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Regioselective Reduction of 1-Aryl-3-arylaminopyrrolidine-2,5-diones by Sodium Borohydride: A Convenient Route to 3-Arylamino-4hydroxybutanamides

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REGIOSELECTIVE REDUCTION OF 1-ARYL-3-ARYLAMINO-

PYRROLIDINE-2,5-DIONES BY SODIUM BOROHYDRIDE:

A CONVENIENT ROUTE TO 3-ARYLAMINO-4-HYDROXYBUTANAMIDES

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<u>ABSTRACT</u>: The hitherto unknown 3-arylamino-4-hydroxybutanamides are prepared in high yields by regioselective reduction of 1-aryl-3-arylaminopyrrolidine-2,5-diones by sodium borohydride in neutral media. Intramolecular hydrogen bonding is proposed to be an important factor in controlling the regioselectivity.

Pyrrolidine-2,5-diones are reduced to 4-hydroxybutanamides and 2-hydroxy-5-pyrrolidones by sodium borohydride in neutral¹ and acidic^{2,3} media respectively. The reductions are highly regioselective when one of the carbonyl groups is flanked by two bulky alkyl/aryl groups⁴⁻⁷. Curiosisly, the more hindered carbonyl group is reduced preferentially. The regioselectivity has been rationalised in terms of the steric inhibition of the amide resonance involving the

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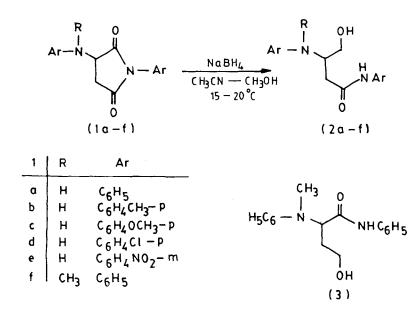
more hindered carbonyl group that makes it more electrophilic and hence more prone to nucleophilic attack by the hydride. Accordingly, the regioselectivity is found to be poor when only one alkyl/aryl group is present adjacent to one of the carbonyl groups. The effect of a heteroatom substituent on the regiochemistry of the reduction has not, however, been reported.

We felt that an adjacent amino group may have considerable effect on the regioselectivity of the reduction and reduction of readily available⁸ 3-aminopyrrolidine-2,5-diones with sodium borohydride in neutral media would offer a convenient route to 3-amino-4-hydroxybutanamides which are otherwise difficult to obtain. It was argued that the loss in the steric control of regioselectivity due to the absence of a second substituent at the 3-position could be effectively compensated by the -I effect as well as intramolecular hydrogen bonding of the amino group with the adjacent carbonyl group, thus leading to the preferential hydride attack at the 2-position. That is what has been realised and is the subject of the present communication.

The 1-Ary1-3-arylaminopyrrolidine-2,5-dione (la-e) were prepared in one step by refluxing a solution of

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maleic anhydride and the appropriate aromatic amines taken in 1:2 molar ratio in acetic acid for 2-3 h⁸. The reaction, however, was not successful with p-nitroaniline and alkyl amines such as butylamine, cyclohexylamine and benzyl amine. The compound (1f) was prepared by the Michael addition of N-methylaniline to N-phenylmaleimide. Reduction of (1a-e) with sodium borohydride in acetonitrile-methanol (4:1) mixture



afforded the hitherto unknown 3-arylamino-4-hydroxybutanamides (2a-e) in high yields. The reduction of (1f), however, proceeded comparatively slowly and yielded a 2:3 mixture of (2f) and (3) as determined by

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the NMR spectroscopy. The compounds (2a-f) were characterised by spectral analysis. Their NMR spectra displayed a doublet around $\delta 2.6$ (J=5-7 Hz) for CH₂CO, another doublet around $\delta 3.7$ (J=5-6 Hz) for CH₂OH and a multiplet around $\delta 3.7-3.8$ for NCH which is partially overlapped with the downfield doublet in the spectra of (1a-d) but is observed as a distinctly separated fivesignal multiplet in the spectra of (1e,f). The reduction can be performed in methanol with little effect on the yield and regioselectivity, however, large excess of sodium borohydride and comparatively longer reaction time are required.

The loss and reversal in regioselectivity in the reduction of (lf) suggest that probably the intramolecular hydrogen-bonding is the more dominant factor in controlling the regiochemistry of the reduction of (la-e). We are not aware of any other study on hydrogen-bond assisted regioselective reduction with sodium borohydride. The method offers a short, convenient and inexpensive route to 3-arylamino-4hydroxybutanamides.

<u>General Procedure</u>: A suspension of (1) (0.005 mole) in a mixture of acetonitrile-methanol (4:1, v/v) (10 ml) was stirred at 15-20° and sodium borohydride (0.2 g, 0.005 mole) was added in one lot. The suspension became

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Reactant (1)	Reaction time (h)	Product (2)	
		% Yield	m.p.(°C)
a	3	90	114
b	3	88	91
с	3	85	82
d	3	98	127-8
e	4	92	155-6
f	10	32*	111

Table

*80% overall as a mixture of (2f) and (3) in 2:3 ratio.

homogeneous as the reaction proceeded. The stirring was continued for the time indicated in the Table. The reaction was then quenched with water (10 ml), acidified with acetic acid and extracted with dichloromethane (3 x 25 ml). The combined organic layer was dried (anhy. K_2CO_3), the solvent evaporated and the residual solid recrystallised from benzene or benzenehexane mixture.

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