A New Simple Route to the Thieno[2,3-*b*]indole Ring System

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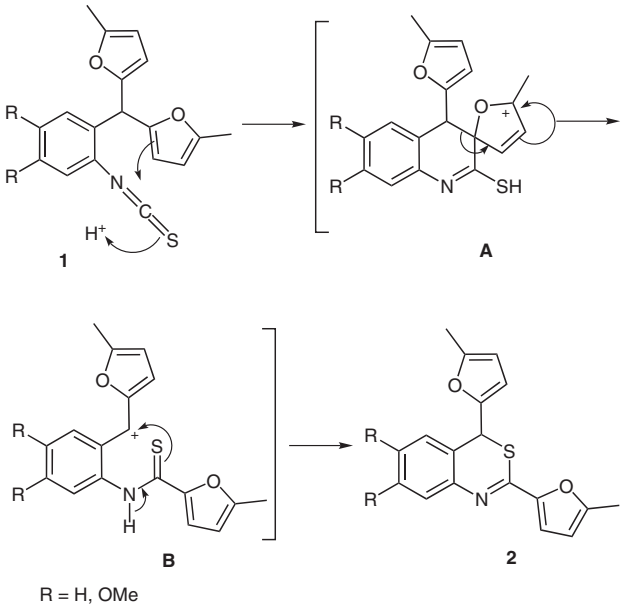
Abstract: A simple and effective method has been elaborated for the synthesis of thieno[2,3-*b*]indole ring system. It is based on the electrophilic recyclization of 2-alkyl-5-(2-isothiocyanoaryl)furans in the presence of anhydrous $AlCl_3$.

Key words: furan, ring opening, ring closure, fused-ring system, thieno[2,3-*b*]indole

The thieno[2,3-*b*]indole ring system has been little studied to date and few methods of its synthesis have been reported.[1–7] Nevertheless, thieno[2,3-*b*]indoles are promising as physiologically active compounds. In particular, thienodolin {6-chlorothieno[2,3-*b*]indole-2-carboxamide} isolated from the culture broth of *Streptomyces albogriseolus*[8] and characterized by Japanese researches was proved to have plant-growth-regulation activity. The parent thieno[2,3-*b*]indole also demonstrates antifungal activity.[9]

In continuation of our studies in furan chemistry[10] we studied intramolecular interactions of the furan ring and isothiocyano group. It is well known that isothiocyanates react with aromatic and heterocyclic compounds under Friedel–Crafts reaction conditions yielding thioamides.[11] In this reaction the carbon atom of isothiocyano group acts as an electrophile with regard to the aromatic ring. When this reaction is performed in intramolecular mode, the cyclic thioamides are usually formed.[12] However, direct thiocarbamoylation of furans with isothiocyanates under the Friedel–Crafts conditions has not been reported, a fact that can be attributed to the known sensitivity of furan compounds to acids. The known furan thioamides are usually synthesized by use of lithiated furan derivatives.[13]

In 1997 we have described the first example of the acid-catalyzed intramolecular reaction of an isothiocyano group with the furan moiety. We found that treatment of 2-[bis(2-furyl)methyl]aryl isothiocyanates with perchloric acid in 1,4-dioxane led to the formation of 2,4-difuryl-4*H*-3,1-benzothiazines derivatives (Scheme 1).[14] In this case the intramolecular *ipso* substitution followed by furan ring migration occurred instead of cyclic thioamide formation which is the usual process for most aromatic and heteroaromatic substrates. Later we showed the generality of this reaction, as it was bound to be applicable to various *o*-isothiocyanotriarylmethanes.[15] The key step of the furan migration is the **A**-to-**B** rearrangement. The formation of the relatively stable carbocation is a prerequisite of this reaction. Otherwise, the furan fails to migrate.



Scheme 1 Synthesis of 2,4-difuryl-4*H*-3,1-benzothiazines via a furan ring migration

It was of interest to study the intramolecular interaction of furan and isothiocyano groups in substrates wherein the furan ring migration is impossible due to structural features of the molecule. For this investigation we chose arylfurans wherein the aryl group and furan ring are linked directly.

