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THE USE OF LITHIUM BOROHYDRIDE FOR DEPROTECTING ACETYLATED ALCOHOLS AND PHENOLS IN THE PRESENCE OF N-ACETYLATED GUANIDINES

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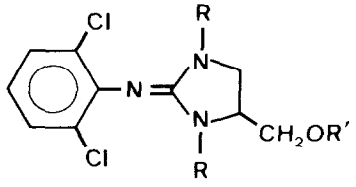
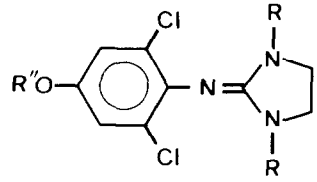
Summary : The behaviour of $LiBH_4$ and $NaBH_4$ on various O- and N-acetylated guanidines has been investigated.

In our study of molecules with adrenergic properties, we carried out alkylation reactions either on the phenol or the alcohol functions. For this type of reaction to succeed, the 2-(imino-2)-imidazolidines of I and II had



I



II

Ia : R = R' = H

Ib : R = R' = Ac

Ic : R = Ac ; R' = H

IIa : R = R" = H

IIb : R = R" = Ac

IIc : R = Ac ; R" = H

Scheme I

to be protected. To date, no entirely satisfactory protecting group has been reported in the literature.

N-benzylation is possible, but deprotection through catalytic hydrogenation (Pd/C) provokes, at least partially, hydrogenolysis of the Ar-Cl links. Protecting the guanidine function with 1,1 dimethylethoxy carbonyl and trichlorethoxy carbonyl residues, often applied in peptide chemistry, did not work.

The most satisfactory technique was to protect the guanidine in its N-acetylated form (1,2). However, this rather harsh method (Ac_2O, 80°C, 18 h or CH_3-COCl in pyridine) did not give selective N-acetylation in the presence of an alcohol function (Ia) or of a phenol one (IIa).

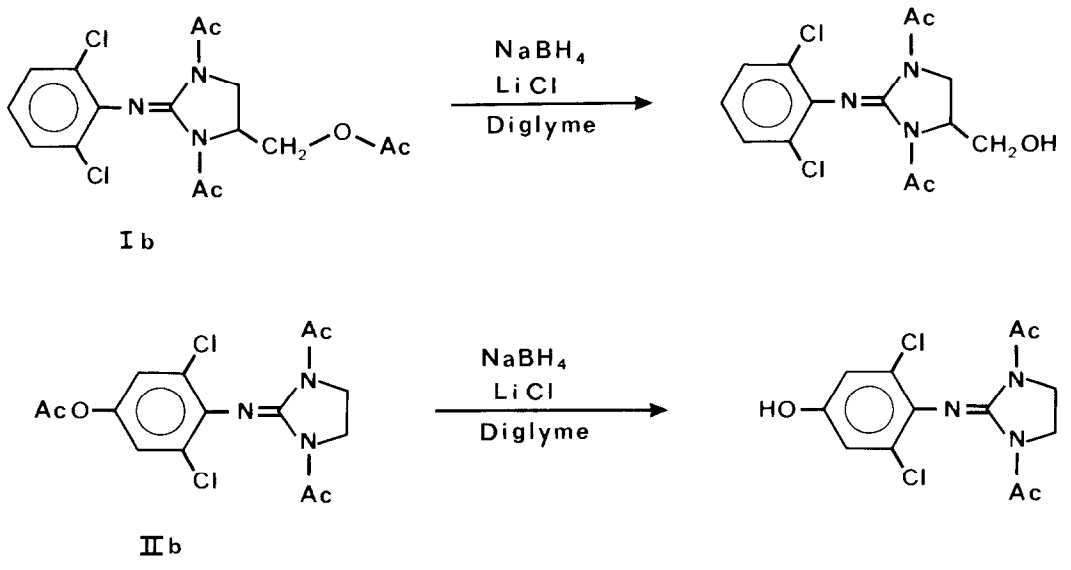
We tried to obtain the diacylated derivatives, Ic and IIc, by treating Ib and IIb with different desacetylating reagents, as described in the literature.

TABLE I

	Initial product	End product	Reference
K_2CO_3/MeOH	Ib	Ia	(3)
$NaHCO_3$/aq. MeOH	IIb	no reaction	(5)
t-$BuNH_2$	Ib	Ia	
	IIb	no reaction	
aq. NaOH 0.1N/THF	Ib	Ia	(1)
	IIb	IIa	(1)
KCN/EtOH 95%	Ib	no reaction	(4)
$NaBH_4$, LiCl/diglyme	Ib	Ic	
	IIb	IIc	

As Table I shows, product Ib was completely desacetylated in the presence of potassium carbonate. This was also the case with a sodium hydroxide/THF mixture. Treating Ib with t-butylamine gave also the completely desacetylated product Ia, whereas IIb did not react.

The reactivity of Ib could be explained by the partial hydrolysis of the ester function by t-$BuNH_2$, followed by the N-desacetylation reaction, facilitated by the assistance of the beta-alcohol function. A similar observation has already been described among acetylated beta-aminoalcohols (9).



Scheme II

Already well known for its reducing properties, sodium borohydride (6) has recently been used for selective deprotection of acetylated phenol in the presence of acetylated alcohol (7). The reducing properties of borohydrides have been shown to vary with the solvent and with nature of the cation (8). Thus, $LiBH_4$ has greater reducing properties than $NaBH_4$ in etheral solvents. It therefore seemed worth studying the reactivity of $NaBH_4$ and $LiBH_4$ on Ib and IIb. Treating Ib with $LiBH_4$ (10) gave the N-diacetylated compound, Ic. Surprisingly, $NaBH_4$, which is supposed to have lower reducing properties than $LiBH_4$, gave a completely desacetylated derivative, Ia.

On the other hand, treating the N,O-triacetylated derivative, IIb, with $NaBH_4$ or $LiBH_4$, gave only the N-diacetylated derivative IIc. No satisfactory explanation has yet been found for this unexpected behaviour of $NaBH_4$ and $LiBH_4$.

We are at present applying this selective desacetylation method to other clonidine-type derivatives.

Our results show, for the first time, that $LiBH_4$ can be used for selective O-desacetylation in the presence of N-diacetylated guanidine.

Acknowledgements

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10. Ib (20 mmoles) was treated with $NaBH_4$ (20 mmoles) and LiCl (20 mmoles) in 50 ml of diglyme for 18 h at room temperature. After usual work-up and chromatography, there was obtained 5.8 g (84%) of Ic. As an example, the spectrometric data of compound Ic are presented here. IIb (20 mmoles) was treated with $NaBH_4$ (20 mmoles) and LiCl (20 mmoles) in 50 ml of diglyme for one night at 50°C. After work-up and chromatography, we obtained 5.2 g (79%) of IIc. ^1H NMR (60 MHz, $CDCl_3$), MS, IR($CHCl_3$, cm^{-1}) spectra were consistent with assigned structure.
Ic : IR 3440, 1680. ^1H NMR 2.1(s, 3H); 2.7(s, 3H); 3.8 - 4.2(m, 5H); 4.8(s, 1H); 6.7 - 7.5(m, 3H). Mass spectrum m/z (%) : 343/345/347 (60), 308/310 (100), 228/230/232 (35).

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