

Masaji Shimadzu, Nobuko Ishikawa, Katsumi Yamamoto and Akira Tanaka*

Faculty of Pharmaceutical Science, Josai University, Keyakidai 1-1,
Sakado, Saitama 350-02, Japan
Received January 17, 1986

Methyl 5-alkoxy-2-furancarboxylates, methyl 5-alkylthio-2-furancarboxylates and methyl 5-phenylthio-2-furancarboxylate were prepared by nucleophilic substitution of methyl 5-nitro-2-furancarboxylates. Also, 5-phenoxyfuran-2-nitriles and 5-phenylthiofuran-2-nitriles were prepared.

J. Heterocyclic Chem., **23**, 1179 (1986).

In the previous paper [2], the preparation of methyl 5-phenoxy-2-furancarboxylates by nucleophilic substitution of methyl 5-nitro-2-furancarboxylate (**1a**) has been reported. In the present paper this work was extended to the reaction of some other nucleophiles with **1a** and 5-nitrofuran-2-nitrile (**1b**).

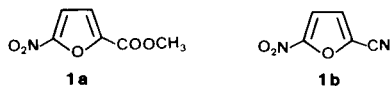


Chart 1

Reaction with Alkoxides and Phenoxides.

It has been reported by Severin *et al* [3] that 2,5-dinitro-furan reacts with potassium alkoxides to give 2-alkoxy-5-nitrofurans. It is interesting to investigate the nucleophilic substitution of 5-nitrofurans which are easily available. Compound **1a** was allowed to react with sodium methoxide in dimethylsulfoxide (DMSO) at various temperatures but the intractable product obtained caused the decomposition of the nitrofuran ring. When **1a** was treated with a hot sodium methoxide-methanol solution methyl 5-methoxy-2-furancarboxylate (**2a**) was obtained in a yield of 29%. Reactions were also carried out using sodium ethoxide, sodium isopropoxide, and sodium *t*-butoxide, respectively but only the reaction with sodium ethoxide gave ethyl 5-ethoxy-2-furancarboxylate (**2b**). The other two alkoxides did not give 5-alkoxy derivatives because of the large steric environment. The reaction of **1b** with sodium ethoxide, however, gave ethyl 5-nitro-2-furancarboximidate instead of 5-ethoxyfuran-2-nitrile. When **1b** also was reacted with potassium phenoxides, the corresponding 5-phenoxyfuran-2-nitriles **4a-e** were obtained (Table I).

Reaction with Thiolates.

Since thiolates ions have strong nucleophilicity, it is expected that the reaction of 5-nitrofurans with thiolates will give good results. Compound **1a** was treated with sodium phenylthiolates in dimethylformamide (DMF) to give a series of methyl 5-phenylthio-2-furancarboxylates **5a-h** in good yield. In these reactions, the yield depended upon

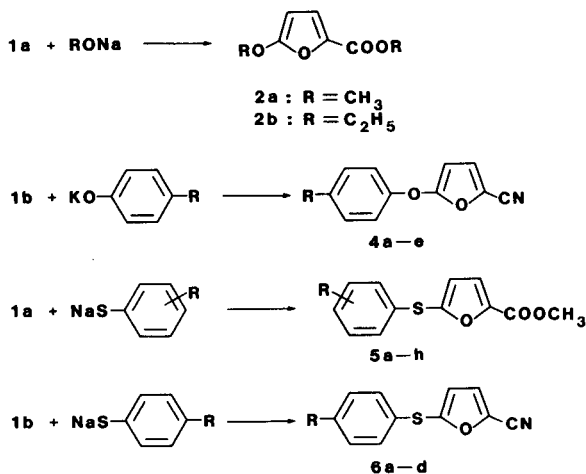


Chart 2

the substituent on the benzene ring of the phenylthiolates, that is, those that possessed an electron-attracting group showed good yields, on the other hand, those that possessed an electron-releasing group showed lower yields in spite of having a longer reaction time. Compound **1b** also was reacted with sodium phenylthiolates to give the corresponding 5-phenylthiofuran-2-nitriles **6a-d** as shown in Table I. The yields were lower than those of **5**.

