A FACILE SYNTHESIS OF HIGHLY FUNCTIONALIZED UNSYMMETRICAL HETEROBIARYLS UTILIZING THE INTRAMOLECULAR ULLMANN COUPLING REACTION DIRECTED BY SALICYL ALCOHOL AS A TEMPLATE

Masami Takahashi, Tooru Kuroda, Tsuyoshi Ogiku, Hiroshi Ohmizu, Kazuhiko Kondo, and Tameo Iwasaki*

Department of Synthetic Chemistry, Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 3-16-89 Kashima, Yodogawa, Osaka 532, Japan

Abstract - The cyclic heterobiaryls (**3**) containing a thenoyl or furoyl group were synthesized in good yields by regioselective acylations of salicyl alcohol (**1**), followed by the intramolecular Ullmann coupling reaction of the diesters (**2**). The cleavage of the two ester bonds of **3** by hydrogenolysis or nucleophilic substitution reactions proceeded regioselectively to afford the highly functionalized unsymmetrical heterobiaryls (**4**-**6**) in good yields.

INTRODUCTION

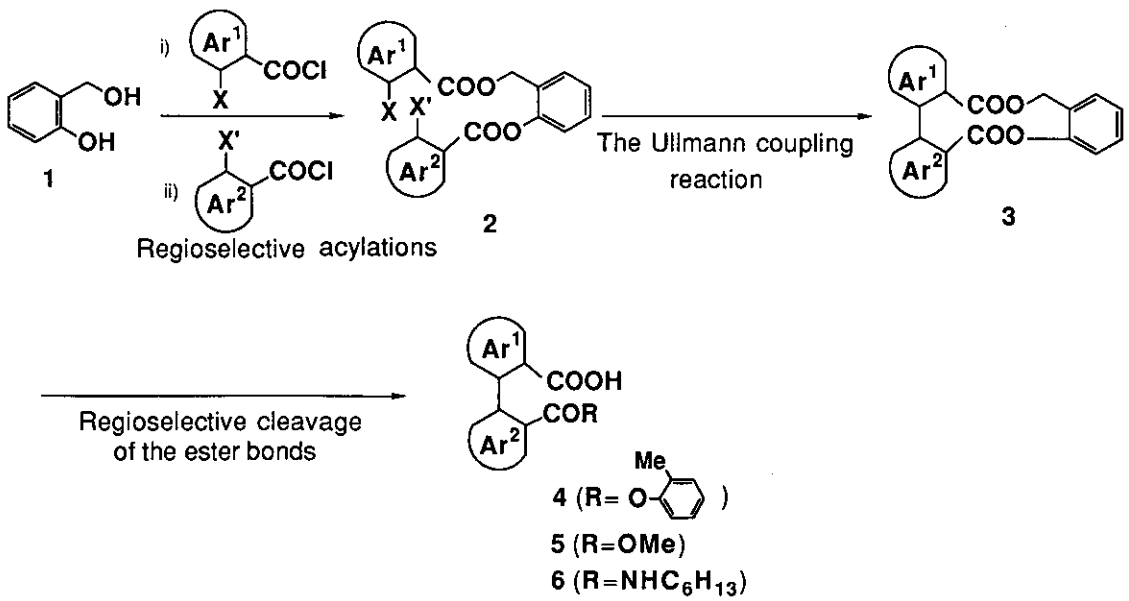
The highly functionalized unsymmetrical heterobiaryls are of considerable interest recently as useful intermediates in the synthesis of the biologically active natural products such as tanshinone.[1] The synthetic methods of the heterobiaryls so far reported include those based on the transition metal-catalyzed cross coupling reaction of an aryl metal with an aryl halide and the intermolecular Ullmann coupling reaction.[2,3] However, difficulties are frequently encountered in the transition metal-catalyzed cross coupling reactions between two aryls having substituents which are incompatible with the organometallic reagents. On the other hand, the

intermolecular Ullmann coupling reaction gives rise to the undesired symmetrical biaryls.[4] We have previously reported our preliminary results[5] of an efficient synthesis of highly functionalized unsymmetrical heterobiaryls utilizing the intramolecular Ullmann coupling reaction as a key step. In this paper, we provide full details of this synthetic method together with new results.

RESULTS AND DISCUSSIONS

Our method consists of the three steps involving the regioselective acylations of salicyl alcohol by two different aroyl chlorides, the intramolecular Ullmann coupling reaction[6] and the regioselective transformation of the two ester groups of **3** into the other functional groups different from each other (Scheme 1).

Scheme 1

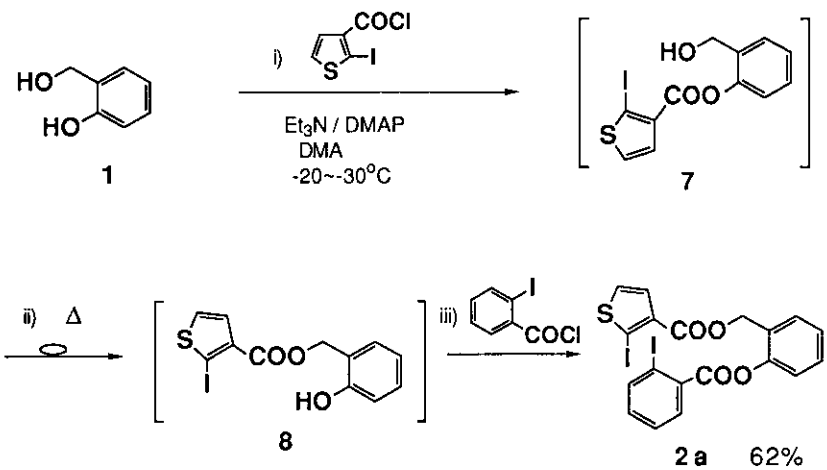


Regioselective acylations of salicyl alcohol

As described in the previous papers,[7] the migration of an aroyl group from the phenolic hydroxyl group of salicyl alcohol to the benzylic one is a key step in this regioselective acylations of salicyl alcohol.[8] We first examined the migration reaction in the acylation of salicyl alcohol using 2-iodo-3-thenoyl chloride as a typical example (Scheme 2). Salicyl alcohol was acylated with 2-iodo-3-thenoyl chloride in *N,N*-dimethylacetamide (DMA) in the presence of triethylamine at -30~-20 °C, and the reaction mixture was then gradually warmed up to

room temperature. On monitoring the reaction by thin layer chromatography (tlc), the first acylated product (**7**) formed at -30~-20 °C was found to be gradually converted into the migration product (**8**) at room temperature; the rate of migration of the thenoyl group is almost the same as that of a benzoyl group having electron-donating substituents.[7] After completion of the migration, **8** was isolated by quenching the reaction; the structure of **8** was determined by the ^{1}H-nmr spectrum. Without isolation of **8**, the second acylation by 2-iodobenzoyl chloride was carried out to afford **2a** in 62% yield.

