Synthesis of 1*H*-Thieno[3,4-*c*]pyrazoles, Thieno[3,4-*b*]furans, Selenolo[3,4-*b*]furans and Pyrrolo[3,4-*d*]thiazoles

A. Shafiee*, M. A. Ebrahimzadeh, J. Shahbazi and S. Hamedpanah

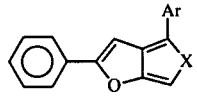
Department of Chemistry, College of Pharmacy, The Medical Sciences University of Tehran, Tehran, Iran

Received August 19, 1997

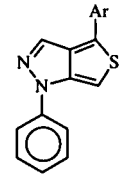
Starting from the readily available aryl 2-methyl-5-phenyl-3-furyl ketones, 5-methyl-1*H*-1-phenylpyrazole-4-yl ketones and 4-methyl-2-phenyl-5-thiazolylcarboxaldehyde, a series of 2-phenyl-4-arylthieno[3,4-*b*]-furan, 2-phenyl-4-(*p*-methoxyphenyl)selenolo[3,4-*b*]furan, 4-aryl-1*H*-1-phenylthieno[3,4-*c*]pyrazole and 5-benzyl-2-phenylpyrrolo[3,4-*d*]thiazole were prepared in high yield.

J. Heterocyclic Chem., **35**, 71 (1998).

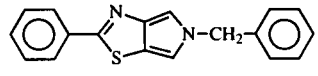
In continuation of the study on the chemistry of selenium heterocyclic compounds and as a part of a program designed to expand the chemistry of fused thiophene and selenophene heterocycles [1,2], it became necessary to synthesize 4-aryl-2-phenylthieno[3,4-*b*]furan (**1**, X = S), its selenium analog **2** (X = Se) and 4-aryl-1*H*-1-phenylthieno[3,4-*c*]pyrazole (**3**) and 5-benzyl-2-phenylpyrrolo-[3,4-*d*]thiazole (**4**) for biological evalution [3].



1, 2



3



4

The starting materials, aryl 2-methyl-5-phenyl-3-furyl ketones **7** could be prepared either from the reaction of aryllithium with 2-methyl-5-phenyl-3-furancarboxylic acid (**5**) or Friedel Crafts reaction of 2-methyl-5-phenyl-3-furoyl chloride (**6**) [4] with aromatic hydrocarbons [5].

Reaction of *N*-bromosuccinimide with compounds **7** afforded aryl 2-bromomethyl-5-phenyl-3-furyl ketones **8** in good yield. Reaction of thioacetamide with the latter gave desired compounds **1**. The reaction of *N,N*-diethylselenopropionamide [6] with compound **8c** afforded compound **2**. However with the other substituents only debromination without the reduction of keto group was observed (Sheme 1).

Compound **9** was prepared according to the reported procedure [7]. The latter was converted to compounds **3** according to Scheme 1. The reaction of compound **12** with *N,N*-diethylselenopropionamide did not give the desired compound **13**. In all cases debromination without cyclization was observed.

Compound **14** was prepared according to the reported procedure [8]. Condensation of diethyl malonate with compound **14** gave the expected compound **15**, which was brominated with *N*-bromosuccinimide to yield compound **16**. Reaction of the latter with benzylamine gave the desired compound **4**. Reaction of compound **16** with thioacetamide gave the intermediate **17**. The latter could not be converted to the desired compound **18** under different experimental conditions (Scheme 2).

The physical constants of all compounds prepared are summarized in Tables 1 and 2.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin Elmer Model 781 spectrograph (potassium bromide disks). The ^{1}H nmr spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

