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Preferred Preparation of Substituted Diphenylacetic Acids

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Abstract. *Synthesis of substituted diphenylacetic acids has been reported in the literature using a variety of methodologies. We now report the results of utilizing these techniques and outline the procedure that proved most reproducible for our particular application.*

Recently we became interested in the preparation of various mono and di phenyl substituted diphenylacetic acids. We needed a procedure which could potentially yield gram amounts. A number of possible synthetic methods were explored, however one method proved to be far superior to others attempted. This is note is intended to summarize out limited evaluation of some literature reports. Our preferred sequence is described first.

Starting with the commercially available mono or di substituted benzophenones, generation of the acid was carried out according to a literature procedure reported by Ronald L. Halterman and Marjorie A. McEvoy (*J. Am. Chem. Soc.* 1990, **112**, 6690-6695). The procedure is outlined in Scheme 1 and has been successfully reproduced in our labs and extended to a number of other substituents. The procedure utilizes trimethylsulfoxonium iodide / NaH to convert the benzophenone **1** to the corresponding epoxide **2,** which then undergoes rearrangement to the aldehyde **3** using BF_3-Et_2O. In our hands, as well as reported in the literature, the aldehydes are unstable. Threfore they were immediately oxidized to the acid **4** using Jones reagent. Yields for the products ranged from 20 to 45% based on the starting benzophenone.

Scheme 1

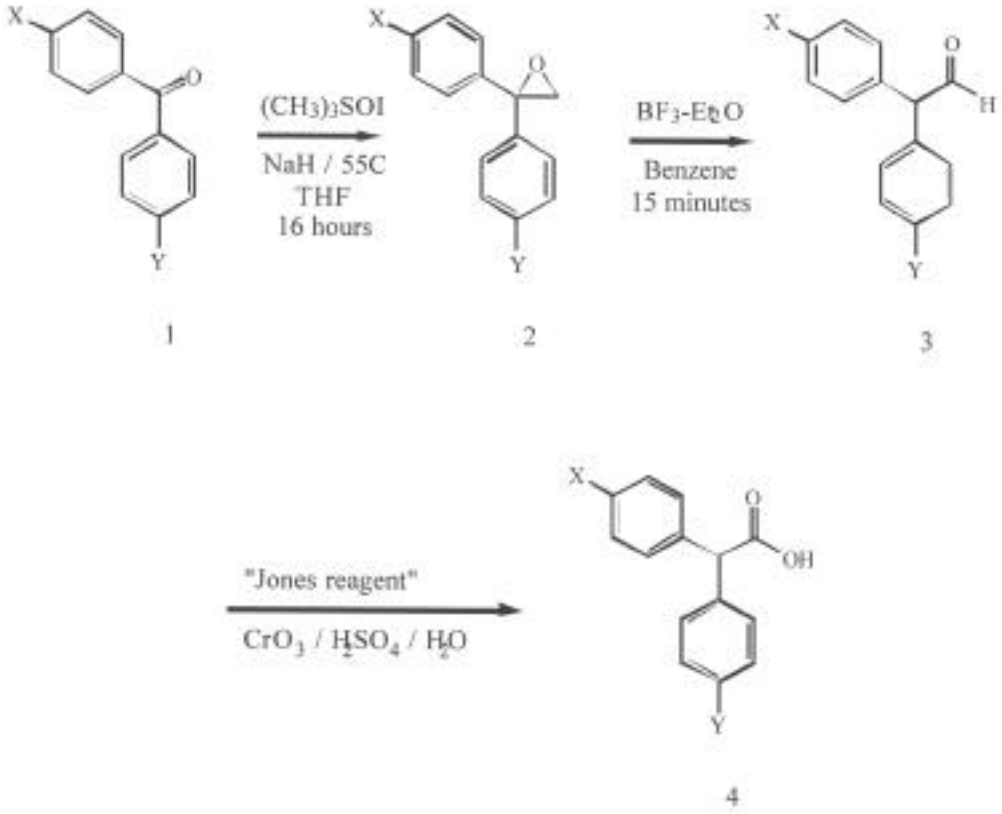


Table 1. Substituted Diphenylacetic Acids from Benzophenones Using the Halterman-McEvoy Procedure

