isolated in the lowest (5%) yield but it should be obtained in higher yield in future work from thienoindole **5c** by hydrolysis of its 1-N-acetyl group.

Thienoindoles **5a,c,d** were prepared by refluxing nitriles **14a,c,d** and sulfur in isopropanol or ethanol in the presence of the excess of triethylamine. Thienoindole **5a** is formed rather readily, for 1 h, while the synthesis of thienoindoles **5c,d** takes not less than 10 h. Under similar conditions, thienoindole **5c** was isolated only in low yield (1–2%) due to strong resinification of the reaction mixture. We managed to increase the yield of thienoindole **5c** up to 25% by heating cyanoester **14c** and sulfur in DMSO at 75°C for 5 h as well as by performing the reaction in DMF or acetonitrile at 20°C for 10 days. All thienoindoles **5** obtained were purified without using any chromatographic methods.

Scheme 7



3a,c **14a,c,e**

3: R^1 =CN (**a**); COOMe (**c**).

14: R^1=CN, R^2=COMe (**a**); R^1=COOMe, R^2=COMe (**c**); R^1=COOMe, R^2=H (**e**).

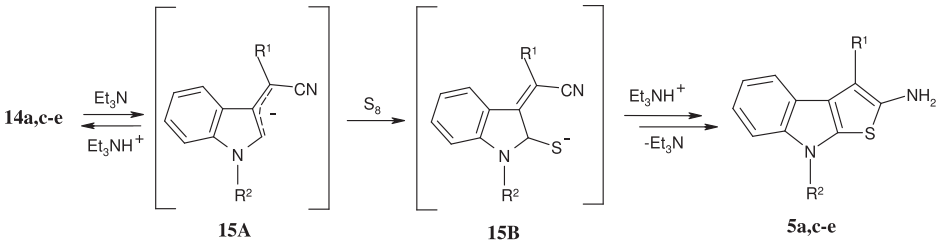
Table 2

(1-R^2-1H-Indol-3-yl)-R^1-acetonitriles (**14a,c,e**).

Comp.	2-H	4-H	5-H	6-H	7-H	CH	R^1	R^2
14a	8.17 (br s)	7.78 (d)	7.50[a]	7.50[a]	8.44 (d)	6.80 (br s, 1H, CH)	–	2.74 (br s, 3H, CH_3)
14c	8.03 (br s)	7.62 (d)	7.38[a]	7.38[a]	8.37 (d)	5.99 (br s, 1H, CH)	3.76 (br s, 3H, CH_3)	2.68 (br s, 3H, CH_3)
14e	7.55 (d)	7.62 (d)	7.08[b](t)	7.16[b](t)	7.48 (d)	5.81 (s, 1H, CH)	3.71 (s, 3H, CH_3)	11.36 (br s, 1H, NH)

[a]Complex overlapping signals.
[b]An alternative assignment of the signals is possible.

Scheme 8



5, **14**: R^1=CN, R^2=COMe (**a**); R^1=COOMe, R^2=COMe (**c**); R^1=R^2=COOEt (**d**);

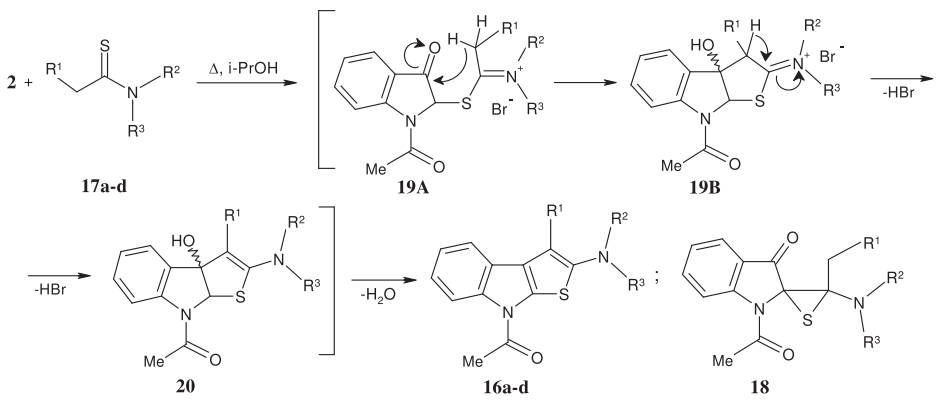
R^1=COOMe, R^2=H (**e**).

We suppose that in the case of thienoindole **5** synthesis from the heteroaryl- activated nitrile **14** and sulfur, the starting nitrile is deprotonated followed by the thiolation in position 2 of the indole ring with subsequent intramolecular cyclization *via* intermediates **15A**,**B**. On the other hand, the reason of the decrease in the yields of thienoindoles **5c–e** can also be the competitive thiolation of 3-indolylcyanoesters at the active α-position.

