Simple One-Pot Synthesis of Thieno[2,3-*b*]thiophene Derivatives under Solid–Liquid PTC Conditions. Useful Starting Material for the Synthesis of Biological Active Compounds

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(Received October 30, 1992)

A variety of thieno[2,3-*b*]thiophenes were prepared under phase-transfer catalysis conditions. The reaction of diethyl 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarboxylate with hydrazine hydrate gave the corresponding hydrazide derivative which was also subjected to react with acetylacetone, ethyl acetoacetate, malononitrile, CS_2, phenyl isothiocyanate, *p*-chlorobenzaldehyde and diazotization to afford the described compounds. Treatment of 2,5-bis(azidocarbonyl)-3,4-dimethylthieno[2,3-*b*]thiophene with ethyl cyanoacetate, diethyl malonate or malononitrile gave the corresponding triazole derivatives.

The reported biological activity of many heterocyclic compounds containing thiophene moiety[1,2] has prompted us to use a series of novel thieno[2,3-*b*]thiophenes compound prepared in our laboratory as a building block for the synthesis of polyfused heterocycles containing different nuclei.

Gompper and Schafer[3] reported alkylation of the dithioic acid derived from methyl cyanoacetate with chloroacetamide under acidic conditions yielded a thiophene arising from S-alkylation followed by closure onto the nitrile.

The introduction of phase-transfer catalysis (PTC) in carbanionic reactions offers one of the most important recent methods of organic synthesis. It is important because it simplifies procedures, eliminates, expensive, inconvenient, and dangerous reactants and solvents, and also allows one to perform many reactions that otherwise proceed in an unsatisfactory way or do not proceed at all. PTC have been reviewed[4—9] but only two reviews deal with chemistry of heterocyclic compounds.[10,11] Most PTC reactions take place in liquid–liquid two phase systems in which both phases, aqueous alkali and organic reactants (neat or in a nonpolar solvent) are mutually immiscible. Despite many advantages, this system has some limitations, one of them being the hydrolytic activity of concentrated aqueous alkali. However, solid–liquid two phase systems offers a convenient alternative. Reactions are catalyzed by tetrabutylammonium bromide or a crown ether. In solid–liquid PTC systems the catalyst are unable to transfer carbonate anions (CO_3^{-2}) into the organic phase.[12] Thus solid–liquid phase-transfer phenomena are not involved here.

We reported here the synthesis of some new functionally substituted thieno[2,3-*b*]thiophenes in a one-pot reaction by using PTC conditions (K_2CO_3/benzene/tetrabutylammonium bromide TBAB, catalyst) starting with acetylacetone, CS_2 and α-chloro compounds in 1:1:2 molar ratios. The reaction of acetylacetone, CS_2 with ethyl chloroacetate, chloroacetonitrile, 2-(chloroacetylamino)thiazole, or (chloroacet)anilide was carried out under PTC conditions by stirring the reactants at different temperatures over different periods of time (cf. Table 2). Where the corresponding thieno[2,3-*b*]thiophenes **1**—**4** were obtained in excellent yields (cf. Scheme 1).

The reaction of compound **1** with hydrazine hydrate gave 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-dicarbohydrazide (**5**), which was treated with acetylacetone, ethyl acetoacetate, or malononitrile. The reaction afforded an exocyclic pyrazole nuclei and 3,4-dimethyl-2,5-bis[(3,5-dimethyl-1-pyrazolyl)carbonyl]thieno[2,3-*b*]thiophene (**6**), 3,4-dimethyl-2,5-bis[(3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)carbonyl]thieno-[2,3-*b*]thiophene (**7**), or 3,4-dimethyl-2,5-bis[(3,5-diamino-1*H*-pyrazol-1-yl)carbonyl]thieno[2,3-*b*]thiophene (**8**), were obtained respectively.

Compound **5**, when was also treated with CS_2, potassium hydroxide and then treated with dil HCl or concd H_2SO_4, afforded 3,4-dimethyl-2,5-bis(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)thieno[2,3-*b*]thiophene (**9**) or 3,4-dimethyl-2,5-bis(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)thieno[2,3-*b*]thiophene (**10**), respectively.

Condensation of compound **9** with hydrazine hydrate yield, 3,4-dimethyl-2,5-bis(4-amino-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)thieno[2,3-*b*]thiophene (**11**) (cf. Scheme 2).