Scheme 2

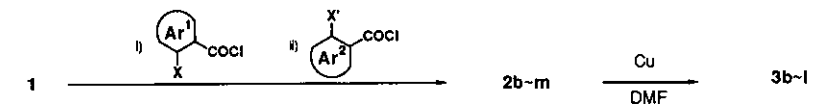


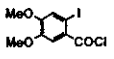
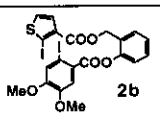
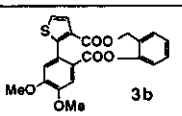
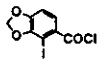
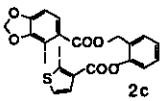
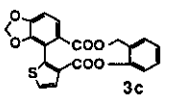
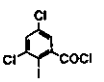
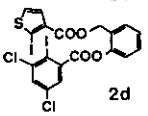
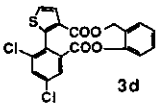
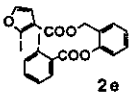
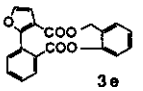
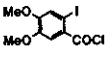
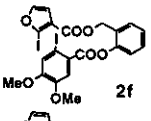
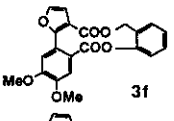
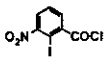
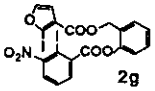
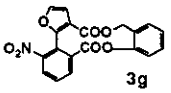
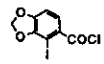
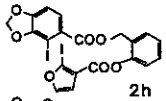
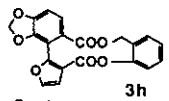
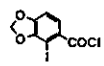
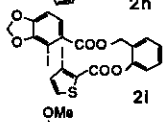
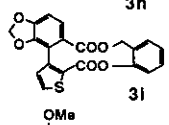
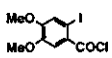
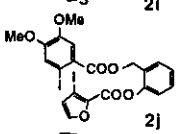
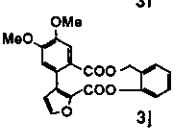
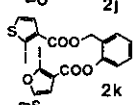
This one-pot procedure for acylations of salicyl alcohol was successfully applied to the synthesis of a variety of the diesters (**2**) having a thenoyl or furoyl group. The results are summarized in Table 1. The melting points and spectral data of **2** are shown in Table 3.

The intramolecular Ullmann coupling reaction of the diesters (**2**)

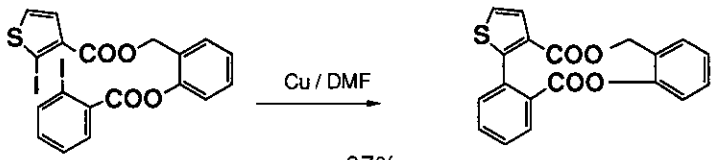
We next examined the intramolecular Ullmann coupling reaction of the diesters (**2**). The coupling reaction of **2a** by the dropwise addition method[9] furnished the corresponding coupling product (**3a**) in 87% yield (Scheme 3); in this reaction, a small amount of polymerization products was formed probably by the intermolecular Ullmann coupling reaction.

Table 1 Regioselective acylations of salicyl alcohol and the intramolecular Ullmann coupling reaction



entry			Regioselective acylations		The intramolecular Ullmann coupling reaction	
			Product	Yield (%)	Product	Yield (%)
1			 2b	65	 3b	87
2			 2c	78	 3c	84
3			 2d	62	 3d	78
4			 2e	61	 3e	80
5			 2f	64	 3f	83
6			 2g	61	 3g	83
7			 2h	68	 3h	78
8			 2i	62	 3i	67
9			 2j	70	 3j	68
10			 2k	69	3k	81
11			2l	65	3l	64
12			2m	64	3l	28

Scheme 3



2a **3a**

As shown in Table 1, in the Ullmann coupling reaction of the diesters containing a 2-iodo-3-thenoyl group and a benzoyl one having electron-donating substituents (**2b, c**) or electron-withdrawing substituents (**2d**) on the benzene ring, the coupling product was obtained in a good yield (entries 1~3). The coupling reaction of the diesters (**2e~h**) containing a 2-iodo-3-furoyl group also gave the corresponding coupling products (**3e~h**) in good yields (entries 4~7); the structure of **3f** was determined by the X-ray crystallographic analysis. Even in the case of the diesters (**2i, j**) having a 3-iodo-2-thenoyl group and a 3-iodo-2-furoyl one which are less reactive than 2-iodo-3-thenoyl group[10] and 2-iodo-3-furoyl one respectively, the corresponding coupling products (**3i, j**) were obtained in satisfactory yields; in the coupling reaction of the diester (**2m**) having a 3-bromo-2-thenoyl group which is much less reactive than a 3-iodo-2-thenoyl group, the yield of the product (**3i**) remarkably decreased (entry 12). Furthermore, the Ullmann coupling reaction of the diesters (**2k, l**) having two heteroaromatics furnished the coupling products (**3k, l**) in good yields (entries 10, 11). The melting points and spectral data are shown in Table 4. From these results, the coupling reactions leading to the heterobiaryls (**3**) were found to proceed efficiently regardless of the nature of substituents on the benzene rings and of heteroaromatics.

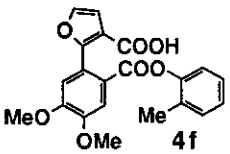
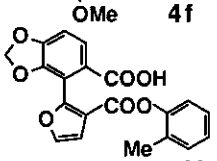
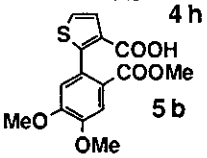
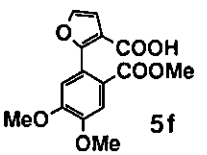
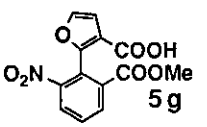
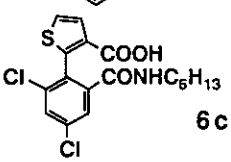
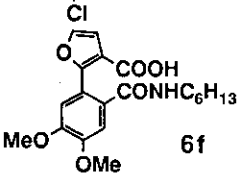
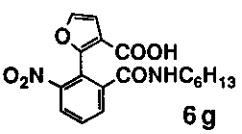
It is noteworthy that the coupling products was obtained in good yields even in the reaction of the diesters (**2c, d, 2g~i**) having the substituents on both of the two *ortho* positions of the reaction site on a benzene ring.

