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A Convenient Preparation of Deuterated Aromatic Compounds

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Received March 3, 1978

The classical procedures for the deuteration of polycyclic aromatics are tortuous and inconvenient,[1] involving heating the arene in D_2O to 350 °C in the presence of a Pt catalyst or exchange with benzene-d_6.[2] A more convenient procedure for the deuteration of benzo[*a*]pyrene was recently published.[3] There also exists an excellent method developed by Makabe, but since it was published in Japanese it has not been used widely in the west.[4] Their elegant method uses a mixture of BF_3·D_3PO_4 and is useful with a variety of organic compounds. This experimental procedure was improved by Heredy and co-workers.[5] The use of liquid deuteriohalides has also been reported.[6] We have developed another technique for preparing deuterated aromatic compounds which is very rapid and convenient, requiring only BF_3 and D_2O.

The liquid acid prepared by blowing BF_3 gas into D_2O to prepare a 1:1 molar solution is a fascinating, strong acid system[7,8] whose chemistry we are exploring. Its preparation is rapid and easy. It can be used for preparing deuterated aromatics simply by stirring the neat aromatic with the BF_3·D_2O system. Reactions with deactivated benzenes are too slow to be useful. The reaction proceeds nicely with polycyclic aromatics and others whose electrophilic reactivity is as great as or greater than benzene. The system has obvious advantages over D_2SO_4. Since the proton is the only electrophile, competing electrophilic reactions such as sulfonation do not occur. Since BF_3 and D_2O are commonly available, the procedure is much more convenient than the use of deuteriohalides such as DBr and $AlBr_3$ or DF or DCl in CF_3COOD.[6] Results with a variety of aromatics are given in Table I.

Experimental Section

All compounds were purchased and were used without further purification.

Preparation of BF_3·D_2O. A weighed amount of D_2O (99.8%) was cooled in a ice–water bath and BF_3 was bubbled into the liquid until a 1:1 molar ratio was reached as measured by the weight increase. BF_3·D_2O is a fuming liquid and was stored in a polyethylene bottle.

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Table I. Deuteration of Aromatic Compounds

compd	registry no.	temp, °C	time, h	H–D exchange, %
benzene	71-43-2	25	61	45
toluene	108-88-3	25	24	74
chlorobenzene	108-90-7	25	120	14
o-xylene	95-47-6	25	48	81
m-xylene	108-38-3	25	48	85
p-xylene	106-42-3	25	48	81
cumene	98-82-8	25	41	78
tert-butylbenzene	98-06-6	25	30	dealkylates
n-butylbenzene	104-51-8	25	48	70
tetralin	119-64-2	25	61	78
naphthalene	91-20-3	90	23	76
phenanthrene	85-01-8	105	20	81

Deuterium Exchange. The hydrocarbon was placed in a flask and a ca. 10 M excess of D_2O·BF_3 was added. A condenser was connected and the reaction mixture was stirred at room temperature. Naphthalene and phenanthrene exchanges were carried out at 90 and 105 °C, respectively, in fuming, slowly decomposing acid. After completion, the organic layer was separated, washed twice with water, and dried with silica gel. Naphthalene and phenanthrene were dissolved in CCl_4 after the reaction, the CCl_4 layer was separated, washed with water, and dried over silica gel, and the CCl_4 was evaporated.

Analysis of Deuterium Exchange. The possibility of deuterium incorporation into the aliphatic groups was examined by looking for aliphatic C–D stretching bands in the IR spectrum. While a diminution of the C_{ar}–H stretch at about 3030 cm^{-1} and a new intense band at 2260 cm^{-1} due to C_{ar}–D stretch was observed, no bands attributable to C_{al}–D stretch were observed. Mass spectra indicated that a mixture of deuterated compounds was present in each reaction product. The extent of deuterium incorporation was measured by comparing the areas of the aromatic and aliphatic NMR peaks in the deuterated products. With benzene, chlorobenzene, naphthalene, and phenanthrene, D incorporation was estimated by adding a known amount of a standard compound (cyclohexane) to the CCl_4 solution of deuterated product and comparing peak areas. Reproducibility of the NMR technique was ±5% of the measured conversion.

Aknowledgment. Research sponsored by the Division of Basic Energy Sciences of the Department of Energy under contract with Union Carbide Corp. The helpful comments of Vernon Raaen and L. Maya are gratefully acknowledged.

Registry No.—D_2O, 7789-20-0; BF_3, 7637-07-2; BF_3·D_2O, 33598-66-2.

