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The synthesis of thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acids using the Fischer indolization reaction

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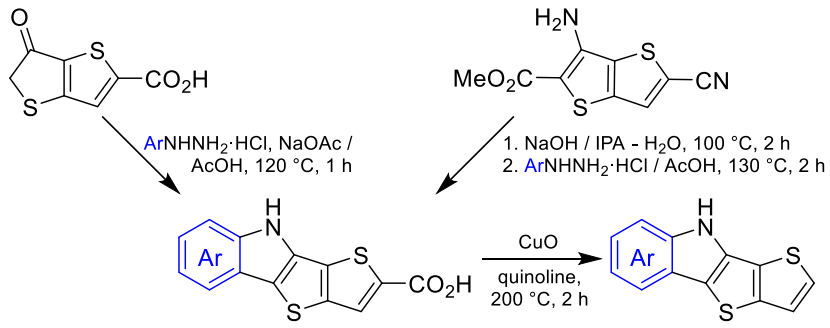
Abstract

Six thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acids were readily synthesized through two distinct ways, both employing Fischer indolization as a key step. In the first way, 6-oxo-5,6-dihydrothieno[3,2-*b*]thiophene-2-carboxylic acid reacted with arylhydrazines hydrochlorides to afford the desired carboxylic acids in 29-82% yields. The second pathway involved the hydrolysis of methyl 3-amino-5-cyanothieno[3,2-*b*]thiophene-2-carboxylate, followed by arylhydrazine hydrochlorides treatment to give the products in 34-73% yields. The starting materials were prepared from dimethyl 3-nitrothiophene-2,5-dicarboxylate in 3 and 5 steps. It was also shown that upon decarboxylation, the 2-unsubstituted thieno[2',3':4,5]thieno[3,2-*b*]indoles are formed in yields of 53-96%.



Keywords: thieno[2',3':4,5]thieno[3,2-*b*]indole, thieno[3,2-*b*]thiophene, arylhydrazines, the Fischer indole synthesis

Introduction

Thienoindoles constitute a family of tricyclic N,S-containing heteroaromatics having thiophene-indole ring-fused system, which attracted the interest of researchers worldwide due to their diverse practical properties and applications.[1] Among them, thieno[3,2-b]indoles found much application for the elaboration of photo- and electroactive materials, thanks to their planar, π-conjugated and highly electron-rich structure.[2,3] Indeed, the thieno[3,2-b]indole ring-system has gained widespread use in engineering organic photovoltaic materials, specifically thieno[3,2-b]indole-based D-π-A dyes for the dye-sensitized solar cells,[4–10] semiconductor materials for perovskite solar cells[11–13] and polymer solar cells[14–16] were previously reported in the literature.

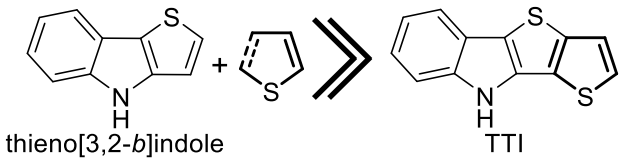


Figure 1. The structure of thieno[3,2-b]indole and thieno[2',3':4,5]thieno[3,2-b]indole

In turn, thieno[2',3':4,5]thieno[3,2-b]indole (TTI) can be considered as a π-extended version of thieno[3,2-b]indole, characterized by the formal addition of an extra thiophene unit to thieno[3,2-b]indole structure (Figure 1), which affects its aromaticity and π-conjugation. Taking into account this fact, TTI derivatives seem promising for application in the field of organic electronics. Thus, TTI is a suitable unit for the design of D-π-A dye molecules with enhanced intramolecular charge transfer compared to their thieno[3,2-b]indole analogs.[17] In addition, the integration of TTI core into molecules of organic semiconductors can improve their mobility of charge carriers by increasing intermolecular S-S interactions[18,19] in its thieno[3,2-b]thiophene part. For example, two types of non-fullerene acceptor materials based on TTI scaffold, namely compounds TTI-2F, TTI-2Cl and TIT-H, TIT-EH, shown in Figure 2, were synthesized and demonstrated promising photovoltaic performance, able to obtain devices with power conversion efficiency of 10.67% for **TTI-2F**[20] and 13.32% for **TIT-EH**.[21] Therefore, TTIs are important targets for organic chemistry.

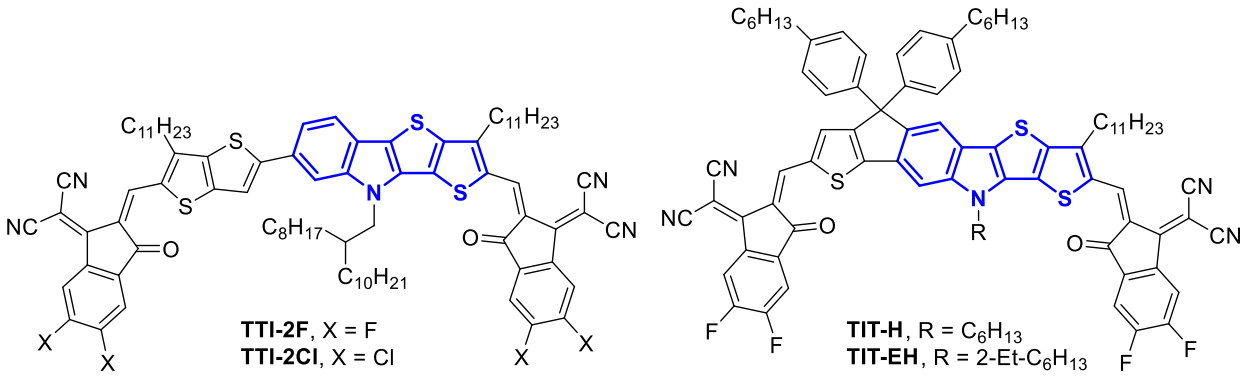
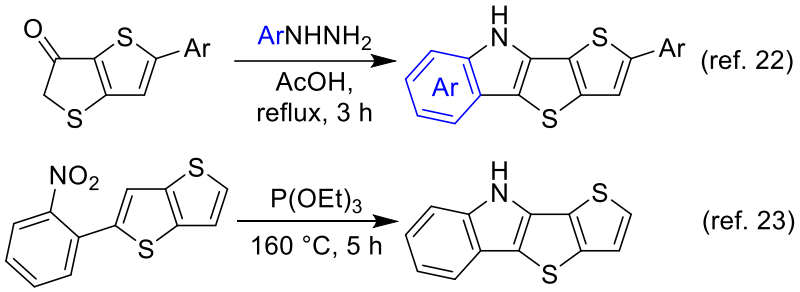


