

ELECTROCHEMICAL ALKYLATION OF SCHIFF BASES

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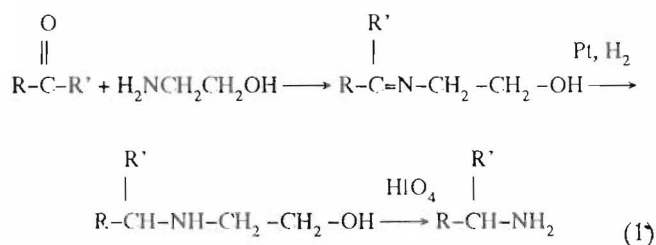
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Alkylation of N-(hydroxyethyl) benzylideneimine, the Schiff base formed from benzaldehyde and ethanolamine under electrochemical conditions mediated by Pb(II)/Pb(O) redox system has been reported. Cathodically (Pt) generated Pb(O) from PbBr₂ reacted with allyl bromide to form allyl lead bromide in THF, in an undivided cell. Tetrabutylammonium bromide was the electrolyte. The anode was aluminium sheet (Sacrificial) which generated AlBr₃ which by complexation with the nitrogen of the Schiff base, catalysed the addition of the organometallic compound to the C-N double bond, to yield, on work up, 1-phenyl-N-(hydroxyethyl) but-3-enylamine. Several side products have been identified. Conditions for optimisation of yield and effective work - up have been developed. The potential application of this reaction for the asymmetric synthesis of amines has been brought out.

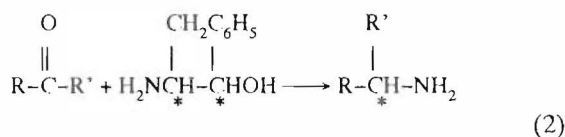
Keywords: Asymmetric synthesis, Schiff base, alkylation

INTRODUCTION

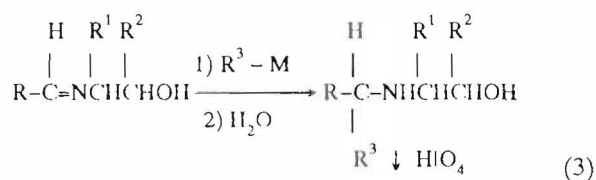
Use of ethanolamine as an ammonia equivalent for the reductive amination of carbonyl compounds has recently been reported [1]. The methodology involved the condensation of ethanolamine with aldehyde or ketone followed by catalytic hydrogenation of the C-N double bond to obtain N-alkylethanolamine. This compound was then oxidised by periodic acid to alkylamine.



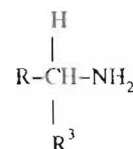
This route was further developed by using the commercially available chiral derivative of ethanolamine, namely, norephedrine, for asymmetric synthesis of amines [2].



This methodology opens up further routes for the synthesis of amines. If instead of hydrogenation, the Schiff base can be alkylated, the following route opens up.

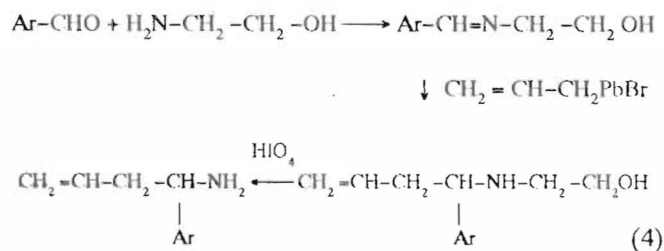


(R³-M is an organometallic compound)



If R¹ and R² are not hydrogen, that is if the ethanolamine is chiral, the final product could be chiral. Grignard addition to Schiff bases is generally unsatisfactory and in any case, the presence of the hydroxy group will interfere. Recently there was a report on the use of insitu generated allyl lead bromide for the reductive allylation of the Schiff base of benzaldehyde and benzylamine [3]. Allyl lead bromide could be generated from lead bromide either chemically [4] using aluminium metal as a reducing agent or electrochemically [5], in either case freshly generated Pb(O) was claimed to

react with allyl bromide to form allyl lead bromide. Al^{3+} from the aluminum (reagent or anode) was believed to activate the Schiff base for RPbBr addition by complexation with the nitrogen of the Schiff base. Benzaldehyde-benzylamine was the only system reported. While there are many reports on the "Barbier Type" allylation of carbonyl compound using various redox couples (Sn(IV)/Sn(O) , Pd(II)/Pb(O) , Ni(II)/Ni(O) , Bi(II)/Bi(O)) this was the first report on the electrochemical allylation of imines [3]. The present study was motivated by the idea that if the Schiff base of benzaldehyde and ethanolamine could be alkylated, it could lead to a new route for primary amine and also for the asymmetric synthesis of amines.