The reaction of compound **5** with phenyl isothiocyanate in ethanol[13] gave 3,4-dimethylthieno-[2,3-*b*]thiophene-2,5-bis[*N'*-(*N*-phenylthiocarbamoyl)-carbohydrazide] (**12**), which was treated with potassium hydroxide and acidification with dil HCl to afford 3,4-dimethyl-2,5-bis(4,5-dihydro-4-phenyl-5-thioxo-1*H*-1,2,4-triazol-3-yl)thieno[2,3-*b*]thiophene (**13**).

Condensation of compound **5** with *p*-chlorobenzaldehyde in ethanol and few drops of piperidine as a catalyst afforded the expected 3,4-dimethylthieno[2,3-*b*]thiophene-2,5-bis[*N'*-(*p*-chlorobenzylidene)carbohydrazide] (**14**).

Also, diazotization of **5** in acetic acid with sodium nitrite (10%) gave the corresponding azide, namely 2,5-bis(azidocarbonyl)-3,4-dimethylthieno[2,3-*b*]thiophene **15** (cf. Scheme 3).

The reaction of azide compound **15** with an active

Table 1. Analitical and Spectral Data of the Reported New Compounds

Product No.	Yield %	Mp[a] °C	Mol.Form. (MW)[b]	IR (Nujol) ν (cm^{-1})[c]	^1H NMR (DMSO-d_6)[d] δ (ppm)
1	93	135	$C_{14}H_{16}S_2O_4$ 312.40	2970—2920 (C–H), 1730 (C=O ester).	4.70—4.20 (q,4H,2CH_2), 2.90 (s,6H,2CH_3), 1.50—1.20 (t,6H,2CH_3 ester).
2	85	165	$C_{10}H_6N_2S_2$ 224.34	2970 (C–H), 2220 (CN).	2.70 (s,6H,2CH_3).
3	78	360	$C_{16}H_{12}N_4S_4O_2$ 420.54	3250 (NH), 2970—2950 (C–H), 1650 (C=O).	10.60 (br,2H,2NH), 9.20—8.90 (dd,4CH-thiazole), 2.20 (s,6H,2CH_3).
4	51	67	$C_{22}H_{18}N_2S_2O_2$ 406.52	3300 (NH), 2970—2950 (C–H), 1650 (C=O).	8.70—8.40 (br,2H,2NH), 7.80—7.20 (m,10H,2Ph), 2.30 (s,6H,2CH_3).
5	96	325	$C_{10}H_{12}N_4S_2O_2$ 284.35	3350, 3310, 3220 (NH,NH_2), 2970—2950 (C–H), 1650.	9.70 (br,2H,2HN), 6.30 (br,4H,2NH_2), 2.65 (s,6H,2CH_3).
6	88	210	$C_{20}H_{20}N_4S_2O_2$ 412.52	2970—2950 (C–H), 1680 (C=O), 1600 (C=N).	6.10 (s,2H,2CH-pyrazole), 2.90 (s,6H,2CH_3), 2.65,2.40 (ss,12H,4CH_3-pyrazole).
7	79	>360	$C_{18}H_{16}N_4S_2O_4$ 416.77	3200 (NH), 2980—2950 (C–H), 1720, 1690 (C=O), 1600 (C=N).	10.60 (br,2H,2NH), 6.70 (s,2H,2CH-pyrazolinone), 2.85 (s,6H,2CH_3), 2.35 (s,6H,2CH_3-pyrazolin one).
8	73	295	$C_{16}H_{16}N_8S_2O_2$ 416.47	3350,3280 (NH_2), 2980—2950 (C–H), 1620 (C=N).	7.30 (br,4H,2NH_2), 6.50 (br,4H,2NH_2), 6.20 (s, 2H,2CH-pyrazole), 2.85 (s,6H,2CH_3).
9	82	315[d]	$C_{12}H_8N_4S_4O_2$ 368.46	3200 (NH), 2980—2950 (C–H), 1620 (C=N).	10.80 (br,2H,2NH), 2.60 (s,6H,2CH_3).
10	85	170	$C_{12}H_2N_4S_6$ 400.58	3200 (NH), 2980—2950 (C–H), 1620 (C=N).	10.60 (br,2H,2NH), 2.65 (s,6H,2NH_3).