We have also studied the preparation of 2-*N*,*N*-dialkylaminothienoindoles **16a–d** through the condensation of bromoacetylindoxyl **2** with cyclic (morpholino- or piperidino-) thioamides of arylacetic acids **17a–c** (where Ar = Ph, 4-CH_3-C_6H_4-, 4-O_2N-C_6H_4-) and cyanoacetic acid **17d** (Scheme 9). *N*,*N*-Disubstituted thioamides are known to react with α-halo ketones in ambiguous fashion depending on the reaction conditions and the nature of components. In 1970, Eschenmoser described the transformation of thiolactams into its vinylogs that occurs under the action of such α-halo ketones as phenacyl bromides in the presence of a base [42] and involves the formation of sulfur-bridged intermediate of the thiirane **18** type (Scheme 9). According to [43, 44], *N*,*N*-dialkylthioamides also react with some α-halo ketones, in particular, phenacylbromides in the presence of a base but affording 2-aminothiophenes. The data for similar interactions of α-halo ketones with cyanoacetic acid thioamides **17a–d** were lacking. So, it was impossible to decide *a priori* what would be a real route for the interaction of thioamides **17a–d** with bromoacetylindoxyl **2**. We carried out the reaction between bromoacetylindoxyl **2** and thioamides **17a–d** by short heating of the components in isopropanol and obtained thienoindoles **16a–d** in yields from 28 to 50%. Thus, the annulation of the thiophene ring took place in all the cases considered.

We ascertained that in the presence of a base where production of 2-aminothiophenes occurred [43], phenylacetic acid thiomorpholide **17a** afforded 2-morpholinothienoindole **16a** both in the presence and absence of triethylamine but in low yield. The reaction was accompanied by resinification that was especially obvious in the presence of a base. When

Scheme 9



16-20: R^1=Ph, R^2+R^3=$CH_2CH_2OCH_2CH_2$ (**a**), R^1=4-CH_3-C_6H_4,

R^2+R^3=$CH_2CH_2OCH_2CH_2$ (**b**), R^1=4-O_2N-C_6H_4, R^2+R^3 = $CH_2(CH_2)_3CH_2$ (**c**),

R^1=CN, R^2+R^3=$CH_2(CH_2)_3CH_2$ (**d**).

Table 3

3-R^1-8-R^2-2-Amino-8H-thieno[2,3-b]indoles (**5a–e**).

Comp.	4-H	5-H	6-H	7-H	8-R^2	2-NH_2	3-R^1
5a	7.64 (br)	7.35 (m)	7.35 (m)	7.85 (m)	2.79 (br s, 3H, CH_3)	7.36 (br s, 2H, NH_2)	–
5b	8.32 (d)	7.30 (m)	7.30 (m)	7.90 (m)	2.81 (s, 3H, CH_3)	7.41 (br s, 2H, NH_2)	1.41 (t, 3H, CH_3), 4.37 (dd, 2H, CH_2)
5c	8.27 (br)	7.33 (m)	7.33 (m)	7.89 (m)	2.83 (s, 3H, CH_3)	7.52 (br s, 2H, NH_2)	3.89 (s, 3H, CH_3)
5d	8.24 (d)	7.29 (m)	7.29 (m)	8.08 (m)	1.42 (m, 3H, CH_3), 4.48 (br, 2H, CH_2)	7.53 (br s, 2H, NH_2)	1.42 (m, 3H, CH_3), 4.37 (m, 2H, CH_2)
5e	8.05 (br)	7.00[a](br)	7.07[a](t)	7.38 (d)	11.23 (br, 1H, NH)	–[b]	3.88 (s, 3H, CH_3)

[a]An alternative assignment of signals is possible.
[b]The signal merges with that of the solvent (DMSO-d_6).

Table 4

8-Acetyl-2-*N*-(R^2,R^3)-3-R^1-8H-thieno[2,3-b]indoles (**16a–d**).

