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One-pot synthesis of 2-substituted thieno[3,2-*b*]indoles from 3-aminothiophene-2-carboxylates through *in situ* generated 3-aminothiophenes

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ABSTRACT

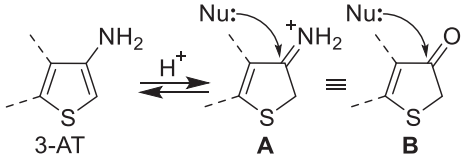
A convenient protocol for one-pot synthesis of thieno[3,2-*b*]indoles, bearing aromatic, thien-2-yl or styryl fragments at C-2 position, from easily accessible 5-substituted 3-aminothiophene-2-carboxylates using the Fischer indolization reaction, was developed during this study. Two main steps of this approach are the saponification of the starting 3-aminoesters with sodium hydroxide and next treatment of the crude 3-aminoacids sodium salts with arylhydrazines in glacial acetic acid solution. The latter step includes *in situ* decarboxylation of the freed 3-aminothiophene-2-caboxylic acids to the 3-aminothiophenes and their acid promoted reaction with arylhydrazines to initially form arylhydrazones of 5-substituted thiophene-3(2*H*)-ones, which smoothly cause indolization to afford the desired thieno[3,2-*b*]indoles.

Over the past decade, thieno[3,2-*b*]indole ring system has been successfully used as electron-rich unit to design π-conjugated molecules of photosensitive and electroactive materials for various types of organic photovoltaic devises [1–6]. In this context, development of facile and convenient methods to obtain thieno[3,2-*b*]indole compounds from available starting substrates is of importance for further engendering new thieno[3,2-*b*]indole-based optical and electronic organic materials.

Thiophene derivatives, bearing amino groups at β-atoms (C-3 or C-3,4 positions), have found wide application in the synthesis of thiophene-fused nitrogen heterocycles [7]. Among them, 2-unsubstituted 3-aminothiophenes (3-ATs) have been used as primary enamine substrates, *e.g.*, reaction of 3-ATs with α-anilinoacetophenones affords thieno[3,2-*b*]pyrroles [8], while their condensation with 1,3-dicarbonyl compounds gives thieno[3,2-*b*]pyridines [9–13]. In regard to synthetic accessibility of 3-ATs, there are known several methods for their preparation, including reduction of 3-nitro- [14,15] or 3-azidothiophenes [16,17], reaction of dihydrothiophen-3(2*H*)-ones with hydroxylamine hydrochloride [18,19], copper-catalyzed amination of 3-bromothiophenes [20,21] or easy decarboxylation of 3-aminothiophene-2-caboxylic acids, that can be obtained from the corresponding 3-aminoesters [22,23].

Besides using 3-aminothiophene unit as three-atom CCN synthon, it can be also considered as two-atom C2 synthon for the construction of thiophene-annulated molecules. Thus, due to enamine character of 3-AT moiety, its protonation proceeds at C-2 position to form thiophene-3(2*H*)-iminium cation **A** [18], which is able to further react with nucleophiles, *e.g.*, treatment of the simplest 3-aminothiophene with acetic acid gives di(thiophen-3-yl)amine through the iminium intermediate formation, followed by its action with initial amine [24]. Therefore, we supposed that 3-AT fragment can be utilized as synthetic equivalent of thiophene-3(2*H*)-one **B** for annulation reactions, which are started from nucleophilic attack at C-3 position (Scheme 1).

Recently, we have described an efficient approach to the synthesis of 2-(hetero)aryl-substituted thieno[3,2-*b*]indoles from 5-(hetero)arylthiophene-3(2*H*)-ones, obtained from the corresponding 3-hydroxythiophene-2-carboxylates, and arylhydrazines *via* the Fischer indolization reaction [25] (Scheme 2). Herein, we wish



Scheme 1. C2-Protonation of 3-aminothiophene moiety.

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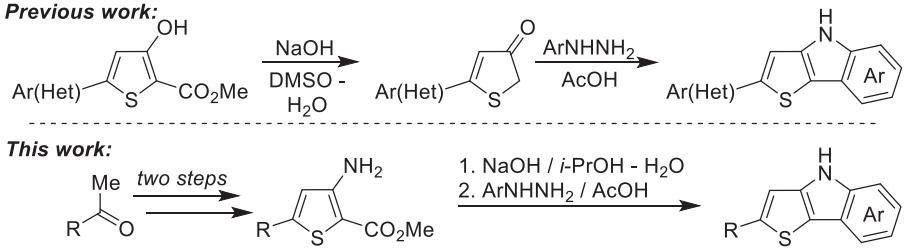


Scheme 2. Previous and current synthetic strategies to construct thieno[3,2-*b*]indoles.