These results clearly show that this intramolecular Ullmann coupling reaction is not influenced by steric hindrance around the reaction sites.[11]

Regioselective cleavage of the two ester bonds of **3**

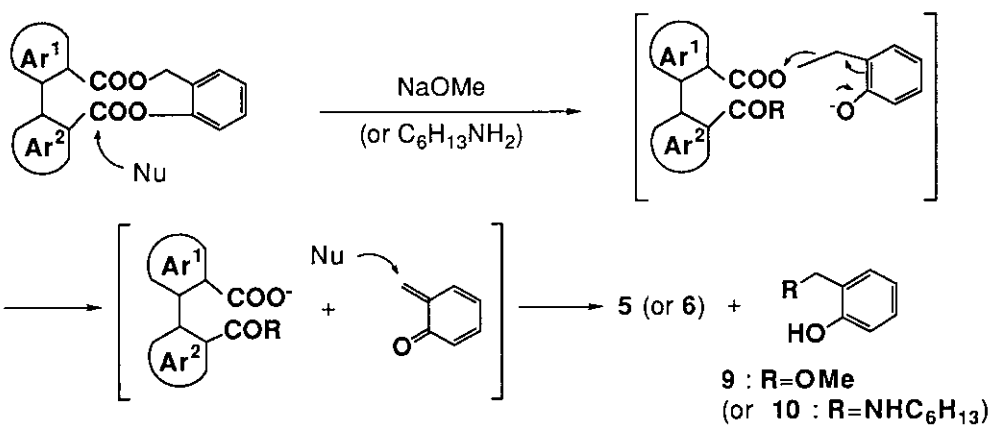
We finally examined the regioselective cleavage of the ester bonds of **3** by hydrogenolysis or nucleophilic substitution reactions.

Table 2 Regioselective cleavage of the ester bonds of 3 by hydrogenolysis and nucleophilic substitution reactions

entry	Substrate	Method	Product	Yield (%)
1	**3f**	H_2 , Pd-C /Dioxane	 **4f**	95
2	**3h**	H_2 , Pd-C /Dioxane	 **4h**	78
3	**3b**	NaOMe / MeOH	 **5b**	81
4	**3f**	NaOMe / MeOH	 **5f**	82
5	**3g**	NaOMe / MeOH	 **5g**	76
6	**3c**	$C_6H_{13}NH_2$ / CH_2Cl_2	 **6c**	91
7	**3f**	$C_6H_{13}NH_2$ / CH_2Cl_2	 **6f**	89
8	**3g**	$C_6H_{13}NH_2$ / CH_2Cl_2	 **6g**	90

Hydrogenolysis of **3f** and **3h** furnished **4f** and **4h** in 95% and 78% yields, respectively (Table 2, entries 1, 2) . We next examined the regioselective conversion of the ester groups of **3** into the other functional groups different from each other by nucleophilic substitution reactions. Treatment of **3b, f, g** with two molar equivalents of sodium methoxide in methanol at room temperature afforded the corresponding monoesters (**5b, f, g**) in good yields, respectively (Table 2, entries 3~5). In this reaction, *o*-methoxymethylphenol (**9**) was obtained; **9** would be formed by the reaction of the intermediately generated *o*-quinone methide[12] with sodium methoxide (Scheme 4). The diesters (**3c, f, g**) were similarly treated with hexylamine in CH_2Cl_2 to afford the corresponding monoamides (**6c, f, g**) in high yields (Table 2, entries 6~8), together with the formation of *o*-hexylaminomethylphenol (**10**). The structures of **5f** and **6f** were confirmed by comparison with the authentic samples which were prepared by treatment of **4f** with sodium methoxide and hexylamine, respectively.

Scheme 4



As described above, the two ester bonds of **3** were readily converted into the other functional groups different from each other. The use of nucleophiles other than sodium methoxide and hexylamine will make it possible to convert the two ester bonds into the functional groups other than methoxycarbonyl and hexylaminocarbonyl groups.

In conclusion, we achieved a remarkably efficient method for the synthesis of highly functionalized heterobiaryls utilizing the intramolecular Ullmann coupling reaction as a key step. This method should find application in a synthesis of a variety of heterobiaryls having interesting biological activities.

Table 3 Analytical data and spectral details of the diesters (2)