Comp.	4-H	5-H	6-H	7-H	8-Ac	2-*N*-R^2,R^3	3-R^1
16a	7.48[a]	7.15 (t)	7.28 (t)	7.90 (m)	2.83 (s, 3H, CH_3)	2.94 (m, 4H, $2CH_2$), 3.68 (m, 4H, $2CH_2$)	7.66 (d, 2H, 2′,6′-Ph), 7.48[a](t, 2H, 3′5′-Ph), 7.38 (t, 1H, 4′-Ph)
16b	7.51 (d)	7.15 (t)	7.27 (t)	7.90 (m)	2.80 (s, 3H, CH_3)	2.93 (m, 4H, $2CH_2$), 3.69 (m, 4H, $2CH_2$)	2.44 (s, 3H, CH_3), 7.56 (d, 2H, 2′,6′-Ph), 7.28 (d, 2H, 3′5′-Ph)
16c	7.44 (d)	7.23(t)	7.36 (t)	8.09 (d)	2.86 (s, 3H, CH_3)	1.53 (m, 2H, CH_2), 1.55 (m, 4H, $2CH_2$), 2.88 (t, 4H, $2CH_2$)	7.94 (d, 2H, 2′,6′-Ph), 8.38 (d, 2H, 3′5′-Ph)
16d	7.64 (m)	7.26[a]	7.29[a]	7.81 (m)	2.70 (br s, 3H, CH_3)	1.47 (m, 2H, CH_2), 1.56 (m, 4H, $2CH_2$), 3.37 (t, 4H, $2CH_2$)	–

[a]The complex overlapping signals.

the same reaction was performed on short heating in an isopropanol solution of the same species, thienoindole **16a** was isolated in 33% yield. Under the same conditions, thienoindoles **16b–d** were obtained in 28, 39, and 50% yields, respectively (Scheme 9).

It is obvious that the first step of the process is S-alkylation of a thioamide with bromoacetylindoxyl **2** to afford the corresponding α-thioiminoketone salts **19A,B** (Scheme 9).

The salt undergoes cyclization to give hydroxydihydrothienoindole **20** followed by both dehydration of the latter and splitting of HBr to furnish thienoindole **16**. This is in line with our earlier findings that cyclic hydroxy-containing intermediates of **20** type are readily formed in the course of the synthesis of thiazolo[5,4-b]indoles and imidazo[4,5-b]indoles from bromoacetylindoxyl **2** [8,45,46]. The above process takes place when the reaction is conducted in the absence of a base. The competitive formation of the Eschenmoser-type thiirane **18** followed by its further transformations seems more likely in the presence of a base.

The IR spectra of thienoindoles **5a–e** show absorption bands in the range of 3200–3420 cm^{-1} associated with the NH_2 groups. The nitrile and ester groups of thienoindoles **5a–e** have typical stretching modes at 2195–2200 and 1650–1660 cm^{-1}, respectively. The N-acetyl groups in aminothienoindoles **5a–c** manifest themselves at 1660–1670 cm^{-1}; those in *N*,*N*-dialkylaminothienoindoles **16a–c, 16d** and the NCOOEt group in thienoindole **5d** have higher frequencies, 1660 and 1740 cm^{-1}, respectively. The ^{1}H- and ^{13}C-NMR data are in accord with the structures of thienoindoles **5** and **16** (Tables 3 and 4).

A general peculiarity of the ^{1}H-NMR spectra of *N*-acetylthienoindoles **16a–d** (Table 3) measured at RT is a remarkable broadening of the signals of the indole protons, which lie at about 200 Hz for the 7-H of the compound **16b** (T = 25°C). Upon increasing the temperature, the signals become narrower indicating that this broadening is associated with a dynamic process, hindered rotation of the acetyl group about the N_8-C_{Ac} amide bond.

CONCLUSIONS

It is of considerable general preparative interest that secondary/primary amines in the presence of elemental sulfur induce the ring opening of acetylindoxyl **1** in a single step, under mild conditions, affording pharmacologically interesting thioamides of 2-acetylaminophenylglyoxylic acid **6** or **7** and, as a rule, in good yields. The pathway of

this process was shown to involve the formation of intermediates 1-acetyl-2-thioisatin **8** and/or 1-acetyl-indoxyldisulfide **9**. Thioamides **6a,b** were demonstrated to undergo cyclization to 2,2-disubstituted indoxyls **13a,b** in moderate yields upon their alkylation with methyl iodide in the presence of potassium hydroxide. This cyclocondensation also shows possibilities of thioamides **6a–e** to serve as the key intermediates in the synthesis of various derivatives of indoxyl and indole series. The thioamides **6a–e** are under study at the Colorado State University as potential antituberculosis drugs. Already some have displayed appreciable antituberculosis activity against *Mycobacterium tuberculosis* $H_{37}Rv$ with the MIC values ranging between 5 and 21 μg/mL. A novel method for 1-acetyl-3-indolylmalononitrile **14a** and methyl 1-acetyl-3-indolylcyanoacetate **14c,e** syntheses based on acetylindoxyl **1** condensation with malononitrile or cyanoacetates is offered. It is rather simple and the process proceeds under mild conditions in high-to-good yields. The protocol may be used for the synthesis of a variety of the compounds of this series. In some key aspects, these protocols are more advantageous than current ones.

