A Convenient One-Pot Synthesis of 2,5-Functionalized Thieno[2,3-*b*]-thiophenes Using Anhydrous Potassium Fluoride in Dimethylformamide

Sabir H. Mashraqui,* Harini Hariharasubrahmanian, Sukeerthi Kumar

Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai 400 098, India
Fax +91(22)6528547; Email: shm@chbu.ernet.in

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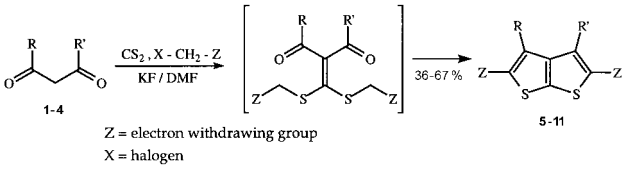
Abstract: A simple one-pot synthesis of 2,5-functionalized thieno[2,3-*b*]thiophenes by the condensation of 1,3-diketones with CS_2 and alkylating agents carrying an electron-withdrawing group such as CO_2Et, COR or CN in the presence of anhydrous potassium fluoride as the condensation promoter in anhydrous DMF is described. The process is mild, convenient and offers reasonable yields.

Key words: 1,3-diketones, carbon disulfide, potassium fluoride, thieno[2,3-*b*]thiophenes, sulfur, condensation reaction



Scheme

Thieno[2,3-*b*]thiophenes,[1,2] structurally related to isoelectronic naphthalene and 10π-pentalene dianion are of potential interest as π-electron donors in several current applications.[3] Of the few syntheses described in the literature for thieno[2,3-*b*]thiophenes, the majority are multistep, proceed in very poor yield, and being target-oriented, offer little or no generality.[4] On the other hand, a two-step synthesis of thienothiophenes based on the Dieckmann type cyclization of the appropriately activated ketene dithioacetals, in spite of its relatively wider use, suffers from variable yields and complications associated with strongly basic conditions, i.e., MeONa, NH_3(liq)/Na, NaH, LDA etc., employed for accomplishing these cyclizations.[5] Recently, synthesis of a limited number of thienothiophenes under phase-transfer catalysis in benzene has also been reported.[6] In view of the aforementioned drawbacks, we deemed it desirable to develop a milder and more convenient synthetic approach to thieno-[2,3-*b*]thiophene systems.

Fluoride ions as non-nucleophilic bases have been widely exploited for the generation of carbanions and heteroatom based nucleophiles.[7] Recently, we reported the application of commercially available anhydrous KF as the condensation promoter between CS_2, active methylene compounds and alkylating agents for a practically useful synthesis of ketene dithioacetals.[8] We envisaged that if in these condensations, the alkylating agent, X–CH_2–Z is endowed with a suitable carbanion stabilizing group (where Z may be COR, CO_2R, CN etc.), then the resultant ketene dithioacetal intermediate might directly cyclize under the conditions shown in the Scheme to provide thieno[2,3-b]thiophenes in a single step process. Precedence for analogous cyclization using the KF/DMF system can be found in the context of thiazoline to thiazine ring expansions reported earlier by us.[9]

Thus, in order to test the validity of the reaction given in the Scheme, we initially investigated a reaction between acetylacetone **(1)**, CS_2 and chloroacetone in anhydrous DMF containing an excess of anhydrous KF at room temperature for 8 hours. The workup of the reaction and purification afforded, though in low yield (ca 11%) a single crystalline compound, unequivocally characterized as the desired 1,5-diacetyl-3,4-dimethylthieno[2,3-*b*]thiophene **(6)** by analytical and spectral data. The yield of **6** was enhanced to 46% (Lit.[4a] yield: 25%) by applying an elevated temperature of 80–100°C for 2 hours (Table 1). Of the several solvents examined, the reaction proved successful in anhydrous DMF; other solvents such as anhydrous dioxane, THF or MeCN were found to be ineffective.

The generality of the KF/DMF conditions was demonstrated using other activated alkylating agents and diketones **1–4** (Table 1). Thus, alkylating agents carrying such activating groups as ester, ketone and nitrile successfully participated in KF assisted thienothiophene synthesis.The structural characterization of new thieno[2,3-*b*]thiophenes (Table 2) is based on elemental analyses and spectral data.