methylene compounds[14] as ethyl cyanoacetate, diethyl malonate or malononitrile in presence of sodium ethoxide afforded the corresponding triazoles **16**—**18**, namely, 2,5-bis(5-amino-4-ethoxycarbonyl-1*H*-1,2,3-triazol-1-ylcarbonyl)-3,4-dimethylthieno[2,3-*b*]thiophene (**16**), 2,5-bis(4-ethoxycarbonyl-4,5-dihydro-5-oxo-1*H*-1,2,3-triazol-1-ylcarbonyl)-3,4-dimethylthieno[2,3-*b*]thiophene (**17**) or 2,5-bis(5-amino-4-cyano-1*H*-1,2,3-triazol-1-ylcarbonyl)-3,4-dimethylthieno[2,3-*b*]thiophene (**18**) (cf. Scheme 4).

Experimental

All melting points were determined on a Kofler melting point apparatus and were uncorrected (Table 1). IR spectra were obtained on a Pye-Unicam SP 1200 infrared spectrophotometer. ^1H NMR spectra were obtained on a Varian EM 360L at 60 MHz using TMS as internal standard. The elemental analyses were carried out on an elemental analyzer 240C.

General Procedure. Acetylacetone (0.05 mol), along with 0.05 mol of CS_2 in 70 ml of dry benzene was treated with 3 g of anhydrous potassium carbonate. The formed dianionic ambident compound was then treated with 0.1 mol of the reactive halo derivative including ethyl chloroacetate, chloroacetonitrile, 2-(chloroacetylamino)thiazole, or (chloroacet)anilide, and a catalytic amount of the tetrabutylammonium bromide (TBAB, 3 mmol). The reaction mixture was stirred for about 5—10 h, whereby a noticeable change in color was observed.

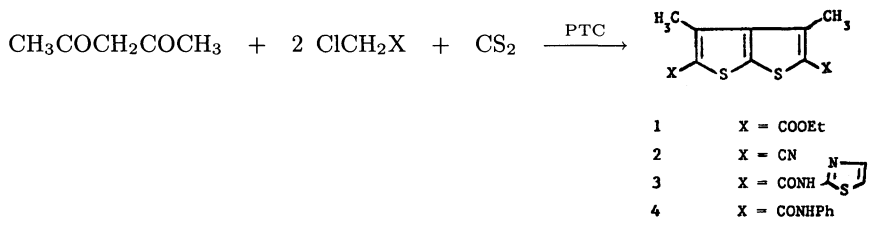
At the end of the reaction, benzene layer was separated, washed thoroughly with water, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was washed with light petroleum ether and collected by filtration.

In the sequence of our studies only one compound was separated from benzene layer, 3,4-dimethyl-2,5-bis(*N*-phenylcarbamoyl)thieno[2,3-*b*]thiophene (**4**). The rest of the prepared products, diethyl 3,4-dimethylthieno[2,3-*b*]thiophen-2,5-dicarboxylate (**1**), 2,5-dicyano-3,4-dimethylthieno[2,3-*b*]-thiophene (**2**), and 3,4-dimethyl-2,5-bis[*N*-(2-thiazolyl)carbamoyl]thieno[2,3-*b*]thiophene (**3**) were precipitated during the course of reaction. They were obtained by filtration along with the potassium carbonate layer and the precipitate was washed thoroughly with water and was recrystallized from appropriate solvent.

Table 1. (Continued)

