Synthesis of Phenyl Furyl Sulfides and Phenyl Furyl Ethers by Nucleophilic Substitution of Nitrofurans

Masayuki Ogawa, Katsuya Sakuma, Hiroshi Okamoto, Jyunichi Koyanagi, Kouji Nakayama, Akira Tanaka, and Katsumi Yamamoto*

Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan

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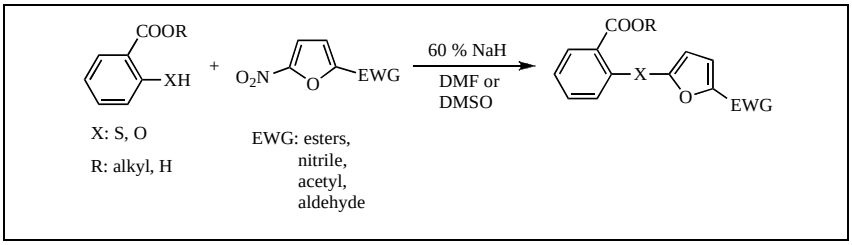

Phenyl furyl sulfides (**3a-j**) and phenyl furyl ethers (**3k-n**), which are useful in synthesizing furo-condensed 3-ring compounds, can be synthesized by nucleophilic substitution of nitrofurans having electron withdrawal groups. In our experiments using 5-nitrofurans having electron withdrawal groups (**2a-i**), nucleophilic substitution readily occurred with the benzenethiolate anion of thiosalicylic acid (**1a**), the benzenethiolate anion of thiosalicylate ester (**1b**), and the phenylate anions of salicylate esters (**1c-d**) to yield phenyl furyl sulfides (**3a-j**) and phenyl furyl ethers (**3k-n**).

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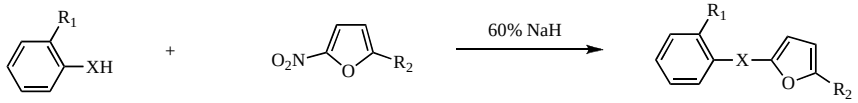
Furan rings, classified as pi-excessive heterocyclic rings, are known to be highly reactive in electrophilic substitution reactions. However, nucleophilic substitution reactions do not readily proceed unless strong electron withdrawal groups are present, and thus such reactions have not been considered important in synthetic chemistry [1]. However, interest in these reactions has gradually increased since 1951, when Bunnett and Zahler [2] published their review article on aromatic nucleophilic substitution. Here, we briefly discuss these reactions of interest in the field of synthetic chemistry.

In 1891, Tiemann [3] synthesized *o*- and *p*-methoxybenzonitrile by reacting 2-chloro-4-nitrobenzaldehyde and sodium methoxide, and in 1899, Reinders and Ringer [4] synthesized the same compound from *p*-nitrobenzonitrile and sodium methoxide. In a 1957 study into the rate of substitution, Bunnett *et al.* [5] reported that in reactions between pipiridine and 1,2,4-trinitrobenzene, 1-chloro-2,4-dinitrobenzene or 1-bromo-2,4-dinitrobenzene in methanol, the relative rate of substitution of the nitro group at position 1 was 200 times faster than that of chlorine or bromine. In 1977, Bartoli and Todesco [6] reported that in reactions of methoxide ions and 1,2,4-trinitrobenzene, 1-fluoro-2,4-dinitrobenzene or 1-chloro-2,4-dinitrobenzene, the relative rate of substitution of the nitro group at position 1 was equivalent to that of fluorine, and 400 times faster than chlorine substitution.

On the other hand, with regard to nucleophilic substitution of nitro groups in heteroaromatic systems, O We then performed nucleophilic substitution of 5-

Scheme 1



1a-d **2a-i** **3a-n**

Compoud No.	R_1	X
1a	COOH	S
1b	$COOCH_3$	S
1c	$COOCH_3$	O
1d	COOBzl	O

Compoud No.	R_2
2a	$COOCH_3$
2b	$COOC_2H_5$
2c	$COOC_3H_7$
2d	COO-*i*-C_3H_7
2e	$COOC_4H_9$
2f	COO-*i*-C_4H_9
2g	CN
2h	$COCH_3$
2i	CHO

see Table 1 and 2 for R_1, R_2, and X

nitrofurans (**2h-i**) with the benzenethiolate anion of thiosalicylate ester (**1b**). The sodium salt of **1b** was prepared with 60% NaH in dimethylsulfoxide (DMSO) at room temperature and was used in the reactions. This yielded the corresponding phenyl furyl sulfides (**3i-j**) (Table 1).chiai and Katada [7] reported in 1943 that 4-phenoxypridine-*N*-oxide and 4-ethoxypridine-*N*-oxide could be obtained from reactions between 4-nitropyridine-*N*-oxide and phenoxide ions and ethoxide ions, respectively. Moreover, in a 1972 study targeting the nucleophilic substitution of nitro groups from nitrofuran derivatives, Lieb *et al.* [8] successfully reacted 5-nitro-2-furancarbaldehyde with sodium azide and sodium chelates, the first examples of this type of reaction. In 1973, Severin and Kullmer [9] obtained a 5-amino and an alkoxide at the 5-position from reactions between secondary amines and alkoxides and 2,5-dinitrofuran, in which the aldehyde group was replaced with a nitro group to act as the electron withdrawal group.