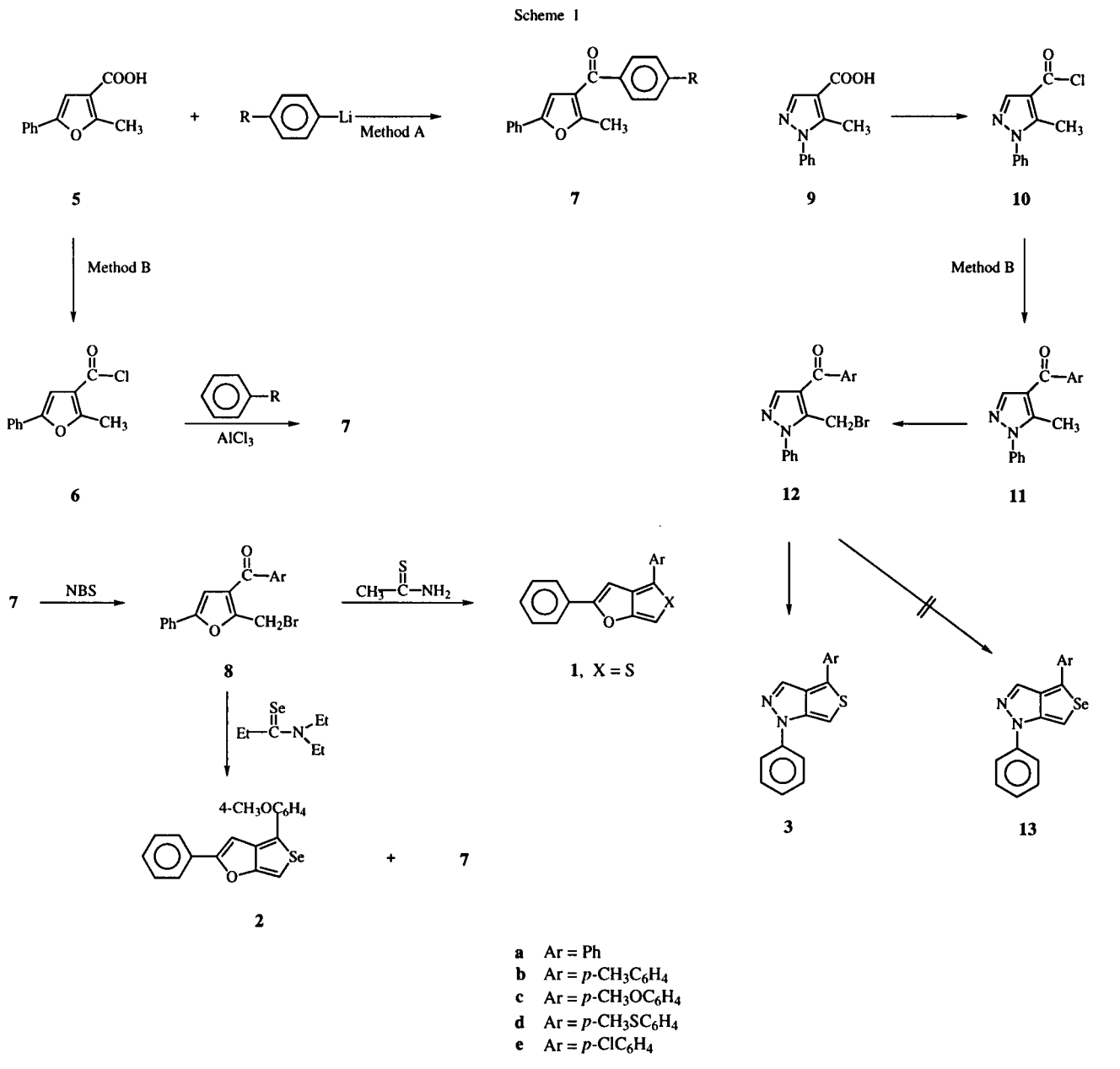
p-Chlorophenyl 2-Methyl-5-phenyl-3-furyl Ketone (**7e**).

Method A.

To a stirring solution of *p*-chlorophenyllithium, which was prepared from *p*-bromobenzene (7.851 g, 0.05 mole) and *n*-buthyllithium (32 ml of 10% solution in hexane, 0.05 mole) according to the literature [9] was added 2-methyl-5-phenyl-3-furancarboxylic acid (**5e**, 2.02 g, 0.01 mole). The mixture was stirred overnight under nitrogen at room temperature. Ice water was added to the mixture followed by extraction with ether. The residue was purified by tlc (silica gel, chloroform-petroleum ether 30:70) and the desired compound was crystallized from petroleum ether to give 1.77 g (60%) of **7e**, mp 55-57°; ir (potassium bromide): ν 1650 cm^{-1} (carbonyl); ^{1}H nmr (deuteriochloroform): 7.77 (d, 2H, aromatic), 7.63 (d, 2H, aromatic), 7.30 (m, 5H, phenyl), 6.75 (s, 1H, H_4) and 2.61 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.38. Found: C, 72.61; H, 4.53.