We also report on a method for the synthesis of thienoindoles **5** in a single step from fully heteroaromatic activated nitriles such as 3-indolylmalononitrile **14a** and the corresponding 3-indolylcyanoacetates, **14c** or **14e**. 2-Aminothienoindoles **5** bearing COMe/COOEt substituent in position 1 of the ring system were prepared from nitriles **14** by means of a novel modification of the Gewald reaction with elemental sulfur in the presence of a tertiary amine in low-to-high yields (80–25%). Although the yield of thieno[2,3-b]indoles from this modification of the Gewald aminothiophene synthesis is somewhat low, the simplicity of the method makes it suitable for preparative purposes. Besides, purification of all fused indoles obtained does not require any chromatographic procedures. The approach offers advantages for application in the synthesis of other sulfur-containing compounds of this series. We also offer a simple, quick, and high- to satisfactory-yielding syntheses of 2-*N*,*N*-dialkylaminothienoindoles **16** from bromoacetylindoxyl **2** (available starting material) and demonstrate their potential as intermediates in the synthesis of other sulfur heterocycles.

Thus, acetylindoxyl **1** and some of its derivatives have been successfully used as available and versatile starting materials in the synthesis of pharmacologically interesting thieno[2,3-b]indoles and "opened" thioamides.

EXPERIMENTAL

Melting points are uncorrected. Mass spectra of all compounds except **9** and **13** were recorded on a Finnigan Polaris Q apparatus (70 eV). FAB mass spectra of compounds **9** and **13** were recorded on a Jeol JMS DX300 in a matrix of *meta*-nitrobenzilic alcohol using xenon as an ionizing gas. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance-600 spectrometer at 600.22 (^{1}H) and 150.93 (^{13}C) MHz in DMSO-d_6 solutions. Chemical shifts are given in ppm from residual proton signals from deuterated solvent as the internal standard (^{1}H-2.54, ^{13}C-40.45 ppm). IR spectra were recorded on a Perkin-Elmer 457 apparatus. Elemental analyses were performed with a Perkin-Elmer recorder.

N*-[2-(2-*N*-(R_1,R_2)-Thioxoacetyl)-phenyl]acetamides (6a–e), 8-acetyl-2-amino-8H-thieno[2,3-b]indole-3-carbonitrile (5a), and *N*-[2-(butylimino-butylthiocarbamoyl-methyl)-phenyl] acetamide (7) (Tables 1 and 3).** ***Method A. A mixture of acetylindoxyl **1** (1.75 g, 10 mmol), sulfur (0.48 g, 15 mmol), malononitrile **3a** (1.0 g, 15 mmol), and morpholine **4a** (1.31 g, 15 mmol) was boiled in 2-propanol (20 mL) for 3 h. After cooling, the crystals were filtered off and washed with dichloromethane (5 mL) and toluene (20 mL). Thienoindole **5a** (0.23 g) was obtained in a yield of 9%, mp 276–278°C (decomp.); IR: 1665 (COMe), 2200 (CN), 3200, 3400 (NH_2) cm^{-1}; ^{13}C-NMR: δ 24.7, 72.0, 115.2, 116.2, 117.7, 120.3, 123.0, 123.6, 124.0, 136.7, 165.0, 167.3 ppm; ms: *m/z* 255 (M^+). Anal. Calcd. for $C_{13}H_9N_3OS$: C, 61.16; H, 3.55; N, 16.46; S, 12.56. Found: C, 61.21; H, 3.54; N, 16.50; S, 12.64.

The filtrate was concentrated by evaporation, and the residue is crystallized from toluene. Thioamide **6a** (1.78 g, 61%) was obtained, mp 192–194°C; IR: 1640 (COMe), 1695 (CO), 3290 (NH) cm^{-1}; ^{13}C-NMR: δ 25.0, 47.1, 52.0, 65.5, 65.8, 118.8, 120.7, 123.0, 133.3, 136.0, 141.6, 169.1, 190.1, 192.4 ppm; ms: *m/z* 292 (M^+). Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; S, 10.97. Found: C, 57.55; H, 5.47; N, 9.60; S, 10.93.

The use of piperidine **4b** (1.28 g, 15 mmol) gave **5a** (0.22 g, 8%) and thioamide **6b** (55%), mp 157–159°C; IR: 1640 (COMe), 1690 (CO), 3300 (NH) cm^{-1}; ms: *m/z* 290 (M^+). Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65; S, 11.04. Found: C, 62.11; H, 6.18; N, 9.69; S, 11.09.

Method B. A mixture of acetylindoxyl **1** (1.75 g, 10 mmol), sulfur (0.48 g, 15 mmol), and morpholine **4a** (1.74 g, 20 mmol) was boiled in 2-propanol (20 mL) for 3 h. After cooling, the crystals were filtered off and recrystallized from toluene. Thioamide **6a** (2.21 g, 76%) was obtained.