Product No.	Yield %	Mp[a] °C	Mol.Form. (MW)[b]	IR (Nujol) ν (cm^{-1})[c]	^{1}H NMR (DMSO-d_6)[d] δ (ppm)
11	78	>360	$C_{12}H_{12}N_8S_4$ 396.52	3350, 3250, 3200 (NH,NH_2), 2990—2970 (C–O), 1620 (C=N).	10.40 (br,2H,2NH), 6.40 (br,2H,$2NH_2$), 2.90 (s,6H,$2CH_3$).
12	67	321	$C_{24}H_{22}N_6S_4O_2$ 554.72	3280 (NH), 2980—2950 (C–H), 1670 (C=O).	11.20 (br,4H,4NH), 8.90 (br,2H,2NH), 8.20—7.80 (m,10H,2Ph), 2.80 (s,6H,$2CH_3$).
13	66	>360	$C_{24}H_{18}N_6S_4$ 518.66	3250 (NH), 2980—2960 (C–H), 1620 (C=N).	10.30 (br,2H,2NH), 8.50—8.00 (m,10H,2Ph), 2.80 (s,6H,$2CH_3$).
14	71	329	$C_{24}H_{18}N_4S_2O_2Cl_2$ 529.56	3300 (NH), 3030 (C-H arom.), 2980—2950 (C–H), 1670 (C=O).	9.70 (br,2H,2NH), 8.30 (s,2H,2CH-phenyl), 8.00—7.70 (m,8H,2Ph), 2.90 (s,6H,$2CH_3$).
15	78	112	$C_{10}H_6N_6S_2O_2$ 306.32	2980—2950 (C–H), 1680(C=O).	2.90 (s,6H,$2CH_3$).
16	81	139	$C_{20}H_{20}N_8S_2O_6$ 532.55	3350 (NH_2), 2990—2950 (C–H), 1750 (C=O ester), 1670 (C=O), 1620 (C=N).	6.70 (br,4H,$2NH_2$), 4.40—4.00 (q,4H,$2CH_2$), 2.90 (s,6H,$2CH_3$-thiophene), 1.50—1.10 (t, 6H,$2CH_3$ ester).
17	65	130	$C_{20}H_{18}N_6S_2O_8$ 534.51	2980—2950 (C–H), 1710, 1670 (C=O), 1620 (C=N).	5.50 (s,2H,2CH), 4.60—4.20 (q,4H,$2CH_2$), 2.90 (s,6H,$2CH_3$), 1.60—1.20 (t,6H,$2CH_3$-ester).
18	86	151	$C_{16}H_{10}N_{10}S_2O_2$ 438.44	3340 (NH_2), 2980—2950 (C–H), 2220 (CN), 1670 (C=O), 1620 (C=N).	6.20 (br,4H,$2NH_2$), 2.90 (s,6H,$2CH_3$).

a) Not corrected. b) Satisfactory microanalysis obtained C, ±0.45; H, ±0.2%; N, ±0.3%; S, ±0.3%. c) Measured on a Pye-Unicam SP 1200 spectrophotometer. d) Measured on a Varian EM 360L spectrometer using TMS as internal standard.



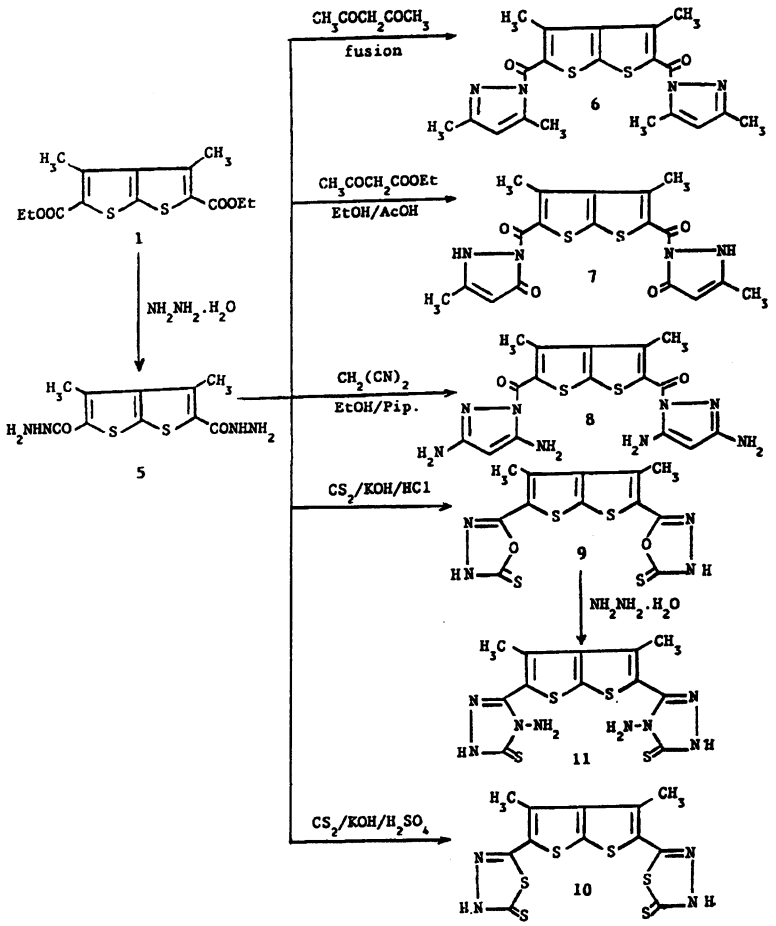
Scheme 1.