As starting compounds for the synthesis of the desired isothiocyanates we used carbonyl derivatives of 2-(*o*-nitroaryl)furans **3** obtained by the arylation of furfural and 2-acetylfuran.[16] Reduction of compounds **3** with $NaBH_4$ in the presence of equimolar amounts of $AlCl_3$ in anhydrous THF led to 2-alkyl-5-(2-nitroaryl)furans **4**[17] and subsequent reduction of the nitro group with Raney Ni and hydrazine furnished amines **5**.[18] Isothiocyanates **6** were obtained by the treatment of compounds **5** with thio-

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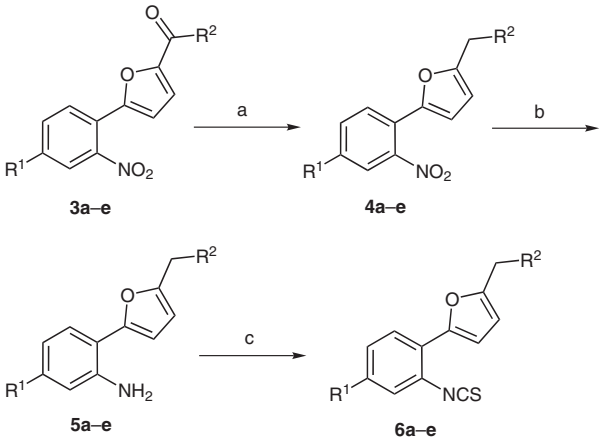


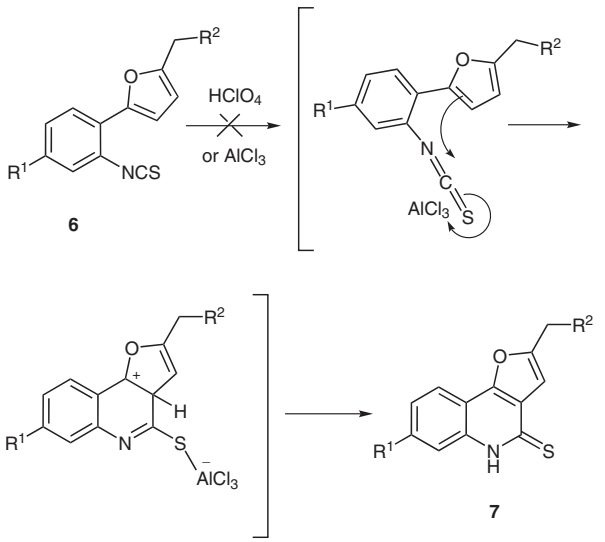
Scheme 2 Synthesis of starting materials. *Reagents and conditions*: a) $NaBH_4$, $AlCl_3$, THF; b) Ra-Ni, NH_2NH_2, EtOH; c) $CSCl_2$, $NaHCO_3$, CH_2Cl_2, H_2O.

Table 1 Yields of Compounds **4**–**6**

Compd **4**–**6**	R^1	R^2	Yield of **4** (%)	Yield of **5** (%)	Yield of **6** (%)
a	H	H	67	76	94
b	H	Me	83	89	77
c	Cl	H	63	78	79
d	Me	H	60	80	52
e	OMe	H	81	78	76

phosgene in the presence of aqueous $NaHCO_3$ and CH_2Cl_2 (Scheme 2, Table 1).[19]

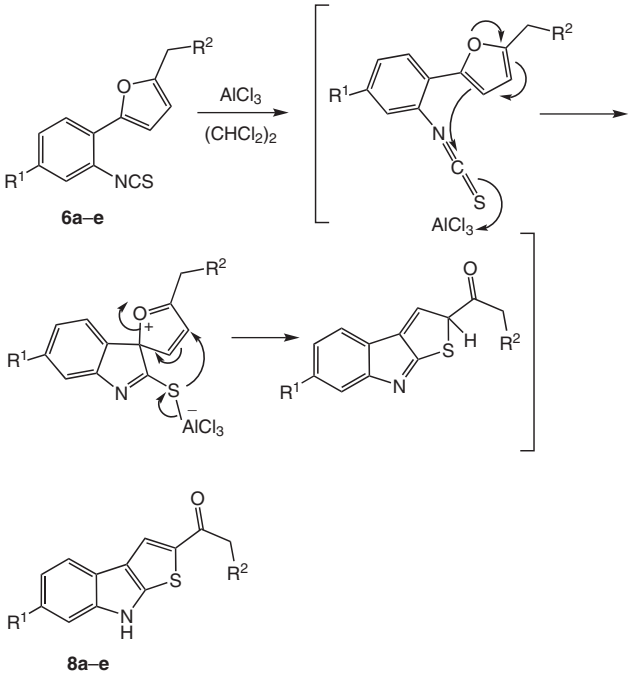
We expected that treatment of isothiocyanates **6** with perchloric acid by procedure similar to that used for 2-[bis(2-furyl)methyl]aryl isothiocyanates[14] should lead to intramolecular Friedel–Crafts cyclization onto the β-position of the furan ring (Scheme 3). However, decomposition largely occurred under these reaction conditions.