Figure 2. TTI-based non-fullerene acceptor materials

In overall, there are few reports in the literature on the chemistry of TTI compounds. Thus, we have described the TTI ring-system for the first time in 2019,[22] namely, 2-aryl-substituted TTI derivatives were prepared in 45–84% yields by the reaction of thieno[3,2-*b*]thiophene-3(2*H*)-ones with arylhydrazines using the

Fischer indole synthesis. The simplest thieno[2',3':4,5]thieno[3,2-*b*]indole was synthesized from 2-(2-nitrophenyl)thieno[3,2-*b*]thiophene by its treatment with $P(OEt)_3$ using the Cadogan cyclization, in 58% yield (Scheme 1).[23] It should be also noted that the Cadogan cyclization was utilized to prepare the key intermediates of the mentioned above TTI-cored organic materials.[17,20,21]



Scheme 1. The known methods for the construction of TTI molecules

In this work, we wish to report the synthesis of thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acids using Fischer indolization, as well as the synthesis of 2-unsubstituted TTIs by decarboxylation of these carboxylic acids (Figure 3).

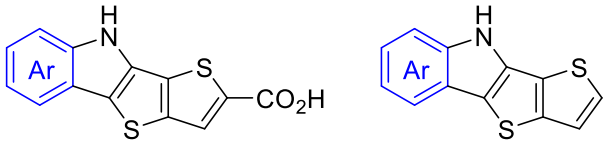
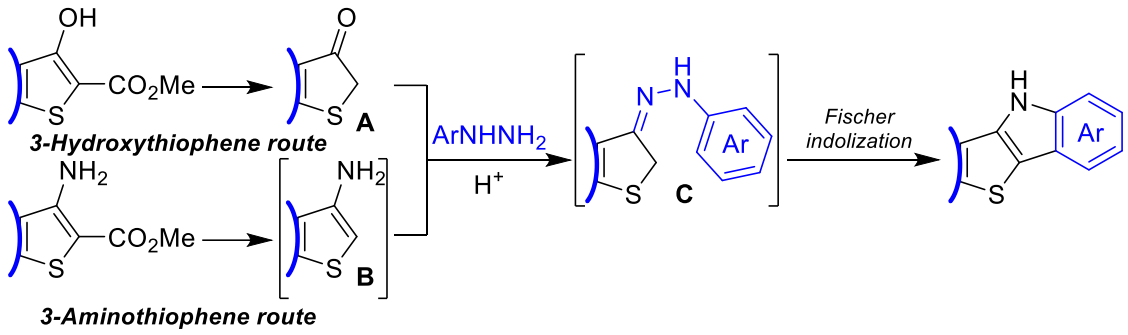


Figure 3. The structure of the synthesized TTI derivatives

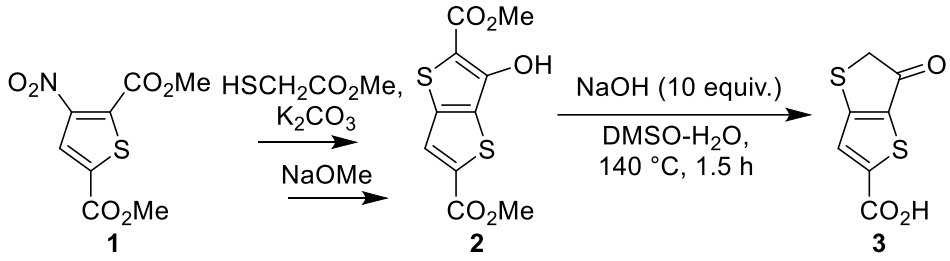
Results and Discussion

Fischer indolization is a very convenient reaction for constructing thieno[3,2-*b*]indole molecules. Thus, we previously proposed a practical strategy for the synthesis of diverse thieno[3,2-*b*]indoles and their fused analogues according to the Fischer indole synthesis. Within this synthetic strategy, we developed two routes to the thieno[3,2-*b*]indole-cored molecules using Fischer indolization of arylhydrazones **C**, which were formed on the spot by reacting either thiophene-3(2*H*)-ones **A**[24–26] or 3-aminothiophenes **B**[27–31] with arylhydrazines in an acidic medium. The thiophene-3(2*H*)-ones **A** are prepared starting from 3-hydroxythiophene-2-carboxylates, while 3-aminothiophenes **B** are generated from 3-amitothiophene-2-carboxylates, and used without their isolation in the reaction with arylhydrazines (Scheme 2). Thus, 3-amitothiophene-2-carboxylates were directly converted to thieno[3,2-*b*]indoles using one-pot two-step procedure.



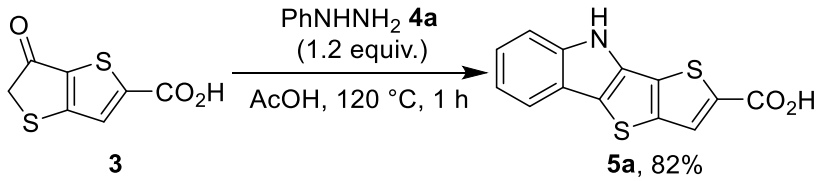
Scheme 2. Fischer indolization based routes to thieno[3,2-*b*]indole framework

In this study, we used both routes to synthesize thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acids. To follow the 3-hydroxythiophene route, we chose thieno[3,2-*b*]thiophene-2,5-dicarboxylate **2** as an accessible substrate with thieno[3,2-*b*]thiophene core that is suitable for the subsequent construction of TTI molecules. Indeed, an effective protocol for the synthesis of compound **2** based on nucleophilic substation of the nitro-group in dimethyl 3-nitrothiophene-2,5-dicarboxylate (**1**) with methyl thioglycolate in the presence of K_2CO_3 was described in our recent work.[32] In turn, thiophene-3(2*H*)-one **3** was obtained in 75% yield from ester **2** by its saponification in the presence of NaOH excess in a mixture of DMSO-water (Scheme 3).