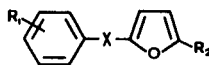
In the reaction of **1a** with aliphatic thiolates, the corresponding 5-alkylthio derivatives were obtained however they were detected as crystalline carboxylic acids by hydrolyzing them with sodium hydroxide.

EXPERIMENTAL [4]

Methyl 5-Methoxy-2-furancarboxylate (**2a**).

Sodium (0.14, 6.0 mg-atoms) was dissolved in 50 ml of methanol. To the solution was added dropwise under an atmosphere of nitrogen 10 ml of an ethanol solution containing 1.0 g (5.85 mmoles) of **1a**. After ten minutes, the reaction mixture was concentrated to one half. The mixture was poured into 200 ml of ice water, then extracted with ether. The ether extract was dried over calcium chloride, and evaporated. The residue was recrystallized from petroleum ether to give 250 mg (29%) of **2a** as colorless prisms, mp 51°. The crystals were identified by mixed melting point and various spectral comparison with an authentic sample [5].

Table I



Compound No.	R ₁	R ₂	X	Time (hours)	Temp (°C)	Yield (%)	bp/(°C)/torr or mp (°C)	Recrystallization solvent	Formula	Analysis (%)		
										Calcd.	(Found)	
										C	H	N
4a	4-NO ₂	CN	O	5	60	27.6	70-72	MeOH	C ₁₁ H ₆ N ₂ O ₄	57.40 (57.32)	2.63 (2.66)	12.17 (12.16)
4b	4-Cl	CN	O	5	60-70	66.2	42-43	MeOH	C ₁₁ H ₆ ClNO ₂	60.15 (60.09)	2.75 (2.70)	6.38 (6.39)
4c	4-H	CN	O	5	60-70	66.7	168/22		C ₁₁ H ₇ NO ₂	71.35 (71.11)	3.81 (3.72)	7.56 (7.48)
4d	4-CH ₃	CN	O	5	60-70	59.1	150-155/7		C ₁₂ H ₇ NO ₂	72.35 (72.02)	4.55 (4.35)	7.03 (7.22)
4e	4-OCH ₃	CN	O	5	60-70	63.03	175-176/7		C ₁₂ H ₇ NO ₃	66.97 (66.86)	4.22 (4.38)	6.51 (6.45)
5a	4-NO ₂	CO ₂ CH ₃	S	3	80	64.5	128-129	MeOH	C ₁₂ H ₇ NO ₃ S	51.61 (51.94)	3.25 (3.43)	5.02 (5.02)
5b	CO ₂ CH ₃	CO ₂ CH ₃	S	3	100	44.3	144-146	MeOH	C ₁₄ H ₁₂ O ₅ S	57.52 (57.59)	4.14 (4.43)	
5c	4-Cl	CO ₂ CH ₃	S	1	80	95.5	92-92.5	benzene- benzene	C ₁₂ H ₆ ClO ₃ S	53.63 (53.47)	3.38 (3.38)	
5d	H	CO ₂ CH ₃	S	1	80	90.5	41.5-42	petroleum benzene	C ₁₂ H ₁₀ O ₃ S	61.52 (61.36)	4.30 (4.48)	
5e	2-CH ₃	CO ₂ CH ₃	S	1	80	91.0	51-52	petroleum benzene	C ₁₃ H ₁₂ O ₃ S	62.88 (62.87)	4.87 (5.07)	
5f	3-CH ₃	CO ₂ CH ₃	S	1	80	88.6	56-56.5	petroleum benzene	C ₁₃ H ₁₂ O ₃ S	62.88 (62.34)	4.87 (5.06)	
5g	4-CH ₃	CO ₂ CH ₃	S	1	80	90.0	65-66	petroleum benzene	C ₁₃ H ₁₂ O ₃ S	62.88 (62.34)	4.87 (4.73)	
5h	2-NH ₂	CO ₂ CH ₃	S	1	80	93.8	67-68	petroleum benzene	C ₁₂ H ₁₁ NO ₃ S	57.81 (57.96)	4.45 (4.47)	5.62 (5.66)
6a	4-NO ₂	CN	S	5	60-70	5.6	120-121	MeOH	C ₁₁ H ₆ N ₂ O ₃ S	53.65 (53.60)	2.46 (2.58)	11.38 (11.13)
6b	4-Cl	CN	S	5	69-70	52.8	158-160/2		C ₁₁ H ₆ ClNOS	56.05 (56.01)	2.57 (2.64)	5.94 (5.70)
6c	H	CN	S	1	60-70	75.5	145/4		C ₁₁ H ₇ NOS	65.65 (65.59)	3.51 (3.49)	6.96 (6.55)
6d	4-CH ₃	CN	S	2	60-70	77.0	155-156/3		C ₁₂ H ₇ NOS	66.95 (66.81)	4.21 (4.09)	6.51 (6.60)

