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A New Synthesis of Unsymmetrical Diphenic Acid Derivatives: Template-directed Intramolecular Ullmann Coupling Reaction

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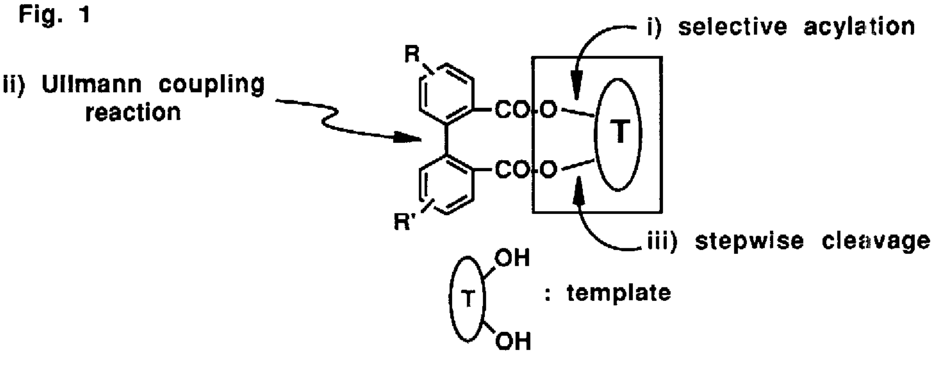
Abstract: Intramolecular Ullmann coupling reaction of the diesters (**6**, **9**), which were prepared by regioselective acylation of salicyl alcohol by using the two different substituted 2-iodobenzoyl chlorides, afforded the unsymmetrical diphenic acid derivatives (**7**, **10**). Hydrogenolysis of the Ullmann coupling product (**7**) afforded the monoester (**12**) in an excellent yield.

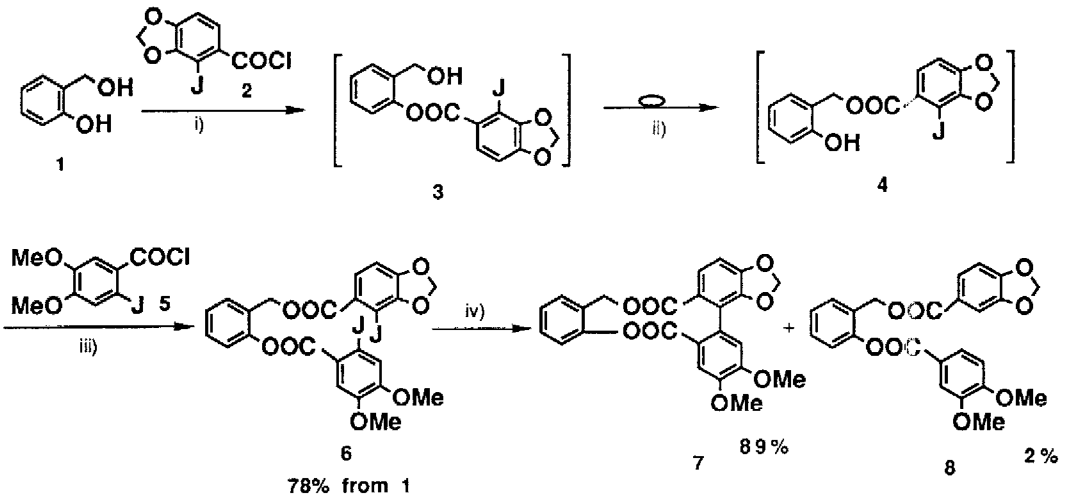
The chemistry of 2,2'-disubstituted unsymmetrical biaryl compounds[1)] has attracted considerable interest recently because of the biological activities of a number of natural products containing these moieties.[2)] The current methods for construction of unsymmetrical biaryl skeletons include those based on the regioselective carbon-carbon bond formation between two different aromatics by transition metal-catalized cross-coupling reaction of an aryl metal with an aryl halide,[3)] the ambient-temperature Ullmann coupling reaction[4)] and the Meyers oxazoline method.[5)] Because of the unsatisfactory yields of these methods in the synthesis of highly functionalized biaryl compounds,[6)] efforts have still been devoted to develop a new methodology for the synthesis of 2,2'-disubstituted unsymmetrical biaryl compounds.[7)] In connection with our efforts in search of compounds having intriguing biological activities, we now report a new synthetic method of unsymmetrical diphenic acid derivatives which are convertible to various 2,2'-disubstituted biaryl compounds, based on a template-directed intramolecular Ullmann coupling reaction.