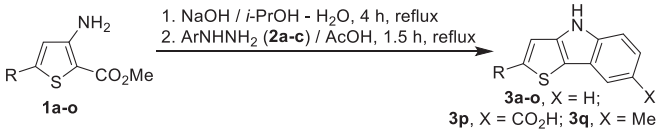
to report an alternative method for the preparation of 2-substituted thieno[3,2-*b*]indoles directly from 5-substituted methyl 3-aminothiophene-2-carboxylates through *in situ* formation of 3-aminothiophenes, followed by their involvement in the Fischer indole synthesis (Scheme 2). In turn, the required 3-aminothiophene-2-carboxylates were prepared in two steps starting from the corresponding methyl ketones (Scheme 2, R = aryl, thien-2-yl or styryl) by their sequential treatment with the Vilsmeier reagent ($POCl_3$-DMF complex) and hydroxylamine hydrochloride to form 3-substituted 3-chloroacrylonitriles [26], which further reacted with methyl thioglycolate in the presence of NaOMe in a methanol solution [27] according to the Fiesselmann method for thiophene ring construction [28] (for experimental details see ESI).

Firstly, we studied behavior of 5-phenyl-3-aminothiophene **1aA**, used as a model compound, in the Fischer reaction with phenylhydrazine **2a**. Amine **1aA** is a known compound [19,22], and it was prepared by us from 3-aminoester **1a** in 95% yield *via* its treatment with NaOH (4 equiv.) in *i*-PrOH-H_2O (9:1, v/v) solution at reflux for 4 h, followed by neutralization of the reaction mixture with acetic acid and its heating at 40 °C for 30 min to perform decarboxylation of the intermediate aminoacid. We found that treatment of substrate **1aA** with phenylhydrazine **2a** (1.5 equiv.) in glacial acetic acid solution at reflux for 1 h give the desired product **3a** in 71% yield (Scheme 3), which confirmed our assumption to use 3-aminothiophenes instead of thiophene-3(2*H*)-ones to construct thieno[3,2-*b*]indoles *via* the Fischer indolization. The presumable mechanism for this transformation includes initial formation of iminium salt **1aB**, its condensation with **2a** to give phenylhydrazone **1aC**, and next Fischer indolization to obtain the desired product **3a** (Scheme 3).

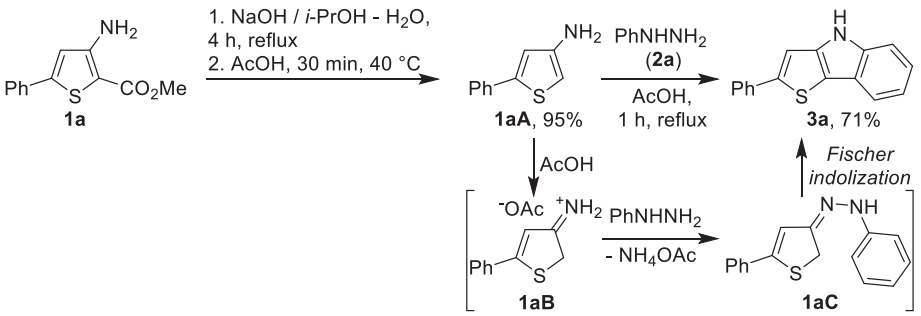
The saponification of 3-aminoester **1a** was carried out with NaOH in aqueous *i*-PrOH instead of aqueous DMSO, which had been previously used as a solvent to saponify the similar 3-hydroxythiophene-2-carboxylate [25], since in that case a higher temperature had been needed to proceed reaction due to initial formation of the sodium 2-(methoxycarbonyl)thiophen-3-olate. In this context, we decided to perform a direct transformation of 3-aminothiophene-2-carboxylates **1** to thieno[3,2-*b*]indoles **3** without isolation of the intermediate 3-aminothiophenes. To this end, ester **1a** was saponified and the reaction mixture was concentrated under reduced pressure. The obtained residue, containing sodium salt of amino acid together with NaOH excess, was treated with phenylhydrazine **2a** (1.5 equiv.) in glacial acetic acid solution at reflux for 1.5 h to afford compound **3a** in 69% yield. In the same manner, other 3-aminothiophene-2-carboxylates **1b-n**, bearing various aromatic as well as thien-2-yl fragments at C-5 position, were successfully converted to 2-substituted thieno[3,2-*b*]indoles **3b-n** in 50–77% yields (Scheme 4, Table 1). Thus, in comparison with our previous protocol for the synthesis of thieno[3,2-*b*]indoles **3** from the thiophene-3(2*H*)-ones [25], the current approach provided us to obtain product **3a-c,e,n** in higher yields (Table 1, entries 1–3,5,14), while comparable yield was received for compound **3d** (Table 1, entry 4).