The use of piperidine **4b** (1.70 g, 20 mmol) gave **6b** (1.94 g, 67%). The use of butylamine **4c** (1.46 g, 20 mmol) results in **7** (1.17 g, 35%), mp 147–149°C; IR: 1660 (COMe), 3160 (NH) cm^{-1}; ^{1}H-NMR: δ 0.92* (3H, CH_3), 0.92* (3H, CH_3), 1.36 (m, 2H, CH_2), 1.44 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 2.11 (s, 3H, $COCH_3$), 3.18, 3.55 (t, 2H, CH_2), 3.68 (br, 2H, CH_2), 7.09 (t, 1H, 4-H), 7.42* (1H, 3-H), 7.42* (1H, 5-H), 8.59 (d, 1H, 6-H), 10.88 (br d, 1H, NH), 13.21 ppm (s, 1H, NH) *complex overlapping signals; ^{13}C-NMR: δ 13.8, 13.9, 20.0, 20.4, 25.2, 29.3, 32.7, 44.0, 51.7, 119.1, 119.6, 122.2, 131.3, 140.7, 167.9, 168.7, 192.5 ppm; ms: *m/z* 333 (M^+). Anal. Calcd. for $C_{18}H_{27}N_3OS$: C, 64.83; H, 8.16; N, 12.60; S, 9.61. Found: C, 64.78; H, 8.08; N, 12.59; S, 9.57.

When the reaction was run in an argon atmosphere, compounds **6a–c** were chromatographically detected using Silufol UV-254 plates and chloroform–acetone (20:1) mixture as an eluent.

Method C. A mixture of **9** (2.05 g, 5 mmol) and morpholine **4a** (1.04 g, 12 mmol) was boiled in dioxane (10 mL) for 2 h. The solvent was removed *in vacuo*, and the residue was crystallized from an ethanol–water mixture. **6a** (2.28 g, 78%) was obtained.

The use of piperidine **4b** (1.02 g, 12 mmol) gave **6b** (2.03 g, 70%). When the reaction was run in the presence of the equimolar amount of malononitrile **3a**, the yields of compounds **4a,b** were 78 and 70%, respectively.

Method D. A mixture of **8** (2.05 g, 10 mmol) and morpholine **4a** (1.04 g, 12 mmol) was mixed for 20 min in dioxane (10 mL) at RT. The solvent was removed *in vacuo*, and the residue was recrystallized from an ethanol–water mixture. **6a** (2.65 g, 91%) was obtained.

The use of piperidine **4b** (1.02 g, 12 mmol) gave **6b** (2.51 g, 87%). The use of *n*-butylamine **4c** (0.88 g, 12 mmol) results in **6c** (2.50 g, 90%), mp 149–151°C; IR: 1650 (COMe), 1675 (CO), 3050, 3200, 3300 (NH) cm^{-1}; ms: *m/z* 278 (M^+). Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06; S, 11.52. Found: C, 60.46; H, 6.46; N, 10.02; S, 11.45.

The use of *N*-methylpiperazine **4d** (1.20 g, 12 mmol) yields in **6d** (2.68 g, 88%), mp 176–179°C; IR: 1640 (COMe), 1700 (CO), 3280 (NH) cm^{-1}; ms: *m/z* 305 (M^+). Anal. Calcd. for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 58.92; H, 6.20; N, 13.79; S, 10.44.

The use of isopropylamine **4e** (0.70 g, 12 mmol) gave **6e** (2.38 g, 90%), mp 212–214°C; IR: 1660 (COMe), 1670 (CO), 3200, 3300 (NH) cm^{-1}; ms: *m/z* 264 (M^+). Anal. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 59.12; H, 6.03; N, 10.61; S, 12.10.

When the reaction was run in the presence of the equimolar amount of malononitrile **3a**, the yields of compounds **6a,b** were 91 and 87%, respectively.

1-Acetyl-2-thioxo-1,2-dihydro-3H-indol-3-one (8). A solution of $Na_2S_2O_3$ pentahydrate (2.0 g, 8.0 mmol) in water (10 mL) was added to a solution of bromoindoxyl **2** (2.0 g, 7.9 mmol) in dioxane (20 mL). The reaction mixture was stirred at RT for 20 min. Sodium acetate (0.66 g, 8 mmol) and iodine (2.10 g, 8.3 mmol) were added to the reaction mixture. The mixture was stirred for 40 min, diluted with water (15 mL), and the precipitated crystals were filtered off. The yield was 72% (1.17 g), mp 182–184°C (decomp.); IR: 1690 (COMe), 1730 (CO) cm^{-1}; ms: *m/z* 205 (M^+). Anal. Calcd. for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82; S, 15.62. Found: C, 58.47; H, 3.40; N, 6.81; S, 15.65.