The two-step synthesis of compound **10** which we recently reported[10] in 43% yield is now available in an improved yield of 61%. It is noteworthy that despite the presence of the reactive pyridyl ring, the conversion of 3-(4-methoxyphenyl)-1-pyridylpropane-1,3-dione, to a unique donor-acceptor *peri*-3,4-disubstituted thienothiophene (Table 1, compound **11**) could be realized successfully in a yield of 36%.

In summary, we have described a one-pot synthesis of 3,5-functionalized thieno[2,3-*b*]thiophenes utilizing anhydrous KF as the condensation promoter.

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-4200 spectrophotometer as KBr discs. ^{1}H NMR spectra were

Table 1 Synthesis of 2,5-Functionalized Thieno[2,3-*b*]thiophenes **5–11** Using Anhydrous Potassium Fluoride

	Diketones	Alkylating agents		Thienothiophenes	Time	Yield	mp (°C)	
		X–CH_2–Z			(h)	(%)	found	reported
1:	R = R' = Me	X = Br, Z = CO_2Et	**5**:	R = R' = Me Z = CO_2Et	4	50	133–135	135[6]
1:	R = R' = Me	X = Cl, Z = COMe	**6**:	R = R' = Me Z = COMe	2	46	157–159	158[4a]
1:	R = R' = Me	X = Cl, Z = COPh	**7**:	R = R' = Me Z = COPh	4	40	252–254	–
1:	R = R' = Me	X = Cl, Z = CN	**8**:	R = R' = Me Z = CN	6	67	220–222	165[a]
2:	R = R' = Ph	X = Cl, Z = COMe	**9**:	R = R' = Ph Z = COMe	2	67	252–254	–
3:	R = R' = 4-MeC_6H_4	X = Br, Z = CO_2Et	**10**:	R = R' = 4-MeC_6H_4 Z = CO_2Et	2	61	154–156	–
4:	R = 4-$OMeC_6H_4$	X = Cl, Z = COMe	**11**:	R = 4-$OMeC_6H_4$ Z = COMe	3	36	238–240	–

[a]Although there is a discrepancy between the reported[6] and our mp, analysis and spectral data are in complete agreement for compound **8**.
^{1}H NMR ($CDCl_3$) : δ = 2.7 (s, CH_3).
IR (KBr): ν = 2910, 2220, 1495, 1394, 1120, 1030 cm^{-1}.
Anal. calcd. for $C_{10}H_6N_2S_2$: C, 55. 05; H, 2. 75; N, 12. 84; S, 29. 36. Found : C, 55. 31; H, 2. 47; N, 13. 02; S, 29. 07.

Table 2 Analytical and Spectral Data of New Thieno[2,3-*b*]-thiophenes **7, 9–11** Prepared

Product[a]	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
7	1620, 1600, 1480, 1411, 1280, 1107, 980, 913, 820	2.7 (3 H, s), 7.5–7.0 (5 H, m)
9	1635, 1503, 1380, 1260, 1003, 925, 885, 814	1.9 (3 H, s), 6.85–7.3 (5 H, br s)
10	2985, 1735, 1680, 1505, 1387, 1285, 1178, 1070, 830	1.2 (3 H, t , *J* = 7), 2.1 (3 H, s), 4.2 (2 H, q , *J* = 7) , 6.7 (4 H, s)
11	2975, 1642, 1603, 1505, 1467, 1350, 1240, 900	1.9 (3 H, s), 2.0 (3 H, s), 3.70 (3 H, s), 6.6–6.9 (8 H, m)

[a]Satisfactory microanalyses obtained: C, ±0.29; H, ±0.29; S, ±0.31.

recorded on a Varian EM-360L (60 MHz) spectrometer with TMS as internal standard.

DMF was dried (CaH_2) and distilled. Anhyd KF was purchased from S.D. Fine Chemical Ltd. (India) and used as such.

Diethyl 3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate (5); Typical Procedure

To anhyd DMF (30 mL) containing KF (8 g, 0.138 mol) were added acetylacetone (**1**; 1.03 mL, 10 mmol) and freshly distilled CS_2 (0.8 mL, 12 mmol). The mixture was vigorously stirred at r.t.for 15 min. Ethyl bromoacetate (2.2 mL, 20 mmol) was then added and the temperature was raised and maintained at 80–100 °C for 4 h. The mixture was allowed to cool to r.t., and then poured onto crushed ice. The precipitated solid was filtered, washed with chilled 50% aq EtOH and crystallized from EtOH to give colorless crystals; yield: 1.43 g (50%); mp 133–135 °C (Lit.[6] mp 135 °C).

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