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The Regioselective Side-Chain Lithiation of 2-Methyl-3-thiophenecarboxylic Acid

Su Hui-Wen, Kazuo Hirose, Kozo Shirai, and Takanobu Kumamoto*
Department of Chemistry, Faculty of Science, Tokai University,
Kitakaname, Hiratsuka, Kanagawa 259-12
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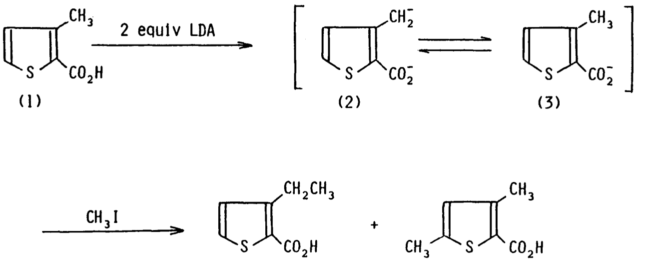
Synopsis. It was found that the dilithium salt (**5**), which was lithiated at the side-chain of 2-methyl-3-thiophenecarboxylic acid (**4**), was produced regioselectively by the reaction of **4** with lithium diisopropylamide (LDA). The reactions of **5** with alkyl halides resulted in the formation of 2-alkyl-3-thiophenecarboxylic acids (**7**). Further, δ-lactone derivatives (**11**) were obtained by the cyclization of the adducts (**10**) which were produced from **5** with aldehydes and ketones.

The side-chain metalation of thiophene derivatives has attracted considerable attention[1a—c] in terms of its usefulness for the synthesis of many types of the thiophene derivatives. However, the selectivity of the side-chain metalation of the thiophene derivatives is reported to be unsatisfactory because of the metalation of the thiophene nuclei. For example, Lee et al.[1c] reported that lithiation of 3-methyl-2-thiophenecarboxylic acid (**1**) with two equivalents of lithium diisopropylamide (LDA) and subsequent treatment with methyl iodide gave a mixture of the products which were formed from the dilithium salts of **2** and **3** respectively, in the ratio of 35 : 65 (Scheme 1).

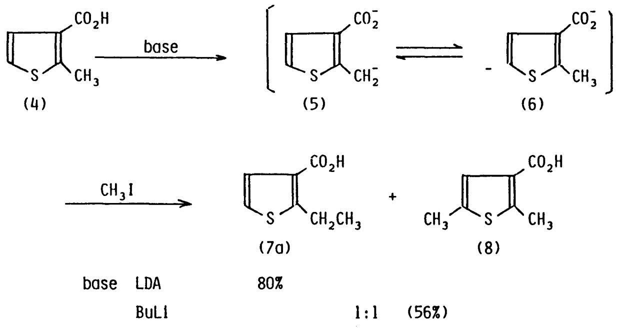


Scheme 1.

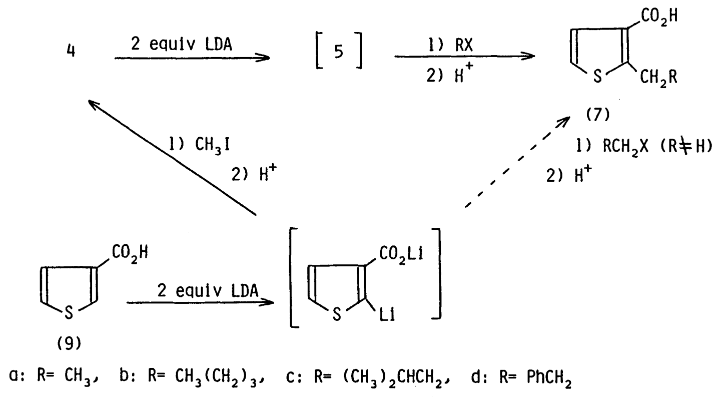
We report herein the selective side-chain lithiation of 2-methyl-3-thiophenecarboxylic acid (**4**) and some reactions of the resulting dilithium salt with electrophiles.