2,2′-Dithiobis(1-acetyl-1,2-dihydro-3H-indol-3-one) (9). A solution of $Na_2S_2O_3$ pentahydrate (2.0 g, 8.0 mmol) in water (10 mL) was added to a solution of bromoindoxyl **2** (2.0 g, 7.9 mmol) in dioxane (20 mL). The reaction mixture was stirred at RT for 20 min. Sodium acetate (0.33 g, 4.0 mmol) and iodine (1.05 g, 4.1 mmol) were added to the reaction mixture. The mixture was stirred for 20 min, and the precipitated crystals were filtered off and recrystallized from dioxane. The yield was 45% (0.73 g), mp 212–214°C (decomp.); IR: 1685 (COMe), 1720 (CO) cm^{-1}; ms: (FAB) *m/z* 412 (M^+). Anal. Calcd. for $C_{20}H_{16}N_2O_4S_2$: C, 58.24; H, 3.91; N, 6.79; S, 15.55. Found: C, 58.30; H, 3.88; N, 6.73; S, 15.58.

1-Acetyl-2-(methylthio)-2-morpholin-1-yl-1,2-dihydro-3H-indol-3-one (13a) and 1-acetyl-2-(methylthio)-2-piperidin-1-yl-1,2-dihydro-3H-indol-3-one (13b). A solution of KOH (0.7 g, 12.5 mmol) in methanol (10 mL) was added to a solution of thioamide **6a** (1.46 g, 5 mmol) and methyl iodide (1.42 g, 10 mmol) in dimethylformamide (15 mL). The reaction mixture was stirred at RT for 30 min and poured into water (50 mL). The reaction product was extracted with dichloromethane (3 × 10 mL); the extract was washed with water and dried over Na_2SO_4. Dichloromethane was evaporated, and the residue was recrystallized from a benzene–petroleum ether mixture. The yield of **13a** was 52% (0.80 g), mp 121–122°C; IR: 1680 (COMe), 1720 (CO) cm^{-1}; ^{1}H-NMR: δ 1.88 (s, 3H, $COCH_3$), 2.71 (s, 3H, SCH_3), 2.90 (br, 4H, $2CH_2$), 3.62 (m, 4H, $2CH_2$), 7.18 (t, 1H, 5-H), 7.64 (t, 1H, 6-H), 7.69 (d, 1H, 4-H), 8.53 ppm (d, 1H, 7-H); ^{13}C-NMR: δ 12.2, 25.4, 47.0, 66.7, 89.1, 118.0, 122.0, 123.8, 125.1, 138.9, 152.4, 171.1, 195.6 ppm; ms: (FAB) *m/z* 306 (M^+). Anal. Calcd. for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14; S, 10.47. Found: C, 58.80; H, 5.89; N, 9.12; S, 10.41.

The use of **6b** (1.45 g, 5 mmol) yielded **13b** (0.68 g, 45%), mp 89–91°C; IR: 1675 (COMe), 1720 (CO) cm^{-1}; ^{1}H-NMR: δ 1.37 (m, 2H, CH_2), 1.45 (m, 4H, $2CH_2$), 1.84 (s, 3H, $COCH_3$), 2.61 (s, 3H, SCH_3), 2.73 (br, 4H, $2CH_2$), 7.28 (t, 1H, 5-H), 7.70 (d, 1H, 4-H), 7.77 (t, 1H, 6-H), 8.43 ppm (d, 1H, 7-H); ms: (FAB) *m/z* 304 (M^+). Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 63.19; H, 6.55; N, 9.17; S, 10.48.

8-Acetyl-2-amino-8H-thieno[2,3-b]indole-3-carbonitrile (5a). ***Method B.*** A mixture of acetylindoxyl **1** (1.75 g, 10 mmol), sulfur (0.48 g, 15 mmol), malononitrile **3a** (1.0 g, 15 mmol), and triethylamine (1.5 g, 15 mmol) was boiled in 2-propanol (20 mL) for 1 h. Dichloromethane (5 mL) was added to the cooled reaction mixture, and the crystals were filtered off and washed with toluene. **5a,** 1.34 g (52%) was obtained.

Method C. A mixture of **14a** (0.5 g, 2.2 mmol), sulfur (0.11 g, 3.4 mmol), and triethylamine (0.33 g, 3.3 mmol) was boiled in 2-propanol (5 mL) for 1 h. The crystals precipitated were filtered off and washed with toluene. **5a,** 0.45 g (80%) was obtained. The use of morpholine as a base gave **5a,** 0.45 g (80%).

