

Synthetic potentiality of α -amino nitrones as oxidizing reagent in the conversion of alkyl halides to aldehydes

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Abstract : α -Amino nitrones have been used successfully as an oxidizing reagent for the synthesis of aldehydes from various alkyl halides with an excellent yield. In addition, hydrolysis of the side product (imines) furnishes starting material amides which are recyclable along with corresponding amines.

Keywords : α -Amino nitron, aldehyde synthesis, recyclable product.

Introduction

Conversion of alkyl halides to aldehydes using *N*-oxide with moderate yield has been reported long time back (Krohnke reaction). In addition to the existing methods available for the synthesis of aldehydes from alkyl halides¹⁻⁵, we would like to incorporate an efficient methodology of synthesis of aldehydes from alkyl halides along with imines for the first time using α -amino nitrones⁶⁻¹¹ as an oxidizing reagent with an excellent yield (Scheme 1, Fig. 1, Table 1).

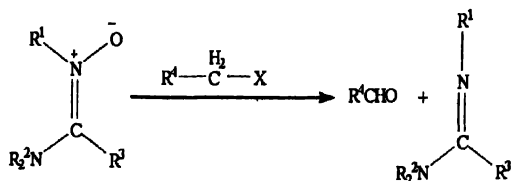


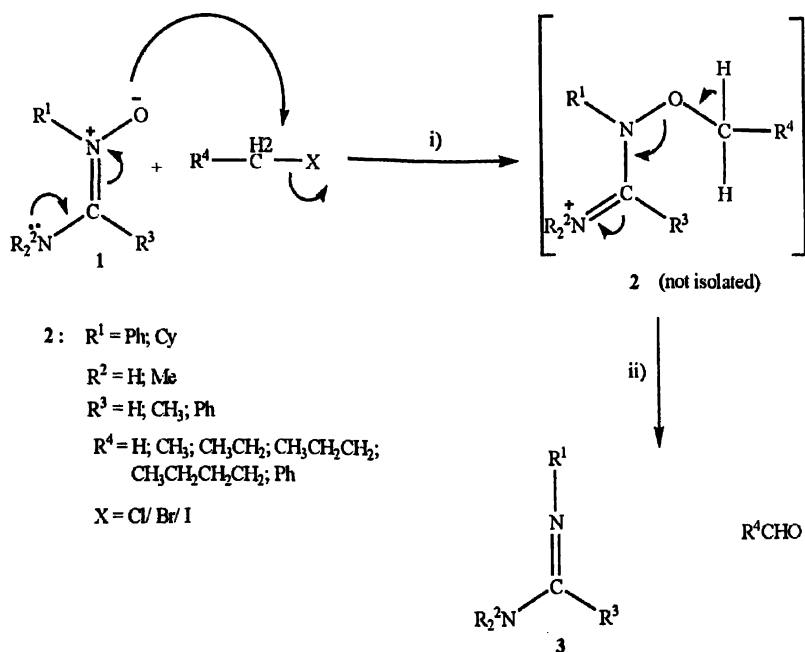
Fig. 1

In addition, the side product (imines) obtained during aldehyde synthesis results starting material amide and amines upon simple hydrolysis (Scheme 2). The duly obtained amides can be successfully reused for the synthesis of nitrones while the amines can be used for further general reaction purposes. Synthesis of aldehydes from alkyl halides and recycling the side product in cycloaddition reactions using α -chloro nitrones have been already reported from this laboratory^{6,12,13}. Literature survey reveals that aldehyde synthesis using α -amino nitrones as an oxidizing reagent has not yet reported and

can be incorporated as an important application in nitron chemistry.

Results and discussion

The present study has been carried out using a variety of α -amino nitrones and alkyl halides (Table 1) in order to generalize the methodology for the aldehyde synthesis. The synthesis and cycloaddition reactions of some α -amino nitrones **1** ($R^1 = \text{Ph, Cy}$; $R^2 = \text{NMe}_2$; $R^3 = \text{H}$ and $R^1 = \text{Ph, Cy}$; $R^2 = \text{NH}_2$; $R^3 = \text{H}$) have been already reported⁶⁻¹¹ following the general methodology of α -amino nitron synthesis from DMF and formamide¹⁴. The remaining α -amino nitrones **1** of Table 1 were prepared following the same methodology. The yield of the isolated aldehydes are extremely high (almost 80–88%) within a short time and are much better in case of active alkyl halides compared to inactive alkyl halides while imines are obtained in almost 11–20% yields as side products. The results are summarized in Table 1. The products especially aldehyde, amide and amines are known compounds and spectral data of these synthesized compounds are almost identical to the values found in literature. For example, sharp singlet signals at δ 9.80 and 198 in the ^1H NMR and ^{13}C NMR spectrum along with molecular ion peak at 106, base peak at 105 and 77, 51 in the MS spectrum give strong evidence in favour of benzaldehyde formation. Spectral data of the imine derivatives **3** also agreed well with the assigned structures. For example, prominent molecular ion peak at 196 and base peak at 103 (due to the formation of PhCN) clearly indicates in favour of imine derivative **3** (entry 8). Similarly strong evidences