Scheme I



a Ar = Ph
b Ar = *p*-$CH_3C_6H_4$
c Ar = *p*-$CH_3OC_6H_4$
d Ar = *p*-$CH_3SC_6H_4$
e Ar = *p*-ClC_6H_4

p-Methoxyphenyl 2-Methyl-5-phenyl-3-furyl Ketone (**7c**).

Method B.

A stirring mixture of 2-methyl-5-phenyl-3-furoyl chloride (**6**, 2.21 g, 0.01 mole), anisole (1.08 g, 0.01 mole) and aluminium chloride (1.335 g, 0.01 mole) in 20 ml of carbon disulfide was refluxed in water bath for 4 hours. After cooling the complex was decomposed with ice water and dilute hydrochloric acid. The organic layer was separated and the mother liquor was extracted with carbon disulfide once more. The combined organic layer was washed with a saturated sodium bicarbonate solution in water. The organic layer was dried, filtered and evaporated. The residue was crystallized from methanol to give 2.5 g (85%) of **7c**, mp 128-130°; ir (potassium bromide): ν 1645 cm^{-1} (carbonyl); ^1H nmr (deuteriochloroform): 7.92 (d, 2H, aromatic), 7.37 (m, 5H, phenyl), 7.00 (d, 2H, aromatic), 6.74 (s, 1H, H_4) and 3.81 ppm (s, 3H, OCH_3).

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.08; H, 5.48. Found: C, 77.97; H, 5.31.

Other aryl 2-methyl-5-phenylfuryl ketones were prepared similarly by method B.

p-Methoxyphenyl 2-Bromomethyl-5-phenyl-3-furyl Ketone (**8c**).

A mixture of **7c** (2.93 g, 0.01 mole) and *N*-bromosuccinimide (1.93 g, 0.011 mole) in 30 ml of carbon tetrachloride was irradiated with a 500W (G.E. Photospot) lamp while heating and stirring at reflux temperature for 4 hours. The reaction mixture was cooled and filtered. The solvent was evaporated and the residue

Scheme 2

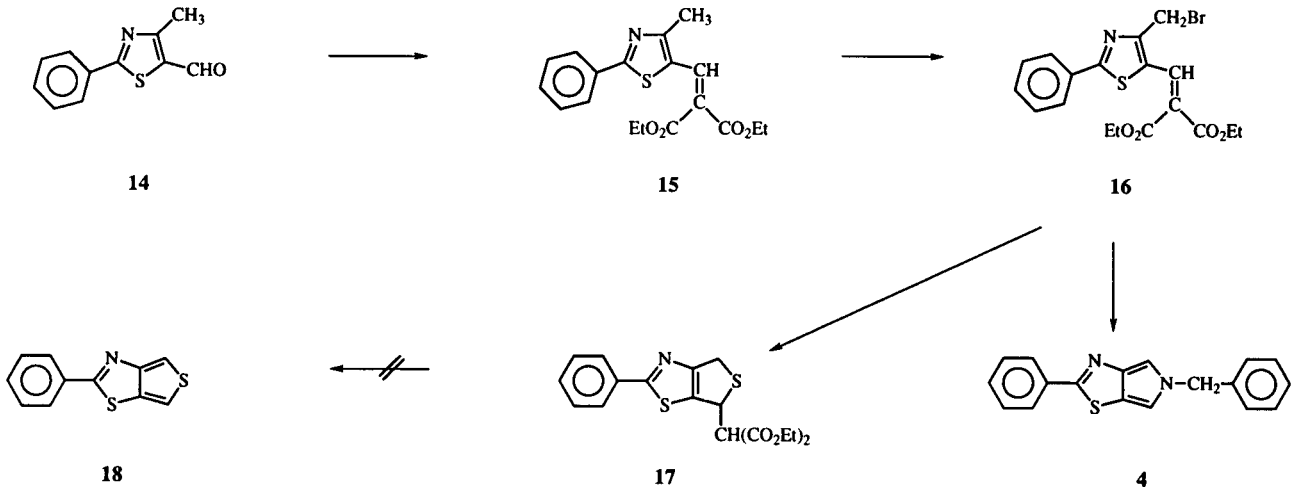
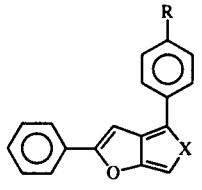


