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PARTIAL ASYMMETRIC SYNTHESIS OF ATROPISOMERIC 1,1'-BINAPHTHYLS *VIA* THE ULLMANN COUPLING REACTION OF CHIRAL ALCOHOL ESTERS OF 1-BROMO-2-NAPHTHOIC ACID

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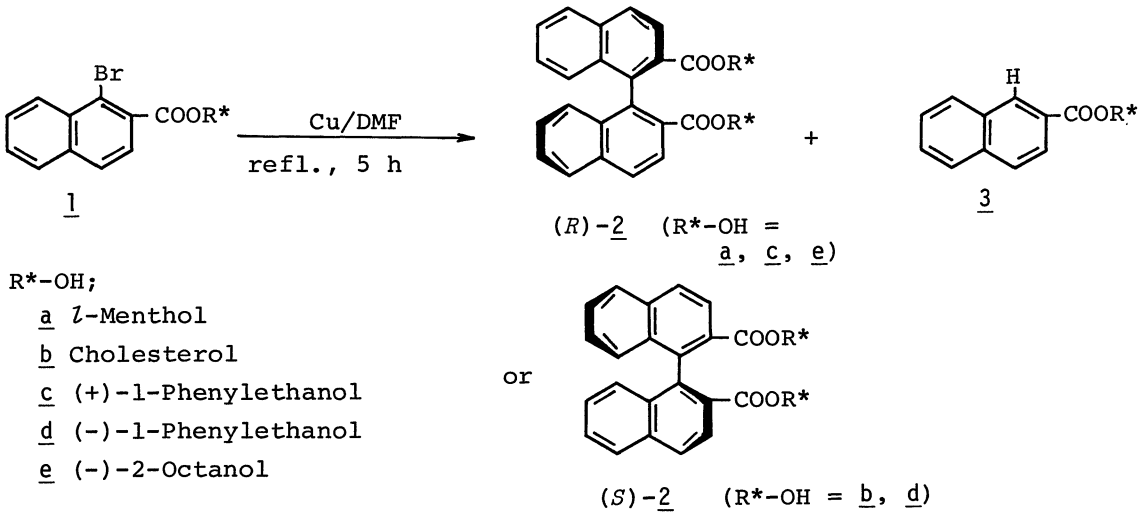
The Ullmann coupling of 1-bromo-2-naphthoates of *C*-chiral alcohols of *R*- and *S*-configuration induced axial dissymmetry of *R*- and *S*-chirality, respectively, in the newly formed 1,1'-bond of the binaphthyls; the optical yield amounted up to 13% where the chiral alcohol was *l*-menthol.

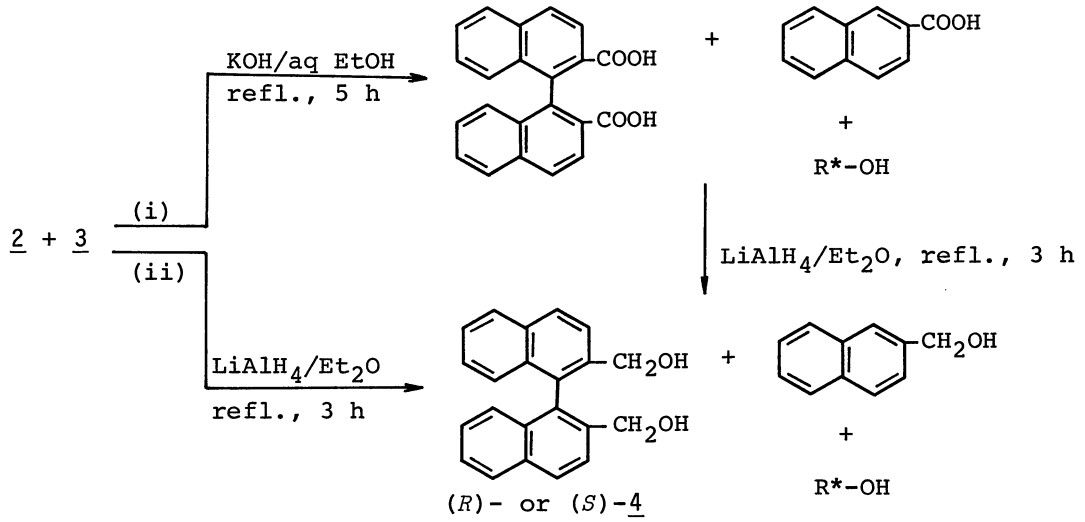
Among various methods for the synthesis of biaryls,[1] the classical Ullmann coupling is still one of the most important procedures for practical use.[2] Although the mechanism of this reaction has been the subject of a large amount of discussion,[3] the precise nature of it is far from fully established, and, to the best of our knowledge, little is known about the stereochemical course of the reaction.[4]

We wish to report here the partial asymmetric synthesis of axially dissymmetric 1,1'-binaphthyls *via* the Ullmann coupling of *C*-chiral alcohol esters of 1-bromo-2-naphthoic acid (Scheme 1).[5]



Scheme 1.