Compound (Formula)	mp (°C)	Ir (Nujol; ν_{max}/cm^{-1})	^{1}H Nmr ($CDCl_3$) δ	Ms, m/z (relatively intensity)	Analysis (%) Found (Calcd) C	H	N
2a ($C_{19}H_{12}O_4I_2S$)	oil	1744, 1720[a]	5.38 (s, 2 H), 7.1~7.65 (m, 8 H), 8.0~8.2 (m, 2 H)	590 (M^+, 16), 231 (100)	38.73 (38.67	2.13 2.05	- -)
2b ($C_{21}H_{16}O_6I_2S$)	118	1750, 1730	3.86 (s, 3 H), 3.90 (s, 3 H), 5.34 (s, 2 H), 7.15~7.7 (m, 8 H)	650 (M^+, 6), 291 (100)	38.63 (38.79	2.44 2.48	- -)
2c ($C_{20}H_{12}O_6I_2S$)	120~121	1720	5.33 (s, 2 H), 6.03 (s, 2 H), 6.67 (d, J=8 Hz, 1 H), 7.15~7.6 (m, 7 H)	634 (M^+, 9), 237 (100)	37.79 (37.88	1.89 1.91	- -)
2d ($C_{19}H_{10}O_4Cl_2I_2S$)	92~93	1754, 1724[b]	5.36 (s, 2 H), 7.25~7.75 (m, 8 H)	658 (M^+, 4), 299 (100)	34.67 (34.63	1.50 1.53	- -)
2e ($C_{19}H_{12}O_5I_2$)	oil	1740, 1727[a]	5.36 (s, 2 H), 6.67 (d, J=2.1 Hz, 1 H), 7.15~7.7 (m, 8 H), 8.08 (dd, J=7.8, 1.7 Hz, 1 H)	574 (M^+, 9), 231 (100),	39.54 (39.75	1.97 2.11	- -)
2f ($C_{21}H_{16}O_7I_2$)	116~117	1740, 1720	3.88 (s, 3 H), 3.92 (s, 3 H), 5.33 (s, 2 H), 6.64 (d, J=1.5 Hz, 1 H), 7.15~7.7 (m, 7 H)	634 (M^+, 9), 291 (100)	39.91 (39.77	2.53 2.54	- -)
2g ($C_{19}H_{11}NO_7I_2$)	93~94	1750, 1716[a]	5.37 (s, 2 H), 6.66 (d, J=2.1 Hz, 1 H), 7.3~7.6 (m, 6 H), 7.75 (dd, J=8.0, 1.7 Hz, 1 H), 8.03 (dd, J=7.7, 1.7 Hz, 1 H)	619 (M^+, 13), 276 (100),	36.91 (36.86	1.89 1.79	2.28 2.26)
2h ($C_{20}H_{12}O_7I_2$)	115~116	1720	5.34 (s, 2 H), 6.04 (s, 2 H), 6.69 (d, J=8 Hz, 1 H), 6.84 (d, J=1 Hz, 1 H), 7.05~7.65 (m, 4 H), 7.48 (d, J=8 Hz, 1 H), 7.60 (d, J=1 Hz, 1 H)	618 (M^+, 12), 221 (100)	38.92 (38.86	2.01 1.96	- -)
2i ($C_{20}H_{12}O_6I_2S$)	134~135	1725	5.35 (s, 2 H), 6.04 (s, 2 H), 6.69 (d, J=8 Hz, 1 H), 7.15~7.65 (m, 7 H)	634 (M^+, 12), 237 (100)	37.86 (37.88	1.97 1.91	- -)
2j ($C_{21}H_{16}O_7I_2$)	134~135	1737[b]	3.87 (s, 3 H), 3.90 (s, 3 H), 5.41 (s, 2 H), 6.70 (d, J=1.8 Hz, 1 H), 7.2~7.65 (m, 4 H), 7.34 (s, 1 H), 7.37 (s, 1 H), 7.53 (d, J=1.8 Hz, 1 H)	634 (M^+, 21), 291 (100)	39.85 (39.77	2.79 2.54	- -)
2k ($C_{17}H_{10}O_5I_2S$)	83~84	1730, 1705	5.36 (s, 2 H), 5.84 (d, J=2 Hz, 1 H), 7.15~7.65 (m, 6 H), 7.61 (d, J=2 Hz, 1 H)	580 (M^+, 6), 231 (100)	35.32 (35.20	1.84 1.74	- -)
2l ($C_{17}H_{10}O_5I_2S$)	68~69	1730, 1715	5.37 (s, 2 H), 6.86 (d, J=2 Hz, 1 H), 7.15~7.7 (m, 7 H)	580 (M^+, 13), 221 (100)	35.33 (35.20	1.62 1.74	- -)
2m ($C_{20}H_{12}O_6BrIS$)	139~140	1740, 1725	5.35 (s, 2 H), 6.04 (s, 2 H), 6.68 (d, J=8.5 Hz, 1 H), 7.05~7.65 (m, 7 H)	585 (M^+, 9), 189 (100)	40.76 (40.91	2.04 2.06	- -)

[a] The infrared spectrum was measured in a liquid film. [b] The infrared spectrum was measured in KBr.

Table 4 Analytical data and spectral details of the coupling products (3)

Compound (Formula)	mp (°C)	Ir (Nujol; ν_{max}/cm^{-1})	^1H Nmr ($CDCl_3$) δ	Ms, m/z (relatively intensity)	Analysis (%) Found (Calcd) C	H	N
3a ($C_{19}H_{12}O_4S$)	169~170	1755, 1710	4.8~5.6 (m, 2 H), 7.15~7.6 (m, 8 H), 7.9~8.05 (m, 2 H)	336 (M^+, 50), 186 (100)	67.92 (67.85	3.71 3.60	- -)
3b ($C_{21}H_{16}O_6S$)	218~221	1745, 1705	3.93 (s, 3 H), 3.98 (s, 3 H), 5.23 (br s, 2 H), 6.98 (s, 1 H), 7.1~7.55 (m, 7 H)	396 (M^+, 13), 78 (100)	63.85 (63.63	4.04 4.07	- -)
3c ($C_{20}H_{12}O_6S$)	169~171	1750, 1710	4.5~6.1 (m, 2 H), 6.01 (s, 2 H), 6.76 (d, J=8 Hz, 1 H) 7.1~7.55 (m, 7 H)	380 (M^+, 34), 230 (100)	63.16 (63.15	3.11 3.18	- -)
3d ($C_{19}H_{10}O_4Cl_2S$)	171~172	1758, 1724[a]	5.14 (d, J=12.1 Hz, 1 H), 5.37 (d, J=12.1 Hz, 1 H), 7.15~7.5 (m, 6 H), 7.70 (d, J=2.2 Hz, 1 H), 7.81 (d, J=2.2 Hz, 1 H)	404 (M^+, 21), 78 (100)	56.19 (56.30	2.38 2.49	- -)
3e ($C_{19}H_{12}O_5$)	189~190	1750, 1719[a]	5.28 (br s, 2 H), 6.85 (d, J=1.9 Hz, 1 H), 7.2~7.7 (m, 7 H), 7.76 (dd, J=7.9, 1.4 Hz, 1 H), 7.96 (dd, J=7.3, 1.4 Hz, 1 H)	320 (M^+, 52), 214 (100)	70.91 (71.25	3.67 3.78	- -)
3f ($C_{21}H_{16}O_7$)	220~222	1755, 1715	3.96 (s, 3 H), 4.01 (s, 3 H), 5.26 (s, 2 H), 6.81 (d, J=1 Hz, 1 H), 7.15~7.65 (m, 7 H)	380 (M^+, 19), 274 (100)	66.51 (66.31	4.30 4.24	- -)
3g ($C_{19}H_{11}NO_7$)	228~229	1762, 1722[a]	4.7~5.8 (m, 2 H), 6.69 (d, J=1.9 Hz, 1 H), 7.2~7.5 (m, 4 H), 7.47 (d, J=1.9 Hz, 1 H), 7.73 (t, J=8.0 Hz, 1 H), 8.07 (dd, J=8.2, 1.3 Hz, 1 H), 8.16 (dd, J=7.8, 1.3 Hz, 1 H)	365 (M^+, 5), 78 (100)	62.62 (62.47	3.02 3.04	3.79 3.83)
3h ($C_{20}H_{12}O_7$)	178~180	1725	5.46 (br s, 2 H), 6.03 (s, 2 H), 6.80 (d, J=8 Hz, 1 H), 6.96 (d, J=1 Hz, 1 H), 6.9~7.45 (m, 5 H), 7.55 (d, J=1 Hz, 1 H)	364 (M^+, 28), 258 (100)	66.08 (65.93	3.24 3.32	- -)
3i ($C_{20}H_{12}O_6S$)	179~180	1735, 1705	4.77 (brd, J=12 Hz, 1 H), 6.02 (brd, J=12 Hz, 1 H), 5.9~6.2 (m, 2 H), 6.77 (d, J=8 Hz, 1 H), 7.05~7.45 (m, 6 H), 7.60 (d, J=8 Hz, 1 H)	380 (M^+, 68), 274 (100)	63.25 (63.15	3.25 3.18	- -)
3j ($C_{21}H_{16}O_7$)	221~223	1730, 1725[a]	3.92(s, 3 H), 3.95 (s, 3 H), 4.7 (br, 1 H), 6.3 (br, 1 H), 6.71 (d, J=1.7 Hz, 1 H), 6.91 (s, 1 H), 7.1~7.45 (m, 5 H), 7.75 (d, J=1.7 Hz, 1 H)	380 (M^+, 25), 274 (100)	66.35 (66.31	4.28 4.24	- -)
3k ($C_{17}H_{10}O_5S$)	177~179	1725, 1705	5.41 (s, 2 H), 6.9~7.6 (m, 8 H)	326 (M^+, 52), 220 (100)	62.29 (62.57	2.89 3.09	- -)
3l ($C_{17}H_{10}O_5S$)	174~175	1726	5.40 (s, 2 H), 6.89 (d, J=2 Hz, 1 H), 7.0~7.6 (m, 7 H)	326 (M^+, 49), 220 (100)	61.98 (62.57	3.01 3.09	- -)