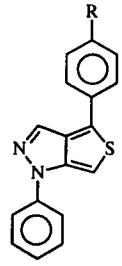
Table 1



Compound	R	X	Yield (%)	Mp°C [a]	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%
1a	H	S	75	115-116	$C_{18}H_{12}OS$	78.26	78.21	4.35	4.32
1b	CH_3	S	45	87-87 [b]	$C_{19}H_{14}OS$	78.62	78.68	4.83	4.79
1c	OCH_3	S	60	113-114	$C_{19}H_{14}O_2S$	74.51	74.43	4.58	4.47
1e	Cl	S	73	136-138	$C_{18}H_{11}ClOS$	69.57	69.59	3.54	3.58
2	OCH_3	Se	30	93-95 [b]	$C_{19}H_{14}O_2Se$	64.59	64.72	3.97	3.84

[a] Unless otherwise mentioned the compound was crystallized from ethanol; [b] This compound was crystallized from acetone.

Table 2



Compound	R	Yield (%)	Mp°C [a]	Formula	Calcd. C%	Found C%	Calcd. H%	Found H%	Calcd. N%	Found N%
3a	H	82	135	$C_{17}N_{12}N_2S$	73.91	73.89	4.35	4.31	10.14	10.10
3b	CH_3	92	145	$C_{18}H_{14}N_2S$	74.48	74.38	4.83	4.79	9.66	9.58
3c	OCH_3	97	154-155	$C_{18}H_{14}N_2OS$	70.59	70.72	4.58	4.72	9.15	8.98
3d	SCH_3	96	158-159	$C_{18}H_{14}N_2S_2$	67.08	66.99	4.35	4.22	8.70	8.86

[a] All compounds were crystallized from ethanol.

was crystallized from ethyl acetate-methanol to give 2.6 g (70%) of **8c**, mp 115-116°; ir (potassium bromide): ν 1645 cm^{-1} (carbonyl); 1H nmr (deuteriochloroform): 7.91 (d, 2H, aromatic), 7.37 (m, 5H, phenyl), 7.00 (d, 2H, aromatic), 6.84 (s, 1H, H_4), 4.76 (s, 2H, CH_2Br) and 3.91 ppm (s, 3H, OCH_3)

Anal. Calcd. for $C_{19}H_{15}BrO_3$; C, 61.46; H, 4.04. Found: C, 61.28; H, 4.17.

4-(*p*-Methoxyphenyl)-2-phenylthieno[3,4-*b*]furan (**1c**).

A solution of **8c** (371 mg, 1 mmole) and thioacetamide (82.5 mg, 1.1 mmoles) in 10 ml of ethanol was refluxed for 7 hours. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform-petroleum ether, 1:1). The desired compound was crystallized from ethanol to give 183 mg (60%) of **1c**, mp 113-114°, ^1H nmr (deuteriochloroform): 7.73 (d, 2H, aromatic), 7.00 (s, 1H, H_6), 6.92 (d, 2H, aromatic), 6.63 (s, 1H, H_3) and 3.84 ppm (s, 3H, OCH_3); ms: m/z (%) 306 (M^+, 100), 291 (47), 202 (16), 189 (11), 105 (23) and 77 (36).

Anal. Calcd. for $C_{19}H_{14}O_2S$: C, 74.51; H, 4.58. Found: C, 74.43; H, 4.47.

Other 4-aryl-2-phenylthieno[3,4-*b*]furan were prepared similarly (Table 1).

4-(*p*-Methoxyphenyl)-2-phenylselenolo[3,4-*b*]furan (**2c**).

A solution of **8c** (371 mg, 1 mmole) and *N,N*-diethylselenopropionamide (211 mg, 1.1 mmoles) [6] in 10 ml of ethanol was refluxed for 4 hours. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform-petroleum ether, 1:1), and desired compound was crystallized from acetone to give 106 mg (30%) of **2c**, mp 93-95°; ^1H nmr (deuteriochloroform): 7.78 (d, 2H, aromatic); 7.44 (m, 5H, aromatic), 7.16 (s, 1H, H_6), 6.94 (d, 2H, aromatic), 6.63 (s, 1H, H_3) and 3.85 ppm (s, 3H, OCH_3); ms: m/z (%) 354 (M+1, 100), 353 (M^+, 12), 339 (26) and 202 (11).

