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ALTERNATIVE METHODS FOR THE ALKYLATION OF ISOQUINOLINE REISSERT COMPOUNDS

Jerry W. Skiles and Michael P. Cava*

Department of Chemistry, University of Pennsylvania,
Philadelphia, Pennsylvania 19104, U. S. A.

A comparative study was made of the alkylation of five representative isoquinoline-type Reissert compounds (1-5) with both benzyl chloride and *o*-nitrobenzyl chloride, using three different base-solvent systems: (A) lithium diisopropylamide in THF/HMPA, (B) KOH with benzene and dicyclohexyl-18-crown-6, and (C) 50% aqueous NaOH with benzene or acetonitrile and cetrimonium bromide. Systems (B) and (C) were clearly the best, the latter being especially advantageous.

The alkylation of isoquinoline-derived Reissert compounds with benzylic halides is an important reaction, since it forms a key step in a widely used synthetic route to benzylisoquinoline and aporphine alkaloids.[1] The required Reissert anion intermediate in these alkylations has almost always been generated using a sodium hydride suspension in dimethylformamide. Although the NaH/DMF method has been of great synthetic value, the literature cites a number of cases in which the expected alkylation product was obtained either in low yield or not at all.[2] In our own laboratory, we have often had difficulty in obtaining satisfactory and reproducible yields, especially when nitrobenzyl halides were employed. In the hope of developing a better Reissert route to benzylisoquinolines, we have now made a comparative stud of the alkylation of five known Reissert compounds (**1**-**5**) by both benzyl chloride (**6**) and *o*-nitrobenzyl chloride (**7**), using three alternate alkylation systems: (**A**) lithium diisopropylamide in tetrahydrofuran in the presence of hexamethylphosphoramide, (**B**) potassium hydroxide and benzene in the presence of a crown ether (dicyclohexyl-18-crown-6), and (**C**) a two phase system of 50% aqueous sodium hydroxide and benzene or acetonitrile in the presence of a phase-transfer catalyst (cetrimonium bromide). Systems **A** and **B** have not been employed previously in benzylisoquinoline synthesis; one example related to System **C** (78% of **8** from **1** and **6** using 50% NaOH and TEBA catalyst, no solvent) has been reported.[3]

The results of our experiments, shown in the Table, indicate that System **A** gave consistently inferior yields of alkylated Reissert compounds than Systems **B** and **C**, both of which functioned extremely well. The phase-transfer System **C** held a slight advantage over crown-ether System **B**, both in yields and economy of reagents. Typical procedures are given below.

Table Alkylation of Reissert Compounds

Reissert Compound	Alkylated Reissert (mp, ° C)	% Yield (Method)		
		A	B	C
1	8 (128-129)[a]	46	95	91
1	9 (142-144)[b]	36	85	83
2	10 (153-155)[c]	38	92	94
2	11 (182-184)[c]	42	81	88
3	12 (138-139)[c]	52	94	96
3	13 (127-128)[d]	34	80	87
4	14 (146-148)[c]	51	93	92
4	15 (177-178)[c]	48	80	86
5	16 (198-200)[e]	44	90	91
5	17 (195-196)[c]	42	85	82

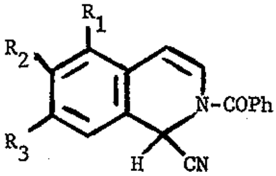
a: lit. mp 129° C [4]

b: lit. mp 143-144° C [5]

c: satisfactory elemental analyses were obtained.

d: reported as an oil [6]

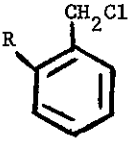
e: lit. mp 185-186° C [7]



1, $R_1 = R_2 = R_3 = H$

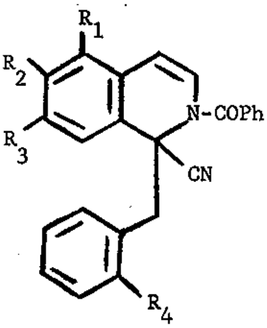
2, $R_1 = H$; $R_2 = R_3 = OMe$

3, $R_1 = R_2 = R_3 = OMe$



6, $R = H$

7, $R = NO_2$



8, $R_1 = R_2 = R_3 = R_4 = H$

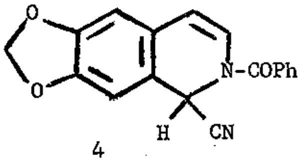
9, $R_1 = R_2 = R_3 = H$; $R_4 = NO_2$

10, $R_1 = R_4 = H$; $R_2 = R_3 = OMe$

11, $R_1 = H$; $R_2 = R_3 = OMe$; $R_4 = NO_2$

12, $R_1 = R_2 = R_3 = OMe$; $R_4 = H$

13, $R_1 = R_2 = R_3 = OMe$; $R_4 = NO_2$



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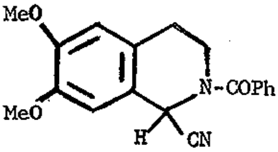

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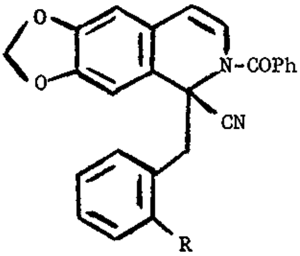
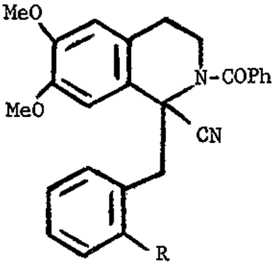


14, $R = H$

15, $R = NO_2$



16, $R = H$

17, $R = NO_2$

Crown-ether Catalysis (System B): A mixture of the Reissert compound (2.5 mmole), the benzyl halide (2.5 mmole), powdered potassium hydroxide (0.60 g) and dicyclohexyl-18-crown-6 (50 mg) was cooled to 0° (argon atmosphere). Dry benzene (30 ml) was added by syringe and the mixture stirred 15 min at 0° and then 90 min at room temperature. After acidification to pH 5 (5% aqueous sulfuric acid) the product was extracted into benzene. After evaporation of the dried solvent, the products were crystallized from methanol, ethanol, or ether either directly or after silica chromatography (benzene eluant).

Phase-transfer Catalysis (System C): A mixture of the Reissert compound (8.6 mmole), the benzyl halide (9.0 mmole), cetyltrimethylammonium bromide ("cetrimonium bromide", 20-50 mg), and benzene (20-30 ml) was flushed with argon. Aqueous 50% sodium hydroxide (5 ml) was added in one portion and the mixture was stirred for 90-120 min at room temperature. After acidification to pH 6 (5% sulfuric acid) the product was isolated as indicated above.

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