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

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Abstract-Heterobiaryls (**4**) were synthesized in good yields utilizing the intramolecular Ullmann coupling reaction directed by salicyl alcohol as a template. The regioselective cleavage of the two ester bonds of **4** gave the highly functionalized unsymmetrical heterobiaryls having substituents which are incompatible with organometallic reagents

The highly functionalized unsymmetrical heterobiaryls are of considerable interest recently as useful intermediates in the synthesis of biologically active natural products such as tanshinone.[1] The synthetic methods of 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 intermolecuar Ullmann coupling reaction.[2,3] However, difficulties are frequently encountered in the transition metal-catalyzed cross coupling reactions between two aryls having subsituents which are incompatible with the organometallic reagents. On the other hand, the intermolecular Ullmann coupling reaction gives rise to the undesired symmetrical biaryls. We recently reported that the template-directed intramolecular Ullmann coupling reaction is quite effective in the synthesis of a variety of diphenic acid derivatives.[4] In connection with our synthetic studies in search of new compounds having intriguing biological activities,[5] we now report a facile synthesis of highly functionalized unsymmetrical heterobiaryls utilizing the intramolecular Ullmann coupling reaction directed by salicyl alcohol as a template, followed by regioselective cleavage of the two ester bonds of **4**.

Scheme 1

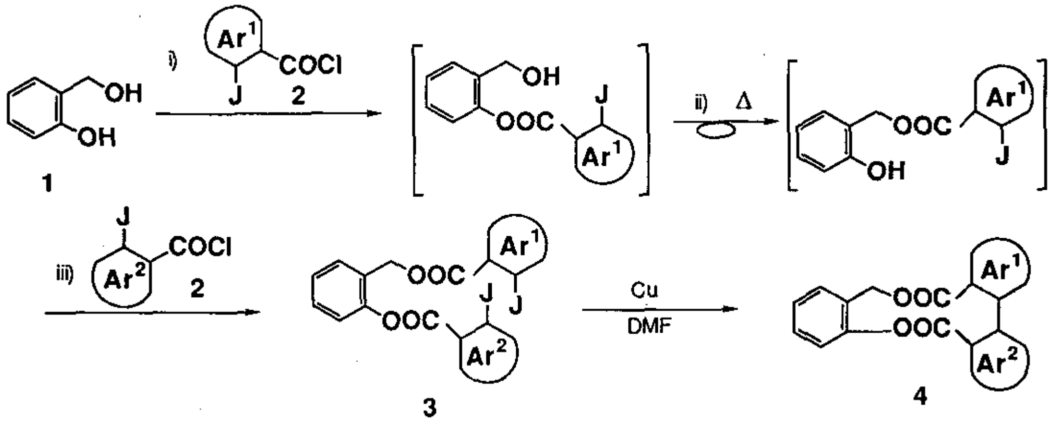
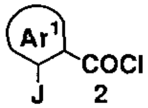
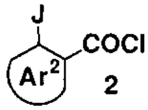
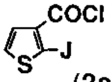
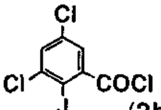
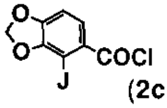
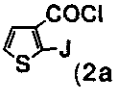
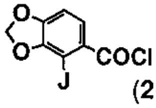
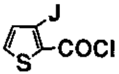
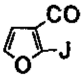
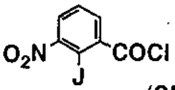
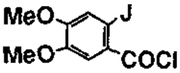
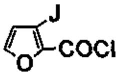
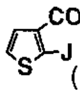
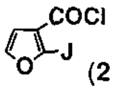


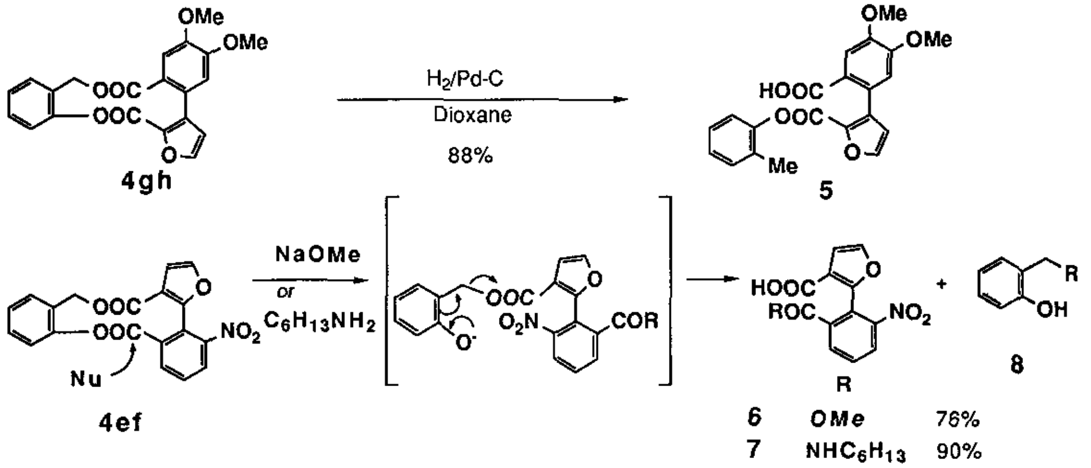
Table 1. Yields of the Diacylations and the Ullmann Coupling Reactions

entry	 2	 2	1 → 3 product	yield (%)*	3 → 4 product	yield (%)*
1	 (2a)	 (2b)	**3ab**	62	**4ab**	78
2	 (2c)	 (2a)	**3ca**	78	**4ca**	84
3	 (2c)	 (2d)	**3cd**	62	**4cd**	67
4	 (2e)	 (2f)	**3ef**	61	**4ef**	83
5	 (2g)	 (2h)	**3gh**	70	**4gh**	63
6	 (2a)	 (2e)	**3ae**	65	**4ae**	81