Substrate chiral esters, 1a - 1e, were obtained by the treatment of respective optically active alcohols (a - e) with 1-bromo-2-naphthoyl chloride[6] in benzene-pyridine, and finally purified by column chromatography (silica gel/benzene-cyclohexane) (Table, footnote c); these were identified by microanalyses and spectral studies. The asymmetric Ullmann reaction was carried out by stirring the esters in DMF in the presence of excess amounts of freshly activated copper powder[8] and heating at gentle reflux for 5 h under nitrogen. The reaction mixtures were worked up as usual to afford solid residues, which were comprised of the coupled products (2) (80 - 95%) and the reduced ones (3) (20 - 5%) as was shown by HPLC and TLC.[9] Negative Beilstein test confirmed the absence of the starting bromo esters.

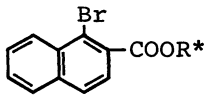
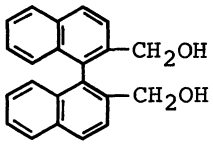


Scheme 2.

According to either ((i) or (ii)) or both of the procedures illustrated in Scheme 2, binaphthyl esters (2) were eventually converted into 2,2'-bis(hydoxymethyl)-1,1'-binaphthyl (4), pure samples of which were isolated by preparative TLC (silica gel/$CHCl_3$-ethyl acetate (4:1)). The %ee's of the resulted 4, and thus the optical yields for the induction of axial dissymmetry in the asymmetric Ullmann coupling are obtainable on the basis of the optical rotations of the recovered 4 with respect to the reported values for the pure enantiomers.[7] Furthermore, one of the samples of 4 was transformed into a diastereomeric mixture of esters of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid ((*R*)-(+)-MTPA), relative amounts of which were determined by PMR using a chiral shift reagent, $Eu(fod)_3$, according to the method by S. Yamaguchi and his coworkers.[10]

From the results summarized in Table, it becomes apparent that *C*-chirality in 1 is capable of exerting appreciable effect on the induction of axial dissymmetry in 2, where alcohols of *R*- and *S*-configuration afforded the binaphthyls of *R*- and *S*-configuration, respectively. It should be noted that *l*-menthyl moiety in 1a, though the *C*-chiral center is relatively distant from the site of the coupling and the conditions for the Ullmann reaction were rather severe, resulted in a substantial optical yield of 13%.

Table. Asymmetric Ullmann Coupling of *C*-Chiral Alcohol Esters of 1-Bromo-2-naphthoic Acid[a)]

	R*-OH	%ee[b)]	(Config)	 (2)[c)] mmol	Cu g	 (4) %ee[b)]	(Config)
a	*l*-Menthol	100	(*R*)	3.5	2	13	(*R*)
b	Cholesterol	100	(*S*)	3.0	2	5.3	(*S*)
c	(+)-1-Phenylethanol	93	(*R*)	3.0	2	5.0(4.6)[d)]	(*R*)
d	(-)-1-Phenylethanol	96	(*S*)	5.0	1.2	7.5	(*S*)
e	(-)-2-Octanol	98	(*R*)	2.7	1.2	1.8	(*R*)

a) The reaction was carried out in 20 ml of DMF at gentle reflux for 5 h under nitrogen.

b) The %ee's were calculated from the observed optical rotations and reported values for the pure enantiomers: a, M. Windholz, Ed., *"The Merk Index"*, 9th Ed., Merk & Co., Ind., Rahway, N. J., p. 757 (1976); b; *ibid.*, p. 283; c and d; R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, 82, 876 (1960); e, S. Miyano, H. Ushiyama, and H. Hashimoto, *Nippon Kagaku Kaishi*, 1977, 138; 4, Ref. 7.

c) 2a, $[\alpha]_D^{23}$ -45.9° (c 1.05, EtOH), mp 62 - 64°C; 2b, $[\alpha]_D^{23}$ +2.4° (c 4.2, $CHCl_3$), mp 197 - 198°C; 2c, $[\alpha]_D^{23}$ -24.5° (c 2.6, acetone), mp 79 - 81°C; 2d, $[\alpha]_D^{23}$ +26.8° (c 2.7, acetone), mp 82 - 83°C; 2e, $[\alpha]_D^{23}$ -28.8° (c 2.92, EtOH), viscous oil.

d) Determined by PMR.[10)]