Ethyl 8-acetyl-2-amino-8H-thieno[2,3-b]indole-3-carboxylate (5b). A mixture of acetylindoxyl **1** (1.75 g, 10 mmol), sulfur (0.64 g, 20 mmol), **3b** (2.26 g, 20 mmol), and triethylamine (2 g, 20 mmol) was boiled in 2-propanol (15 mL) for 3 h. The reaction mixture was cooled and kept overnight. The crystals precipitated were filtered off and recrystallized from toluene and then from dioxane. The yield was 10% (0.3 g), mp 220–222°C (decomp.); IR: 1660 br (COMe, COOEt), 3300, 3420 (NH); ms: *m/z* 302 (M^+). Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27; S, 10.60. Found: C, 59.65; H, 4.61; N, 9.30; S, 10.63.

(1-Acetyl-1H-indol-3-yl)malononitrile (14a). A mixture of acetylindoxyl **1** (1.75 g, 10 mmol), triethylamine (1.5 g, 15 mmol), and malononitrile **3a** (0.99 g, 15 mmol) was boiled in acetonitrile (20 mL) for 1 h. Then, acetic acid (2.0 mL) and water (15 mL) were added to the reaction mixture. After cooling, the crystals were filtered off. The yield was 88% (1.96 g). The yield in 2-propanol was 73% (1.63 g), mp 164–166°C; ^{13}C-NMR: δ 20.1, 24.3, 107.4, 113.2, 116.9, 118.8, 124.7, 126.6, 126.7, 127.8, 135.6, 170.2 ppm; ms: *m/z* 223 (M^+). Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.82; H, 4.05; N, 18.89.

Methyl (1-acetyl-1H-indol-3-yl)cyanoacetate (14c). A mixture of acetylindoxyl **1** (1.75 g, 10 mmol), triethylamine (1.5 g, 15 mmol), and **3c** (1.49 g, 15 mmol) was boiled in acetonitrile (20 mL) for 5 h. Acetic acid (2.0 mL) was added to the reaction mixture. The solvent was removed *in vacuo*. The residue was recrystallized from a 2-propanol–water mixture. The yield was 72% (1.84 g). The yield in 2-propanol was 67% (1.72 g), mp 124–126°C; IR: 1720 (COMe), 1750 (COOMe), 2260 (CN) cm^{-1}; ms: *m/z* 256 (M^+). Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.65; H, 4.70; N, 10.91.

Methyl (1H-indol-3-yl)cyanoacetate (14e). ***Method A.*** A mixture of acetylindoxyl **1** (1.75 g, 10 mmol), triethylamine (1.5 g, 15 mmol), and **3c** (1.49 g, 15 mmol) was boiled in

methanol (20 mL) for 5 h. A solution of acetic acid (2.0 mL) in water (40 mL) was added to the reaction mixture. After cooling, the crystals were filtered off and recrystallized from a methanol–water mixture. The yield was 62% (1.33 g), mp 122–124°C; IR: 1740 (COOMe), 2260 (CN), 3420 (NH) cm^{-1}; ms: *m/z* 214 (M^+). Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.25; H, 4.70; N, 13.02.

Method B. A solution of **14c** (0.5 g, 2.0 mmol) and triethylamine (0.20 g, 2.0 mmol) in methanol (5 mL) was kept at RT for 24 h. Then, acetic acid (0.3 mL) and water (15 mL) were added to the reaction mixture. The crystals precipitated were filtered off and recrystallized from a methanol–water mixture. The yield was 21% (0.09 g).

Ethyl (1-carboethoxy-1H-indol-3-yl)cyanoacetate (14d). Compound **14d** (mp 71–73°C) was obtained from 3-indolylacetonitrile and diethylcarbonate by the method given in ref. 38.

Methyl 8-acetyl-2-amino-8H-thieno[2,3-b]indole-3-carboxylate (5c). ***Method A.*** A mixture of **14c** (1.0 g, 3.9 mmol), sulfur (0.5 g, 15.6 mmol), and triethylamine (0.73 g, 7.2 mmol) was boiled in 2-propanol (7 mL) for 10 h. The solvent was removed *in vacuo*. The reaction product obtained was recrystallized from toluene and then from a toluene–dioxane mixture. **5c** (0.022 g, 2%) was obtained, mp 236–238°C (decomp.); IR: 1650 (COMe), 1670 (COOMe), 3310, 3440 (NH_2) cm^{-1}; ms: *m/z* 288 (M^+). Anal. Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72; S, 11.12. Found: C, 58.34; H, 4.16; N, 9.69; S, 11.18.