Scheme 3

We tested different Brønsted and Lewis acids and finally found that transformation of compounds **6** was the most efficient when treated with anhydrous $AlCl_3$ in 1,2-dichloroethane. To our surprise, the spectroscopic data showed that we obtained thieno[2,3-*b*]indoles **8** instead of the target furoquinolines **7** (Scheme 4, Table 2).[20] Structures of these products were unambiguously confirmed by single-crystal X-ray data for **8a** (Figure 1).[21]

A possible mechanism for the formation of thieno[2,3-*b*]indoles **8** is shown in Scheme 4. The first step of this re-



Scheme 4 Synthesis of thieno[2,3-*b*]indoles **8**

Table 2 Yields of Compounds **8**

Entry	Compd	R^1	R^2	Yield of **8** (%)
1	**8a**	H	H	67
2	**8b**	H	Me	83
3	**8c**	Cl	H	63
4	**8d**	Me	H	60
5	**8e**	OMe	H	81

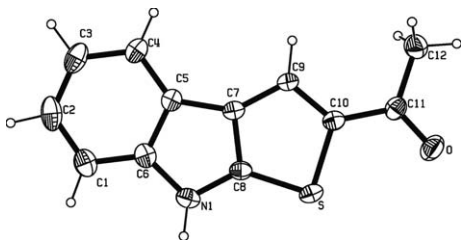


Figure 1 ORTEP Diagram of **8a**.

action is electrophilic attack by the carbon of the isothiocyano group activated with anhydrous $AlCl_3$ onto the α-position of the furan ring. Furan ring opening followed by cyclization due to intramolecular attack of the sulfur atom on the carbocation intermediate furnishes the final products **8**.

In summary, we have studied the transformation of 2-alkyl-5-(2-isothiocyanoaryl)furans under the Friedel–Crafts conditions. It has been demonstrated that this reaction proceeds via electrophilic recyclization of the furan ring rather than direct intramolecular cyclization. The transformation is a simple and elegant method for the synthesis of rare thieno[2,3-*b*]indole derivatives.

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(16) (a) Compounds **3** were prepared using the Meerwein method. For a typical procedure, see ref. 16b.
General Procedure for the Arylation Reaction
A mixture of substituted 2-nitroaniline (0.3 mol), H_2O (400 mL) and 36% HCl (200 mL) was stirred for 30 min at 80 °C. The solution was then cooled to 0 °C to –10 °C. The resulting suspension of aniline hydrochloride was treated with $NaNO_2$ (25 g, 0.36 mol) in H_2O (120 mL). The resulting solution of the diazonium salt was stirred for 40 min at 0 °C to –5 °C and filtered. A solution of furfural or 2-acetylfuran (0.3 mol) in acetone (150 mL) was added, followed by $CuCl_2$ (8 g, 0.06 mol) in H_2O (100 mL). The reaction mixture was stirred for 12 h at r.t. When the reaction was complete, the resulting precipitate was filtered off and crystallized from EtOH–acetone; yields of 5-arylfurfurals **3a**,**c**–**e**: 45–53%; yield of 2-acetyl-5-phenylfuran (**3b**): 41%. (b) Janda, L.; Voticky, Z. *Chem. Zvesti* **1984**, *38*, 507.
(17) (a) Compounds **4** were synthesized according to the reported procedure, see ref. 17b.
General Procedure for the Preparation of Compounds 4a–e
To a cooled (0–5 °C) solution of compound **3** (17 mmol) in THF (120 mL), anhyd $AlCl_3$ (4.5 g, 34 mmol) and $NaBH_4$ (1.3 g, 34 mmol) were added portionwise under stirring. The resulting suspension was stirred at 0–5 °C for 20 min and then brought to reflux. After 1–2 h when the starting compound **3** vanished (TLC monitoring), the reaction mixture was cooled and poured into H_2O (400 mL). The organic layer was separated and the water layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhyd Na_2SO_4, treated with activated charcoal, and the solvent evaporated under the reduced pressure. The residue **4** was used in the next step without further purification. (b) Ono, A.; Suzuki, N.; Kamimura, J. *Synthesis* **1987**, 736.
(18) **General Procedure for the Preparation of Compounds 5a–e**
To an ethanolic solution (50 mL) of compound **4** (6 mmol),

Raney Ni (1.5 g) and hydrazine hydrate (2.5 mL) were added and the reaction mixture was refluxed for 1–2 h. After completion of the reaction (TLC monitoring), the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in benzene–PE (1:1), filtered through a pad of silica gel, and the solvent evaporated under reduced pressure. The residue **5** was used in the next step without further purification.
WARNING: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.