Synthesis and reaction of *l*-menthyl 1-bromo-2-naphthoate (1a) is illustrative: A solution of *l*-menthol (4.20 g, 26.9 mmol) and 1-bromo-2-naphthoyl chloride[6)] (7.05 g, 26.2 mmol) in benzene (70 ml)-pyridine (12 ml) was stirred overnight in a water bath, and then heated at reflux for 3 h. The reaction was quenched with 50 ml of 2 *M* HCl, and extracted with portions of benzene. The combined extracts were washed successively with 2*M* HCl, 1*M* Na_2CO_3, and then water, and dried over Na_2SO_4. Solvent was removed *in vacuo*, giving a pale yellow residue, which was chromatographed on silica gel column (Wako Gel C-200) with benzene-cyclohexane (1:3). After removal of the eluent, the residue was dissolved in small amount of ether and chilled in a dry ice-methanol bath to give 7.98 g of 1a as a white precipitate; yield, 78.2%. Found(Calcd): C, 64.81(64.78); H, 6.53(6.47); Br, 20.36(20.53)%. IR(KBr): 1720, 1280, 1130 cm^{-1} (νCOO).

Just prior to the Ullmann reaction, the solvent DMF was distilled from CaH_2 under nitrogen. To a 100-ml round-bottomed flask equipped with magnetic stirrer and reflux condenser topped with nitrogen inlet were placed freshly activated copper (prepared from 2.0 g of 200-mesh copper powder),[8)] and 1.34 g of 1a (3.45

mmol). The whole system was flushed with nitrogen, and 20 ml of DMF was added. The well-stirred mixture was heated at gentle reflux for 5 h under nitrogen. The cooled mixture was diluted with 50 ml of benzene; solids were filtered off and washed well with portions of benzene. The filtrate was washed with 2*M* HCl and then water, and dried over Na_2SO_4. Removal of the solvent afforded pale yellow residue, 1.01 g, $[\alpha]_D^{23}$ -102° (c 1.15, PhH). This was comprised of 93% of 2a and 7% of 3a by HPLC peak area (JASCO SC-01 column/MeOH, 254 nm absorption); analytical samples of each component were obtained by preparative TLC (Kiesel Gel G (Type 60)/PhH-cyclohexane (1:1)). 2a: $[\alpha]_D^{23}$ -103° (c 1.09, PhH), mp 170 - 172 °C. Found(Calcd): C, 81.52(81.52); H, 8.04(8.14)%. 3a: IR(KBr); 1700, 1280, 1190 cm^{-1} (νCOO).

A mixture of the Ullmann products (2a + 3a) (0.844 g) and lithium aluminum hydride (0.5 g) in 50 ml of ether was boiled for 3 h, and worked up as usual. The organic phase was freed of the solvent, and then heated up to 100 °C *in vacuo* to remove bulk of the regenerated menthol by sublimation, affording 0.456 g of a residue. This was in turn subjected to preparative TLC (Kiesel Gel G (Type 60)/$CHCl_3$-ethyl acetate (4:1)) to give a sample of partially active 4, 0.352 g, $[\alpha]_D^{24}$ +10.5° (c 1.02, acetone), mp 180 - 185.5 °C. NMR and IR spectrum supported the structure.

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References and Notes

1) For example, a) K. Tamao, A. Minato, N. Miyake, T. Matsuda, Y. Kiso, and M. Kumada, *Chem. Lett.*, 1975, 133, b) R. L. Clough, P. Mison, and J. D. Roberts, *J. Org. Chem.*, 41, 2252 (1976), c) A. McKillop, A. G. Turrell, and E. C. Taylor, *J. Org. Chem.* 42, 764 (1977).

2) P. E. Fanta, *Synth.*, 1974, 9.

3) For example, a) Y. Mugnier and E. Laviron, *J. Chem. Soc., Perkin 2*, 1979, 1264, b) F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuno, and N. D. Sinha, *J. Am. Chem. Soc.*, 102, 790 (1980), and literatures cited therein.

4) Stereospecific phenol coupling reactions of chiral substrates have appeared; a) J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Am. Chem. Soc.*, 93, 3551 (1971); *J. Org. Chem.*, 41, 845 (1976), b) B. Feringa and H. Wynberg, *J. Am. Chem. Soc.*, 98, 3372 (1976).

5) *Cf.* a) K. Tamao, H. Yamamoto, H. Matsumoto, N. Miyake, T. Hayashi, and M. Kumada, *Tetrahedron Lett.*, 1977, 1389, b) Ref. 1a).

6) The acid chloride was prepared from 1-bromo-2-naphthoic acid[7] and thionyl chloride; mp 82.4 - 83.9 °C (cyclohexane).

7) D. M. Hall and E. E. Turner, *J. Chem. Soc.*, 1955, 1242.

8) R. C. Fuson and E. A. Cleveland, *"Organic Syntheses"*, Coll. Vol. III, p.339 (1955).

9) The coupled products 2 should be comprised of diastereomeric mixtures, while no appreciable chromatographic separation of each diastereomer was observed.

10) a) K. Kabuto, F. Yasuhara, and S. Yamaguchi, *Tetrahedron Lett.*, 1980, 307, b) *Cf.* J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 95, 512 (1973).

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