During this study, we also were able to synthesize 2-styryl-substituted thieno[3,2-*b*]indoles. To this end, 3-aminothiophene-2-carboxylate **1o** with styryl group at C-5 position was prepared starting from benzylideneacetone in two steps similar to esters **1a-n** (for experimental details see ESI). The standard saponification of ester **1o**, followed by treatment with phenylhydrazine **2a** as well as 4-carboxy- and 4-methylphenylhydrazines **2b** and **2c** afforded 2-styryl derivatives **3o-q** in 42%, 40% and 44% yields, respectively (Scheme 4, Table 1, entries 15–17). It should be noted, that all thieno[3,2-*b*]indoles **3a-q**, prepared using this approach, were isolated in analytically pure form by filtration of the reaction mixtures without any additional purification.

In summary, we have demonstrated new synthetic application of 3-aminothiophenes as reagents for the preparation of thieno



Scheme 4. Synthesis of 2-substituted thieno[3,2-*b*]indoles **3a-q.**



Scheme 3. Transformation of amine **1aA** to thieno[3,2-*b*]indole **3a** and its possible mechanism.

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Table 1
Substrate scope of 2-substituted thieno[3,2-*b*]indoles **3**.

Entry	3-Aminoester **1** (R)	**3** (yield %)
1	**1a** (phenyl)	**3a** (69/58[a])
2	**1b** (4-fluorophenyl)	**3b** (70/65[a])
3	**1c** (4-bromophenyl)	**3c**[b] (67/61[a])
4	**1d** (2-methoxyphenyl)	**3d** (65/66[a])
5	**1e** (2-bromophenyl)	**3e** (73/38[a])
6	**1f** (4-chlorophenyl)	**3f** (71)
7	**1g** (4-methylphenyl)	**3g** (57)
8	**1h** (3-methoxyphenyl)	**3h** (51)
9	**1i** (4-(*tert*-butyl)phenyl)	**3i** (62)
10	**1j** (4-ethoxyphenyl)	**3j**[b] (52)
11	**1k** (naphthalen-2-yl)	**3k**[b] (72)
12	**1l** (2,5-dimethylphenyl)	**3l** (50)
13	**1m** (3,4-dimethoxyphenyl)	**3m** (76)
14	**1n** (thien-2-yl)	**3n** (77/72[a])
15	**1o** (styryl)	**3o** (42)
16	**1o** (styryl)	**3p** (40)
17	**1o** (styryl)	**3q** (44)

[a] Yield of product **3** previously obtained in reaction of the corresponding thiophene-3(2*H*)-ones with $PhNHNH_2$ [25].
[b] A mixture of *N*,*N*-dimethylacetamide and AcOH (1:1, v/v) was used as a solvent for the second step due to poor solubility of the intermediated sodium salt in AcOH.

[3,2-*b*]indole derivatives *via* the Fischer indolization reaction. To this end, 5-substituted 3-aminothiophenes, *in situ* generated from the corresponding readily available 3-aminothiophene-2-carboxylates, were treated with arylhydrazines in glacial acetic acid solution, similarly to the thiophene-3(2*H*)-one derivatives [25], to afford 2-substituted thieno[3,2-*b*]indoles. Thus, the present method is able to provide easy access to thieno[3,2-*b*]indole-based compounds directly from the 3-aminothiophene-2-carboxylate-containing sources, and further study of its synthetic potential is in progress now.

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Appendix A. Supplementary data

Supplementary data (experimental procedures, characterization data for new compounds, copies of ^{1}H and ^{13}C NMR spectra) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151185.