Scheme 1. Reaction conditions : (i) dry ether, RT, N_2 atmosphere, 1–2 h, (ii) dry ether, Na_2CO_3 , RT, N_2 atmosphere, 3–4 h.Table 1. Aldehyde synthesis using α -amino nitrones

Entry	Nitrone	Alkyl halide ^a	Aldehyde ^b	Time (h)	Yield ^c (%)
1	$R^1 = \text{Ph; } R^2 = \text{H; } R^3 = \text{Ph}$	$R^4 = \text{Ph}$	$\text{C}_6\text{H}_5\text{CHO}$	5	88
2	$R^1 = \text{Ph; } R^2 = \text{H; } R^3 = \text{H}$	$R^4 = \text{Ph}$	$\text{C}_6\text{H}_5\text{CHO}$	4	86
3	$R^1 = \text{Ph; } R^2 = \text{H; } R^3 = \text{Ph}$	$R^4 = \text{CH}_3\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CHO}$	6	84
4	$R^1 = \text{Ph; } R^2 = \text{H; } R^3 = \text{H}$	$\text{ClCH}_2\text{C}_6\text{H}_4\text{OH}$	$\text{OHCC}_6\text{H}_4\text{OH}$	4	83
5	$R^1 = \text{Ph; } R^2 = \text{Me; } R^3 = \text{H}$	$R^4 = \text{CH}_3\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CHO}$	5	82
6	$R^1 = \text{Ph; } R^2 = \text{H; } R^3 = \text{CH}_3$	$\text{ClCH}_2\text{C}_6\text{H}_4\text{Cl}$	$\text{OHCC}_6\text{H}_4\text{Cl}$	5	82
7	$R^1 = \text{Cy; } R^2 = \text{Me; } R^3 = \text{H}$	$R^4 = \text{CH}_3\text{CH}_2\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}$	5	81
8	$R^1 = \text{Ph; } R^2 = \text{H; } R^3 = \text{H}$	$R^4 = \text{H}$	HCHO	6	80
9	$R^1 = \text{Cy; } R^2 = \text{H; } R^3 = \text{H}$	$R^4 = \text{Ph}$	$\text{C}_6\text{H}_5\text{CHO}$	4	80

^aReaction conditions : α -amino nitrone (2–3 mmol), alkyl halide (1 equivalent), dry ether, sodium carbonate, N_2 atmosphere, RT.^bAll the compounds were characterized by IR, ^1H NMR, ^{13}C NMR, MS, HRMS spectral data.^cIsolated yield after purification.

are also obtained from HRMS spectra in favour of the aldehyde and other known compounds formation. The proposed mechanism for the aldehyde synthesis using α -amino nitrone is very interesting. Nitrone 1 undergoes $\text{S}_{\text{N}}2$ reaction readily with alkyl halides and develops an intermediate compound 2 which was not isolated. The reaction rate is much more faster compared to the $\text{S}_{\text{N}}2$ reactions of α -chloro nitrones^{6,15–18} due to the involvement of available electron pairs of amino or dimethyl

amino group. The N–O bond of the intermediate compound 2 breaks¹⁹ when the reaction mixture is stirred with solid sodium carbonate which plays an important role for the development of aldehyde and imines in a Kornblum type reaction with a very good yield (Scheme 1, Table 1). The imine derivative 3 on hydrolysis results starting amide 5 (55–60%) and amines 4 (35–40%) where amides are the material for α -amino nitrone synthesis. In the course of the study, major difficulties were faced dur-

ing isolation and identification of formaldehyde because of its volatility and GC-MS has been used to identify it (m/z 30, M^+ 75.52%). The products were characterized from their spectroscopic (IR, ^1H NMR, ^{13}C NMR, HRMS) data. No catalyst or co organic solvent was required.

Finally, we developed a new atom economical methodology for the aldehyde synthesis using α -amino nitrones and considered further reaction carried out by hydrolysing the imine derivatives in acid medium for the regeneration of starting material amide and corresponding amines. The isolated amide (starting material for α -amino nitrones) and amines are equally good in quality as obtained from commercial suppliers and thereby offering greater scope for the present methodology. The notable advantages offered by this method are simple operation, easy workup, mild and faster reaction conditions with high yield of products. Therefore, the present methodology may be incorporated as a general method of aldehyde synthesis from alkyl halides for extremely good yield and also as an important application of nitrones.