Results and Discussion

In the course of our studies on the Birch reduction of thiophene derivativs,[2a,b] we examined the alkylation of 2-methyl-3-thiophenecarboxylic acid (**4**) and found the remarkably high regioselective side-chain lithiation of **4**. When the formation of a dilithium salt from **4** with two equivalents of lithium diisopropylamide (LDA) at -30 °C in THF was followed by alkylation with methyl iodide, 2-ethyl-3-thiophenecarboxylic acid (**7a**) was obtained in 80% yield without the formation of 2,5-dimethyl-3-thiophenecarboxylic acid (**8**). This result shows that the side-chain lithiation occurred selectively in sharp contrast to the reaction of 3-methyl-2-thiophenecarboxylic acid (**1**) with LDA. However, when butyllithium was used as the base instead of the LDA, regioselectivity was decreased and the mixture of **7a** and **8** was obtained in the ratio of 1 : 1. It is not clear at the present time why the selectivity of the lithiation is decreased by the use of the butyllithium.



. The reactions of the dilithium salt **5** with several alkyl halides were carried out to yield 2-alkyl-3-thiophenecarboxylic acids (**7**). The results are summarized in Table 1. These reactions may be useful



Scheme 2.

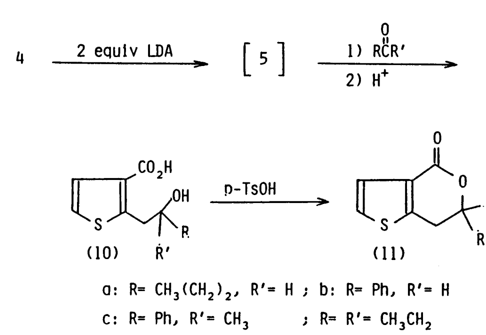


Table 1. Preparation of 2-Alkyl-3-thiophenecarboxylic Acid (**7**)

	R	Yields of **2**
7a	CH_3	80%
7b	$CH(CH_2)_3$	83%
7c	$(CH_3)_2CHCH_2$	70%
7d	$PhCH_2$	70%

Table 2. Preparation of 2-(2-Hydroxyalkyl)-3-thiophenecarboxylic Acid (**10**) and δ-Lactone Derivatives (**11**)

R	R′	Yields of **10** (%)		Yields of **11** (%)	
$CH_3(CH_2)_2$	H	**10a**	77	**11a**	86
Ph	H	**10b**	63	**11b**	87
Ph	CH_3	**10c**	61	**11c**	99
CH_3CH_2	CH_3CH_2	**10d**	81	**11d**	92

because the yields of the reaction of dilithium salt of 3-thiophenecarboxylic acid (**9**) with alkyl halides are not satisfactory for the practical synthesis of **7**, except for the case of the methyl iodide[1b] (Scheme 2).

Furthermore, the reactions of dilithium salt **5** with aldehydes or ketones produced the adducts (**10**) which were easily cyclized to δ-lactone derivatives **11** in refluxing benzene in the presence of *p*-toluenesulfonic acid. The results are summarized in Table 2.

Experimental

Preparation of 2-Ethyl-3-thiophenecarboxylic Acid (7a). Into a solution of LDA in 20 ml of THF, prepared from diisopropylamine (3.60 g, 35.6 mmol) and butyllithium (36.0 mmol), a solution of 2-methyl-3-thiophenecarboxylic acid (**4**) (2.53 g, 17.8 mmol) in 5 ml of THF was added at −30 °C under nitrogen. After the reaction mixture had been stirred for 1 h at −30 °C, a solution of methyl iodide (2.53 g, 17.8 mmol) in 5 ml of THF was added and stirring was continued for 2.5 h at −30 °C. The reaction mixture was quenched with 10% hydrochloric acid and extracted with ether. The ethereal layer was washed with small amounts of sodium sulfite solution and dried over magnesium sulfate. After removal of the ether, the resulting residue was chromatographed on a silica-gel column. From the elution with benzene-ether (5 : 1), 2.24 g (80%) of 2-ethyl-3-thiophenecarboxylic acid (**7a**) was obtained, mp 58—60 °C.[3] IR (KBr): 3300—2300 cm^{-1} (CO_2H), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=1.47 (3H, t), 3.46 (2H, q), 7.33 (1H, d), 7.73 (1H, d), 11.6 (1H, brs); MS: *m/z* 156 (M^+).