[a] The infrared spectrum was measured in KBr.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Yamato MP-21 melting point apparatus and were uncorrected. Infrared spectra were obtained using a Perkin Elmer 1640 infrared spectrometer. Nmr spectra were recorded on a Hitachi R-90 or a Bruker AC-200 instrument using Me_4Si as the internal standard. Mass spectra were obtained on a Hitachi M-60 or Hitachi M-2000A spectrometers. Tlc was carried out on silica gel (Merck type 60H). DMF and DMA, purchased from Katayama Kagaku, were dried over molecular sieves 4 A and used without further purification. All other solvents were purchased from Katayama Kagaku and used without purification. Copper powder was purchased from Katayama Kagaku and used immediately after purification.[13] A 1.6 *M* BuLi in hexane was purchased from Asia Lithium.

Preparation of the aroyl chlorides—2-Iodobenzoyl chlorides were prepared according to the reported methods.[5,14]

3-Iodo-2-thenoic acid was prepared according to the reported method.[15] 2-Iodo-3-thenoic acid was prepared as follows. To a solution of lithium diisopropylamide (105 mmol), prepared from 1.6*M* BuLi in hexane (66 ml) and diisopropylamine (10.6 g) in tetrahydrofuran (THF) (40 ml), was added dropwise a solution of 3-thenoic acid[16] (6.4 g, 50 mmol) in THF (40 ml) at -78 °C. The mixture was stirred for 20 min at the same temperature. To the reaction mixture was added dropwise a solution of iodine (12.7 g, 50 mmol) in ether (10 ml). The resulting mixture was poured into water (300 ml) and the solution was washed with ether (100 ml). The aqueous layer was acidified with 10% hydrochloric acid. The mixture was extracted with ethyl acetate (100 ml x 3). The combined organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol-water to give 2-iodo-3-thenoic acid (10.7 g, 42 mmol); mp 176~177 °C (lit.,[17] mp 178 °C). 2-Iodo-3-furoic acid[18] was prepared from 3-furoic acid under the same reaction conditions as above; mp 146~147 °C (lit.,[19] mp 150 °C). 3-Bromo-2-thenoic acid was prepared as follows. To a solution of lithium diisopropylamide (55 mmol) in THF (40 ml) was added dropwise a solution of 3-bromothiophene (8.2 g, 50 mmol) in THF (40 ml) at -78 °C. The mixture was stirred for 20 min at the same temperature and then poured into a stirred slurry of crushed solid CO_2 in ether. To the reaction mixture was added water (300 ml), and the mixture was washed with ether (100 ml). The aqueous layer was acidified with 10% hydrochloric acid. The mixture was extracted with ethyl acetate (100 ml x 3). The combined organic layer was dried over $MgSO_4$. The mixture was evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate-hexane to give 3-bromo-2-thenoic acid (8.4 g, 42 mmol); mp 155~156 °C; ir (nujol) ν_{max} 3100, 1670 cm^{-1}; ^1H nmr ($CDCl_3$, 90