Scheme 3. The synthesis of fused thiophene-3(2*H*)-one **3**

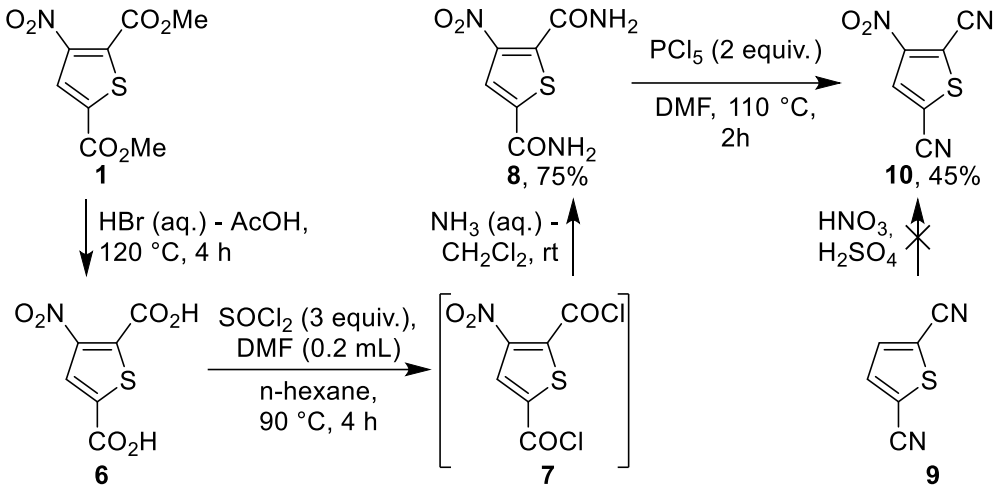
To evaluate the efficiency of the Fischer indolization method using thiophene-3(2*H*)-one **3** as a carbonyl substrate, we tested its reaction with phenylhydrazine (**4a**). The experiment was carried out at heating reagents in glacial acetic acid solution at 120 °C for 1 h to give TTI-2-carboxylic acid **5a** in 82% yield (Scheme 4). Product **5a** was obtained in the same yield, when an equimolar mixture of phenylhydrazine hydrochloride and NaOAc was used instead of phenylhydrazine base.



Scheme 4. The synthesis of TTI-2-carboxylic acid **5a**

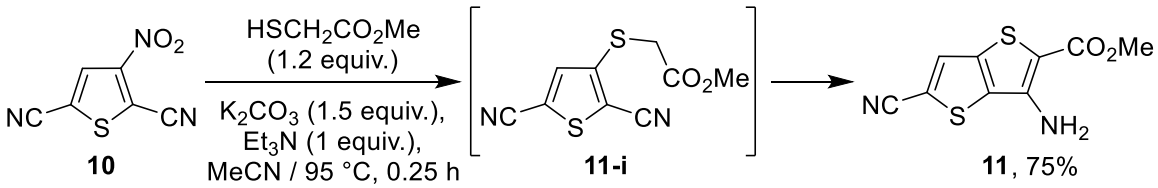
The construction of TTI molecules was also carried out through the 3-aminothiophene route, show in Scheme 1. To achieve this, we first synthesized 3-nitrothiophene-2,5-dicarbonitrile (**10**), which is a necessary

precursor for constructing 3-amino-substituted thieno[3,2-*b*]thiophene substrate. It is important to note that we were unable to obtain compound **10** by direct nitration of thiophene-2,5-dicarbonitrile (**9**), in contrast to the previous synthesis of 3-nitrothiophene-2,5-dicarboxylate **1** by the nitration of dimethyl thiophene-2,5-dicarboxylate.[32] In this regard, the synthesis of required dinitrile **10** was realized starting from available 3-nitrothiophene-2,5-dicarboxylate **1** in 4 steps (Scheme 5). Diester **1** was hydrolyzed in a mixture hydrobromic acid and glacial acetic acid to form dicarboxylic acid **6** followed by its treatment with $SOCl_2$ to obtain dicarbonyl dichloride **7**. Dicarboxamide **8** was formed by treatment of substrate **7** with excess of aqueous ammonia. Product **8** was obtained in 75% yield based on starting diester **1**, while intermediates **6** and **7** were used without purification. The dehydration of dicarboxamide **8** was performed with PCl_5 in a DMF solution to give desired dinitrile **10** in 45% yield.



Scheme 5. The synthesis of 3-nitrothiophene-2,5-dicarbonitrile (**10**)

Thieno[3,2-*b*]thiophene compound **11** was synthesized from 3-nitrothiophene **10** in 75% yield by its reaction with methyl thioglycolate in the presence of K_2CO_3 and Et_3N (Scheme 6). It should be noted that nucleophilic replacement of the nitro group in substrate **10** by -SCH_2CO_2Me fragment in the presence of K_2CO_3 proceeds smoothly. However, it became clear that the addition of Et_3N was crucial for next successful cyclization of intermediate **11-i**. This is evidenced by the fact that in the experiment with K_2CO_3 alone, we obtained a mixture of product **11** and intermediate **11-i**, which emphasizes the importance of Et_3N.