Experimental

^1H NMR spectra were recorded with a Bruker Avance DPX 400 spectrometer (400 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. The coupling constants (J) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q-ToF micro instrument (YA-105). GC-MS was recorded using Clarus 500 gas chromatograph with built in MS detector Perkin-Elmer machine. TLC was carried out on Fluka silica gel TLC cards. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-Cyclohexyl, *N*-phenylhydroxylamines were prepared following standard methods available in the literature^{20,21}.

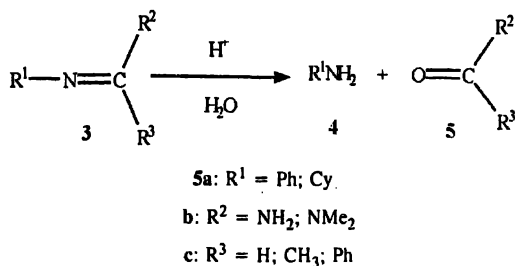
General procedure for preparation of aldehyde (benzaldehyde) and imine derivative 3 (entry 8; Table 1) :

In a 100 ml conical flask, *N*-phenyl- α -amino nitron⁶ (500 mg, 2.3570 mmol), benzyl chloride (295.8670 mg, 1 equivalent) and diethyl ether (25 ml) was added and stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 h. The progress of the reaction was monitored by TLC (R_f = 0.38). 2 g of solid Na_2CO_3 was added at this stage and the reaction mixture was stirred for further 3 h and monitored by TLC. The N-O bond

was easily cleaved¹⁹ under basic medium in a Kornblum type mechanism and developed benzaldehyde (R_f = 0.43) and imine derivative (R_f = 0.54) respectively. The reaction mixture was filtered and concentrated on a rotary evaporator. Basic work-up followed by silica gel column chromatography using ethyl acetate-hexane results benzaldehyde as colourless liquid (706 mg, 88%) and imine derivative (3) as pale yellow gummy liquid (84 mg, 11%, Scheme 1). This general procedure was followed for all the substrates listed in Table 1.

General procedure for acid hydrolysis of imine derivative 3 (substituted formidamide/acetimidamide/benzimidamide, entry 8) :

In a 100 mL R.B flux, imine derivative 3 (70 mg), 20 ml 10% HCl was taken and refluxed in water bath for 30 min. The formation of the desired hydrolysed products were monitored by TLC. During the hydrolysis process, the double bond between carbon and nitrogen of the imine derivative was cleaved²² and benzamide 5 (R^2 = NH_2 ; R^3 = Ph; R_f = 0.42) and aniline 4 (R^1 = Ph; R_f = 0.64) was formed (entry 8). The products were extracted with ether (2 \times 25 ml) when aniline passes into organic layer while benzamide remains in aqueous phase. The ether extract containing aniline was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator and finally purified by silica gel column chromatography using ethyl acetate-hexane as pale yellow liquid (24 mg, 34%). Benzamide was obtained as white crystalline solid when aqueous part of the solution was evaporated in a temperature controlled water bath and was crystallized from ethanol (42 mg, 60%; m.p. 126 $^\circ\text{C}$; Scheme 2). This general hydrolysis procedure was followed for all the imine derivatives 3.



Scheme 2. Reaction condition : 10% HCl, hydrolysis, 30 min.

Spectral data for benzaldehyde (entry 8) :

Yield 706 mg, 88%; HRMS-EI : Calcd. for $\text{C}_6\text{H}_5\text{CHO}$ (M), 106.1240, Found : M^+ , 106.1228; IR (CHCl_3) : 2825 (s), 1695 (s), 1320 (m), 780 (s) cm^{-1} ; ^1H NMR

(CDCl₃) : δ 9.80 (1H, s, CHO), 7.30–7.16 (5H, m, C₆H₅); ¹³CNMR (CDCl₃) : δ 198 (CHO), 136.00, 134.00, 132.50, 131.00 (aromatic carbons); FAB-MS : m/z 106 (M⁺), 105 (B.P), 78, 77, 51.

Spectral data for N'-phenylbenzimidamide (imine derivative 3; entry 8) :

Yield 84 mg, 11%; HRMS-EI : Calcd. for C₁₃H₁₂N₂ (M), 196.2530, Found : M⁺, 196.2519; IR (CHCl₃) : 3450 (m), 1682 (s), 780 (s); ¹H NMR (CDCl₃) : δ 7.32–7.22 (5H, m, C₆H₅), 6.76–6.63 (5H, m, C₆H₅), 3.75–3.62 (2H, br, NH₂); ¹³C NMR (CDCl₃) : δ 136.84, 135.24, 134.50, 132.80, 131.25, 130.00, 128.50, 127.45 (phenyl carbons), 87.00 (C=N); FAB-MS : m/z 196 (M⁺), 119, 103 (B.P), 77.