Entry	X	Y	Isolated yield **4**	Literature yield **4**
A	H	Cl	45	52
B	H	Br	not attempted	53
C	H	CH_3	40	not reported
D	H	OCH_3	31	46
E	H	O-benzyl	21	not reported
F	H	O-t-butylacetate	in progress	not reported
G	Cl	Cl	25	not reported

Several other procedures to prepare substituted diphenylacetic acids were evaluated in our limited study. Our observations are described below.

1) Takemura, S., et. al; *Chem. Pharm Bull*, **1983**, *31*(8) 2632-2683 (Scheme 2).

As a model case, X = CH_3, Y = H, generation of the benzhydrol **5** proceeded cleanly as well as the subsequent conversion to the chloride **6** using thionyl chloride or oxalyl chloride (conversion to the bromide using HBr / AcOH worked equally well). Formation of the nitrile by treatment of the chloride (or bromide) with NaCN in DMF at 80 C for 2 hours, however, proved to be irreproducible and gave extremely low yields in our limited attempts. Subsequent formation of the acid **4** was difficult due to the insolubility of the nitrile in the acidic media.

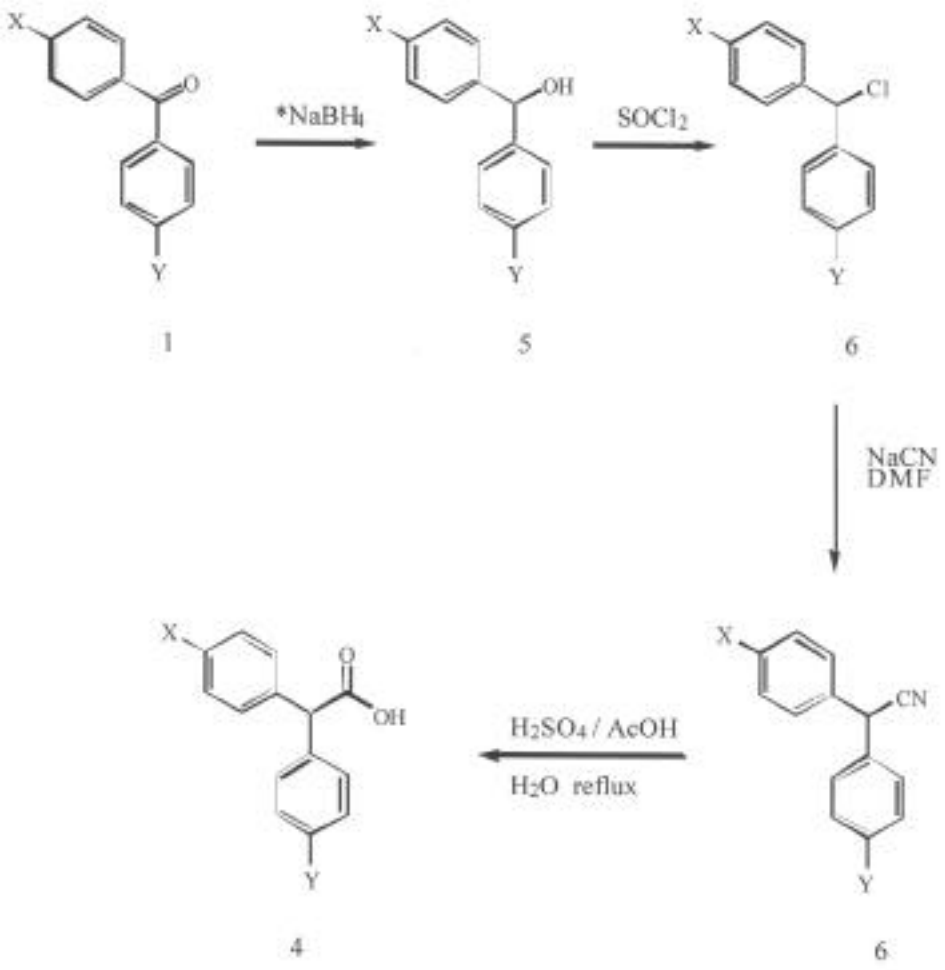
2) Davis, R., et. al.; *J. Org. Chem*, **1981**, *46*, 2985-2987 (Scheme 3).