Method B. Sulfur (0.5 g, 15.6 mmol) and triethylamine (0.73 g, 7.2 mmol) were added to a solution of **14c** (1.0 g, 3.9 mmol) in DMSO (7 mL). The reaction mixture was stirred at 75°C for 5 h. Triethylamine was removed *in vacuo*, unreacted sulfur was filtered off, then benzene (10 mL) was added to the filtrate, and the reaction mixture was diluted with water (15 mL). The mixture was stirred for 30 min, and the crystals precipitated were filtered off, washed with methanol, and recrystallized from dioxane. The yield was 20% (0.22 g).

Method C. A mixture of **14c** (0.5 g, 2 mmol), sulfur (0.25 g, 7.8 mmol), and triethylamine (0.37 g, 3.6 mmol) in dimethylformamide (2.5 mL) was stirred at RT for 10 days, the sulfur residue was filtered off, benzene (5 mL) was added to the filtrate, and the reaction mixture was diluted with water (10 mL). The mixture was stirred for 30 min, and the crystals precipitated were filtered off and washed with methanol. The yield was 21% (0.12 g).

Method D. A mixture of **14c** (0.5 g, 2 mmol), sulfur (0.25 g, 7.8 mmol), and triethylamine (0.37 g, 3.6 mmol) in acetonitrile (2.5 mL) was stirred at RT for 10 days. The reaction mixture was diluted with water (3 mL), and the crystals precipitated were filtered off, washed with methanol, and put into boiling toluene (10 mL). The suspension was boiled for 5 min, cooled, and the product obtained was filtered off. The yield was 25% (0.14 g).

Ethyl 2-amino-8-carboethoxy-8H-thieno[2,3-b]indole-3-carboxylate (5d). A mixture of **14d** (1.0 g, 3.3 mmol), sulfur (0.16 g, 5 mmol), and triethylamine (0.50 g, 5 mmol) was boiled in ethanol (7 mL) for 10 h. The solvent was removed *in vacuo*. The residue was recrystallized from an ethanol–petroleum ether mixture. **5e** (0.36 g, 33%) was obtained, mp 145–147°C; IR: 1660, 1740 (COOEt), 3310, 3410 (NH_2) cm^{-1}; ms: *m/z* 332 (M^+). Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 57.88; H, 4.79; N, 8.41; S, 9.69.

Methyl 2-amino-8H-thieno[2,3-b]indole-3-carboxylate (5e). A mixture of **14e** (0.43 g, 2 mmol), sulfur (0.25 g, 7.8 mmol), and triethylamine (0.37 g, 3.6 mmol) in dimethylformamide (2.5 mL) was stirred at RT for 5 days. The sulfur residue was filtered off, a benzene–petroleum ether (1:1) mixture (5 mL) was added to the filtrate, and the reaction mixture was diluted with water (15 mL). The crystals precipitated were filtered off and recrystallized twice from a benzene–petroleum ether mixture. The yield of **5e** was 5% (0.025 g), mp 179–181°C; IR: 1660 (COOMe), 3290, 3400 (NH, NH_2) cm^{-1}; ms: *m/z* 246 (M^+). Anal. Calcd. for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.61; H, 4.07; N, 11.42; S, 13.07.

8-Acetyl-2-*N*-(R_3,R_4)-3-R_2-8H-thieno[2,3-b]indoles (16a–d) (Table 4). Bromoindoxyl **2** (2.54 g, 10 mmol) was added to a boiling solution of a corresponding thioamide **17a–d** (10 mmol) in 2-propanol (40 mL), and the mixture was boiled for 7 min. After cooling, the product was crystallized for several hours. The crystals precipitated were filtered off and washed with isopropanol. The yield of **16a** was 33% (1.24 g), mp 182–184°C; IR: 1675 (COMe) cm^{-1}; ms: *m/z* 376 (M^+). Anal. Calcd. for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44; S, 8.52. Found: C, 70.25; H, 5.32; N, 7.41; S, 8.50.

The yield of **16b** was 28% (1.09 g), mp 164–166°C; IR: 1680 (COMe) cm^{-1}; ms: *m/z* 390 (M^+). Anal. Calcd. for $C_{23}H_{22}N_2O_2S$: C, 70.74; H, 5.68; N, 7.17; S, 8.21. Found: C, 70.82; H, 5.63; N, 7.20; S, 8.19.

The yield of **16c** was 39% (1.63 g), mp 204–206°C; IR: 1680 (COMe) cm^{-1}; ms: *m/z* 419 (M^+). Anal. Calcd. for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.05; N, 10.02; S, 7.64. Found: C, 65.86; H, 4.99; N, 9.97; S, 7.69.

The yield of **16d** was 50% (1.62 g), mp 212–215°C; IR: 1720 (COMe), 2195 (CN) cm^{-1}; ms: *m/z* 323 (M^+). Anal. Calcd. for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99; S, 9.91. Found: C, 66.89; H, 5.26; N, 13.03; S, 10.00.

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