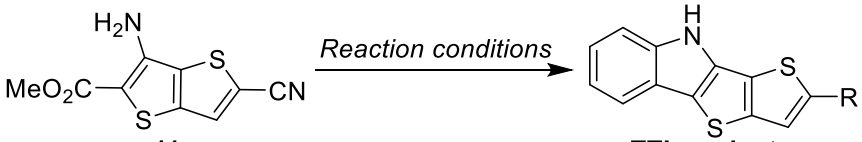


Scheme 6. The synthesis of amino-substituted thieno[3,2-*b*]thiophene derivative **11**

Given the presence of a cyano group in molecule **11**, we naturally expected to obtain 2-cyano-substituted TTI derivatives using this substrate for the construction of the TTI scaffold *via* Fischer indolization following the aforementioned 3-aminothiophene route in Scheme 1. Thus, the typical procedure[27] previously used to convert 3-aminothiophene-2-carboxylates to thieno[3,2-*b*]indoles was studied first to achieve the same conversion of

ester **11**. To this end, ester **11** was heated with NaOH (4 equiv.) in a mixture of isopropanol (IPA) and water to carry out its saponification. A reaction mixture was concentrated under reduced pressure, the residue was dissolved in glacial acetic acid and treated with phenylhydrazine hydrochloride. However, it was found that instead of the expected TTI-2-carbonitrile, TTI-2-carboxylic acid **5a** is only formed under these reaction conditions, in yield of 73% (Table 1, entry 1). It became clear that both methoxycarbonyl and cyano groups in molecule **11** undergo cleavage to the carboxylate function in the presence of alkali. Unfortunately, we were unable to find suitable reaction conditions for the selective hydrolysis of CO_2Me group in ester **11**, which would allow the cyano group to be retained in the structure. A mixture of TTI-2-carboxylic acid **5a** and its carboxamide **5a'** was obtained in the experiments, wherein for the saponification of ester **11** was used small excess of NaOH (1.1 equiv.) at 100 °C for 0.5 h (Table 1, entry 2), or LiOH (4 equiv.) at ambient temperature for 24 h (Table 1, entry 4). Ester **11** remained unchanged upon treatment with NaOH (4 equiv.) at room temperature for 4 h (Table 1, entry 3) as well as during attempts to hydrolyze it under acidic reaction conditions (Table 1, entries 4 and 6).

Table 1. Attempts to synthesize 2-cyano-substituted TTI from ester **11**

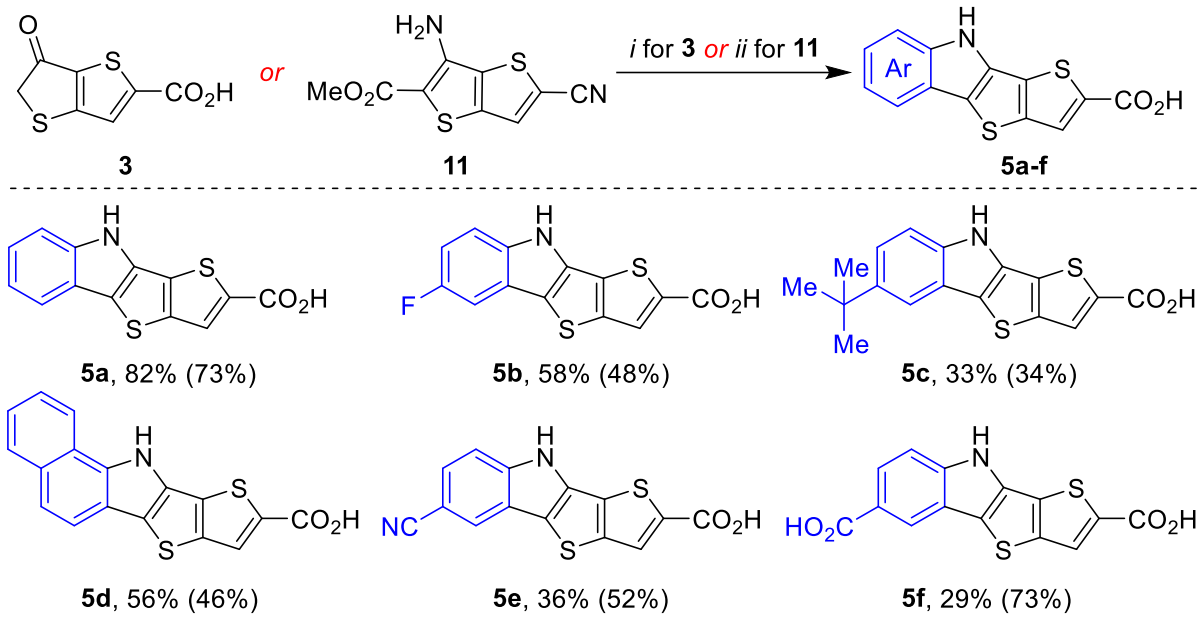


11 **TTI product**

Entry	Reaction conditions	TTI product
1	1. NaOH (4 equiv.) / IPA - H_2O, 100 °C, 2 h 2. $PhNHNH_2$·HCl **4a** (1.2 equiv.) / AcOH, 130 °C, 2 h	**5a**, R = CO_2H (73%)
2	1. NaOH (1.1 equiv.) / IPA - H_2O, 100 °C, 0.5 h 2. $PhNHNH_2$·HCl **4a** (1.2 equiv.) / AcOH, 130 °C, 2 h	**5a**, R = CO_2H **5a'**, R = $CONH_2$
3	1. NaOH (4 equiv.) / IPA - H_2O, rt, 4 h 2. $PhNHNH_2$·HCl **4a** (1.2 equiv.) / AcOH, 130 °C, 2 h	no reaction
4	1. LiOH (4 equiv.) / IPA - H_2O, rt, 24 h 2. $PhNHNH_2$·HCl **4a** (1.2 equiv.) / AcOH, 130 °C, 2 h	**5a**, R = CO_2H **5a'**, R = $CONH_2$
5	$PhNHNH_2$ **4a** (1.2 equiv.) / HCO_2H, 120 °C, 2 h	no reaction
6	1. CF_3CO_2H, rt, 24 h 2. $PhNHNH_2$ **4a** (1.2 equiv.) / CF_3CO_2H-AcOH, 130 °C, 2 h	no reaction