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An Improved General Synthesis of 1-Aryl-1-cyclopropanols

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Received March 8, 1978

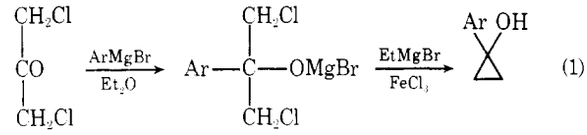
The most general procedure for the synthesis of 1-aryl-1-cyclopropanol previously available was that of De Puy and his co-workers[2] (eq 1). An alternative procedure, based on 1-

0022-3263/78/1943-3602$01.00/0

Table I. Synthesis of 1-Aryl-1-cyclopropanols[a]

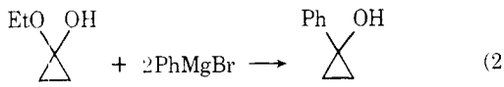
1-Aryl-1-cyclopropanol[b]	Registry no.	Bp (mm) or mp, °C	Yield,[c] %	3,5-DNB[b] mp, °C	Registry no.
p-(Dimethylamino)phenyl	66826-74-2	113–114	57 (0)	137–138	66826-75-3
[5-Coumaranyl]	66859-36-7	130–132 (0.3)	51 (0)	147–148	66826-76-4
p-Methoxyphenyl	15973-65-6	75–78 (0.5)[d]	52 (35)	109–110[g]	65109-90-2
p-Methylphenyl	40122-37-0	38–39[e]	71 (55)	114–115[g]	65109-92-4
Phenyl	29526-96-3	106–107 (20)[f]	75 (48)	104–105[g]	66826-77-5

[a] Complete spectral characterization confirms the structural assignments. [b] Satisfactory microanalytical data were obtained for all of the 1-aryl-1-cyclopropanols and their 3,5-DNB derivatives. [c] The figures in parentheses indicate the percent yields obtained using the De Puy method.[2,5] [d] Lit.[5] bp 75–78 °C (0.5 mm). [e] Lit.[2] mp 39–40 °C. [f] Lit. bp 119–121 °C (26 mm): S. Murai, T. Aya, and N. Sonoda, *J. Org. Chem.*, **38**, 4354 (1973). [g] Melting point is identical with those of products prepared earlier by the De Puy procedure.[5]



(1)

ethoxycyclopropanol, has recently become available[3,4] (eq 2).

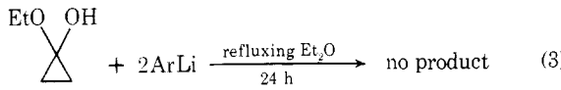


(2)

In our hands the De Puy synthesis proved satisfactory for the preparation of a series of 1-aryl-1-cyclopropanols containing moderately activating substituents in the aryl group (*p*-CH_3, *p*-SCH_3, *p*-OCH_3).[5] However, in attempting to synthesize 1-aryl-1-cyclopropanols containing even more activating substituents (*p*-$N(CH_3)_2$, 5-coumaranyl), this synthetic procedure failed, in spite of considerable experimental effort.

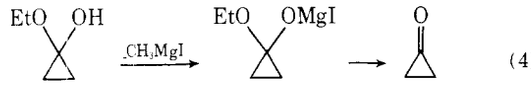
First, these reactive aryl derivatives are converted into the Grignard reagents only with difficulty. The corresponding lithium compounds are far more accessible. However, these aryllithiums failed to add to 1,3-dichloro-2-propanone over a variety of conditions. Instead, preferential enolization of the ketone invariably occurred.

Attempts to use 1-ethoxycyclopropanol with these aryllithiums likewise failed. Apparently the lithium salt of 1-ethoxycyclopropanol is formed, but further reaction does not occur even in refluxing ether over 24 h (eq 3).

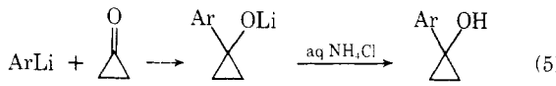


(3)

Experiments revealed a simple solution to the difficulty. Treatment of the reagent, 1-ethoxycyclopropanol, with an equimolar amount of methylmagnesium iodide converted it into a species which readily reacts with the desired aryllithium to give the desired products in high purity and satisfactory yields. Although we did not attempt to identify the intermediate, we believe that the magnesium salt readily breaks down into cyclopropanone, whereas the intermediate lithium salt does not (eq 4 and 5). A further advantage of this procedure



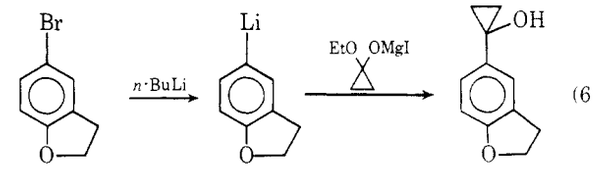
(4)



(5)

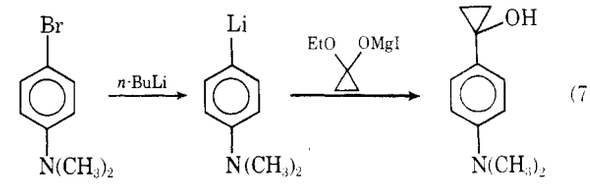
is the fact that it requires only 1 mol of the desired aryllithium.