Synthesis of 3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-dicarbohydrazide (5): Fusion of compound **1** (3.12 g, 0.1 mol) with hydrazine hydrate (12.5 g, 0.25 mol) for 3 h gave a solid product which was washed thoroughly with cold water and was recrystallized from ethanol into white needles.

Synthesis of 3,4-Dimethyl-2,5-bis[(3,5-dimethyl-1-pyrazolyl)carbonyl]thieno[2,3-*b*]thiophene (6): A mixture of compound **5** (1.42 g, 0.005 mol) and acetylacetone (1 g, 0.01 mol) were heated without solvent for 1 h. On cooling, the precipitated solid was filtered off, washed with ethanol, and recrystallized from ethanol as white crystals.

Synthesis of 3,4-Dimethyl-2,5-bis[(3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)caronyl]thieno[2,3-*b*]-thiophene (7): A mixture of compound **5** (1.42 g, 0.005 mol) and ethyl acetoacetate (1.5 ml, 0.01 mol) were refluxed in ethanol (10 ml) containing few drops of glacial acetic acid for 3 h. The solid precipitated on cooling was filtered off and was recrystallized from acetic acid into pale yellow crystals.

Synthesis of 3,4-Dimethyl-2,5-bis[(3,5-diamino-1*H*-pyrazol-1-yl)carbonyl]thieno[2,3-*b*]thiophene (8): A mixture of compound **5** (0.8 g, 0.0028 mol) and ethanol (20 ml) and malononitrile (0.37 g, 0.0056 mol) with catalytic amount of piperidine was refluxed for 3 h. The solid product was collected by filtration and recrystallized from methanol into white crystals.



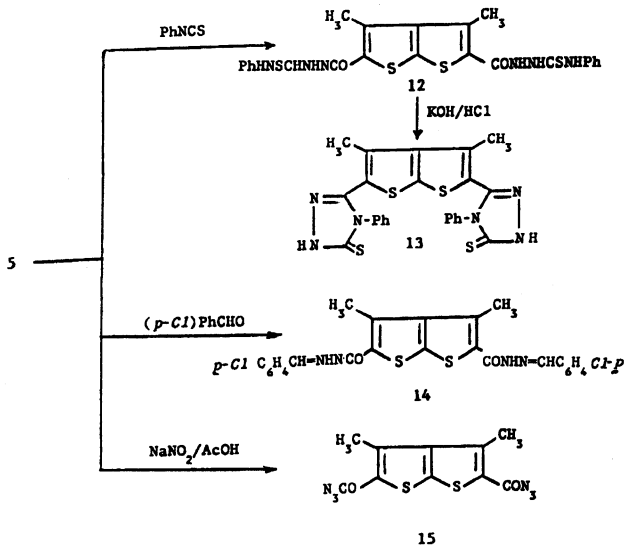
Scheme 2.

Table 2.

Product No.	Reaction temp (°C)	Reaction time (h)	Reaction solvent	Catalyst
1	60	6	Benzene	TBAB
2	60	5	Benzene	TBAB
3	60	10	Benzene	TBAB
4	60	10	Benzene	TBAB