Taking into account the above, we used both thieno[3,2-*b*]thiophene derivatives **3** and **11** to synthesize TTI-2-carboxylic acids *via* the Fischer indolization method (Scheme 7). Treatment of keto-acid **3** with a mixture of arylhydrazines hydrochlorides **4b-f** (1.2 equiv.) and NaOAc (1.2 equiv.) in a solution of glacial acetic acid allowed us to obtain TTI-2-carboxylic acids **5b-f** in 29-82% yields. In addition, compounds **5b-f** were also prepared from ester **11** in 33–73% yields, shown in parentheses in Scheme 7, by saponification of ester **11** with NaOH followed by treatment of the resulting sodium salt with arylhydrazines **4b-f** in glacial acetic acid, as was shown for derivative **5a**. Thus, keto-acid **3** appears to be a more suitable substrate for the synthesis of TTI-2-carboxylic acids **5** compared to ester **11**, since these products are generally obtained in higher yields from substrate **3** than from **11**, except compounds **5e,f** when 4-cyanophenylhydrazine **4e** and 4-hydrazinobenzoic acid **4f** are used. Moreover, it is evident that keto-acid **3** is a more accessible compound than ester **11**, since keto-acid **3** was prepared from dimethyl 3-nitrothiophene-2,5-dicarboxylate (**1**) in 3 steps, whereas ester **11** was prepared from the same starting material in 5 steps. However, ester **11** can be utilized for the preparation of TTI-2-carboxylic

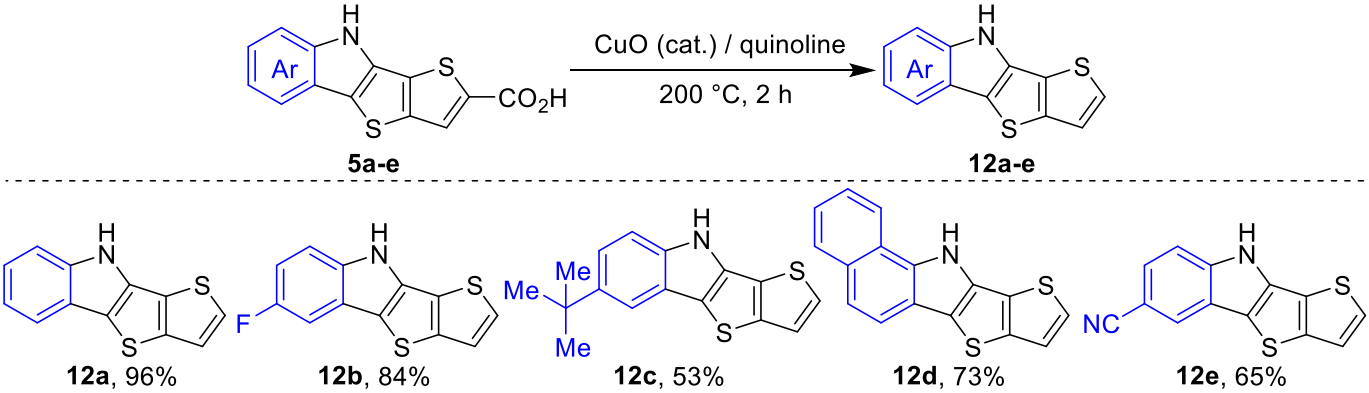
acids bearing electron-withdrawing groups in the benzene ring of their framework due to the higher yields of products **5e,f** from ester **11** compared to keto-acid **3**.



i: ArNHNH$_2$·HCl **4a-f** (1.2 equiv.), NaOAc (1.2 equiv) / AcOH, 120 °C, 1 h.
ii: NaOH (4 equiv.) / IPA - H$_2$O (9:1, v/v), 100 °C, 2 h; ArNHNH$_2$·HCl **4a-f** (1.2 equiv.) / AcOH, 130 °C, 2 h.

Scheme 7. The synthesis of TTI-2-carboxylic acids **5**, scope and yields of products

We were also able to perform the decarboxylation of TTI-2-carboxylic acids **5a-f** (Scheme 8). To this end, a mixture of acid **5a** and catalytic amounts of CuO was heated in a quinoline solution at 200 °C for 2 h affording TTI **12a** in 96% yield. In the same manner, TTI derivatives **12b-e** were obtained from carboxylic acids **5b-f** in 53-84% yields. It should be noted that compound **12a** was previously synthesized by the Cadogan cyclization of 2-(2-nitrophenyl)thieno[3,2-*b*]thiophene, which was prepared by the Stille cross-coupling reaction of 1-iodo-2-nitrobenzene and 2-Me$_3$Sn-thieno[3,2-*b*]thiophene.[23] In contrast, our approach allows the synthesis of TTIs **12** without the use of transition metal-catalyzed reactions, toxic organotin and organophosphorus(III) compounds.



Scheme 8. The decarboxylation of TTI-2-carboxylic acids **5**, scope and yields of products **12**

Conclusions

In summary, we have presented an efficient strategy for the synthesis of TTI-2-carboxylic acids, which is based on the key step of fusing the indole moiety onto the thieno[3,2-*b*]thiophene scaffold by the Fischer indolization reaction, employing various arylhydrazines. Within this approach, two procedures for the synthesis of these acids were elaborated from either fused thiophene-3(2*H*)-one **3** or fused 3-aminothiophene-2-carboxylate **11**. It is important to note, that both substrates, **3** and **11**, were prepared starting from dimethyl 3-nitrothiophene-2,5-dicarboxylate, avoiding the use of halogen-containing thiophene derivatives, that increasing the synthetic attractiveness of the present approach. The obtained TTI-2-carboxylic acids were also shown to undergo the decarboxylation, providing access to the corresponding 2-unsubstituted TTIs. This convenient and halogen-free synthetic access to the functionalized TTI derivatives provides a valuable basis for the future applications of TTI molecules in various fields, including medicinal chemistry and materials science.