Spectral data for aniline (product 4; entry 8) :

Yield 24 mg, 34%; HRMS-EI : Calcd. for C₆H₇N (M), 93.0690, Found : M⁺, 93.0682; IR (CHCl₃) : 3440 (m), 3205 (s), 1635 (s), 1280 (m), 910 (m), 774 (s); ¹H NMR (CDCl₃) : δ 6.88–6.72 (5H, m, C₆H₅), 3.82–3.66 (2H, br, NH₂); ¹³CNMR (CDCl₃) : δ 134.00, 132.50, 129.42, 128.00 (phenyl carbons); FAB-MS : m/z 93 (M⁺).

Spectral data for benzamide (product 5; entry 8) :

Yield 42 mg, 60%; m.p. 126 °C; HRMS-EI : Calcd. for C₇H₇NO (M), 121.0690, Found : M⁺, 121.0681; IR (CHCl₃) : 3455 (s), 1675 (s), 1630 (m), 776 (s); ¹H NMR (CDCl₃) : δ 7.14–7.02 (5H, m, C₆H₅), 6.90–6.76 (br, CONH₂); ¹³C NMR (CDCl₃) : δ 177.50 (C=O), 130.50, 129.00, 128.00, 127.20 (phenyl carbons); FAB-MS : m/z 121 (M⁺), 77.

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References

1. V. Bertini, F. Lucchesini, M. Pocci and S. Alfei, *Tetrahedron*, 2005, 61, 9519.

2. J. Tang, J. Zhu, Z. Shen and Y. Zhang, *Tetrahedron Lett.*, 2007, 48, 1919.
3. A. R. Katritzky, M. J. Cook, S. B. Brown, R. Cruz, G. H. Millet and A. Anani, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2493.
4. G. Cardillo, M. Orena and S. Sandri, *J. Chem. Soc., Chem. Commun.*, 1976, 190.
5. S. V. Lieberman, *J. Am. Chem. Soc.*, 1954, 77, 1114.
6. B. Chakraborty, P. Sharma, N. Rai, S. Kafley and M. S. Chhetri, *J. Chem. Res.*, 2010, 34, 147.
7. B. Chakraborty and M. S. Chhetri, *Indian J. Chem., Sect. B*, 2010, 49, 182.
8. B. Chakraborty and M. S. Chhetri, *Indian J. Heterocycl. Chem.*, 2008, 18, 201.
9. B. Chakraborty and M. S. Chhetri, *Indian J. Heterocycl. Chem.*, 2008, 17, 243.
10. B. Chakraborty, P. J. De Britto and A. R. Ghosh, *Indian J. Heterocycl. Chem.*, 1996, 6, 77.
11. B. Chakraborty, *Indian J. Heterocycl. Chem.*, 1999, 9, 79.
12. B. Chakraborty and M. S. Chhetri, *Indian J. Chem., Sect. B*, 2008, 46, 485.
13. B. Chakraborty, M. S. Chhetri and S. Kafley, *Indian J. Chem., Sect. B*, 2010 (in press).
14. F. Heinzer, M. Saukup and A. Eschenmoser, *Helv. Chim. Acta*, 1978, 61, 2851.
15. B. Chakraborty, S. Kafley and M. S. Chhetri, *Indian J. Chem., Sect. B*, 2009, 48, 447.
16. B. Chakraborty, S. Kafley and M. S. Chhetri, *Indian J. Chem., Sect. B*, 2010, 49, 209.
17. B. Chakraborty, S. Kafley and M. S. Chhetri, *Indian J. Heterocycl. Chem.*, 2009, 18, 283.
18. B. Chakraborty, B. S. Kafley and M. S. Chhetri, *Indian J. Heterocycl. Chem.*, 2008, 18, 203.
19. W. R. Hoffmann, G. Eichler and A. Endesfelder, *Liebigs Ann. Chem.*, 1983, 2000.
20. B. Chakraborty and A. R. Ghosh, *Indian J. Chem., Sect. B*, 1994, 33, 1113.
21. F. Heaney, O. Rooney and D. Cunningham, *J. Chem. Soc., Perkin Trans. 2*, 2001, 373.
22. A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford and P. N. G. Smith, "Vogel's Textbook of Practical Organic Chemistry", 5th ed., 1996, Prentice Hall, 1996.