Fig. 1



In Fig. 1 are illustrated the main features of our strategy for construction of unsymmetrical diphenic acid derivatives. The requirements imposed on the template are threefold as follows. The template must (i) have two hydroxyl groups with different reactivity, which are regioselectively acylated by two different substituted 2-iodobenzoyl chlorides; (ii) enable the intramolecular Ullmann coupling reaction to proceed efficiently by stabilizing the conformation of a transition state leading to the cyclized product;[8] (iii) be removed stepwise from the coupling product, thereby contributing to the conversion of each of the ester groups into a functional group different from one another. We envisioned that the use of salicyl alcohol as a template would meet the above three requirements.

Scheme 1

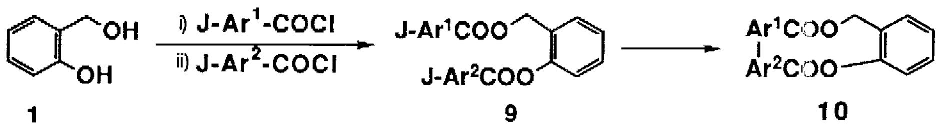


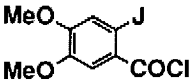
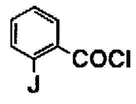
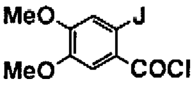
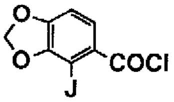
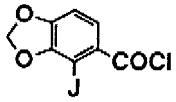
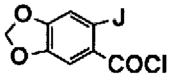
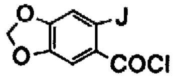
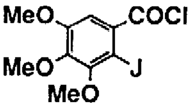
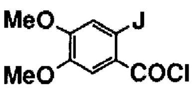
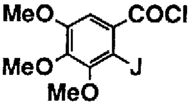
i) 2(1.0eq), Et_3N(2.0eq), DMAP(0.05eq), DMA-CH_2Cl_2(4:1), -20~-30°C, 1hr; ii) r t, 5hr;
iii) 5(1.0eq), Et_3N(1.0eq), -20~-30°C→ r t, 1hr; iv) Cu powder(10eq), DMF, reflux.

We first examined the regioselective acylations of salicyl alcohol (**1**) with two different iodobenzoyl chlorides (**2** and **5**). Acylation of **1** with **2** in a mixed solvent containing N,N-dimethylacetamide(DMA) and dichloromethane(4:1) in the presence of two molar equivalent of triethylamine and a catalytic amount of dimethylaminopyridine(DMAP) at -20~-30°C took place initially at the phenolic hydroxy group to form the ester (**3**); when the reaction was quenched at this stage, a mixture of **3** and **4** was obtained due to the readily conversion of **3** to **4** during the work up procedure. Upon warming the reaction mixture to room temperature, the monoester thus formed rearranged completely to **4** (mp. 89~91°C); this rearrangement process was clearly observed on TLC. Without isolation of **4**, the second acylation was carried out by addition of another benzoyl chloride (**5**) to the reaction mixture at -20~-30°C.[9] By this procedure, the desired diester (**6**, mp. 123~124°C)[10] was obtained in 78% yield in one pot from salicyl alcohol.

We next examined the intramolecular Ullmann coupling reaction of the diester (**6**). When the reaction was carried out in a refluxing N,N-dimethylformamide(DMF) containing **6** and copper powder, the coupling product (**7**, mp. 178~180°C) was obtained only in 44% yield. The yield was readily improved by employing the dropwise-addiotion method. Thus, dropwise addition of a solution of the diester (**6**, 0.01mol) dissolved in DMF(100ml) to a refluxing DMF(50ml) containing copper powder(0.1mol) over a period of 3hr furnished the coupling product (**7**) in 89% yield; the chemical structure was unequivocally determined based on X-ray crystallographic analysis and ^{1}H-NMR spectrum.[11] In this method, a small amount of the reduced product (**8**, mp. 130~131°C) was formed.[12] The method involving the regioselective diacylation and the intramolecular Ullmann coupling reaction described above is also effective for synthesis of the other diphenic acid derivatives(Table 1).