Ethyl 5-Ethoxy-2-furancarboxylate (2b).

Sodium (0.14 g 6.0 mg-atoms) was dissolved in 50 ml of ethanol. To the sodium ethoxide solution was added dropwise under an atmosphere of nitrogen 10 ml of an ethanol solution containing 1.0 g (5.58 mmoles) of **1a**. After ten minutes, the reaction mixture was concentrated to one half. The concentrated mixture was poured into 200 ml of ice water, then extracted with ether. The extract was dried over calcium chloride, and evaporated. The residue was chromatographed on silica gel, eluting with benzene to give 240 mg (24%) of **2b** as colorless needles, mp 37.5-38.0°. The crystals were identified by mixed melting point and various spectral comparisons with an authentic sample [5].

5-Phenoxyfuran-2-nitriles 4a-d (Table I).

A mixture of potassium phenoxides (0.07 mole), 8.0 g (0.058 mole) of **1b** and 100 ml of DMSO was heated at 60-70° for five hours under stirring. The mixture poured into ice water and extracted with benzene. The benzene extract was washed 5% potassium hydroxide solution and water,

dried over calcium chloride and evaporated. Compounds **4a** and **4b** were obtained by recrystallization from an appropriate solvent. Compounds **4c** and **4d** were purified by distillation under vacuum.

Methyl 5-Phenylthio-2-furancarboxylates 5a-h (Table I).

A solution of thiophenols (0.0117 mole) in DMF was treated with 0.78 g (0.02 mol) of 60% sodium hydride with stirring, and the mixture was cooled to room temperature. Then, 2.0 g (0.0117 mole) of **1a** dissolved in 5 ml of DMF was added dropwise and stirring was continued for one to three hours at 80-100°. The mixture was then poured into ice water. With **5d-g**, the resulting suspension was extracted with ether. The ether extract was washed with 5% potassium hydroxide solution and water, dried over sodium sulfate and evaporated. The resulting crystals were filtered and recrystallized from petroleum benzene. With **5a-c, h** the resulting precipitate was filtered and recrystallized from suitable solvents to give the pure product.

5-Phenylthiofuran-2-nitriles 6a-d.

A solution of thiophenols (0.014 mole) in acetonitrile was treated with

Table II

Spectral Data for Methyl 5-Phenylthio-2-furancarboxylates, 5-Phenoxy-2-furonitrile, and 5-Phenylthio-2-furonitriles