Anal. Calcd. for $C_{19}H_{14}O_2Se$: C, 64.59; H, 3.97. Found: C, 64.72; H, 3.84.

p-Methoxyphenyl 5-Methyl-1*H*-1-phenylpyrazole-4-yl Ketone (**11c**).

This compound was prepared similar to **7c** in 81% yield by method B, mp 125-126°; ir (potassium bromide): ν 1640 cm^{-1} (carbonyl); ^1H nmr (deuteriochloroform): 7.89 (s, 1H, H_3), 7.49 (s, 5H, phenyl), 7.44 (ABq, 4H, aromatic), 3.90 (s, 3H, OCH_3) and 2.61 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.97; H, 5.48; N, 9.59. Found: C, 73.84; H, 5.62; N, 9.53.

p-Methoxyphenyl 5-Bromomethyl-1*H*-1-phenylpyrazole-4-yl Ketone (**12c**).

This compound was prepared similar to **8c** in 87% yield, mp 99-100°; ir (potassium bromide): ν 1635 cm^{-1} (carbonyl); ^1H nmr (deuteriochloroform): 7.94 (s, 1H, H_3), 7.58 (s, 5H, phenyl), 7.46 (ABq, 4H, aromatic), 4.41 (s, 2H, -CH_2Br) and 3.90 ppm (s, 3H, OCH_3).

Anal. Calcd. for $C_{18}H_{15}BrN_2O_2$: C, 58.22; H, 4.04; N, 7.55. Found: C, 58.08; H, 4.16; N, 7.41.

4-(*p*-Methoxyphenyl)-1*H*-1-phenylthieno[3,4-*c*]pyrazole (**3c**).

This compound was prepared similar to **1c** in 97% yield, mp 154-155°; ^1H nmr (deuteriochloroform): 7.96 (s, 1H, H_3), 7.79-6.92 (m, 9H, aromatic), 6.82 (s, 1H, H_6) and 3.85 ppm (s, 3H, OCH_3); ms: m/z (%) 306 (M^+, 100), 291 (10), 151 (12) and 177 (87).

Anal. Calcd. for $C_{18}H_{14}N_2OS$: C, 70.59; H, 4.58; N, 9.15. Found: C, 70.72; H, 4.72; N, 8.98.

Other 4-aryl-1*H*-1-phenylthieno[3,4-*c*]pyrazoles were prepared similarly (Table 2).

Diethyl 4-Methyl-2-phenyl-5-thiazolylmethylidenemalonate (**15**).

To a stirring solution of **14** (2.03 g, 0.01 mole) in anhydrous pyridine was added diethyl malonate (1.76 g, 0.011 mole) and 5-6 drops of piperidine. The mixture was stirred for 2 hours then warmed to 80° for 8 hours. The solvent was evaporated and the residue was crystallized from water-ethanol to yield 2.59 g (75%) of **15**, mp 89-90°; ir (potassium bromide): ν 3060, 1725 (C=O), 1715 (C=O) and 1655 cm^{-1} (C=C); ^1H nmr (deuteriochloroform): 8.01-7.93 (m, 2H, aromatic), 7.90 (s, 1H, vinylic H), 7.47-7.39 (m, 3H, aromatic), 4.44 (q, 2H, -CH_2), 4.31 (q, 2H, -CH_2), 2.63 (s, 3H, CH_3), 1.40 (t, 3H, -CH_3) and 1.34 ppm (t, 3H, -CH_3); ms: m/z (%): 345 (M^+, 89), 299 (69), 254 (25), 227 (100), 199 (38), 168 (28), 152 (19) and 124 (26).

Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.61; H, 5.51; N, 4.06. Found: C, 62.58; H, 5.64; N, 4.05.

Diethyl 4-Bromomethyl-2-phenyl-5-thiazolylmethylidenemalonate (**16**).

This compound was prepared similar to **8c** in 85% yield, mp 101-103°; ir (potassium bromide): ν 3060, 1725 (C=O), 1710 (C=O) and 1620 cm^{-1} (C=C); ^1H nmr (deuteriochloroform): 8.02-7.90 (m, 2H, aromatic), 7.81 (s, 1H, vinylic H), 7.50-7.40 (m, 3H, aromatic), 4.73 (s, 2H, CH_2Br), 4.44 (q, 2H, -CH_2), 4.34 (q, 2H, -CH_2), 1.41 (t, 3H, -CH_3) and 1.38 ppm (t, 3H, -CH_3); ms: m/z (%) 425 (M^++1, 30), 380 (12), 378 (12), 344 (48), 305 (20), 298 (45), 270 (74), 244 (26), 198 (100), 123 (31), 95 (42) and 67 (29).