Experimental Section

General. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained on Bruker DRX-400 and AVANCE-500 spectrometers with Me_4Si as an internal standard for ^{1}H and ^{13}C NMR or C_6F_6 as an internal standard for ^{19}F NMR. Mass spectrometry was performed using a high-resolution Q-TOF LC-MS/MS spectrometer. Melting points were determined on Boetius combined heating stages and were not corrected. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Compound **2** was synthesized starting from dimethyl 3-nitrothiophene-2,5-dicarboxylate according to our previously described procedure.[32] Phenylhydrazine (**4a**), 4-fluorophenylhydrazine (**4b**), 4-(*tert*-butyl)phenylhydrazine (**4c**), naphthalen-1-ylhydrazine (**4d**), 4-cyanophenylhydrazine (**4e**), 4-hydrazinobenzoic acid (**4f**) (hydrochlorides) were used in this study.

Procedure for the synthesis of 6-oxo-5,6-dihydrothieno[3,2-*b*]thiophene-2-carboxylic acid (3). NaOH (8.41 g, 210 mmol) in water (30 ml) was added in one portion to the dimethyl 3-hydroxythieno[3,2-*b*]thiophene-2,5-dicarboxylate (5.73g, 21 mmol) in DMSO (60 ml) and the obtained solution was flushed with argon; then it was stirred and heated at 140 °C for 1.5 h under an argon atmosphere. The reaction mixture was cooled to room temperature, poured into water (75 ml) with conc. HCl (18 mL, 37% wt.) and extracted with CH_2Cl_2 (50 ml). The organic extract was washed with saturated aqueous $NaHCO_3$ solution (15 ml), water (2 × 25 ml), and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by crystallization from 50% aqueous EtOH (25 ml).

To obtain single-valued ^{1}H and ^{13}C NMR spectra of compound **3**, the NMR measurements were carried out in DMSO-d_6 solution, where the exclusively enol form of these compounds was detected, since a tautomeric mixture of both 6-oxo-5,6-dihydrothieno[3,2-*b*]thiophene-2-carboxylic acid (ketonic) and 6-hydroxythieno[3,2-*b*]thiophene-2-carboxylic acid (enolic) forms of **3** was observed in its ^{1}H NMR spectrum recorded in a $CDCl_3$ solution.

6-Oxo-5,6-dihydrothieno[3,2-*b*]thiophene-2-carboxylic acid (3). Brown powder, yield 3.16 g (75%), m.p. 210-212 °C (50% aqueous EtOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.22 (br.s, 1H), 10.46 (s, 1H), 8.00 (s, 1H), 6.68 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.4, 147.3, 136.2, 135.1, 134.5, 127.0, 104.8. HRMS (ESI) calcd for $C_7H_3O_3S_2$ m/z 198.9529 $[M-H]^-$, found m/z 198.9528 $[M-H]^-$.

Step to step procedure for the synthesis of 3-nitrothiophene-2,5-dicarboxamide (8).
*3-Nitrothiophene-2,5-dicarboxylic acid (**6**).* 3-nitrothiophene-2,5-dicarboxylate **1** (30 g, 0.12 mol) was added to a mixture of conc. HBr (40 mL, 48% wt., 0.36 mol) and glacial AcOH (50 mL). The obtained mixture was stirred and heated at 120 °C for 3 h under reflux. After this time, the reflux condenser was replaced with a distillation condenser and approximately 40 ml of distillate (mainly water and methyl acetate) was carefully distilled off. Then, conc. H_2SO_4 (20 mL, 96% wt.) is added dropwise to the reaction mixture while cooling with ice, and it was kept under stirring and ice cooling for 2 h. The precipitate was filtered, washed with conc. HCl (3 × 15 ml, 37% wt.) and air-dried to obtain acid **6** in almost quantitative yield.
*3-Nitrothiophene-2,5-dicarbonyl dichloride (**7**).* The air-dried acid **6** was added portion wise to a stirred mixture of $SOCl_2$ (27 mL, 0.36 mol), DMF (0.2 mL) and hexane (30 mL) at room temperature. The reaction mixture was stirred and heated at 90 °C for 4 h, and excess of $SOCl_2$ together with hexane were distilled off under normal pressure. The dark-brown syrupy residue was dissolved in CH_2Cl_2 (50 ml), passed through silica gel (30 mL, 0.032-0.063 mm) on glass filter, and washed CH_2Cl_2 (50 ml), to obtain a yellowish solution of dichloride **7**.
*3-Nitrothiophene-2,5-dicarboxamide (**8**).* The solution of compound **7** was added dropwise to a stirred mixture of aq. NH_3 (35 mL, 13.5 M) and water (175 ml) while cooling with ice. The reaction mixture was evaporated under reduced pressure to remove CH_2Cl_2 phase. The formed precipitate was filtered, washed with hot water and dried at 110 °C to give compound **8** in analytically pure form.
3-Nitrothiophene-2,5-dicarboxamide (8). White microcrystals, yield 19.6 g (75%), m.p. 283-284 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 8.34 (s, 1H), 8.31 (s, 2H), 8.10 (s, 1H), 7.89 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.0, 160.7, 143.0, 142.2, 139.0, 123.2. HRMS (APCI) calcd for $C_6H_4N_3O_4S$ m/z 213.9928 $[M-H]^-$, found m/z 213.9929 $[M-H]^-$.

Procedure for the synthesis of 3-nitrothiophene-2,5-dicarbonitrile (10). Crashed PCl_5 (25 g, 0.12 mol) was added in portion wise to DMF (100 mL) under ice cooling and stirred until the solid was completely dissolved. Then compound **8** (12.9 g, 0.06 mol) was added to this solution, and the obtained mixture was stirred and heated at 110 °C for 2 h. During this process, HCl gas was released and the solution darkens. The reaction mixture was poured into a cold water (600 mL), and the formed precipitate of colorless crystals was filtered, washed with water and dried to give dinitrile **10** in analytically pure form.

3-Nitrothiophene-2,5-dicarbonitrile (10). Light-cream microcrystals, yield 4.83 g (75%), m.p. 159-160 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.7, 134.3, 115.1, 115.0, 111.7, 110.0. HRMS (APCI) calcd for $C_6N_3O_2S$ m/z 177.9717 $[M-H]^-$, found m/z 177.9717 $[M-H]^-$.