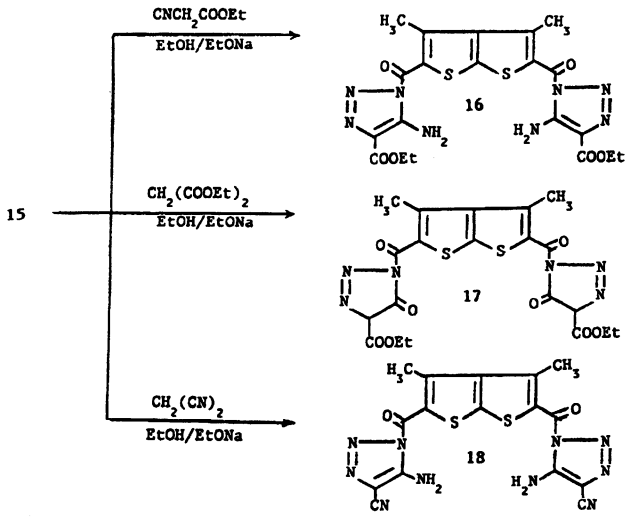
Synthesis of 3,4-Dimethyl-2,5-bis(4,5-dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)thieno[2,3-*b*]thiophene (9): To a solution of KOH (1.12 g, 0.02 mol) in ethanol (20 ml), compound **5** (2.84 g, 0.01 mol) was added, followed by the addition of CS_2 (2.28 g, 0.03 mol). The reaction mixture was refluxed on a steam bath for 4 h, then filtered off. The filtrate was neutralized with dil HCl, and the obtained solid product was washed several times with water and recrystallized from ethanol giving yellow crystals.

Synthesis of 3,4-Dimethyl-2,5-bis(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)thieno[2,3-*b*]thiophene (10): To a solution of KOH (1.12 g, 0.02 mol) in ethanol (20 ml), compound **5** (2.84 g, 0.01 mol) was added, followed by the addition of CS_2 (2.28 g, 0.03 mol). The reaction mixture was refluxed on a steam bath for 4 h, then filtered off. The filterate was acidified with concd H_2SO_4, and the obtained solid product was washed several times with water and recrystallized from ethanol giving yellow crystals.



Scheme 3.

Synthesis of 3,4-Dimethyl-2,5-bis(4-amino-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl)thieno[2,3-*b*]-thiophene (11): A mixture of compound **9** (1.84 g, 0.005 mol) and hydrazine hydrate 95% (2 g, 0.04 mol) was refluxed in ethanol (20 ml) for 8 h. The precipitated product was collected by filtration and recrystallized from ethanol



Scheme 4.

into brown crystals.

Synthesis of 3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-bis[*N*′-(*N*-phenylthiocarbamoyl)carbohydrazide] (12): A mixture of **5** (2.84 g, 0.01 mol) and phenyl isothiocyanate (2.7 g, 0.02 mol) was heated in ethanol (20 ml) for about 4 h. The precipitated product was collected by filtration and recrystallized from benzene into white crystals.

Synthesis of 3,4-Dimethyl-2,5-bis(4,5-dihydro-4-phenyl-5-thioxo-1*H* -1,2,4-triazol-3-yl)thieno[2,3-*b*]-thiophene (13): Compound **12** (5.55 g, 0.01 mol) was dissolved in 2 M (M =mol dm^{-3}) alcoholic KOH (20 ml) and heated on a steam bath for 1 h. The solution was filtered, cooled and acidified with dil HCl. The solid product was collected by filtration and recrystallized from dioxane into white needles.

Synthesis of 3,4-Dimethylthieno[2,3-*b*]thiophene-2,5-bis[*N*′-(*p*-chlorobenzylidene)carbohydrazide] (14): A mixture of compound **5** (2.84 g, 0.01 mol) and *p*-chlorobenzaldehyde (2.83 g, 0.02 mol) was refluxed in ethanol (20 ml) cotaining few drops of piperidine for 4 h. The precipitated product was filtered off and recrystallized from benzene into white crystals.

Synthesis of 2,5-Bis(azidocaronyl)-3,4-dimethylthieno[2,3-*b*]thiophene (15): Compound **5** (5.68 g, 0.02 mol) in (10 ml) acetic acid was treated with sodium nitrite (10%) (5.52 g, 0.08 mol) which was added drop by drop at −5 °C with stirring for 1 h. The solid product was filtered off and recrystallized from ethanol into white crystals.

Synthesis of Compounds 16, 17 and 18. General Procedure: A solution of Na (0.15 g, 0.0065 mol) in ethanol (20 ml) is added in one-portion to an ice-cold of compound **15** (1 g, 0.0033 mol) and an active methylene compounds (0.0066 mol). The mixture was stirred overnight and then the solvent evaporated in vaduo, the concentrated ethanol solution then poured into cold water and corresponding products was collected by filtration and recrystallized from ethanol.

compound **16** and **17**	yellow
compound **18**	gray

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