Tetrahedron Letters,Vol.28,No.51,pp 6453-6456,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE 3,4-DIMETHOXYBENZYL GROUP: A PROTECTIVE GROUP FOR NEW 2-IMINO-IMIDAZOLIDINE DERIVATIVES

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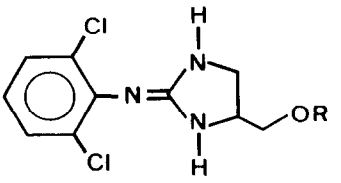
Abstract *- The 3,4-dimethoxybenzyl group has been used to protect 2-imino-imidazolidine derivatives, so we could realize selective O-alkylation, to obtain new clonidine derivatives.*

In our studies of molecules with adrenergic properties, we have tried to obtain new clonidine derivatives[1a] containing either an oxypropanolamine 11[1b,1c] or an imino-oxy-propanolamine moiety 12[1b]. Compound 12 could be synthesized readily from p-acetyl clonidine[2] and 3-(aminoxy)-N-tert-butyl-2-hydroxy-propanamine[3,4].



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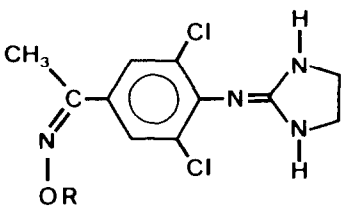

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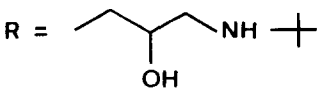
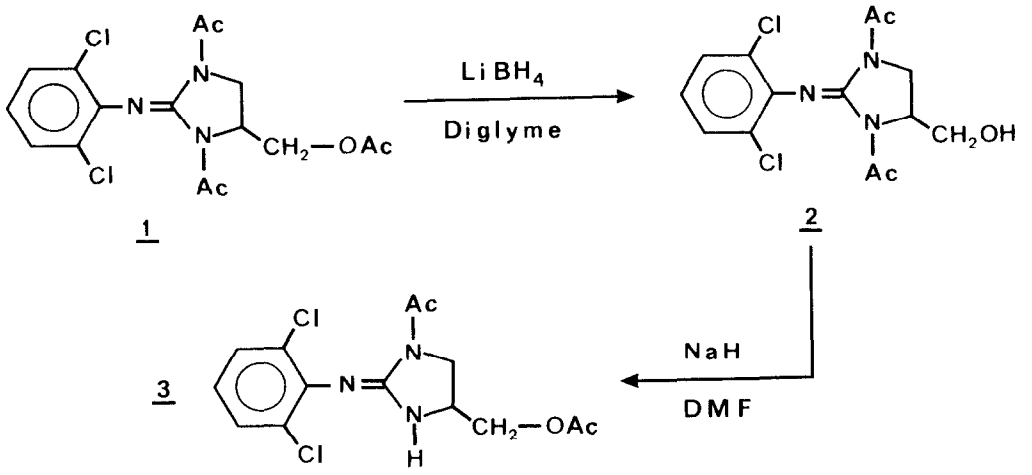


However, the synthesis of 11 proved to be much more difficult. The most feasible approach to 11 involved selective alkylation of an alcohol function in the presence of a 2-imino-imidazolidine. For that type of reaction, the 2-imino-imidazolidine group had to be protected. To date, the most satisfactory protection technique is to transform the guanidine into its N-acetylated form[5]. In an effort to apply this technique to the current problem, we first transformed 1 into 2 by selective O-deacetylation[6].

However, as outlined in Scheme 1, treating the diacetylated compound

2 with NaH in DMF gave 3, in 40% yield, via an N -> O acetyl transfer. The



Scheme 1

structure of 3 was confirmed by the appearance of a methyl ester singlet at 2.2 ppm and the disappearance of an N-acetyl singlet at 2.7 ppm, in the NMR spectrum. A similar migration has been reported for acetylated aminoalcohols[7]. To avoid this reaction, we sought another protective group which would be stable under basic conditions.Recently, Jones et al.[8] have advocated the use of a 3,4-dimethoxybenzyl derivative to protect a pyrrole-NH group, subsequent cleavage of which occurs under acid conditions. The use of the acid labile 3,4-dimethoxybenzyl unit as a "blocking group", for 2-imino-imidazolidine derivatives appeared preferable to the use of an N-benzyl group whose removal through catalytic hydrogenation (Pd/C) provokes, at least partially, hydrogenolysis of the Ar-Cl bonds[5].