2-Pentyl-3-thiophenecarboxylic acid (**7b**), 2-(3-methylbutyl)-3-thiophenecarboxylic acid (**7c**), and 2-(2-phenylethyl)-3-thiophenecarboxylic acid (**7d**) were obtained by the similar procedure from **4** and the corresponding alkyl bromides. Yields and spectral data are as follows:

7b: Yield 83%; mp 62.5—63 °C; IR (KBr): 3500—2350 cm^{-1} (CO_2H), 1690 cm^{-1} (C=O); ^1H NMR($CDCl_3$): δ=0.89 (3H, t), 1.24—1.88 (6H, m), 3.22 (2H, t), 7.02 (1H, d), 7.46 (1H, d), 11.1 (1H, brs); MS: *m/z* 198 (M^+).

7c: Yield 70%; mp 64.5—65 °C; IR (KBr): 3500—2400 cm^{-1} (CO_2H), 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=0.95 (6H, d), 1.60 (3H, t), 3.22 (2H, t), 7.02 (1H, d), 7.46 (1H, d), 11.1 (1H, brs); MS: *m/z* 198 (M^+).

7d: Yield 70%; mp 96—97 °C; IR (KBr): 3500—2400 cm^{-1} (CO_2H), 1700 cm^{-1} (C=O); ^1H NMR($CDCl_3$): δ=2.86—3.11 (2H, m), 3.38—3.62 (2H, m), 7.02 (1H, d), 7.12—7.33 (5H, m), 7.46 (1H, d), 11.1 (1H, brs); MS: *m/z* 236 (M^+).

Preparation of 2-(2-Hydroxypentyl)-3-thiophenecarboxylic Acid (10a). Into a solution of LDA in 20 ml of THF, prepared from diisopropylamine (1.78 g, 17.6 mmol) and butyllithium (17.0 mmol), a solution of **4** (1.14 g, 8.0 mmol) in 5 ml of THF was added at −30 °C under nitrogen. The reaction mixture was stirred for 1 h at −30 °C. A solution of butanal (0.58 g, 8.1 mmol) in 5 ml of THF was added to the reaction mixture and the resulting mixture was stirred for 2 h at −30 °C. The reaction mixture was acidified with 10% hydrochloric acid and extracted with ether. The ethereal layer was washed with saturated sodium chloride solution and dried over magnesium sulfate. After removal of the ether, the resulting residue was chromatographed on a silica-gel column. From the elution with benzene-ether (5 : 1), 1.32 g (77%) of the acid **10a** was obtained, mp 73—75 °C. IR (KBr): 3400 cm^{-1} (OH), 3100—2300 cm^{-1} (CO_2H), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=0.73—1.87 (7H, m), 3.39 (1H, dd), 3.48 (1H, dd), 3.79—4.21 (1H, m), 7.1 (1H, brs), 7.30 (1H, d), 7.69 (1H, d); MS: *m/z* 194 (M^+−H_2O, −H_2). Found: C, 56.24; H, 6.84%. Calcd for $C_{10}H_{14}O_3S$: C, 56.04; H, 6.59%.