In this way we successfully synthesized 1-[5-coumaranyl]-1-cyclopropanol (eq 6), which had previously eluded us in spite



(6)

of exhaustive efforts.[5] Similarly, we were successful in extending the procedure to the synthesis of the highly activated *p*-(dimethylamino)phenyl derivative (eq 7). This method



(7)

appears to provide a highly convenient general synthetic route to the 1-aryl-1-cyclopropanols.

Experimental Section

Melting and boiling points are uncorrected. ^1H NMR spectra were determined on a Varian T-60 spectrometer.

Synthesis of 1-ethoxycyclopropanol was done from 1-ethoxy-1-trimethylsiloxycyclopropane[6] according to the method of Salaün[3] in 90% yield, bp 60–61 °C (18 mm) [lit.[7] bp 60–62 °C (20 mm)].

Preparation of Aryllithiums. The aryllithiums were made by the treatment of the corresponding aryl bromides with *n*-butyllithium.[8]

Synthesis of 1-Aryl-1-cyclopropanols: 1-[*p*-(Dimethylamino)phenyl]-1-cyclopropanol. To an oven-dried, nitrogen-flushed, 250-mL three-neck flask fitted with a septum inlet, a magnetic stirring bar, a pressure equalizing dropping funnel, and a reflux condenser and topped with a connecting tube leading to a mercury bubbler was added magnesium (0.243 g, 10 mmol) and diethyl ether (20 mL). To this stirred suspension was added dropwise methyl iodide (1.42 g, 10 mmol) in ether (20 mL). After all of the magnesium was dissolved, the flask was cooled in an ice bath. To this was added dropwise 1-ethoxycyclopropanol (1.02 g, 10 mmol) in ether (20 mL). A gas, presumably methane, evolved, and a white suspension was observed. To a 100-mL flask fitted with a septum inlet and a magnetic stirring bar and topped with a connecting tube leading to a mercury bubbler was added *p*-(dimethylamino)bromobenzene (2.0 g, 10 mmol) and diethyl ether (20 mL). To this stirred solution at room temperature was added dropwise a solution of 10 mmol of *n*-butyllithium in hexane (1.9 M, 5.3 mL) with the help of a syringe. Stirring was continued for 2 h.[9] This solution was added dropwise with a double-ended needle to the white suspension prepared above, maintained at 0 °C. After the addition was over, the reaction mixture was brought to room temperature (30 min) and then maintained (oil bath) under reflux for 12 h. It was cooled to 0 °C and saturated ammonium chloride solution added. After the usual workup and removal of solvents, the solid obtained was recrystallized from a 90:10 mixture of hexane–ethyl acetate. There was obtained 1.01 g (57%) of pale yellow crystals, mp 113–114 °C.

This procedure was applied to the synthesis of a representative group of 1-aryl-1-cyclopropanols, and these were converted into the corresponding 3,5-dinitrobenzoates.[5] The results are summarized in Table I.

Registry No.—1-Ethoxycyclopropanol, 13837-45-1; *p*-(dimethylamino)bromobenzene, 586-77-6; 5-bromocoumarin, 66826-78-6; *p*-(methoxy)bromobenzene, 104-92-7; *p*-(methyl)bromobenzene, 106-38-7; bromobenzene, 108-86-1.

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Preparation of Optically Pure *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine and Its Antipode

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Received March 27, 1978

O-Benzyl-L-serine derivatives are useful in peptide synthesis. The currently available methods for preparing these compounds are laborious and not convenient for large-scale preparation. Okawa[1] prepared *O*-benzyl-L-serine via bromination of methyl acrylate and resolved the racemate of the *N*-acetyl derivative by acylase. The other method is benzylation of N-*tert*-butyloxycarbonyl-L-serine in sodium–liquid ammonia[2] or in sodium hydride–dimethylformamide.[3] The acylase method can obtain optically pure *O*-benzyl-L-serine but the amino-protecting group should be introduced again for peptide synthesis. The enzyme, however, is not cheap and is hard to obtain. The second method, benzylation of *N-tert*-butyloxycarbonyl-L-serine, is only around 50% in yield and racemization might occur in the benzylation process.