(19) **General Procedure for the Preparation of Compounds 6a–e**

A solution of thiophosgene (0.5 mL, 6.5 mmol) in CH_2Cl_2 (10 mL) and $NaHCO_3$ (1.3 g, 15.5 mmol) in H_2O (50 mL) were simultaneously added at r.t. to a stirred solution of compound **5** (5 mmol) in CH_2Cl_2 (15 mL). When the reaction had finished (TLC monitoring), the mixture was poured into H_2O (200 mL) and stirred for 6 h. The organic layer was separated and water layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhyd Na_2SO_4, the dried extract was reduced to the half of its volume, and PE was added until the solution became cloudy. The solution was filtered through a pad of silica gel, evaporated to one third of its volume, and left to allow crystallization of the compounds **6**.

Selected Analytical Data of 6e

Mp 85–86 °C. IR: ν_{max} = 2136, 1616, 1600, 1568, 1548, 1496, 1296, 1200, 1176, 1032, 976, 880, 804, 788 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 6.10 (d, *J* = 3.3 Hz, 1 H, H_{Fur}), 6.67 (d, *J* = 3.3 Hz, 1 H, H_{Fur}), 6.78 (d, *J* = 2.6 Hz, 1 H, H_{Ar}), 6.84 (dd, *J* = 2.6, 8.8 Hz, 1 H, H_{Ar}), 7.62 (d, *J* = 8.8 Hz, 1 H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 55.6, 108.0, 109.0, 112.4, 114.6, 120.5, 126.2, 127.3, 134.7, 148.0, 152.0, 158.7. MS: *m/z* (%) = 245 (85) [M^+], 230 (37), 212 (23), 202 (29), 188 (32), 171 (20), 160 (17), 159 (19), 127 (13), 116 (13), 115 (26), 76 (14), 59 (23), 43 (38). Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.86; H, 4.38; N, 5.79.

(20) **General Procedure for the Preparation of Compounds 8a–e**

Aluminum chloride (1.6 g, 12 mmol) was added to a solution of compound **6** (6 mmol) in 1,2-dichloroethane (30 mL). The reaction mixture was stirred for 30 min at 50 °C (TLC monitoring), then poured into H_2O (200 mL) and extracted with CH_2Cl_2 (2 × 40 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was crystallized from the appropriate solvent: benzene–PE for **8a**; benzene for **8b**; EtOH for **8c**; EtOAc–PE for **8d**; EtOH for **8e**.
WARNING: Care should be taken when handling benzene as a solvent because of its carcinogenic properties.

Selected Analytical Data of 8e

Mp 225–226 °C. IR: ν_{max} = 1628, 1608, 1584, 1508, 1480, 1472, 1400, 1280, 1236, 1196, 1156, 1092, 1024, 936, 824, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 6.81 (dd, *J* = 2.3, 8.6 Hz, 1 H, H_{Ar}), 7.04 (d, *J* = 2.3 Hz, 1 H, H_{Ar}), 7.73 (d, *J* = 8.6 Hz, 1 H, H_{Ar}), 8.29 (s, 1 H, H_{Th}), 11.86 (s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7, 55.3, 96.1, 109.2, 115.9, 120.1, 124.7, 126.2, 135.8, 143.5, 146.6, 156.8, 190.5. MS: *m/z* (%) = 245 (85) [M^+], 231 (22), 230 (100), 203 (11), 202 (57), 188 (13), 187 (18), 160 (17), 159 (16), 158 (17), 115 (11), 69 (18), 57 (12). Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.69; H, 4.41; N, 5.77.

(21) **Crystal Data of Compound 8a**

$C_{12}H_9NOS$, orthorhombic, space group P_{bca}; *a* = 11.982(2) Å, *b* = 10.837(2) Å, *c* = 15.752(3) Å, *V* = 2045.4(6) $Å^3$, *Z* = 8, D_{calcd} = 1.398 Mg/m^3, *F*(000) = 896; 1797 reflections collected, 1797 unique (R_{int} = 0.0000); final *R* indices (935 observed collections $I > 2\sigma I$): R_1 = 0.0309, wR_2 = 0.0924; final *R* indices (all data): R_1 = 0.0859, wR_2 = 0.1005. Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 657300. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uc]. Each request should be accompanied by the complete citation of this paper.