By a similar procedure, 2-(2-hydroxy-2-phenylethyl)-3-thiophenecarboxylic acid (**10b**), 2-(2-hydroxy-2-phenylpropyl)-3-thiophenecarboxylic acid (**10c**) and 2-(2-ethyl-2-hydroxybutyl)-3-thiophenecarboxylic acid (**10d**) were obtained from **4** and corresponding aldehydes or ketones. The yields, spectral and analytical data are as follows:

10b: Yield 63%; mp 143—148 °C; IR (KBr): 3300 cm^{-1} (OH), 3100—2300 cm^{-1} (CO_2H), 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=3.36—4.03 (2H, m), 5.12 (1H, q), 7.26 (1H, d), 7.65 (1H, d), 7.36—7.81 (5H, m); MS: *m/z* 248 (M^+). Found: C, 62.74; H, 4.66%. Calcd for $C_{13}H_{12}O_3S$: C, 62.90; H, 4.58%.

10c: Yield 61%; mp 115—117 °C; IR (KBr): 3400—2400 cm^{-1} (CO_2H), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=1.60 (3H, s), 3.50 (1H, d), 3.78 (1H, d), 7.01 (1H, d), 7.17—7.56 (6H, m); MS: *m/z* 244 (M^+−H_2O). Found: C, 63.99; H, 5.44%. Calcd for $C_{14}H_{14}O_3S$: C, 64.11; H, 5.38%.

10d: Yield 81%; mp 95—97 °C; IR (KBr): 3400—2200 cm^{-1} (CO_2H), 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=0.91 (6H, t), 1.54 (4H, q), 3.31 (2H, s), 7.09 (1H, d), 7.37 (1H, d); MS: *m/z* 210 (M^+−H_2O). Found: C, 57.65; H, 7.11%. Calcd for $C_{11}H_{16}O_3S$: C, 57.88; H, 7.07%.

Preparation of 6,7-Dihydro-6-propyl-4*H*-thieno[3,2-*c*]pyran-4-one (11a). A solution of **10a** (1.16 g, 54.2 mmol) and a catalytic amount of *p*-toluenesulfonic acid in 100 ml of benzene was refluxed for 3 h with a water separating apparatus. The mixture was evaporated and the resulting residue was chromatographed on a silica-gel column. From the elution with benzene, 0.91 g (86%) of the pyrane **11a** was obtained as an oil. IR (NaCl): 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=0.96 (3H, t), 1.31—2.04 (4H, m), 2.92—3.10 (2H, m), 4.42—4.76 (1H, m), 7.14 (1H, d), 7.41 (1H, d); MS: *m/z* 196 (M^+). Found: C, 61.38; H, 6.35%. Calcd for

$C_{10}H_{12}O_2S$: C, 61.21; H, 6.17%.

By a similar procedure, 6,7-dihydro-6-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one (**11b**), 6,7-dihydro-6-methyl-6-phenyl-4*H*-thieno[3,2-*c*]pyran-4-one (**11c**), and 6,6-diethyl-6,7-dihydro-4*H*-thieno[3,2-*c*]pyran-4-one (**11d**) were formed from the corresponding acids **10**. The yields, spectral and analytical data are as follows:

11b: Yield 87%; mp 130 °C; IR (KBr): 1700 cm^{-1}(C=O); ^1H NMR ($CDCl_3$): δ=3.33 (2H, d), 5.64 (1H, t), 7.20 (1H, d), 7.36—7.60 (6H, m); MS: *m/z* 230 (M^+). Found: C, 67.72; H, 4.27%. Calcd for $C_{13}H_{10}O_2S$: C, 67.82; H, 4.38%.

11c: Yield 94%; oil; IR (NaCl): 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=1.64 (3H, s), 3.41 (1H, d), 3.67 (1H, d), 7.05 (1H, d), 7.20—7.53 (6H, m); MS: *m/z* 244 (M^+). Found: C, 68.66; H, 5.04%. Calcd for $C_{14}H_{12}O_2S$: C, 68.84; H, 4.95%.

11d: Yield 92%; oil; IR (NaCl): 1700 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ=0.93 (6H, t), 1.86 (4H, q), 3.06 (2H, s), 7.14 (1H, d), 7.44 (1H, d); MS: *m/z* 210 (M^+). Found: C, 62.93; H, 6.88%. Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71%.

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