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Stereoselective synthesis of optically active phenyl ethers

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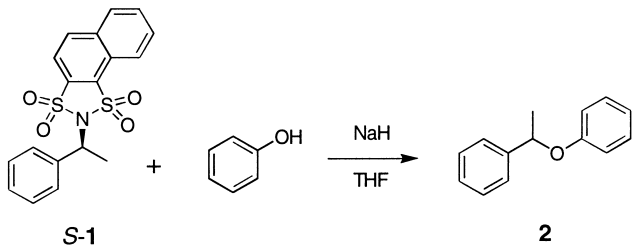
Abstract

Reacting the 1,2-naphthalenedisulfonimide of (*S*)-α-methylbenzylamine with phenol gave the corresponding α-methylbenzyl phenyl ether with 46% *e.e.* Synthesis of the authentic optically active phenyl ethers was accomplished under mild, neutral conditions by generating benzyne in the presence of optically active (*R*)-α-methylbenzyl alcohol. Benzyne was generated by reacting anthranilic acid with *tert*-butyl nitrite in refluxing monoglyme.

The stereochemistry of the nucleophilic reactions of 1,2-benzenedisulfonylimide derivatives of optically active amines has been studied.[1] Similarly, the naphthalene-1,2-disulfonylimide-derivative of (*S*)-α-methylbenzylamine, (*S*)-**1**,[2] was reacted with phenol under basic conditions in THF to yield the corresponding α-methylbenzyl phenyl ether, **2**.[3] However, we were not able to determine the optical purity of the product by chiral chromatography or by NMR, Scheme 1. The difficulty of determining the *e.e.* of phenyl ethers has been recognized by other groups.[4] It was therefore decided to prepare an optically active reference compound of **2**, starting from the readily available (*R*)-α-methylbenzyl alcohol, (*R*)-**3**. A number of nucleophilic displacement and aromatic



S-1 2

Scheme 1.

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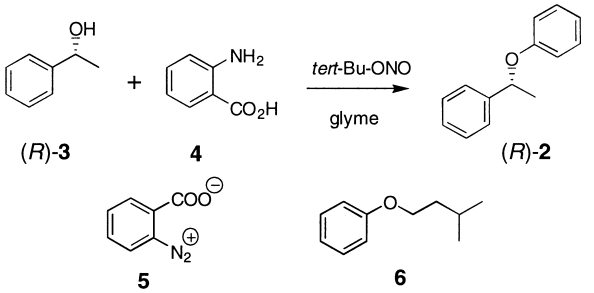
substitution procedures were tested. However, as expected, all were either unreactive or not stereoselective. The methods for the formation of the alkyl phenyl ether required mild, basic, neutral or eventually slightly acidic conditions. Strong acid conditions readily cleaved the benzylic ether bonds or resulted in racemization of the stereogenic carbon. Radical mechanisms were also avoided, ruling out Cu-promoted reactions.[5]

To ensure that the chiral alcohol (*R*)-**3** did not racemize during ether formation, the ideal reaction must occur away from the chiral center and not involve any C–O bond cleavage. Nucleophilic aromatic substitution is only possible if an activating group is present in the aromatic halide or exceedingly strenuous conditions are employed.[6] Formation of aryl ethers is generally difficult and yields are low.[7] The Pd-catalyzed formation of phenyl ethers has also been reported.[8] However, our objective may be accomplished by the addition of alcohol (*R*)-**3** to unsubstituted benzyne,[9] addressing the limitations mentioned above. The benzyne can be generated by diazotization of anthranilic acid, **4**. The use of this compound for generating benzyne has been described earlier.[10] In most of the described reactions the corresponding 2-diazoniumbenzoate, **5**, was isolated and thermolyzed.[11,12] However, examples where benzyne was generated directly from anthranilic acid by treatment with amyl nitrite in the presence of an acid catalyst and trapping agents have been reported.[12] The addition of nucleophiles to benzyne has been studied.[11,13] However, syntheses of aryl ethers by the addition of alcohols to benzyne were never really successful and have not found widespread use. Carrying out the reaction in an alcohol presented a potential risk of alcoholysis of the diazonium group. Thus, most of the described methods suffer from cumbersome experimental techniques and low yields of the desired products. The procedures using the isolated diazonium salt also have the disadvantage that this compound is dangerously explosive when dry.

Despite these apparent disadvantages, the benzyne route appeared most appealing to our specific problem, making it worthwhile to reinvestigate. As a result of this study we can report a modification of the anthranilic–benzyne procedure that proved successful for our system. Initially the reaction was carried out with isoamyl nitrite.[14] Thus, when isoamyl nitrite was added to a solution containing anthranilic acid together with (*R*)-**3**, and refluxed overnight, the benzyne was formed as the anthranilic acid disappeared. However, the major addition product isolated was the isoamyl phenyl ether, **6**, together with minute amounts of **2**. This was encouraging, as the alcohol formed from the nitrite actually appeared to have added to the benzyne. Formation of the byproduct was eliminated by employing *tert*-butyl nitrite instead for generating the benzyne in order to reduce the reactivity of the alcohol formed from the nitrite. The only product observed was the desired product, which was assigned the structure (*R*)-**2** (Scheme 2).