References

[1] X.-H. Zhang, Y. Cui, R. Katoh, N. Koumura, K. Hara, J. Phys. Chem. C 114 (2010) 18283–18290.
[2] H. Huang, M. Qiu, Q. Li, S. Liu, X. Zhang, Z. Wang, N. Fu, B. Zhao, R. Yang, W. Huang, J. Mater. Chem. C 4 (2016) 5448–5460.
[3] I. Jeong, S. Chae, A. Yi, J. Kim, H.H. Chun, J.H. Cho, H.J. Kim, H. Suh, Polymer (Guildf) 109 (2017) 115–125.
[4] L. Liu, Y. Wu, M. Li, X. Zong, Z. Sun, M. Liang, S. Xue, Chem. Commun. 54 (2018) 14025–14028.
[5] A.S. Steparuk, R.A. Irgashev, G.L. Rusinov, E.V. Krivogina, P.I. Lazarenko, S.A. Kozyukhin, Russ. Chem. Bull. 68 (2019) 1208–1212.
[6] X. Zhou, J. Lu, H. Huang, Y. Yun, Z. Li, F. You, B. Zhao, T. Qin, D. Gao, W. Huang, Dyes Pigm. 160 (2019) 16–24.
[7] C. Paulmier, Sulfur Rep. 19 (1996) 215–284.
[8] V.I. Shvedov, A.N. Grinev, V.K. Vasil'eva,, Chem. Heterocycl. Compd. 6 (1970) 257–258.
[9] P.I. Abramenko, Chem. Heterocycl. Compd. 7 (1971) 436–438.
[10] R. Benoit, G. Dupas, J. Bourguignon, G. Quéguiner, Synthesis (Stuttg) 1987 (1987) 1124–1126.
[11] M. Berkaoui, F. Outurquin, C. Paulmier, Tetrahedron 54 (1998) 9055–9066.
[12] D. Brugier, F. Outurquin, C. Paulmier, Tetrahedron 56 (2000) 2985–2993.
[13] A. Mityuk, S. Kolodych, S. Mytnyk, Y. Dmytriv, D. Volochnyuk, P. Mykhailiuk, A. Tolmachev, Synthesis (Stuttg) 2010 (2010) 2767–2770.
[14] R.L. Elliott, P.J. O'hanlon, N.H. Rogers, Tetrahedron 43 (1987) 3295–3302.
[15] G. Malicorne, J. Bompart, L. Giral, E. Despaux, Eur. J. Med. Chem. 26 (1991) 3–11.
[16] P. Spagnolo, P. Zanirato, S. Gronowitz, J. Org. Chem. 47 (1982) 3177–3180.
[17] V.N. Yarovenko, N.G. Smirnova, V.N. Bulgakova, I.V. Zavarzin, M.M. Krayushkin, Russ. J. Org. Chem. 39 (2003) 1161–1163.
[18] E. Campaigne, P.A. Monroe, J. Am. Chem. Soc. 76 (1954) 2447–2450.
[19] J.M. Barker, P.R. Huddleston, M.L. Wood, Synth. Commun. 32 (2002) 2565–2568.
[20] X. Zeng, W. Huang, Y. Qiu, S. Jiang, Org. Biomol. Chem. 9 (2011) 8224.
[21] S. Fantasia, J. Windisch, M. Scalone, Adv. Synth. Catal. 355 (2013) 627–631.
[22] I. Abdillahi, G. Revelant, Y. Datoussaid, G. Kirsch, Synthesis (Stuttg) 2010 (2010) 2543–2546.
[23] F. Derridj, K. Si Larbi, J. Roger, S. Djebbar, H. Doucet, Tetrahedron 68 (2012) 7463–7471.
[24] F. Outurquin, C. Paulmier, Tetrahedron Lett. 34 (1993) 5719–5722.
[25] R.A. Irgashev, A.S. Steparuk, G.L. Rusinov, Org. Biomol. Chem. 16 (2018) 4821–4832.
[26] J. Liebscher, B. Neumann, H. Hartmann, J. Für Prakt. Chem. 325 (1983) 915–918.
[27] H. Hartmann, J. Liebscher, Synthesis (Stuttg) 1984 (1984) 275–276.
[28] H. Fiesselmann, G. Pfeiffer, Chem. Ber. 87 (1954) 848–856.

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