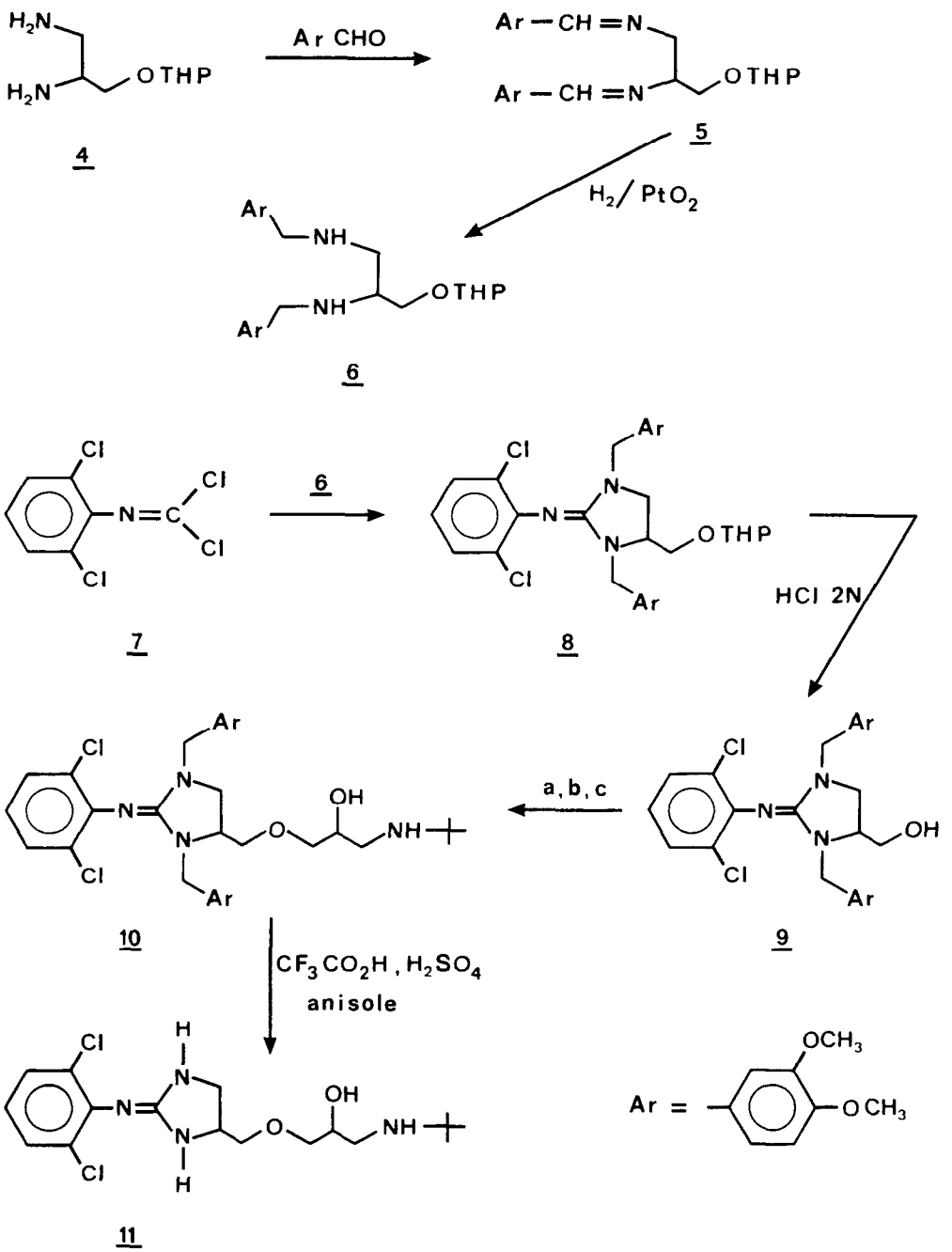
The utilization of the 3,4-dimethoxybenzyl group for guanidine protection in the synthesis of 11 is illustrated in Scheme 2.