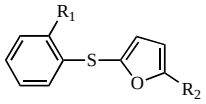
We have conducted a series of nucleophilic substitution reactions in nitrofurans using electron withdrawal groups, including 5-nitro-2-furaldehyde [10], methyl 5-nitro-2-furancarboxylate [11,12] and 5-nitrofuran-2-nitrile [12]. Research on the synthesis of furo-condensed 3-ring compounds has since led to the discovery of furoindoles [13] and furobenzothiazepines [14,15], which have anti-inflammatory effects, and furonaphthoquinones [16], which have cytotoxic effects. In addition, nucleophilic substitution products can be very useful as synthetic intermediates for furo-condensed 3-ring compounds [14].

In this study, we prepared alkyl 5-nitro-2-furancarboxylates (**2a-f**), 5-nitrofuran-2-nitrile (**2g**), 5-nitro-2-acetylfuran (**2h**) and 5-nitro-2-furaldehyde (**2i**) as 5-nitrofurans with electron withdrawal groups at the 2-position. Nucleophilic substitution was carried out using the benzenethiolate anion of thiosalicylic acid (**1a**), the benzenethiolate anion of thiosalicylate ester (**1b**), the phenylate anions of salicylate esters (**1c-d**), and the phenylate anion of salicylic acid (**1e**) as nucleophilic reagents to give phenyl furyl sulfides and phenyl furyl ethers. The phenyl furyl sulfides (**3a-j**) and phenyl furyl ethers (**3k-o**) (including those previously reported) are shown in Tables 1 and 2. We now report our findings on the reactivity of these reactions (Scheme 1)

We first performed nucleophilic substitution of 5-nitrofurans (**2a-h**) with the benzenethiolate anion of thiosalicylic acid (**1a**). A solution of **1a** in *N*,*N*-dimethylformamide (DMF) was dropped into a suspension of 60% sodium hydride (NaH) in DMF at <5 ℃ to form the disodium salt of **1a**. This solution was heated to 80 ℃, and DMF solutions of **2a-h** were then dropped in and allowed to react for 3 h to yield the corresponding phenyl furyl sulfides (**3a-h**). With the exception of **3e** and **3f**, which did not require recrystallization, the yields of the nucleophilic substitution reactions did not markedly differ. This demonstrates the absence of any effects due to the type of electron withdrawal group at the 2-position of the furan ring.

We then performed nucleophilic substitution of 5-nitrofurans (**2h-i**) with the benzenethiolate anion of thiosalicylate ester (**1b**). The sodium salt of **1b** was prepared with 60% NaH in dimethylsulfoxide (DMSO) at room temperature and was used in the reactions. This yielded the corresponding phenyl furyl sulfides (**3i-j**) (Table 1).

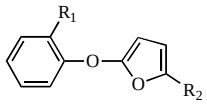
Table 1 Phenyl furyl sulfides **3a-j**



Compoud No.	R_1	R_2	Yield (%)	Mp (°C)	Recrystallization solvent
3a[15]	COOH	$COOCH_3$	52	224-225	methanol
3b	COOH	$COOC_2H_5$	50	193-194	ethanol
3c	COOH	$COOC_3H_7$	54	176-178	benzene
3d	COOH	COO-*i*-C_3H_7	63	182-183(dec.)	benzene
3e	COOH	$COOC_4H_9$	88	183-186	-
3f	COOH	COO-*i*-C_4H_9	90	183-186	-
3g	COOH	CN	66	183-184	methanol
3h	COOH	$COCH_3$	61	225(dec.)	benzen-hexane
3i[12]	$COOCH_3$	$COOCH_3$	44	144-146	methanol
3j	$COOCH_3$	CHO	68	85-86	methanol

Next, we performed nucleophilic substitution of 5-nitrofurans (**2a, 2g, 2i**) with the phenylate anion of salicylate esters (**1c-d**). As with **1b**, the sodium salts of **1c-d** were prepared with 60% NaH in DMSO at room temperature and were used in the reactions. This yielded the corresponding phenyl furyl ethers (**3k-n**) (Table 2).