Table 1. Synthesis of diphenic acid derivatives



Entry	J-Ar^1-COCl	J-Ar^2-COCl	Yield of **9**(%)^{a,b}	Yield of **10**(%)^{a,b}
1			74	71
2			84	89
3			76	75
4			81	78
5			80	83

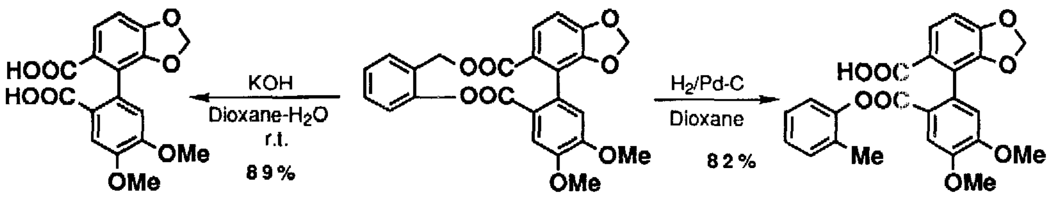
a) Isolated yield. b) All products were unequivocally identified by 200MHz ^{1}H-NMR, IR, and Mass spectra, and elemental analyses.

We then examined the regioselective cleavage of the two ester groups of the cyclized products. Under alkali-hydrolysis conditions, **7** could not be hydrolyzed regioselectively, resulting in the formation of the substituted diphenic acid (**11**) in 89% yield. On the other hand, hydrogenolysis of **7** using palladium on charcoal proceeded regioselectively to afford the monoester (**12**) in 82% yield.

This successful transformation involving the reactions consisting of regioselective diacylation, efficient intramolecular Ullmann coupling reaction and regioselective ester-cleavage should offer a new entry to the synthesis of a variety of 2,2'-disubstituted unsymmetrical biaryl compounds.

The scope and limitation of this new transformation are now under investigation.

Scheme 2



11 7 12

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References and Notes

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6. The presence of electron-donating groups on aromatics generally reduces the yields of coupling products. Hiyama et al. recently reported the preparation of highly functionalized biaryl compounds. See, ref. 3(b).
7. Intramolecular aryl-aryl coupling reactions have been reported. see: (a) Miyano, S.; Fukushima, H.; Handa, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249 and references citied therein; (b) Semmelhach, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460; (c) Newman, M. S.; Cella, J. A. *J. Org. Chem.* **1974**, *39*, 2084; (d) Fanta, P. E. *Synthesis* **1974**, 9.
8. The ring size is a critical factor to make the Ullmann coupling reaction proceed efficiently . For example, the intramolecular Ullmann reaction of bis(2-iodobenzoyl)catechol afforded the coupling product in only 35% yield. The details will be reported elsewhere.
9. The chemical structure of **6** was determined based on X-ray crystallographic analysis
10. **6**: IR (Nujol) 1755, 1705 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 3.86(s, 3H), 3.90(s, 3H), 5.35(s, 2H), 6.02(s, 2H), 6.67(d, 1H, *J*=8Hz), 7.1~7.7(m, 7H).
11. **7**: IR (KBr) 1745, 1730 cm^{-1}; ^1H-NMR (DMSO-d^6) δ 3.85(s, 3H), 3.87(s, 3H), 4.78(d, 1H, *J*=11Hz), 5.90(d, 1H, *J*=11Hz), 6.12(brs, 2H), 6.88(d, 1H, *J*=8Hz), 7.06(d, 1H, *J*=8Hz), 7.2~7.6(m, 6H).
12. **8**: IR (Nujol) 1734, 1716 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 3.88(s, 3H), 3.93(s, 3H), 5.33(s, 2H), 5.96(s, 2H), 6.74(d, 1H, *J*=8Hz), 6.87(d, 1H, *J*=8Hz), 7.1~7.65(m, 7H), 7.81(dd, 1H, *J*=8, 1.5Hz).

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