The direct resolution of *N-tert*-butyloxycarbonyl derivatives of racemic amino acids would be a better way of preparing optically pure protected amino acids rather than incorporating the protecting group onto optically active amino acids or derivatives.

We present here a new method for the preparation of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode. Both enantiomers appeared optically pure and the yields are higher than the published values.

Starting from methyl acrylate, *O*-benzyl-DL-serine obtained[1] was converted to *N-tert*-butyloxycarbonyl derivative[4] and then methylated by diazomethane.[5] The butyloxycarbonyl group might be introduced to the amino acid methyl ester prepared by thionyl chloride in methanol. The racemic acyl amino acid methyl ester was then hydrolyzed under papain catalysis to afford the L acid in 72% yield; its antipode was recovered in 81% yield from the unreacted D ester by mild alkaline treatment.

The same approach to other amino acids including threonine derivative, which has two optical centers, is under investigation.

Experimental Section

***N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine Dicyclohexylammonium Salt.** *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine (mp 90–91 °C, from ether/*n*-hexane) (5.9 g, 20 mmol) prepared from *O*-benzyl-DL-serine was dissolved in ether (100 mL). The ethereal solution of diazomethane[7] was dropped in until the solution remained pale yellow. The mixture was then washed twice with 20-mL portions of 1 N $NaHCO_3$, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to dryness. The oily ester (6.0 g, 98%) obtained was dissolved in 10 mL of dimethylformamide and then added to a phosphate buffer solution (0.05 M, pH 6.0) containing 5 mmol of β-mercaptoethanol, 5 mmol of EDTA and 500 mg of crude papain. The mixture was kept at 35 °C with stirring and the pH was maintained at 6.0 by addition of 1 N NaOH. After 4 h and with no decrease in pH, the mixture was extracted twice with 50-mL portions of ether to recover the unreacted ester. The aqueous solution was then acidified to pH 3.0 with 3 N HCl and extracted three times with 50-mL portions of ethyl acetate. The combined ethyl acetate was washed with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure to give a colorless oil. The oil was dissolved in 30 mL of ether/*n*-hexane (1:1 v/v) followed by addition of dicylcohexylamine (1.6 mL). The precipitates formed after cooling were collected by filtration to give the title compound (3.4 g, 72%): mp 135–136 °C; R_f 0.78 (system A), 0.20 (system B); $[\alpha]^{25}_D$ +25.0 (*c* 2, MeOH) [lit.[7] mp 135.5–136 °C, $[\alpha]^{25}_D$ +24.3 (*c* 2.94, MeOH)].

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 8.92; N, 6.03.

***N-tert*-Butyloxycarbonyl-*O*-benzyl-D-serine Dicyclohexylammonium Salt.** The unreacted ester obtained above in ether was washed with water, dried, and evaporated to give an oil (3.4 g, 11 mmol), which was further digested with papain (50 mg) in the same way as described above (in 100 mL of solution) for 4 h and the unreacted ester was isolated again (2.5 g, 8.1 mmol): R_f 0.88 (system B); $[\alpha]^{25}_D$ +2.5 (C 2, MeOH). It was hydrolyzed by stirring in a mixture of dioxane–1 N NaOH (1:1 v/v) (30 mL) with 1.5 equiv of alkali for 20 min. The solution was then acidified and followed by extraction to prepare the dicyclohexylammonium salt of *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine (3.8 g, 8 mmol): mp 133–134 °C; $[\alpha]^{25}_D$ −24.2 (*c* 2, MeOH) [lit.[7] mp 130–131 °C; $[\alpha]^{25}_D$ −23.6 (*c* 2.28, MeOH)]; TLC data were the same as for the L isomer.

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 9.11; N, 6.06.

The Steric Purity. An aliquot of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode obtained by the above procedure were dissolved in 5 mL of 2 N HCl–AcOH, respectively. After 1 h at room temperature, the reaction mixture was evaporated under reduced pressure at 25 °C to yield a residue which was then diluted to 5 mL with 1 N HCl for optical rotation determination. The samples showed the same optical rotation in absolute value, respectively, as a sample of *O*-benzyl-L-serine[1] similarly treated, $[\alpha]^{25}_D$ =7.4 (*c* 2, 1 N HCl).

Registry No.—*N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine dicyclohexylammonium salt, 30200-52-3; *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine, 53317-22-9; *O*-benzyl-DL-serine, 5445-44-3; dicyclohexylamine, 101-83-7; *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine dicyclohexylammonium salt, 10342-02-6.

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Synthesis of β-Dihydrothebaine

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Received April 6, 1978

The 6,14-*endo*-etheno and 6,14-*endo*-ethanotetrahydrooripavines are among the most potent analgesics known.[1]

0022-3263/78/1943-3604$01.00/0