Procedure for the synthesis of methyl 3-amino-5-cyanothieno[3,2-*b*]thiophene-2-carboxylate (11). K_2CO_3 (2.3 g, 16.75 mmol) and Et_3N (1.54 mL, 11.17 mmol) were added to a stirred solution of dinitrile **2** (2 g, 11.17 mmol) and methyl thioglycolate (1.42 g, 13.4 mmol) in MeCN (30 mL) under ice cooling, since a noticeable exothermic reaction occurs at this step of process. The color of the solution turns green-violet. The reaction mixture was stirred and heated at 95 °C for 15 min, and then poured into water (50 mL). The resulting precipitate was filtered, washed with MeCN-water (10 mL, v/v 1:1), water and dried at 110 °C to give ester **11** in analytically pure form.

Methyl 3-amino-5-cyanothieno[3,2-*b*]thiophene-2-carboxylate (11). Greenish crystals, yield 2.01 g (75%), m.p. 234-235 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.25 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.2, 146.4, 138.9, 132.8, 132.4, 114.2, 112.7, 102.0, 51.4. HRMS (APCI) calcd for $C_9H_5N_2O_2S_2$ m/z 236.9798 $[M-H]^-$, found m/z 236.9798 $[M-H]^-$.

General procedure for the synthesis of thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acids (5a-f) from substrate 3. NaOAc (100 mg, 1.2 mmol) and an appropriate arylhydrazine hydrochloride **4** (1.2 mmol) were added to a stirred solution of ketone **3** (200 mg, 1 mmol) in glacial AcOH (7 ml). The reaction mixture was stirred and heated at 120 °C for 1 h. Then it was cooled to room temperature, and the formed precipitate was filtered, washed with warm water (10 ml), MeOH (3 × 4 ml), and dried at 120 °C to afford product **5**. Compounds **5** were obtained in an analytically pure form without additional purification.

General procedure for the synthesis of thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acids (5a-f) from substrate 11. NaOH (0.16 g, 4 mmol) in water (1 mL) was added to a stirred suspension of ester **11** (1 mmol) in IPA (9 mL), and the mixture was stirred and heated at reflux (100 °C) for 2 h. The resulting solution was then concentrated to dryness under reduced pressure. The solid residue was dissolved in glacial AcOH (7 ml), and an appropriate arylhydrazine hydrochloride **4** (1.2 mmol) was added to this solution. The reaction mixture was stirred and heated at reflux (130 °C) for 2 h. The precipitate was filtered, washed with warm water (10 ml), MeOH (3×4 ml) and dried at 120 °C to give product **5** in analytically pure form.

9*H*-Thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acid (5a). Dark yellow powder, yield 225 mg (82%) from **3**, 200 mg (73%) from **11**, m.p. > 350 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (br.s, 1H), 11.98 (s, 1H), 8.21 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.17 – 7.12 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.4, 140.7, 140.1, 134.2, 133.6, 128.0, 127.7, 123.5, 121.9, 121.0, 119.7, 118.9, 112.8. HRMS (ESI) calcd for $C_{13}H_6NO_2S_2$ m/z 271.9845 $[M-H]^-$, found m/z 271.9847 $[M-H]^-$.

6-Fluoro-9*H*-thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acid (5b). Dark yellow powder, yield 169 mg (58%) from **3**, 141 mg (48%) from **11**, m.p. > 350 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.28 (br.s, 1H), 12.06 (s, 1H), 8.22 (s, 1H), 7.69 (dd, *J* = 9.7, 2.6 Hz, 1H), 7.57 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.14 (td, *J* = 9.2, 2.6 Hz, 1H). ^{19}F NMR (471 MHz, DMSO-d_6) δ 39.26 (td, *J* = 9.6, 4.6 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.3, 156.85 (d, J_{CF} = 233.1 Hz), 140.8, 137.3, 135.7, 134.1, 128.0, 127.4, 122.02 (d, J_{CF} = 11.0 Hz), 120.64 (d, J_{CF} = 4.6 Hz), 113.76 (d, J_{CF} = 9.6 Hz), 111.41 (d, J_{CF} = 26.0 Hz), 104.11 (d, J_{CF} = 25.0 Hz). HRMS (ESI) calcd for $C_{13}H_5FNO_2S_2$ m/z 289.9751 $[M-H]^-$, found m/z 289.9753 $[M-H]^-$.

6-(*tert*-Butyl)-9*H*-thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acid (5c). Dark green powder, yield 110 mg (33%) from **3**, 111 mg (34%) from **11**, m.p. 333-335 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.21 (br.s, 1H), 11.82 (s, 1H), 8.20 (s, 1H), 7.76 (d, *J* = 1.6 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.38 (dd, *J* = 8.7, 1.9 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.4, 142.3, 139.9, 138.9, 134.2, 133.2, 128.0, 127.8, 121.7, 121.2, 114.7, 112.3, 34.4, 31.7 (1$C_{aromatic}$ signal no detected due to peak overlap). HRMS (ESI) calcd for $C_{17}H_{14}NO_2S_2$ m/z 328.0471 $[M-H]^-$, found m/z 328.0470 $[M-H]^-$.

11*H*-Benzo[*g*]thieno[2',3':4,5]thieno[3,2-*b*]indole-9-carboxylic acid (5d). Dark yellow powder, yield 180 mg (56%) from **3**, 148 mg (46%) from **11**, m.p. 292-294 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.25 (br.s, 1H), 12.92 (s, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.24 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.55 – 7.50 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.4, 139.6, 135.6, 132.9, 132.7, 130.5, 128.8, 128.2, 127.9, 126.1, 124.9, 122.9, 122.3, 120.8, 120.6, 118.7, 117.6. HRMS (ESI) calcd for $C_{17}H_8NO_2S_2$ m/z 322.0013 $[M-H]^-$, found m/z 322.0010 $[M-H]^-$.