MHz) δ 7.06 (1 H, d, *J*=5.5 Hz), 7.45 (1 H, d, *J*=5.5 Hz), 9.45 (1 H, br s); ms m/z (relative intensity), 206 (M^+, 85%), 189 (100), 82 (69). 3-Bromo-2-furoic acid[20] was prepared from 3-bromofuran under the same reaction conditions as above. 3-Bromo-2-furoic acid; mp 159~161 °C (lit.,[21] mp 159.5~160 °C). 3-Iodo-2-furoic acid was prepared as follows. To a solution of lithium diisopropylamide (105 mmol), prepared from 1.6*M* BuLi in hexane (66 ml) and diisopropylamine (10.6 g), in THF (40 ml), was added dropwise a solution of 5-trimethylsilyl-2-furoic acid[17] (9.2 g, 50 mmol) in THF (40 ml) at -78 °C, and the mixture was stirred for 20 min at the same temperature. To the reaction mixture was added dropwise a solution of iodine (12.7 g, 50 mmol) in ether (10 ml). To the reaction mixture was added water (300 ml) . The mixture was washed with ether (100 ml). The aqueous layer was acidified with 10% hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried over $MgSO_4$. The mixture was evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate-hexane to afford 3-iodo-5-trimethylsilyl-2-furoic acid (12.4 g, 43 mmol); mp 123~126 °C; ir (nujol) ν_{max} 3050, 1675 cm^{-1}; ^1H nmr ($CDCl_3$, 90 MHz) δ 0.32 (9 H, s), 6.84 (1 H, s), 10.2 (1 H, br s); ms m/z (relative intensity), 310 (M^+, 28%), 75 (100). To a solution of 3-iodo-5-trimethylsilyl-2-furoic acid in THF (40 ml) was added 1 *M* tetrabutylammonium fluoride in THF (40 ml), and the mixture was refluxed for 5 h. The solvent was evaporated to dryness *in vacuo*. To the residue was added 1% hydrochloric acid (100 ml). The mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate-hexane to afford 3-iodo-2-furoic acid (8.8 g, 37 mmol); mp 132~135 °C; ir (nujol) ν_{max} 3400, 1680 cm^{-1}; ^1H nmr ($CDCl_3$, 90 MHz) δ 6.73 (1 H, d, *J*=2 Hz), 7.48 (1 H, br s), 7.58 (1 H, d, *J*=2 Hz); ms m/z (relative intensity), 238 (M^+, 100%). The carboxylic acids obtained above were converted to the corresponding acid chlorides as follows. A carboxylic acid (50 mmol) was refluxed in dioxane (15 ml) containing thionyl chloride (15 ml, 0.2 mol) for 30 min. The mixture was evaporated to dryness *in vacuo*. To the residue was added toluene (50 ml) and the solvent was evaporated to dryness *in vacuo*. This evaporation procedure was repeated twice, and the residue was used in the next step without further purification.

Preparation of 8 —To a solution of salicyl alcohol (**1**) (1.24 g, 10 mmol), Et_3N (3.34 ml, 24 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in DMA (50 ml) was added dropwise 2-iodo-3-thenoyl chloride (2.7 g, 10 mmol) in methylene chloride (10ml) at -30~-20 °C. The reaction mixture was warmed to room temperature and stirred for 6 h at the same temperature. The reaction mixture was poured into 10% aqueous citric acid solution (300 ml). The solution was extracted with ethyl acetate (3 x 100 ml). The organic layer was

dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was crystallized from diisopropyl ether to afford **8** (2.2 g, 61%) as colorless crystals; mp 68~70 °C; ir (KBr) 3500, 1725 cm^{-1}; ^1H nmr ($CDCl_3$, 90 MHz) δ 5.32 (2 H, s, $ArCH_2$), 7.25~7.75 (7 H, m, ArH); ms m/z (relative intensity) 348 (M^+, 27), 106 (100); Anal. Calcd for $C_{11}H_9O_3IS$: C, 37.95; H, 2.61. Found: C, 37.93; H, 2.59.

Preparation of the diesters (**2**) —To a solution of salicyl alcohol (**1**) (1.24 g, 10 mmol), Et_3N (3.34 ml, 24 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in DMA (50 ml) was added dropwise a solution of 2-iodo-3-thenoyl chloride (2.7 g, 10 mmol) in methylene chloride (10ml) at -30~-20 °C. The reaction mixture was warmed to room temperature, and stirred for 6 h at the same temperature. The mixture was again cooled to -30~-20 °C. To the mixture was added 2-iodobenzoyl chloride (2.7 g, 10 mmol). The reaction mixture was warmed to room temperature and stirred for 14 h at the same temperature. The mixture was poured into water (200 ml) and extracted with ethyl acetate (200 ml x 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The mixture was evaporated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, hexane-chloroform-ethyl acetate) to afford **2a** (4.0 g, 62%) as a colorless oil. The other diesters (**2**) were prepared under the same reaction conditions as above. Their melting points and spectral data are shown in Table 3.

The Ullmann coupling reaction of the diesters (**2**)—A solution of the diester (**2a**) (1.3 g, 2.0 mmol) in DMF (10 ml) was added dropwise over a period of 3 h to a refluxing DMF (10 ml) in the presence of the activated copper powder (1.27 g, 20 mmol). After the addition was over, the reaction mixture was refluxed for an additional hour. The reaction mixture was cooled and the insoluble materials were filtered off. The solvent was evaporated to dryness *in vacuo*. To the residue was added ethyl acetate (50 ml). The solution was washed with water and dried over $MgSO_4$. After the solution was evaporated to dryness *in vacuo*, the residue was purified by column chromatography (silica gel, hexane-chloroform-ethyl acetate) to afford **3a** (690 mg, 87%) as colorless crystals. The other cyclization products (**3**) were prepared from respective diesters (**2**) under the same reaction conditions as above. The melting points and the spectral data are shown in Table 4.

On the other hand, the yield markedly decreased when the reaction was carried out under the following reaction conditions. A solution of **2a** (1.3 g, 2.0 mmol) in DMF (10 ml) in the presence of the activated copper powder (1.27 g, 20 mmol) was refluxed for 3 h. The reaction mixture was cooled and the insoluble materials were filtered off. The solvent was evaporated to dryness *in vacuo*. To the residue was added ethyl acetate (50 ml).

The solution was washed with water and dried over $MgSO_4$. After the solvent was evaporated to dryness *in vacuo*, the residue was purified by column chromatography (silica gel, hexane-chloroform-ethyl acetate) to afford **3a** (220 mg, 28%).

Hydrogenolysis of 3f and 3h—A solution of **3f** (760 mg, 2.0 mmol) in dioxane (50 ml) containing 10% palladium on charcoal (100 mg) was shaken for 5 h under the hydrogen atmosphere (2.0 kg/cm^2). The insoluble materials were filtered off. The filtrate was evaporated to dryness *in vacuo*. The residue was crystallized from diisopropyl ether to give **4f** (726 mg, 95%) as colorless crystals; mp 182~183 °C; ir (nujol) 3150, 2700, 1730, 1665 cm^{-1}; ^{1}H nmr ($CDCl_3$, 90 MHz) δ 2.10 (s, 3 H), 3.89 (s, 3 H), 3.96 (s, 3 H), 6.76 (d, *J*=2 Hz, 1 H), 6.9~7.3 (m, 5 H), 7.38 (d, *J*=2 Hz, 1 H), 7.71 (s, 1 H), 9.8 (br, 1 H); ms m/z (relative intensity) 382 (M$^+$, 2), 108 (100). Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.97; H, 4.74. Found: C, 65.84; H, 4.79.

