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# SELECTIVE BENZYLATION OF ALCOHOLS AND AMINES UNDER MILD CONDITIONS

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Abstract -- A new synthesis of benzyl ethers and N-benzylamines is described under nonbasic conditions using the fluoboric acid catalyzed reaction of phenyldiazomethane.

The protection of alcohols and amines as O- and N-benzyl derivatives has long played a central role in organic synthesis. Numerous aryl-substituted benzylating reagents have now been developed which extend the range of available protecting groups.[1] Recently we needed to O-benzylate a monosaccharide derivative which also contained migratory ester and sensitive primary bromide functionality. Thus the conventional method employing strongly basic conditions was not applicable. The use of benzyl and allyl trichloroacetimidates has been reported,[2] although this method involves prolonged exposure to triflic acid at room temperature. We reasoned that phenyldiazomethane, whose preparation is now a convenient *Organic Syntheses* procedure,[3] might achieve the desired benzylation at low temperature in the presence of an appropriate co-reagent.

Unfortunately the reaction of aryldiazoalkanes with many transition metal catalysts leads exclusively to dimeric or cyclopropane-containing products.[4,5] Lewis acids such as $SnCl_2$ or $SnCl_4$ catalyze the O-benzylation of ribonucleosides using $PhCHN_2$ in $CH_3OH$,[6] however this process occurs through cyclic diol chelates[7] and fails, obviously, with simple alcohols. We now describe a general method for the O-benzylation of alcohols with $PhCHN_2$ *at -40°C under near-neutral conditions* using $HBF_4$ as catalyst. The technique works well on primary, secondary, tertiary and benzylic alcohols and is compatible with ester, acetal and reactive halide functionalities. Under the same conditions $PhCHN_2$ also N-benzylates primary and secondary amines, albeit more slowly. As a consequence we are able to O-benzylate aminoalcohols like piperidine-2-methanol cleanly in good yield. Thus $HBF_4$-mediated benzylations using $PhCHN_2$ achieves a kinetic selectivity not customarily possible in the standard Williamson ether synthesis.

The benzylation of several representative alcohols using $HBF_4$ as catalyst is summarized in Entries 1-5 of the Table. Optimal yields were obtained when commercially available 48% fluoboric acid was concentrated to 3/4ths its original volume on a rotary evaporator so as to minimize any hydrolysis of $PhCHN_2$ to benzyl alcohol. Both pyridinium fluoborate and $BF_3{\cdot}OEt_2$ gave consistently poorer results. Isolated yields of benzyl ethers were generally excellent. In each example, minor amounts of diazo coupling products were also formed which could conveniently be removed by flash column chromatography. Attempts to S-benzylate t-butylthiol, benzenethiol or cysteine ethyl ester were only marginally successful (10-15% yields).

The special utility of the method is illustrated in Entry 5. Under Williamson conditions (NaH-$PhCH_2Br$), diol 9 underwent benzoyl migration, whereas the acetimidate method[2] produced several undesired byproducts. With $PhCHN_2$, an acceptable yield of dibenzylated D-glucopyranoside 10 was obtained.

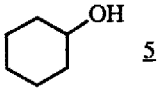
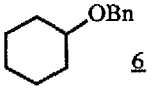
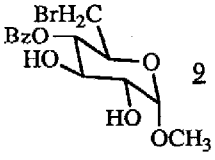
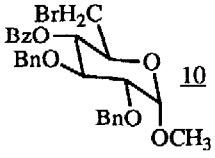
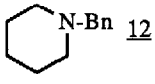
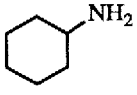
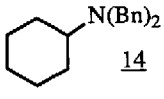
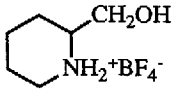
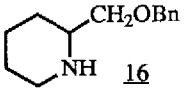
Amines underwent a slow, solvent-independent N-benzylation with $PhCHN_2$ even in the absence of catalyst (e.g. 50% yield of 12 from 11 after 5.5 d at rt). Neither $SnCl_2$ nor $BF_3{\cdot}OEt_2$ accelerated this process. Fluoboric acid markedly promoted N-benzylation (Entries 6 and 7), although the reaction was considerably slower than benzyl ether formation. Thus in Entry 8, the selective O-benzylation of piperidine-2-methanol could be achieved by reacting its $HBF_4$ salt 15 with 5 equiv of $PhCHN_2$ (-40°C, 15 min). Since the benzylation of alcohols in the presence of nucleophilic amines is otherwise impossible, this method should prove useful in synthesis. A representative procedure follows:

**CAUTION! -- All manipulations should be carried out in a well-ventilated hood. Diazo compounds are potentially explosive, and experiments should be conducted behind a safety shield. After distillation, $PhCHN_2$ must be kept cold and under nitrogen; it is best handled in solution. Consult Ref. 3 for a detailed discussion of the stability of this substance.**

To a solution of the alcohol (1 mmol) in $CH_2Cl_2$ (1.5 mL) was added one drop of concentrated 48% $HBF_4$ (see above). The mixture was stirred under argon at -40°C during dropwise addition of $PhCHN_2$ (2.2 mmol) in $CH_2Cl_2$ (1 mL) over 10 min. Nitrogen was evolved. When the red color disappeared, the bath was removed and a saturated solution of $NaHCO_3$ (2 mL) was added. The two-phase mixture was separated and the aqueous layer extracted with $CH_2Cl_2$ (4 x 3 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, concentrated in vacuo, and the crude products purified by flash silica gel chromatography. Isolated yields refer to purified samples whose IR and NMR spectra were identical with authentic standards.

# TABLE

*BENZYLATION OF ALCOHOLS AND AMINES USING PHENYLDIAZOMETHANE*

| Entry | Reactant | Conditions | Product | Yield |
|---|---|---|---|---|
| 1 | n-$C_8H_{17}OH$ 1 | 2.2 equiv, 60 min, -40°C | n-$C_8H_{17}OBn$ 2 | 92% |
| 2 | $PhCH_2OH$ 3 | 2.2 equiv, 35 min, -40°C | $PhCH_2OBn$ 4 | 81% |
| 3 |  5 | 2.2 equiv, 25 min, -40°C |  6 | 85% |
| 4 | $(CH_3)_3C$-OH 7 | 2.2 equiv, 80 min, -40°C | $(CH_3)_3C$-OBn 8 | 66% |
| 5 |  9 | 6.7 equiv, 30 min, -40°C |  10 | 42%[b] |
| 6 |  11 | 1.2 equiv, 12 h, 0°C to rt |  12 | 60% |
| 7 |  13 | 2.4 equiv, 2.5 h, 0°C to rt |  14 | 57% |
| 8 |  15[a] | 5 equiv, 15 min, -40°C |  16 | 68%[c] |

(a) Prepared using a slight excess of $HBF_4$. (b) Both monobenzyl ethers of 9 are also formed; recycling increased the yield of 10 to 55%. (c) Based on ca. 20% recovered 15.

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