Compound No.	MS (M ⁺)	Nujol		Solvent [a]	NMR [b] Chemical shift (δ)
		IR	ν max cm ⁻¹		
4a	230	2230	(C=N)	C	5.82 (1H, d, J = 3.5 Hz, F H-4), 7.11 (1H, d, J = 3.5 Hz, F H-3) 7.17 (2H, d, J = 9.0 Hz, P H), 8.26 (2H, d, J = 9.0 Hz, P H)
4b	219	2230	(C=N)	C	5.55 (1H, d, J = 3.9 Hz, F H-4), 7.06 (1H, d, J = 3.9 Hz, F H-3), 7.06 (2H, d, J = 9.0 Hz, P H), 7.36 (2H, d, J = 9.0 Hz, P H)
4c	185	2220	(C=N)	C	5.37 (1H, d, J = 3.9 Hz, F H-4), 7.02 (1H, d, J = 3.9 Hz, F H-3), 7.00-7.55 (5H, m, P H)
4d	199	2235	(C=N)	C	2.32 (3H, s, CH ₃), 5.41 (1H, d, J = 3.7 Hz, F H-4), 6.80-7.30 (6H, m, F H-3 and P H)
4e	215	2230	(C=N)	C	3.78 (3H, s, OCH ₃), 5.35 (1H, d, J = 3.8 Hz, F H-4), 6.70-7.30 (6H, m, F H-3 and P H)
5a	279	1732	(C=O)	A	3.88 (3H, s, CH ₃), 7.18 (1H, d, J = 3.4 Hz, F H-4), 7.39 (1H, d, J = 3.4 Hz, F H-3), 7.44 (1H, dd, J = 7.79 Hz, P H), 7.68 (1H, dd, J = 8.79 Hz, P H), 8.18 (1H, dd, J = 7.79 Hz, P H), 8.26 (1H, dd, J = 8.79 Hz, P H)
5b	292	1722, 1700	(C=O)	A	3.66 (3H, s, CH ₃), 3.95 (3H, s, CH ₃), 6.85 (1H, dd, J = 9.23 Hz, P H), 7.10 (1H, d, J = 3.42 Hz, F H-4), 7.28 (1H, dd, J = 8.79 Hz, P H), 7.80 (1H, d, J = 3.42 Hz, F H-3), 7.51 (1H, dd, J = 8.79 Hz, P H), 8.03 (1H, dd, J = 9.23 Hz, P H)
5c	268	1734	(C=O)	A	3.86 (3H, s, CH ₃), 6.94 (1H, d, J = 3.9 Hz, F H-4), 7.30 (1H, d, J = 3.9 Hz, F H-3), 7.36 (4H, s, P H)
5d	234	1736	(C=O)	A	3.88 (3H, s, CH ₃), 6.92 (1H, d, J = 3.9 Hz, F H-4), 7.30 (1H, d, J = 3.9 Hz, F H-3), 7.37 (5H, s, P H)
5e	248	1735	(C=O)	A	2.48 (3H, s, CH ₃), 3.87 (3H, s, CH ₃), 6.83 (1H, d, 3.9 Hz, F H-4), 7.23-7.30 (5H, m, F H-3 and P H)
5f	248	1735	(C=O)	A	2.30 (3H, s, CH ₃), 3.74 (3H, s, CH ₃), 6.91 (1H, d, J = 3.9 Hz, F H-4), 7.15-7.30 (5H, m, F H-3 and P H)
5g	248	1735	(C=O)	A	2.37 (3H, s, CH ₃), 3.86 (3H, s, CH ₃), 6.85 (1H, d, J = 3.6 Hz, F H-4), 7.27-7.37 (5H, m, F H-3 and P H)
5h	249	1734	(C=O) 3360, 3460 (NH ₂)	A	3.80 (3H, s, CH ₃), 5.19 (2H, bs, NH ₂), 6.55 (1H, d, J = 3.4 Hz, F H-4), 6.66 (1H, dd, J = 9.28 Hz, P H), 6.84 (1H, dd, J = 9.28 Hz, P H), 7.18 (1H, d, J = 3.41 Hz, F H-3), 7.39 (1H, dd, J = 9.28 Hz, P H)
6a	246	2230	(C=N)	C	6.89 (1H, d, J = 3.8 Hz, F H-4), 7.21 (1H, d, 3.8 Hz, F H-3), 7.30 (1H, d, J = 9.0 Hz, P H), 8.18 (2H, d, J = 9.0 Hz, P H)
6b	235	2230	(C=N)	C	6.59 (1H, d, J = 3.7 Hz, F H-4), 7.02 (1H, d, J = 3.7 Hz, F F-3), 7.26 (4H, s, P H)
6c	201	2235	(C=N)	C	6.58 (1H, d, J = 3.8 Hz, F H-4), 7.06 (1H, d, J = 3.8 Hz, F H-3)
6d	215	2235	(C=N)	C	2.30 (3H, s, CH ₃), 6.48 (1H, d, J = 3.7 Hz, F H-4), 7.02 (1H, d, J = 3.7 Hz, F H-3)

[a] A: perdeuterioacetone; c: deuteriochloroform. [b] s = singlet, d = doublet, dd = double doublet, m = multiplet, b s = broad singlet, F = furan ring, P = benzene ring.