The compound (**4h**) (570 mg, 78%) was prepared from **3h** (730 mg, 2.0 mmol) under the same reaction conditions as above. The conpound (**4h**); mp 177~178 °C; ir (nujol) 3120, 2620, 1724, 1686 cm^{-1}; ^{1}H nmr ($CDCl_3$, 90 MHz) δ 2.04 (s, 3 H), 5.96 (s, 2 H), 6.83 (d, *J*=8 Hz, 1 H), 6.96 (d, *J*=2 Hz, 1 H), 6.9~7.3 (m, 4 H), 7.52 (d, *J*=2 Hz, 1 H), 7.67 (d, *J*=8 Hz, 1 H), 9.75 (br, 1 H); ms m/z (relative intensity) 366 (M$^+$, 9), 259 (100). Anal. Calcd for $C_{20}H_{14}O_7$: C, 65.14; H, 3.85. Found: C, 65.34; H, 3.76.

Regioselective cleavage of the ester bonds of 3b, f, g by NaOMe-MeOH—To a solution of **3b** (400 mg, 1.0 mmol) in methanol (40 ml) was added NaOMe (135 mg, 5.0 mmol) at 5 °C and the mixture was stirred for an hour. The mixture was poured into 10% aqueous citric acid solution (100 ml). The mixture was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was crystallized from diisopropyl ether to give **5b** (260 mg, 81%) as colorless crystals; mp 181~182 °C; ir (nujol) 2600, 1696, 1678 cm^{-1}; ^{1}H nmr ($CDCl_3$, 90 MHz) δ 3.64 (s, 3 H), 3.88 (s, 3 H), 3.96 (s, 3 H), 6.78 (s, 1 H), 7.23 (d, *J*=5 Hz, 1 H), 7.47 (d, *J*=5 Hz, 1 H), 7.51 (s, 1 H), 7.60 (br, 1 H); ms m/z (relative intensity) 322 (M$^+$, 100); Anal. Calcd for $C_{15}H_{14}O_6S$: C, 55.89; H, 4.38; S, 9.95. Found: C, 55.73; H, 4.30; S, 9.93. The mother liquor was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane-ethyl acetate) to give **9** (100 mg, 73%).

The compound **5f** and **5g** were prepared from **3f** and **3g**, respectively under the same reaction conditions as above. The compound (**5f**); colorless crystals; mp 179~181 °C; ir (nujol) 2850, 1695, 1675 cm^{-1}; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 3.71 (s, 3 H), 3.92 (s, 3 H), 3.98 (s, 3 H), 6.86 (d, *J*=2.0 Hz, 1 H), 6.99 (s, 1 H), 7.2 (br, 1H), 7.45 (d, *J*=2.0 Hz, 1 H), 7.58 (s, 1 H); ms m/z (relative intensity) 306 (M$^+$, 100). Anal. Calcd for

$C_{15}H_{14}O_7$: C, 58.83; H, 4.61. Found: C, 58.94; H, 4.52. The compound (**5g**); colorless crystals; mp 169~170 °C; ir (nujol) 2900, 1734, 1676, 1535, 1300, 760 cm^{-1}; ^1H nmr ($CDCl_3$, 200 MHz) δ 3.74 (s, 3 H), 6.87 (d, *J*=1.9 Hz, 1 H), 7.53 (d, *J*=1.9 Hz, 1 H), 7.5 (br, 1 H), 7.69 (t, *J*=8.0 Hz, 1 H), 8.16 (dd, *J*=8.0, 1.3 Hz, 1 H), 8.23 (dd, *J*=8.0, 1.3 Hz, 1 H); ms m/z (relative intensity) 291 (M^+, 16), 145 (100). Anal. Calcd for $C_{13}H_9NO_7$: C, 53.62; H, 3.12; N, 4.81. Found: C, 53.52; H, 3.09; N, 4.70.

Regioselective cleavage of the ester bonds of 3c, f, g by hexylamine—To a solution of **3c** (380 mg, 1.0 mmol) in methylene chloride (40 ml) was added $C_6H_{13}NH_2$ (2.0 g, 20 mmol) at 5 °C and the mixture was stirred at room temperature for four days. The reaction mixture was poured into 10% aqueous citric acid solution (100 ml). The mixture was extracted with methylene chloride (2 x 100 ml). The combined organic layer was dried over $MgSO_4$. The organic layer was evaporated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, hexane-ethyl acetate) to give **6c** (364 mg, 91%) and **10**[22] (140 mg, 68%). The compound (**6c**); colorless crystals; mp 183~185 °C; ir (KBr) 3419, 2913, 1630, 1570, 1421, 1340, 713 cm^{-1}; ^1H nmr ($CDCl_3$+D_2O, 200 MHz) δ 0.85 (t, *J*=6.7 Hz, 3 H), 1.0~1.4 (m, 8 H), 2.8~3.2 (m, 2 H), 7.16 (d, *J*=5.2 Hz, 1 H), 7.3~7.45 (m, 3 H); ms m/z (relative intensity) 399 (M^+, 4), 256 (100). Anal. Calcd for $C_{18}H_{19}NO_3Cl_2S$: C, 54.01; H, 4.78; N, 3.50; S, 8.01. Found: C, 54.03; H, 4.79; N, 3.35; S, 7.91.

The compounds **6f** and **6g** were prepared from **3f** and **3g** respectively under the same reaction conditions as above. The compound (**6f**); colorless crystals; mp 188~190 °C; ir (KBr) 3420, 1628 cm^{-1}; ^1H nmr ($CDCl_3$, 200 MHz) δ 0.87 (t, *J*=6.9 Hz, 3 H), 1.05~1.5 (m, 8 H), 3.24 (q, J=7.1 Hz, 2 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 5.6~5.75 (m, 1 H), 6.86 (d, *J*=1.9 Hz, 1 H), 6.97 (s, 1 H), 7.20 (s, 1 H), 7.45 (d, *J*=1.9 Hz, 1 H); ms m/z (relative intensity) 375 (M^+, 5), 203 (100). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.87; H, 6.73; N, 3.75. The compound (**6g**); colorless crystals; mp 134~137 °C; ir (nujol) 3400, 1625 cm^{-1}; ^1H nmr ($CDCl_3$, 200 MHz) δ 0.87 (t, *J*=6.5 Hz, 3 H), 1.1~1.5 (m, 8 H), 3.1~3.35 (m, 2 H), 3.70 (br, 1 H), 5.8~5.95 (m, 1 H), 6.85 (d, *J*=1.9 Hz, 1 H), 7.55 (d, *J*=1.9 Hz, 1 H), 7.69 (t, *J*=7.9 Hz, 1 H), 7.87 (dd, *J*=7.9, 1.3 Hz, 1 H), 8.16 (dd, *J*=7.9, 1.3 Hz, 1 H); ms m/z (relative intensity) 360 (M^+, 3), 212 (100). Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.85; H, 5.48; N, 7.70.