Table 2 Phenyl furyl ethers **3k-n**



Compoud No.	R_1	R_2	Yield (%)	Bp(°C) / torr
3k[10]	$COOCH_3$	CHO	23	180-182 / 3
3l[11]	$COOCH_3$	$COOCH_3$	52	185 / 2
3m	$COOCH_3$	CN	80	169-171 / 2
3n[15]	COOBzl	$COOCH_3$	69	not measured

In conclusion, we successfully synthesized phenyl furyl sulfides (**3a-j**) and phenyl furyl ethers (**3k-n**), which are useful in synthesizing furo-condensed 3-ring compounds, by nucleophilic substitution of nitrofurans. Using methyl thiosalicylate (**1b**) and salicylate esters (**1c-d**),

nucleophilic substitution reactions readily occurred with 5-nitrofurans using electron withdrawal groups, similar to previous reports of nucleophilic substitution with 5-nitrofurans [10-12]. Using the disodium salt of thiosalicylic acid (**1a**), we found that nucleophilic substitution reactions readily proceeded with several 5-nitrofurans having electron withdrawal groups.

EXPERIMENTAL

All melting points (open capillaries) were determined using a Yamato MP-21 and are uncorrected. ^{1}H-NMR spectra were determined at 60 MHz using a Nippon Denshi JNM PMX60 SI spectrometer with tetramethylsilane as an internal reference. IR spectra were measured using a JASCO IR-810 spectrometer. MS spectra were measured with a Nippon Denshi DX-300 spectrometer at 70 eV.

General procedure for nucleophilic substitution of 5-nitrofurans with disodium salt of thiosalicylic acid. A solution of thiosalicylic acid (15.4 g, 0.1 mol) in *N,N*-dimethylformamide (DMF) (120 ml) was added to a suspension of 60% sodium hydride (8 g, 0.333 mol) in DMF (120 ml) with stirring at <5℃, and the mixture was warmed to 80℃. To this mixture, a solution of 5-nitrofurans (0.1 mol) in DMF (50 ml) was added, and stirring was performed for 3 h at 80℃. The solution was then cooled to room temperature and poured into ice-cold water. The solution was acidified with 10% hydrochloric acid and the resulting product was collected by filtration and purified by recrystallization (Table 1).

Ethyl 5-(2-Carboxyphenylthio)-2-furancarboxylate (3b). The product was pale yellow needles; IR (potassium bromide): 3200-2800 (OH), 1730 ($COOCH_3$), 1670 (COOH) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 8.10-6.83 (4H, m, Ph-H), 7.50 (1H, d, *J*=4 Hz, F-3), 7.24 (1H, d, *J*=4 Hz, F-4), 4.38 (2H, q, *J*=7 Hz, CH_2), 1.25 (3H, t, *J*=7 Hz, CH_3); MS m/z: 292 (M^+). *Anal*. Calculated for $C_{14}H_{12}O_5S$: C, 57.53; H, 4.14. Found: C, 57.48; H, 4.06.

Propyl 5-(2-Carboxyphenylthio)-2-furancarboxylate (3c). The product was pale yellow needles; IR (potassium bromide): 3200-2800 (OH), 1730 (COOCH3), 1680 (COOH) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 8.01-6.65 (4H, m, Ph-H), 7.22 (1H, d, *J*=4 Hz, F-3), 6.85 (1H, d, *J*=4 Hz, F-4), 4.25 (2H, t, *J*=7 Hz, OCH_2), 1.36 (2H, m, CH_3), 1.00 (3H, t, *J*=7 Hz, CH_3); MS m/z: 306 (M^+). *Anal*. Calculated for $C_{15}H_{14}O_5S$: C, 58.81; H, 4.61. Found: C, 58.76; H, 4.75.

Isopropyl 5-(2-Carboxyphenylthio)-2-furancarboxylate (3d). The product was colorless needles; IR (potassium bromide): 3200-2800 (OH), 1725 ($COOCH_3$), 1690 (COOH) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 8.30-6.63 (4H, m, Ph-H), 7.36 (1H, d, *J*=4 Hz, F-3), 7.12 (1H, d, *J*=4 Hz, F-4), 5.25-4.93 (1H, m, CH), 1.30 (6H, d, *J*=6 Hz, CH_3 x 2); MS m/z: 306 (M^+). *Anal*. Calculated for $C_{15}H_{14}O_5S$: C, 58.81; H, 4.61. Found: C, 58.89; H, 4.57.

Butyl 5-(2-Carboxyphenylthio)-2-furancarboxylate (3e). The product was pale yellow needles; IR (potassium bromide): 3200-2800 (OH), 1725 ($COOCH_3$), 1675 (COOH) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 8.06-6.60 (4H, m, Ph-H), 7.41 (1H, d, *J*=4 Hz, F-3), 7.15 (1H, d, *J*=4 Hz, F-4), 4.23 (2H, t, *J*=6 Hz, OCH_2), 1.83-1.20 (4H, m, CH_2 x 2), 0.90 (3H, t, *J*=6 Hz, CH_3); MS m/z: 320 (M^+). *Anal*. Calculated for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03. Found: C, 59.92; H, 5.06.