Scheme 2.

The crude reaction mixture contained **2** together with 9% of unreacted (*R*)-**3**.[15] The pure product was obtained in 42% isolated yield after flash chromatography. The spectroscopic properties were in agreement with the structure. The optical rotation was determined to $[\alpha]_D^{20} = 5.55$ (*c* 2.0, $CHCl_3$).

The starting material (*R*)-**3** had *e.e.* >99%. As it is reasonable to assume that isomerization of the stereogenic center does not take place during the transformations described here, the enantiomeric purity of ether **2** also corresponds to *e.e.* >99%. From the measured optical rotation of the authentic product we can calculate the degree of racemization taking place in the reactions between (*S*)-**1** and phenol. The data and the results including the degree of inversion in the nucleophilic displacement reactions with (*S*)-**1** are shown in Table 1.

Table 1
Measurements of the degree of inversion in the reaction between (*S*)-**1** and phenol

Reaction	**Product** (yield, %)	$[\alpha]_D^{20}$ (c=2.0, $CHCl_3$)	***e.e*** %	**Inversion** %
(*S*)-**1** to **2**	(*R*)-**2**, (57)	+ 4.05	46	73
(*R*)-**3** + **4** to **2**	(*R*)-**2**, (42)	+ 5.55	99	0

These data show that partial racemization takes place during the nucleophilic displacement reaction. The nature of this reactivity and its synthetic applications is currently being further investigated.

In conclusion, a new method is described for the synthesis of alkyl phenyl ethers under mild, neutral conditions by generating benzyne in the presence of the optically active (*R*)-α-methylbenzyl alcohol. Benzyne was formed from anthranilic acid by the reaction with *tert*-butyl nitrite in refluxing monoglyme.

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3. Methylbenzyl phenyl ether **3**: To a stirred solution containing phenol (19.54 mg) and NaH (16.5 mg) in dry THF (15 ml) in a round bottom flask under nitrogen was added drop wise a solution of (*S*)-*N*,*N*-1,2-naphthalenedisulfonyl-1-phenylethylamine, **1**, (70 mg) in THF (5 ml) and the resulting reaction mixture was stirred overnight at ambient temperature. Ether (20 ml) was added and the resulting solution was washed with water (25 ml), 0.1 M NaOH and finally with water. The ether phase was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to yield a yellow oil, 54 mg, which was purified by flash chromatography to give 21 mg (57%) of product **2**. The spectroscopic properties were all in agreement with those of an authentic sample. The optical rotation was measured to $[\alpha]_D^{20} = 4.05$ (*c* 2, $CHCl_3$).

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14. Isoamyl phenyl ether **5**: was prepared using the procedure described in Ref. 7 in 74% yield together with 2–3% of the target compound **2**. Compound **6** exhibited the following spectroscopic properties: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.0 (d, $J = 6.6$ Hz, 6H), 1.74 (q, $J = 6.7$ Hz, 2H), 1.91 (m, 1H), 4.05 (q, $J = 6.7$ Hz, 2H), 6.97 (m, 3H), 7.33 (m, 2H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 22.8, 25.3, 38.2, 66.4, 114.7, 120.7, 129.6, 159.3 ppm.
15. (*R*)-Methylbenzyl phenyl ether (*R*)-**3**: To a refluxing solution of (*R*)-methylbenzyl alcohol **3** (1 ml, 1.01 g, 8.3 mmol) in 5 ml of monoglyme was added simultaneously solutions of anthranilic acid, **4**, (3.4 g, 24.8 mmol) in 10 ml of glyme and *tert*-butyl nitrite (90 % pure, 3.3 ml, 2.9 g, ca. 25 mmol) in 10 ml of glyme, respectively, from two separate syringes over 10 min. The reaction mixture was then refluxed overnight. After cooling 50 ml of diethyl ether was added and the resulting mixture stirred with aqueous potassium hydroxide (3 M). The aqueous phase was extracted once with ether and the combined ether extracts were washed with water, dried (Na_2SO_4) and the solvent evaporated to give the crude product which was purified by flash column chromatography to yield 693 mg (42%) of pure ether **2**. The optical rotation was measured to $[\alpha]_D^{20} = 5.55$ (*c* 2.0, $CHCl_3$). The product exhibited the following spectroscopic properties: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 4H), 7.19 (m, 3H), 6.86 (m, 3H), 5.30 (q, $J = 6.4$ Hz, 1H), 1.63 (d, $J = 6.4$ Hz, 3H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 24.7, 76.1, 116.1, 120.8, 125.8, 127.6, 128.8, 129.5, 143.5, 158.2 ppm. IR (NaCl): 3058, 3028, 2972, 2869, 1628, 1600, 1510, 1485, 1389, 1258, 1217, 1181, 1103, 837, 747, 700 cm^{-1}. MS [*m*/*z*, (% rel. int.)]: 198 (M^+, 2), 106 (9), 105 (100), 104 (45), 103 (14), 94 (26), 79 (14), 78 (8), 77 (22).