By using norephedrine or other chiral amines, such as amino acid derivatives, for the formation of Schiff base chiral aryl butenylamines of the type shown could be synthesised. An electrochemical route for the final step (periodic acid oxidation) has already been developed in this laboratory [6]. In this, oxidation has been done by electrogenerated periodate in a $\text{IO}_3^-/\text{IO}_4^-$ redox cycle. Thus this study was part of the attempted application of electrochemical reactions to several stages of the reductive amination of carbonyl compounds.

EXPERIMENTAL

The reactions were done in a beaker-type undivided cell of 250 ml capacity. A platinum wire (15 cm long) coiled around a glassrod was the cathode. The anode was a perforated aluminium sheet (5 cm x 7 cm) rolled into a cylindrical shape. The cathode was positioned inside the cylindrical anode and properly fixed to prevent contact between the two. Dry THF was used as the solvent, (Analar THF was dried over precalcined 3A molecular sieve) Tetrabutylammonium bromide (6.6 mmol/100 ml of solvent) was the electrolyte. Schiff base formed from benzaldehyde and ethanolamine was purified by distillation under vacuum. Allyl bromide was prepared from allyl alcohol by reported procedure. In a typical experiment a solution of 2.98 g (20 mmol) of the Schiff base, 7.26 g (60 mmol) of allyl bromide, 0.367 g (1 mmol) of PbBr_2 and 2.13 g (6.6 mmol)

of tetrabutylammonium bromide in 100 ml of THF was taken in the cell. Electrolysis was done under constant current conditions (0.1 A for 10 hrs). Stirring was done magnetically. Variations were done by (i) replacing platinum cathode by lead (ii) replacing allyl bromide by allyl chloride and (iii) increasing the potential current. After the electrolysis the solvent was removed by distillation and a small portion of the residue was dissolved in dichloromethane and washed with water to remove the electrolytes and directly analysed by gas chromatography. (Chemito GC 8610 HR. SE 30 column; temperature programmed from 373 to 523 K flame ionization detector). The bulk of the product mixture was treated with dilute HCl, washed with dichloromethane to remove neutral components. The HCl extract was neutralized with alkali and extracted with dichloromethane to recover the basic components. This mixture was once again analyzed by GC and then subjected to column chromatography by successively eluting with hexane, hexane/ethylacetate with increasing proportion of ethylacetate and finally with ethylacetate/methanol mixtures. All the fractions were analysed by GC and those fractions which gave single peaks in GC were appropriately combined to obtain four fractions which were homogeneous. These were analysed by proton NMR and mass spectroscopy. Some of the reaction products (total mixture) were subjected to GC-MS analysis. Some components which could not be separated by column chromatography were identified by GC retention time comparison with suspected authentic samples. The results are presented in Table I.

RESULTS AND DISCUSSION

Choice of electrodes

In the reported procedure aluminium was chosen as the anode because it has an anodic dissolution potential less positive than the oxidation potential of the starting materials and products of the reaction, thereby reducing undesired anodic reactions. The metal ion formed by anodic dissolution had the added role of functioning as Lewis acid to activate the Schiff base as shown in the Scheme 1. Among other anodes reported in [3] zinc was also found to be suitable but not Ni, Sn, Pb or Pt. In the present study aluminium was chosen as anode and found to be satisfactory. In the present study platinum and lead were tried as cathode and platinum was found to be superior (Table I)

Redox mediator

In the reported procedure [3] PbBr_2 was selected after trying various mediators (PbCl_2 , ZnCl_2 , SnCl_2). While PbCl_2 and BiCl_3 also gave satisfactory results, PbBr_2 was definitely the

TABLE I: Pb(II)/Pb(O) mediated allylation

Serial No	Reactants		PbBr ₂ in 1 mmol	Electrolyte	Products (GC yields, %)				% yield of III (9)
	in 20 mmol				III (5)	I (6)	II (7)	(8)	
1	2.98 g	7.26 g (60 mmol)	0.367 g	2.13 g (6.6 mmol)	5.0	9.0	52.0	37.0	80
2(10)	2.98 g	7.26 g (60 mmol)	0.367 g	2.13 g (6.6 mmol)	4.5	19.0	9.5	65.0	60
3	2.98 g	7.26 g (60 mmol)	0.367 g	2.13 g (6.6 mmol)	2.0	30.0	5.0	56.0	25
4	2.98 g	Allyl chloride 4.5 g (59 mmol)	0.367 g	3.2 g (9.9 mmol)	1.0	14.0	37.0	44.0	20

(1) $\text{PhCH} = \text{NCH}_2\text{CH}_2\text{OH}$ (2) $\text{CH}_2 = \text{CH} - \text{CH}_2\text{Br}$ (3) $(n - \text{C}_4\text{H}_9)_4\text{N}^+\text{Br}^-$ (4) Anode is Al in all cases
(5) $\text{CH}_2 = \text{CH} - \text{CH}_2 - \text{CH}(\text{Ph}) - \text{NH} - \text{CH}_2\text{CH}_2\text{OH}$ (6) $(n - \text{C}_4\text{H}_9)_3\text{N}$ (7) $(\text{CH}_2 = \text{CHCH}_2)_2\text{N} - \text{CH}_2\text{CH}_2\text{OH}$
(8) Mainly neutral products arising from benzaldehyde (9) Taking into account loss of Schiff base by hydrolysis
(10) Serial No. 1 repeated at a higher cell potential
Solvent: 100 ml THF cathode Pt

better catalyst. This was the only mediator used in the present study.