0.68 g (0.017 mole) of 60% sodium hydride stirring and the mixture was cooled to room temperature. Then, 2.0 g (0.014 mole) of **1b** was added and stirring was continued for one to five hours at 60-70°. The mixture was then poured into ice water. With **6a**, the resulting crystals were filtered and recrystallized from methanol. With **6b-d**, the resulting oil was extracted with benzene. The benzene extract was washed with 5% potassium hydroxide and water, dried over sodium sulfate and evaporated. The residual oil was distilled under vacuum.

5-Cyclohexyl-2-furancarboxylic Acid (**7a**).

A solution of 1.36 g (0.0117 mole) of cyclohexanethiol in 15 ml of DMF was treated with 0.78 g (0.02 mole) of 60% sodium hydride with stirring and the mixture was cooled to room temperature. Then, 2 g (0.0117 mole) of **1a** dissolved in 5 ml of DMF was added dropwise and the stirring was continued for five hours at 80°. The mixture was then poured into ice water, and extracted with ether. The ether extract was washed with 5% potassium hydroxide solution and water, dried over sodium sulfate and

evaporated. The residual yellow oil was heated in 10% sodium hydroxide solution. The reaction mixture was acidified with dilute hydrochloric acid to deposit a white precipitate. The precipitate was filtered, and recrystallized from benzene to give 1.55 g (59%) of **7a** as colorless needles, mp 109-110°; ms: m/e 226 (M⁺); ir (Nujol): ν max cm⁻¹ 2580 (COOH), 1680 (C=O); nmr (acetone-d₆): 1.29-1.95 (11H, m, cyclohexane H), 6.69 (1H, d, J = 3.4 Hz, furan-4H), 7.72 (1H, d, J = 3.4 Hz, furan-3H).

Anal. Calcd. for C₁₁H₁₄O₅S: C, 58.38; H, 6.24. Found: C, 58.00; H, 6.12.

5-Benzylthio-2-furancarboxylic Acid (**7b**).

A solution of 1.45 g (0.0117 mole) of benzylmercaptan in 15 ml of DMF with 0.78 g (0.02 mole) of 60% sodium hydride with stirring and the mixture was cooled to room temperature. Then, 2 g (0.0117 mole) of **1a** dissolved in 5 ml of DMF was added dropwise and the stirring was continued for two hours at 80°. The remainder of directions are identical with those described above for **7a**. The precipitate was filtered and recrystallized from benzene to give 1.97 g (72%) of **7b** as colorless needles,

mp 128-129°; ms: m/e 234 (M⁺); ir (Nujol): ν max cm⁻¹ 2560 (COOH), 1680 (C=O); nmr (acetone-d₆): 4.21 (2H, s, CH₂), 6.57 (1H, d, J = 3.42 Hz, furan-4H), 7.17 (1H, d, J = 3.4 Hz, furan-3H), 7.29 (5H, s, phenyl H), 7.36 (1H, s, COOH).

Anal. Calcd. for C₁₂H₂₀O₃S: C, 61.52; H, 4.30. Found: C, 61.53; H, 4.49.

REFERENCES AND NOTES

[1] Part XIII of this series, A. Tanaka and T. Usui, *Heterocycles*, **16**, 963 (1981).

[2] A. Tanaka, T. Usui and M. Shimadzu, *Chem. Pharm. Bull.*, **28**, 2846 (1980).

[3] T. Severin and H. Kullmer, *Chem. Ber.*, **106**, 1688 (1973).

[4] All melting points and boiling points are uncorrected. The following instruments were used to obtain physical data. The nmr spectra were obtained on JEOL 60HL and PS-100 spectrophotometers with TMS as an internal standard. The ir spectra were obtained with a Jasco IRA-1 spectrophotometer. Mass spectra were obtained on a direct inlet Shimadzu LKB-9000 machine.

[5] D. C. Manly and E. D. Amstutz, *J. Org. Chem.*, **21**, 516 (1956).