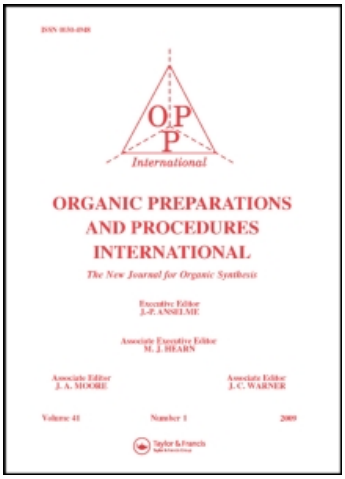

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PREPARATION OF AN *o*-SUBSTITUTED BENZAMIDINE BY THE PINNER METHOD. A LITERATURE CLARIFICATION

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Submitted by (02/05/90)

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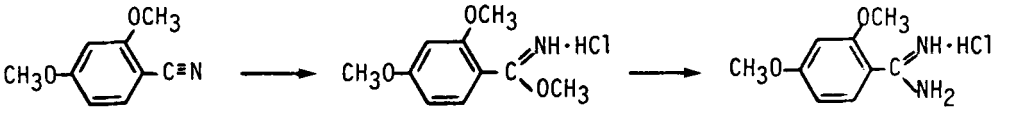
The Pinner amidine synthesis[1] consisting of formation of imino esters (imidates) by the addition of anhydrous hydrogen chloride to a solution of the appropriate nitriles in an alcohol and followed by treatment with ammonia (or primary or secondary amines), is the most practical and widely used method for the preparation of a variety of amidines. However, it has been repeatedly stated[2] that o-substituted benzamidines cannot be prepared by this method and they can only be obtained[3] by O-alkylation of their imidate salts. Nevertheless, reports on the synthesis of 2-hydroxy- and 2,4-dihydroxybenzamidines in low yields by the Pinner process have been reported.[4]



1 2 3

2,4-Dimethoxybenzamidinium chloride (3) which was required as an intermediate for another study,[5] has not been reported although the free amidine was mentioned in a biological study, albeit without any information of its synthesis.[6] In spite of the fact that other approaches were suggested for the synthesis of o-substituted benzamidines,[2,3,7] it was decided to study the feasibility of using

the Pinner method. After several carefully planned experimental trials, the required 2,4-dimethoxybenzamidinium chloride (3) could indeed be obtained in 63% overall yield. The problem of o-substituted steric hindrance was minimized by the use of methanol instead of ethanol for the imino ester (2) formation. In view of these results, previousstatements of the impossibilty of the formation of o-substituted benzamidines from the corresponding benzonitriles by the Pinner process[2] certainly need to be reexamined.

EXPERIMENTAL SECTION

2,4-Dimethoxybenzamidinium Chloride (3).- In a 2-1 round bottom flask fitted with drying tube and containing a solution of 22 g (0.14 mole) of 2,4-dimethoxybenzonitrile (1, thoroughly dried over silica gel) in 400 ml of dry chloroform was added 10 g (0.31 mole) of anhydrous methanol. The stirred solution was cooled to 0° and saturated with dry hydrogen chloride. The resulting solution was kept at 0° for an additional 4 hrs. Then the mixture was gradually allowed to become ambient overnight, the drying tube replaced by a glass stopper and the reaction mixture allowed to stand at room temperature for 48 days with intermittent stirring. The mixture was then evaporated to dryness at room temperature under reduced pressure. To the solid residue 2 was added 800 ml of methanolic ammonia (saturated with NH_3 at 0°). The resulting solution was allowed to stand at room temperature with stirring for 4 days. It was then evaporated to dryness under reduced pressure. The solid was extracted repeatedly with anhydrous ether (5 x 100 ml) in order to remove unreacted benzonitrile (a total of 6 g of starting nitrile was recovered). The remaining insoluble solid was recrystallized from n-butanol. The white crystalline solid, which deposited on cooling, was collected and washed with anhydrous ether to give 18.4 g (63% yield based on unrecovered nitrile) of pure 3, mp. 238-239°. An additional recrystallization from n-butanol yielded analytically pure 3, mp. 239-239.5°. MS: 180 (M^+).

Anal. Calcd. for $C_9H_{12}N_2O_2 \cdot HCl$: C, 49.89; H, 6.05; N, 12.93

Found : C, 49.92; H, 6.09; N, 13.18

The experimental was repeated several times to insure the reproducibility of the reported experimental conditions.

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AN IMPROVED SYNTHESIS OF 4,8,9,10-TETRAARYL-1,3-DIAZAADAMANTANES

Submitted by (05/30/89) S. Sivasubramanian*, M. Sundaravadivelu and N. Arumugam

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In continuation of our ^{1}H nmr spectral studies on 2,6-diphenylpiperidones and their bicyclic derivatives, viz. 3-azabicyclo[3.3.1]nonan-9-ones,[1,2] we were interested in the ^{1}H nmr spectra of 4,8,9,10-tetraaryl-1,3-diazaadamantane systems.[3] The synthesis of several 1,3-diazaadamantanes and their derivatives is reported here.

The most important and versatile route to the above tetraaryl-1,3-diazaadamantane system involves the preparation of the corresponding 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]- nonane and connecting the two nitrogen functions in this system through a methylene group. Although Quast and Muller[4] adopted this route to prepare some of the above compounds, one of their procedures [Method A] involves refluxing a solution of the 3,7-diazabicyclo[3.3.1]nonane in tetrachloromethane with excess of paraformaldehyde for 6 hrs, the addition of paraformaldehyde being sequential [i. e. 1/4th was added initially followed by another 1/4th of the total quantity of paraformaldehyde being added after 1.5, 3.0 and 4.5 hrs] followed by work-up. With method B,[4] the 3,7-diazabicyclo[3.3.1]nonan-9-one in dichloromethane was boiled with excess paraformaldehyde for 3-4 hrs. The solution was filtered hot and worked up.

In our method, to a solution of the 3,7-diazabicyclo[3.3.1]nonan-9-one in hot dimethyl sulfoxide, paraformaldehyde was added slowly over a period of 10 min. and the mixture was heated for another 5 min. Water was then added and the resulting adamantanone was extracted into chloroform to give, after drying and evaporation, the corresponding 1,3-diazaadamantanone. Thus