* Isolated yield

The requisite diester (**3**) was prepared in a good yield in a one-pot procedure by the successive acylations of salicyl alcohol in dimethylacetamide at -30~-20 °C by using two different aroyl chlorides *via* the intramolecular rearrangement of the aroyl group (Scheme 1).[4] We first examined the intramolecular Ullmann coupling reaction of **3ab**[6] containing the 2-iodo-3,5-dichlorophenyl moiety and the 2-iodothiophene one, a reactive halide for the Ullmann coupling reaction. The dropwise addition of DMF (dimethylformamide) solution of **3ab** to a refluxing DMF containing copper powder afforded the coupling product (**4ab**)[7] in 78% yield (entry 1). The Ullmann coupling reaction of **3ca** containing the 2-iodophenyl moiety having electron-donating substituents and the 2-iodothiophene one also proceeded in a good yield (entry 2). Even in the coupling reaction of the diester (**3cd**) having the 3-iodothiophene moiety that is less reactive than the 2-iodothiophene one for the Ullmann coupling reaction,[8] the coupling product (**4cd**) was obtained in 67% yield. This intramolecular coupling reaction was nicely applied to the synthsesis of **4ef** and **4gh** having the furan moieties (entries 4, 5). The coupling reaction of the diester (**3ae**) having two 2-iodoheteroaryls also furnished the coupling product (**4ae**) in a good yield (entry 6).

Scheme 2



We next examined the conversion of the two ester groups of the coupling products (**4**) into the other functional groups different from one another (Scheme 2). Hydrogenolysis of **4gh** using palladium on charcoal afforded the monoester (**5**) in 88% yield. On the other hand, treatment of **4ef** with two molar equivalents of NaOMe in MeOH gave the monoester (**6**) in 76% yield. The reaction of **4ef** with $C_6H_{13}NH_2$ also gave the monoamide (**7**) in 91% yield. In these reactions, the nucleophiles probably attack on the carbonyl carbon of the phenyl ester moiety, resulting in the formation of the monocarboxylic acids by elimination of *o*-quinone methide.[9]

As described above, this new method involving the intramolecular Ullmann coupling reaction, followed by the regioselective cleavage of the two ester groups of the coupling products should find application in the synthesis of a variety of highly functionalized heterobiaryls having ester, nitro and amide groups which are incompatible with the organometallic reagents.

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1. J. Lee and J. K. Snyder, J. Org. Chem., 1990, 55, 4995.
2. a) V. N. Kalinin, Synthesis, 1992, 413. b) Y. Hatanaka, S. Fukushima, and T. Hiyama, Heterocycles, 1990, 30, 303. c) A. Minato, K. Tamao, T. Hayashi, K. Suzuki, and M. Kumada, Tetrahedoron Lett., 1981, 22, 5319.
3. P. E. Fanta, Synthesis, 1974, 9.
4. a) M. Takahashi, T. Kuroda, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, Tetrahedron Lett., 1991, 32, 6919. b) M. Takahashi, Y. Moritani, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, Tetrahedron Lett., in press.
5. a) T. Ogiku, M. Seki, M. Takahashi, H. Ohmizu, and T. Iwasaki, Tetrahedrn Lett., 1990, 31, 5487. b) T. Kuroda, M. Takahashi, T. Ogiku, H. Ohmizu, K. Kondo, and T. Iwasaki, J. Chem. Soc., Chem. Comm., 1991, 1635.
6. mp 92~93 °C ; ir (KBr) ν_{max} 1754, 1724 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ 5.36 (s, 2H), 7.25~7.75 (m, 8H) ; ms (m/z) 658 (M$^+$) ; Anal. Calcd for $C_{19}H_{10}O_4Cl_2I_2S$: C, 34.63; H, 1.53. Found: C, 34.67; H, 1.50.
7. mp 171~172 °C; ir (KBr) ν_{max} 1758, 1724 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ 5.14 (d, J=12.1 Hz, 1H), 5.37 (d, J=12.1 Hz, 1H), 7.15~7.5 (m, 6H), 7.70 (d, J=2.2 Hz, 1H), 7.81 (d, J=2.2 Hz, 1H); ms (m/z) 404 (M$^+$); Anal. Calcd for $C_{19}H_{10}O_4Cl_2S$: C, 56.30; H, 2.49; Cl, 17.50; S, 7.91. Found: C, 56.19; H, 2.39; Cl, 17.48; S, 7.65.
8. The Ullmann coupling reaction using 2-halothiophene derivatives usually gives better results than that using 3-halothiophene derivatives; see: A. Wiersema and S. Gronowitz, Acta Chem. Scand., 1970, 24, 2593.
9. *o*-Quinonemethide was isolated as *o*-methoxymethylphenol or *o*-hexylaminomethylphenol which would be formed by the Micheal addition of the nucleophile to *o*-quinonemethide; see: A. B. Turner, Quart. Rev., 1964, 18, 347.

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