Anal. Calcd. for $C_{18}H_{18}BrNO_4S$:C, 50.94; H, 4.25; N, 3.30. Found: C, 50.81; H, 4.19; N, 3.19.

5-Benzyl-2-phenylpyrrolo[3,4-*d*]thiazole (**4**).

To stirring solution of **16** (4.24 g, 0.01 mole) in absolute ethanol was added benzylamine (3.21 g, 0.03 mole). The mixture was stirred for 24 hours at room temperature and then refluxed for 4 hours. The solvent was evaporated and to the residue water was added .The mixture was extracted with chloroform. The organic layer was dried and evaporated. The residue was purified on column (silica gel, chloroform/methanol, 90:10). The desired compound was crystallized from chloroform to yield 2.32 (80%) of **4**, mp 140-142°; ^1H nmr (deuteriochloroform): 7.98-7.95 (m, 2H, aromatic), 7.22 (d, 1H, H_4, J = 2 Hz), 7.18-7.15 (m, 2H, aromatic), 6.73 (d, 1H, H_6, J = 2 Hz) and 5.24 ppm (s, 2H, -CH_2-); ms: m/z (%): 290 (M^+, 100), 257 (10), 213 (12), 199 (41), 186 (23), 91 (100), 69 (88) and 65 (52).

Anal. Calcd. for $C_{18}H_{14}N_2S$: C, 74.48; H, 4.83; N, 9.66. Found: C, 74.31; H, 4.71; N, 9.48.

6-Diethylmalonyl-4,6-dihydro-2-phenylthieno[4,3-*d*]thiazole (**17**).

To a stirring solution of **16** (4.24 g, 0.01 mole) in absolute ethanol was added thioacetamide (8.25 g, 0.011 mole). The mixture was refluxed for 4 hours. The solvent was evaporated and the residue was purified by preparative tlc (chloroform/meth-

anol, 90:10). The desired compound was crystallized from ether-petroleum ether to give 0.94 g, (25%) of **17**, mp 40-41°; ir (potassium bromide): ν 3060, 1730 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): 7.96-7.74 (m, 2H, aromatic), 7.52-7.35 (m, 3H, aromatic), 5.19 (dq, 1H, H_6, J = 9.3 Hz, $J_{4,6}$ = 4.0 Hz, $J_{4,6}$ = 2.0 Hz), 4.41-4.21 (m, 6H, $-OCH_2-$, $-CH_2-S$), 3.81 (d, 1H, CH $(COOC_2H_5)_2$, J = 9.3 Hz) and 1.97-1.40 ppm (m, 6H, $-CH_3$); ms: m/z (%) 377 (M^+, 18), 303 (18), 258 (49), 231 (51), 218 (100), 115 (39), 71 (27) and 69 (36).

Anal. Calcd. for $C_{18}H_{19}NO_4S_2$: C, 57.29; H, 5.04; N, 3.71. Found: C, 57.16; H, 5.17; N, 3.82.

Acknowledgment.

This work was partially supported by a grant from the research council of the Medical Sciences University of Tehran and the International Organization for Chemical Sciences in Development (IOCD).

REFERENCES AND NOTES

[1] A. Shafiee and M. Rezayazdi, *J. Heterocyclic Chem.*, **32**, 177 (1995) and references cited therein.

[2] A. Shafiee and M. Etebari, *J. Sci. I. R. Iran*, **6**, 223 (1995).

[3] G. T. Seaborg, *Science*, **223**, 9 (1984).

[4] A. Tanaka and K. Yamamoto, *J. Heterocyclic Chem.*, **15**, 301 (1978).

[5] A. Shafiee and E. Behnam, *J. Heterocyclic Chem.*, **15**, 589 (1978).

[6] F. Malek-Yazdi and M. Yalpani, *Synthesis*, 328 (1977).

[7] G. Menozzi, L. Mosti and P. Schenone, *J. Heterocyclic Chem.*, **14**, 1669 (1987).

[8] I. Simiti and A. Muresan, *Rev. Roum. Chim.*, **21**, 1073 (1976); *Chem. Abstr.*, **86**, 29697u (1977).

[9] H. Gilman, W. Langham and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940).