Preparation of 5f from 4f—The compound **5f** (270 mg, 89%) was prepared from **4f** (380 mg, 1.0 mmol) under the same reaction conditions as above.

Preparation of 6f from 4f—The compound **6f** (310 mg, 90%) was prepared from **4f** (380 mg, 1.0 mmol) under the same reaction conditions as above.

ACKNOWLEDGEMENT

We thank Dr. Tetsuya Tosa, director of our company and Dr. Kazuo Matsumoto, general manager of Research Coordination Division for their encouragement and interest. We thank Dr. Tadamasa Date and Mr Kimio Okamura, Research Laboratory of Organic Chemistry, Tanabe seiyaku Co. Ltd., who carried out the X-ray analysis.

REFERENCES AND NOTES

1 J. Lee and J. K. Snyder, J. Org. Chem., 1990, 55, 4995.

2 M. Sainsbury, Tetrahedron, 1980, **36**, 3327; A. Minato, K. Tamao, T. Hayashi, K. Suzuki, and M. Kumada, Tetrahedron Lett., 1981, **22**, 5319; Y. Hatanaka, S. Fukushima, and T. Hiyama, Heterocycles, 1990, **30**, 303; G. Bringmann, R. Walter, and R. Weirich, Angew. Chem., Int. Ed. Engl., 1990, **29**, 977; V. N. Kalinin, Synthesis, 1992, 413.

3 P. E. Fanta, Chem. Rev., 1946, **38**, 139; P. E. Fanta, ibid., 1964, **64**, 613; P. E. Fanta, Synthesis, 1974, 9.

4 W. Baker, W. Barton, and J. F. W. McOmie, J. Chem. Soc., 1948, 2658; E. Brown, J. -P. Robin, and R. Dhal, Tetrahedron, 1982, **38**, 2569; J. Forrest, J. Chem. Soc., 1960, 594; M. Nilsson and O. Wennerstrom, Acta. Chem. Scand., 1970, **24**, 482.

5 M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, Heterocycles, 1992, **34**, 2061.

6 M. S. Newman and J. A. Cella, J. Org. Chem., 1974, **39**, 2084; S. Miyano, S. Handa, K. Shimizu, K. Tagami, and H. Hashimoto, Bull. Chem. Soc. Jpn., 1984, **57**, 1943; S. Miyano, H. Fukushima, S. Handa, H. Ito, and H. Hashimoto, Bull. Chem. Soc. Jpn., 1988, **61**, 3249.

7 M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, Tetrahedron Lett., 1991, **32**, 6919; M. Takahashi, Y. Moritani, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, ibid., 1992, **33**, 5103.

8 It is well documented that a phenolic hydroxyl group is acylated more readily than a benzylic hydroxyl group. See, M. P. Paradisi, G. P. Zecchini, and I. Torrini, Tetrahedron Lett., 1986, **27**, 5029; M. S. Van Dyk, J. P. Steynberg, P. J. Steynberg, and D. Ferreira, Tetrahedron Lett., 1990, **31**, 2643.

9 To a refluxing DMF containing copper powder was added dropwise **2a** in DMF. On the other hand, when a DMF solution containing **2a** was refluxed in the presence of copper powder, the yield remarkably decreased, probably due to the formation of polymerization products by the intermolecular Ullmann coupling reaction. The details are shown in the experimental section.

10 A. Wiersema and S. Gronowitz, Acta Chem. Scand., 1970, **24**, 2593.

11 In the palladium-catalyzed cross coupling reaction of an aryl metal with an aryl halide having substituents on the *ortho* positions, the yields remarkably decreased. See, for example, D. A. Widdowson and Y.-Z. Zhang, Tetrahedron, 1986, **42**, 2111.

12 The generation *o*-quinone methide was suggested in the reaction of *o*-chloromethylphenol with a base. See, M. Wakselman and M. Vilkas, Compt. Rend., 1964, **258**, 1526.

13 R. C. Fuson and E. A. Cleveland, Organic Synthesis, Coll. Vol. 3, 1962, 339.

14 M. Takahashi, T. Ogiku, K. Okamura, T. Da-te, H. Ohmizu, K. Kondo, and T. Iwasaki, J. Chem. Soc., Perkin Trans. 1, in press.

15 A. J. Carpenter and D. J. Chadwick. J. Chem. Soc., Perkin Trans. 1, 1985, 173; A. J. Carpenter and D. J. Chadwick. J. Org. Chem., 1985, **50**, 4362.

16 The lithiation of 3-thenoic acid was reported. See, D. W. Knight and A. P. Nott, J. Chem. Soc., Perkin Trans. 1, 1983, 791.

17 R. Guilard, P. Fournari, and M. Person, Bull. Soc. Chim. Fr., 1967, 4121.

18 The lithiation of 2-furoic acid was reported. See, D. W. Knight and A. P. Nott, J. Chem. Soc., Perkin Trans. 1, 1981, 1125.

19 R. Sornay, J.-M. Meunier, and P. Fournari, Bull. Soc. Chim. Fr., 1971, 990.

20 The lithiation of 3-bromofuran was reported. See, N. D. Ly and M. Schlosser, Helv. Chim. Acta, 1977, **60**, 2085.

21 Ya. L. Gol'dfarb, M. A. Marakatkina, and L. I. Belen'kii, Khim. Geterotsikl. Soedin., 1970, 132.

22 Zh. V. Molodykh, L. A. Kudryavtseva, R. A. Shagidullina, L. V. Shtanova, A. B. Teitel'baum, A. M. Zotova, I. S. Ryzhkina, M. A. Kudrina, N. N. Anisimova, and B. E. Ivanov, Khim.-Farm. Zh., 1987, **21**, 182 (Chem. Abstr., 1987, **106**, 192593x).

Received, 2nd March, 1993