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A NEW METHOD FOR THE REDUCTION OF AMIDES TO AMINES WITH SODIUM BOROHYDRIDE

Atta-ur-Rahman*, Anwer Basha and Nighat Waheed,
H.E.J. Postgraduate Institute of Chemistry,
University of Karachi, Karachi-32, Pakistan.

&

Shahid Ahmed,
Department of Chemistry,
University of Karachi,
Karachi-32, Pakistan.

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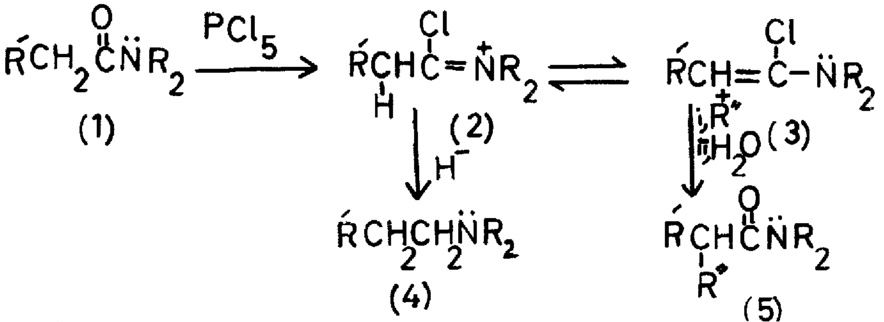
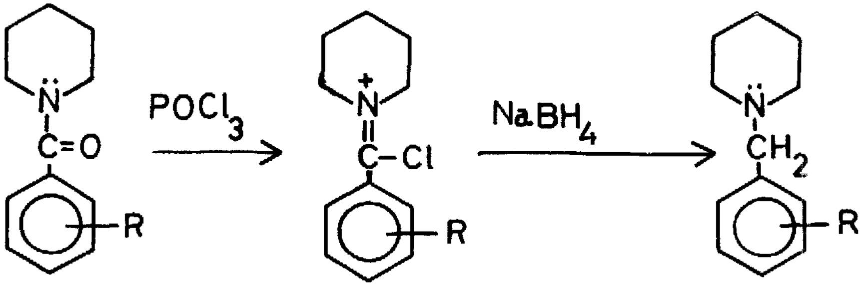
We have recently described a new procedure[1] for the activation at α-carbons of amides and imides thus making possible alkylation, bromination etc. at carbon atoms adjacent to amide and imide carbonyls. This reaction involved the generation of the Vilsmeir complex (2) of an amide/imide with PCl_5 which could react via the chlorenamine (3) with appropriate electrophiles.



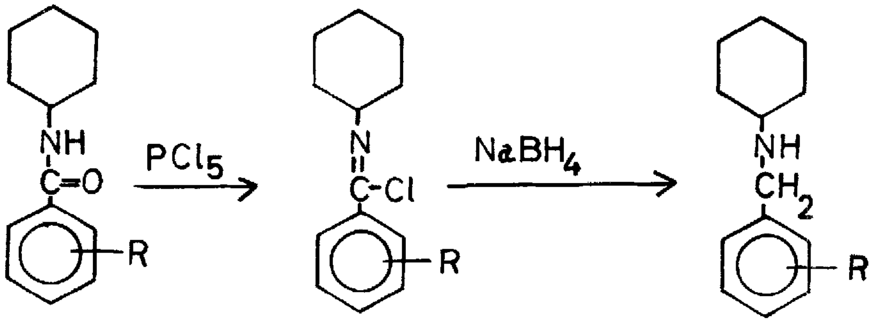
We report here a new procedure for the reduction of amides involving the reduction of the complex (2) with sodium borohydride in ethanol. The tertiary amides on which the reductive procedure was examined were prepared by the reaction of piperidine with aromatic acid chlorides. The Vilsmeir complexes were prepared by heating the amides in refluxing anhydrous toluene with equimolar amounts of phosphorusoxychloride for 2 to 5 hours. The resulting brownish complexes were cooled to 0°to 5°C and suspensions of sodium borohydride (five fold excess) in absolute ethanol were added dropwise over 15 to 20 minutes with vigorous stirring and cooling. The solutions were then refluxed on a water bath for about 30 minutes, the ethanol was evaporated off, and the residue partitioned between water and ethyl acetate. The organic layers were extracted with

1% acetic acid, the acid layers basified with aqueous ammonia and extracted with ethyl acetate. Drying (sodium sulphate) and evaporation of the organic solvent afforded the corresponding amines which appeared as slower moving single spots on t.l.c. The isolated yields were between 75-90%.



	Substrate		Reagent	Reaction Time	Yields	M.Pt. or Picrate of base	Molecular ion
	R	m.p./b.p.	a) POCl$_3$ b) NaBH$_4$				
1.	o-Cl	b.p. 100-105°	a) 1.1 mole b) 5 mole	a) 3 hrs b) ½ hr.	80%	184-85°	209/211
2.	m-Br	m.p. 95-100°	a) 1.1. mole b) 5 mole	a) 4 hrs b) 1 hr	85%	188-90°	253/255
3.	p-Cl	m.p. 80-82°	a) 1.2 mole b) 5 mole	a) 5 hrs b) ½ hr	78%	160-61°	209/211
4.	p-NO$_2$	m.p. 122-25°	a) 1.1 mole b) 5 mole	a) 4 hrs b) ½ hr	88%	176-78°	220
5.	m-NO$_2$	m.p 78-80°	a) 1.1 mole	a) 5 hrs	85%	210°	220
6.	H	b.p 140°	a) 1.1 mole b) 5 mole	a) 5 hrs b) ½ hr	90%	184-85°	175

The applicability of this procedure for the reduction of secondary amides was similarly investigated. The secondary amides were prepared by the reaction of cyclohexylamine with the appropriate acid chlorides. The amides were then treated with phosphorus pentachloride in refluxing chloroform and the resulting complexes were treated with a suspension of sodium borohydride in absolute ethanol. Subsequent work up afforded the corresponding amines in high yields.



	Substrate		Reagent	Reaction Time (in minutes)	Yields	Molecular ion
	R	m.p.	(a)PCl_5(b) $NaBH_4$			
1.	H	146°C	a) 1.2 mole	(a) 5	85%	189
			b) 3 mole	(b) 15		
2.	o-NO_2	154°C	a) 1 mole	(a) 7	80%	234
			b) 4 mole	(b) 10		
3.	m-NO_2	166°C	a) 1.2 mole	(a) 5	87%	234
			b) 4 mole	(b) 8		
4.	p-NO_2	200-202°C	a) 1.1 mole	(a) 5	77%	234
			b) 3 mole	(b) 10		
5.	o-Cl	118°-120°C	a) 1.2 mole	(a) 5	90%	223
			b) 3 mole	(b) 15		
6.	m-Br	142°C	a) 1.3 mole	(a) 5	86%	267/269
			b) 3 mole	(b) 15		

When the reaction was attempted with primary amides, such as benzamide, the corresponding cyanides were obtained quantitatively.

The above procedure offers a novel approach for the reduction of amides to amines. A survey of the literature of the various reductive procedures[2-12] for converting amides to amines indicates that our method may possess distinct advantages in selectivity of reaction and yields. An extension of this approach involving the use of other nucleophiles is under investigation.

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