6-Cyano-9*H*-thieno[2',3':4,5]thieno[3,2-*b*]indole-2-carboxylic acid (5e). Brownish powder, yield 107 mg (36%) from **3**, 155 mg (52%) from **11**, m.p. > 350 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.35 (br.s, 1H), 12.57 (s, 1H), 8.48 (s, 1H), 8.25 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.63 (dd, *J* = 8.5, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.3, 142.3, 141.7, 135.9, 134.9, 128.0, 127.1, 126.0, 124.5, 121.8, 121.1, 120.2, 113.9, 101.6. HRMS (ESI) calcd for $C_{14}H_5N_2O_2S_2$ m/z 296.9798 $[M-H]^-$, found m/z 296.9796 $[M-H]^-$.

9*H*-Thieno[2',3':4,5]thieno[3,2-*b*]indole-2,6-dicarboxylic acid (5f). Brownish powder, yield 91 mg (29%) from **3**, 230 mg (73%) from **11**, m.p. 335-337 °C (dec.). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.96 (br.s, 2H), 12.36 (s, 1H), 8.48 (s, 1H), 8.24 (s, 1H), 7.89 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.8, 163.3, 143.1, 140.9, 135.3, 134.2, 128.0, 127.3, 124.5, 122.2, 121.8, 121.5, 121.2, 112.5. HRMS (ESI) calcd for $C_{14}H_6NO_4S_2$ m/z 315.9744 $[M-H]^-$, found m/z 315.9740 $[M-H]^-$.

General procedure for the synthesis of 9*H*-thieno[2',3':4,5]thieno[3,2-*b*]indoles (12a-e). An appropriate TTI-2-carboxylic acid **5** (1 mmol) was dissolved in quinoline (3 mL), and CuO (3 mg) was added to this solution. The reaction mixture was heated at 200 °C for 2 h, while active evolution of CO_2 and strong darkening of the solution were observed in the first 0.5 h. Then, the reaction mixture was cooled to room temperature, neutralized with conc. HCl (3 mL, 37% wt.), diluted with water (50 ml) and extracted with CH_2Cl_2 (3 × 15 mL). The organic extract was dried with Na_2SO_4, passed through silica gel (5 mL, 0.032-0.063 mm) on glass filter, and the filtrate was concentrated in vacuum and the residue was triturated with hexane (10 ml). The formed precipitate was filtered, washed with hexane and dried at 110 °C to afford product **12**.

9*H*-Thieno[2',3':4,5]thieno[3,2-*b*]indole (12a). Cream microcrystals, yield 220 mg (96%), m.p. 226-227 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 5.2 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.25 – 7.19 (m, 1H), 7.15 – 7.09 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 140.9, 140.0, 134.6, 126.7, 123.3, 122.3, 122.2, 121.6, 119.4, 118.0, 117.3, 112.5. HRMS (APCI) calcd for $C_{12}H_6NS_2$ m/z 227.9947 $[M-H]^-$, found m/z 227.9947 $[M-H]^-$.

6-Fluoro-9*H*-thieno[2',3':4,5]thieno[3,2-*b*]indole (12b). Cream scaly crystals, yield 208 mg (84%), m.p. 208-209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 7.71 (d, *J* = 5.2 Hz, 1H), 7.58 (dd, *J* = 9.8, 2.6 Hz, 1H), 7.55 (d, *J* = 5.2 Hz, 1H), 7.51 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.06 (td, *J* = 9.2, 2.6 Hz, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ 38.87 (td, *J* = 9.6, 4.6 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.80 (d, J_{CF} = 232.6 Hz), 141.7, 136.6, 136.3, 127.3, 123.1, 122.46 (d, J_{CF} = 11.0 Hz), 121.7, 117.12 (d, J_{CF} = 4.4 Hz), 113.31 (d, J_{CF} = 9.8 Hz), 110.01 (d, J_{CF} = 25.8 Hz), 103.39 (d, J_{CF} = 24.9 Hz). HRMS (APCI) calcd for $C_{12}H_5FNS_2$ m/z 245.9853 $[M-H]^-$, found m/z 245.9850 $[M-H]^-$.

6-(*tert*-Butyl)-9*H*-thieno[2',3':4,5]thieno[3,2-*b*]indole (12c). Cream scaly crystals, yield 151 mg (53%), m.p. 210 - 211 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 5.2 Hz, 1H), 7.53 (d, *J* = 5.2 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.31 (dd, *J* = 8.7, 1.9 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 141.9, 140.6, 138.2, 134.7, 126.4, 123.3, 122.1, 121.7, 120.4, 117.5, 113.9, 111.9, 34.3, 31.7. HRMS (APCI) calcd for $C_{16}H_{14}NS_2$ m/z 284.0573 $[M-H]^-$, found m/z 284.0575 $[M-H]^-$.

11*H*-Benzo[*g*]thieno[2',3':4,5]thieno[3,2-*b*]indole (12d). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 5.2 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.57 (d, *J* = 5.2 Hz, 1H), 7.51 – 7.45 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 140.3, 134.4, 133.2, 129.9, 128.6, 126.2,

125.8, 124.1, 123.5, 122.4, 121.7, 120.5, 120.2, 119.3, 118.4, 117.9. HRMS (ESI) calcd for $C_{16}H_8NS_2$ m/z 278.0104 $[M-H]^-$, found m/z 278.0107 $[M-H]^-$.

6-Cyano-9*H*-thieno[2',3':4,5]thieno[3,2-*b*]indole (12e). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 8.38 (d, *J* = 1.5 Hz, 1H), 7.76 (d, *J* = 5.2 Hz, 1H), 7.70 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.61 – 7.54 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) 142.6, 141.8, 136.7, 128.1, 125.0, 123.5, 122.9, 122.2, 121.7, 120.4, 117.6, 113.5, 101.3. HRMS (APCI) calcd for $C_{13}H_5N_2S_2$ m/z 252.9900 $[M-H]^-$, found m/z 252.9903 $[M-H]^-$.

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Supplementary Material

^{1}H, ^{19}F and ^{13}C NMR spectroscopic data of synthesized compounds are available in the Supplementary material file associated with this manuscript.

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