The tetrahydropyranyl derivative 4 was synthetized from 2,3-dibromopropanol, as described by Okamoto and Barefield[9]. Condensation of the diamino compound 4, with 3,4-dimethoxybenzaldehyde in refluxing toluene gave a 70% yield of diimine 5 which was reduced by catalytic hydrogenation to the N,N'-di(3,4-dimethoxybenzyl)ethylene diamine derivative 6.

The dichloro isocyanide 7, was obtained according to Toldy and Rados[10,11], from 2,6-dichloro-aniline by formylation with formic-acetic anhydride mixture and then treatment with thionyl chloride and sulfuryl chloride.

Treating 7 with the protected aminoalcohol 6, gave the 2-imino-imidazolidine 8, which was transformed into alcohol 9, by removal of the tetrahydropyranyl-protective group.

Sequential treatment of 9 with MeONa (NaH gave lower yields) (1.1 equiv., 25°C), epibromohydrin in DMF (1.1 equiv.) and tert-butylamine



a = MeONa/MeOH, b = Epibromohydrin/DMF, c = tert-Butylamine/EtOH

Scheme 2

in ethanol (3.3 equiv.) gave 10, in 61% yield.

As expected, compound 10 was cleaved in CF_3COOH-H_2SO_4-anisole, which finally permitted the preparation of the target derivative, 11[12].

In conclusion, our results show, for the first time, that the 3,4-dimethoxybenzyl group can be used as a protective group for 2-imino-imidazolidine derivatives.

ACKNOWLEDGMENT. We thank ALCON/POS Laboratories for financial support.

REFERENCES AND NOTES

1a. A preliminary communication of this work was presented at the "22ème Rencontre internationale de chimie thérapeutique, Clermont-Ferrand, Sept.1986 under the title: "New drugs in the treatment of open angle glaucoma". This work forms part of a thesis for the degree of Doctorat to be submitted by D. HUBER at the University Louis Pasteur, Strasbourg.

1b. Patent pending.

1c. Part of this work was presented at the : "3rd Cyprus Conference on New Methods in Drug Research", Limasol, Cyprus, 26 April-2 May 1987, under the title : "The 3,4-dimethoxybenzyl group : A novel protective group for new drugs to lower intraocular pressure".

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12. **2-(2,6-dichlorophenylimino)-4-(3-tert-butylamino-2-hydroxy-propyloxymethyl)imidazolidine 11.** To a solution of 10 ml of CF_3COOH, 2.5 ml of concentrated H_2SO_4 and 3.4 ml of anisole was added 1.8 g (2.6 mmol) of 10 dissolved in a 3 ml of CF_3COOH. The solution was stirred for 2 h. After that time, the trifluoroacetic acid was evaporated. To the residue was added 20 ml of water. The mixture was basified with $KHCO_3$ and extracted with EtOAc. After usual work up, and silica gel column, we obtained 0.77 g of 11 (76%). ^1H NMR ($CDCl_3$) 1.1 (s, 9H, -NH-(CH_3)$_3$), 2.4-2.8 (broad s, 2H, -NH-CH_2-CHOH -), 3.0-4.1 (m, 8H), 4.5-5.0 (broad s, 4H, -N<u>H</u>-CH_2-CH<N<u>H</u>-, -CH_2-CHO<u>H</u> -CH_2-N<u>H</u>-), 6.6-7.4 (m, 3H, Ar). Mass spectrum, m/z 388/390/392/ (M^+), 373/375/377 (M-CH_3), 353/355 (M-Cl). 11 difumarate salt : mp 104°C; Anal. Calcd for $C_{25}H_{34}Cl_2N_4O_{10}$: C, 48.32; H, 5.51; N, 9.02. Found : C, 48.13; H, 5.90; N, 8.66.

(Received in France 7 September 1987)