Choice of allyl bromide

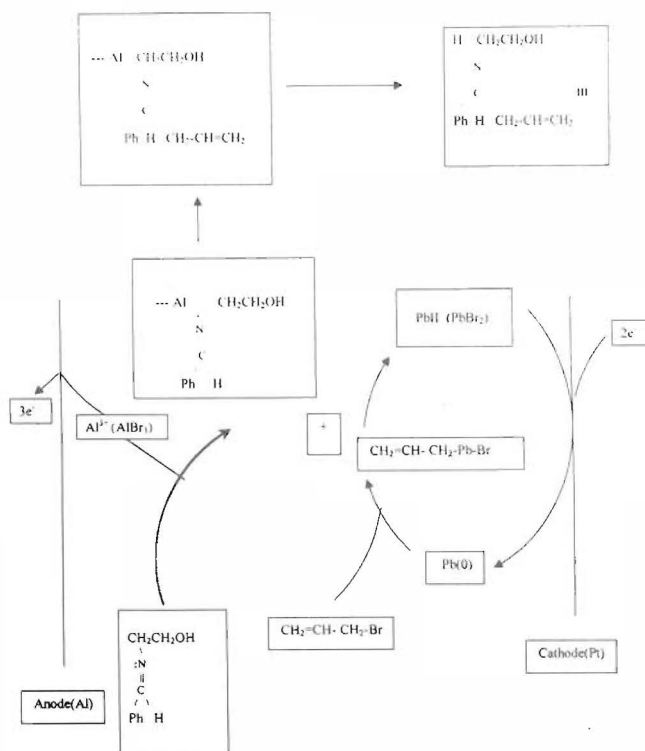
Allyl chloride (Ser No. 4, Table I) gave very poor results. Hence, allyl bromide was used as the allylating agent.

Analysis of products

Gas chromatography of the crude reaction product showed more than 10 peaks. These include benzaldehyde, benzyl alcohol and neutral products arising from these which were removed by chemical separation from the desired compounds (basic fraction). From the basic fraction three components could be isolated by column chromatography over silica gel and identified by NMR and mass spectra, to be I, tributylamine (4.6) II, N, N- Diallylethanolamine (7.3) and III, the desired product 1-phenyl- N-(hydroxyethyl) but 3-enylamine (14.8). The numbers in brackets refer to gas chromatographic retention times under the specified conditions of analysis.

Compound I, arose either by cathodic reduction of the electrolyte (tetrabutylamine) or by Hofmann elimination brought about by electrogenerated base. This product could be somewhat reduced by controlling the applied potential as indicated in Table I. Product II is due to the allylation of ethanolamine and benzaldehyde (which appeared as neutral products) arose due to the breakdown of the Schiff base, probably due to hydrolysis by residual water in the solvent. This has to be controlled in future experiments. Due to the various side reactions, the yield of the desired product III

was low. However if the hydrolysis of the Schiff base which was an avoidable side reaction was corrected for, the yield



Scheme 1: Pb(II)/Pb(O) mediated allylation

of III based on available Schiff base was 80%. It is expected that further refinements of the electrolysis conditions will improve selectivity and yield.

Spectroscopic identification of products

Product I: (Tributylamine)-GC retention time 4.6, Fraction No.7, on column chromatography (Solvent mixture - EtoAc/Methanol).

Mass spectrum m/z 185 ($M+5\%$) 142(100%), 100(95%), 58(30%); Product II: N,N - Diallylethanolamine-GC retention time 7.3, Fraction No.5 on column chromatography (Solvent mixture - EtoAc/Methanol); Mass spectrum: m/z 141 ($M+$, 5%), 110(100%) 86(26%), 60(30%); NMR spectrum: As expected; Product III: I - Phenyl - N (Hydroxyethyl) - but -3-enylamine. GC. Retention time 14.8, Fraction No.3 on column chromatography (Solvent Mixture Hexane / EtoAc); Mass Spectrum: m/z 191 ($M+3\%$), 160(50%)150(4%), 131(5%), 120(2%)105(5%), 91(100%), 77(4%) 65(12%). NMR spectrum: As expected.

CONCLUSION

Allylation of the Schiff base of benzaldehyde and ethanolamine could be done by allyl lead bromide generated electrochemically using Pb (II)/Pb (O) redox mediator. Prominent side reactions were (i) breakdown of the electrolyte (tetrabutylammonium bromide) and loss of Schiff

base by hydrolysis by residual water. Further studies are in progress to minimise these side reactions and to extend these studies to asymmetric synthesis of amines.

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