Isobutyl 5-(2-Carboxyphenylthio)-2-furancarboxylate (3f). The product was pale yellow needles; IR (potassium bromide): 3200-2800 (OH), 1720 ($COOCH_3$), 1685 (COOH) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 8.06-6.60 (4H, m, Ph-H), 7.40 (1H, d, *J*=4 Hz, F-3), 7.14 (1H, d, *J*=4 Hz, F-4), 4.28-3.97 (2H, m, CH_2), 2.17-1.76 (1H, m, CH), 0.96 (6H, d, *J*=6 Hz, CH_3 x 2); MS m/z: 320 (M^+). *Anal*. Calculated for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03. Found: C, 60.05; H, 4.95.

5-(2-Carboxyphenylthio)furan-2-nitrile (3g). The product was pale yellow prisms; IR (potassium bromide): 3000-2500 (OH), 2230 (CN), 1630 (CO) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 8.08-6.67 (4H, m, Ph-H), 7.78 (1H, d, *J*=4 Hz, F-3), 7.27 (1H, d, *J*=4 Hz, F-4); MS m/z: 245 (M^+). *Anal*. Calculated for $C_{12}H_7NO_3S$: C, 58.77; H, 2.88; N, 5.71. Found: C, 58.57; H, 2.72; N, 5.93.

5-(2-Carboxyphenylthio)-2-acetylfuran (3h). The product was pale yellow needles; IR (potassium bromide): 3100-2600 (OH), 1780 (CO) cm^{-1}; ^{1}H-NMR (deuteriochloroform) δ: 8.00-6.60 (4H, m, Ph-H), 7.52 (1H, d, *J*=4 Hz, F-3), 7.15 (1H, d, *J*=4 Hz, F-4), 2.42 (3H, s, CH_3); MS m/z: 262 (M^+). *Anal*. Calculated for $C_{13}H_{10}O_4S$: C, 59.53; H, 3.84. Found: C, 59.50; H, 3.95.

5-(2-Methoxycarbonylphenylthio)-2-furancarbaldehyde (3j). A solution of methyl salicylate (16.8 g, 0.1 mol) in dimethylsulfoxide (DMSO) (150 ml) was added to a suspension of 60% sodium hydride (4 g, 0.167 mol) in DMSO (50 ml) with stirring at room temperature, and the mixture was warmed to 50-55℃. To this mixture, a solution of 5-nitro-2-furancarbaldehyde (14.1 g, 0.1 mol) in DMSO (50 ml) was added, and stirring was performed for 30 min. The solution was then cooled to room temperature and poured into ice-cold water. The resulting product was collected by filtration and purified by recrystallization (Table 1). The product was pale yellow needles; IR (potassium bromide): 1710, 1680 (CO) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 9.56 (1H, s, CHO), 8.01-6.70 (4H, m, Ph-H), 7.61 (1H, d, *J*=4 Hz, F-3), 7.21 (1H, d, *J*=4 Hz, F-4), 3.80 (3H, s, CH_3); MS m/z: 262 (M^+). *Anal*. Calculated for $C_{13}H_{10}O_4S$: C, 59.53; H, 3.84. Found: C, 59.86; H, 3.66.

5-(2-Methoxycarbonylphenoxy)furan-2-nitrile (3m). A solution of methyl salicylate (10.6 g, 0.07 mol) in dimethylsulfoxide (DMSO) (50 ml) was added to a suspension of 60% sodium hydride (2.8 g, 0.117 mol) in DMSO (50 ml) with stirring at room temperature, and the mixture was warmed to 60-70°C. To this mixture, a solution of 5-nitrofuran-2-nitrile (8 g, 0.058 mol) in DMSO (50 ml) was added, and stirring was performed for 3 h. The solution was then cooled to room temperature and poured into ice-cold water. The resulting oil was extracted with benzene. The benzene layer was washed with brine and dried over anhydrous sodium sulfate. The solution was evaporated and the residue was distilled under reduced pressure to give 11.3 g (80.2%). The product was a colorless liquid.; IR (neat): 2230 (CN), 1736 (CO) cm^{-1}; ^{1}H-NMR (dimethyl-d_6 sulfoxide) δ: 8.00-6.94 (4H, m, Ph-H), 6.98 (1H, d, *J*=4 Hz, F-3), 5.32 (1H, d, *J*=4 Hz, F-4), 3.81 (3H, s, CH_3); MS m/z: 243 (M^+). *Anal*. Calculated for $C_{13}H_9NO_4S$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.12; H, 3.61; N, 5.56.

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