Starting with the benzhydrol **5** (X = CH_3, Y = H), a one pot synthesis was attempted whereby a mixture of **5**, TMSCl, NaI, NaCN, DMF and acetonitrile were heated at 60 C for several hours. TLC analysis of the reaction showed complex mixtures with little or no desired product formation occurring. Because of the problems with nitrile hydrolysis described above, this method was not further pursued.

3) Independent results (Scheme 4)

Starting with the benzhydrol **5** (X = CH_3, Y = H), treatment with mesyl chloride in either pyridine or THF / Hunigs base did not give the expected product **7** rather quantitative formation of the dibenzylether **8** was observed. Subsequent treatment of the mesylate **7** would have been followed by treatment with NaCN and then converted to the acid via acidic hydrolysis of the nitrile.

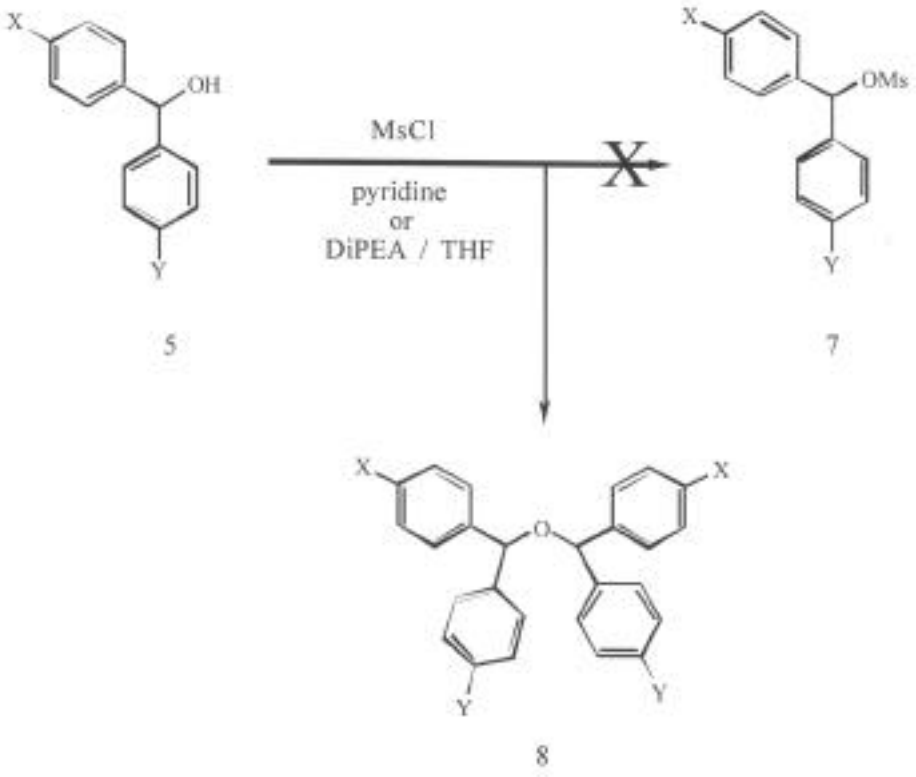
Scheme 2



* this step was not reported in the reference

Scheme 3

Scheme 4



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