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DEOXIMATION OF OXIMES, SODIUM OXIMATES AND O-BENZOYLOXIMES WITH COPPER (II) CHLORIDE DIHYDRATE

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ABSTRACT: Oximes, O-benzoyloximes and sodium salt of aldoximes and ketoximes were deoximated to their parent carbonyl compounds with copper (II) chloride dihydrate in acetonitrile as well as water. This method works well with both aldoximes and ketoximes without any risk of overoxidation in the former case. In addition, sensitive groups like ester, acetamido, isolated as well as conjugated carbon-carbon double bond and phenolic and ether linkages could survive the reaction conditions. The yields and reaction rates were increased in case of aromatic oximes when the reaction was carried out in aqueous acetonitrile. A novel deoximation procedure using sodium oximate which showed considerable rate enhancement over that of oximes, and tolerance to hydrolytically labile ester and amide groups is also described.

INTRODUCTION

The deoximation reaction to liberate carbonyl compounds is an important step in exploiting oximes as protecting[1] and selective α-activating[2] groups. Since many valuable reactions have been developed to prepare oximes[3], an efficient deoximation reaction could lead to new methods of preparing carbonyl compounds as well[4].

Experimentation over the years has yielded various deoximation methods. On the basis of their mechanism of action these can be assorted into three categories involving (i) acid catalysed hydrolysis and transoximation[5] (ii) oxidative deoximation[6-13] and (iii) reductive deoximation [4b,14-16]. Recently, a new method involving enzymatic hydrolysis[17] has been reported.

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Recovery of parent aldehydes or ketones classically involved acid hydrolysis. This limited the scope of the reactions to exclude acid sensitive ketones. The same drawback was encountered if acid was used during the course of the reaction or at any time later on in the oxidative or reductive regeneration modes[10,11a,16b-d]. Though it was due to non-tolerance of acid sensitive groups that led to the discovery of methods other than those involving acid hydrolysis, yet most of the methods cited in the literature do not demonstrate the effect of the reaction conditions on the sensitive groups and some do not show tolerance to common functionalities[11,12a]. Many of the reports either do not describe the deoximation of aldoximes[4b,7f,12a-c,14c,16a,b] or give low yields of aldehydes[5c,8,9,10b,12e,f,14] or the liberated aldehydes are overoxidised[6,13a]. These methods are, therefore, unsuitable for aldehyde regeneration. Moreover, the reagents used are often hazardous or very toxic[11a,12f,13,14b] and expensive[12,14d,15]. In some cases the reagents need to be freshly prepared[9,10a,12a,14c,16d] or the reactions require anaerobic conditions[4b,11c,12d,13b,14c,d,15a] and long reaction times[5f,6a,12f,13a,14b-d,15a,17]. Thus a milder, selective, non-hazardous and inexpensive reagent is still in demand. We describe herein a simply, efficient, selective, non-hazardous and inexpensive mode of deoximation. Recently, a chelation assisted regeneration of carbonyl compounds from semicarbazones with copper(II) chloride dihydrate in refluxing acetonitrile was reported from this laboratory[18]. This prompted us to investigate the deoximation of oximes using this reagent.

RESULTS AND DISCUSSION

Oximes/sodium oximates/O-benzoyloximes (1) were effectively deoximated on heating under reflux with copper (II) chloride dihydrate (2) in acetonitrile or aqueous acetonitrile. The regenerated solid carbonyl compounds were easily isolated in high state of purity. The liquid carbonyl compounds were derivatized as semicarbazone or DNP derivatives to minimize the loss during distillation. The results are shown in Table I.

Deoximation of Oximes (1) in Acetonitrile (Method A). The corresponding carbonyl compounds were obtained in high yields when the oximes were heated under reflux with (2) in acetonitrile. Aldoximes could also be cleaved without any risk of overoxidation. It is noteworthy that ester and acetamido groups, isolated as well as conjugated carbon-carbon double bond, phenolic group and ether linkages could survive under the present conditions. The alcoholic group also appears to survive under these reaction conditions as shown by the recovery of benzyl alcohol even on prolonged heating under reflux with (2) in acetonitrile. The proposed mechanism of the reaction is shown in Scheme 1.

Table I. Deoximation of Oximes, Sodium Oximates and O-Benzoyloximes (1) with Copper (II) Chloride Dihydrate (2)

Entry	Oxime/Sodium Oximate/ Benzoyloxime (1) of	Mode[a]	Molar Ratio (1) : (2)	Reaction Time Refluxing (h)	Yield(%)
1.	Benzaldehyde	A	1:1.1	3.00	74[b]
2.	4-Methoxybenzaldehyde	A	1:1.0	2.50	73[b]
3.	4-Methylbenzaldehyde	A	1:1.1	6.50	88[b]
4.	4-Hydroxy-3-methoxy-benzaldehyde	A	1:1.1	1.50	73[c]
5.	3, 4-Dimethoxybenzal-dehyde	A	1:1.1	1.50	94[c]
6.	4-Chlorobenzaldehyde	A	1:1.0	5.00	46[c]
7.	4-Chlorobenzaldehyde	A	1:1.5	3.00	67[c]
8.	4-Nitrobenzaldehyde	A	1:1.0	5.50	72[c]
9.	4-Nitrobenzaldehyde	A	1:2.0	3.00	86[c]
10.	Cinnamaldehyde	A	1:1.1	2.00	57[b]
11.	Heptaldehyde	D	1:1.1	2.00	11[b]
12.	Acetophenone	A	1:1.0	3.00	77[b]
13.	Acetophenone	B	1:1.1	0.75	79[b]
14.	Acetophenone	D	1:1.1	0.50	62[b]
15.	Propiophenone	A	1:1.1	2.25	68[b]
16.	Propiophenone	B	1:2.2	0.50	98[b]
17.	4-Hydroxyacetophenone	A	1:1.1	2.00	36[c]
18.	4-Hydroxy acetophenone	B	1:2.2	0.50	77[c]
19.	4-Methylacetophenone	A	1:1.0	2.00	92[b]
20.	4-Methylacetophenone	D	1:1.1	0.75	62[b]
21.	4-Acetamidoacetophenone	A	1:1.1	1.00	46[c]
22.	4-Acetamidoacetophenone	C	1:1.1	1.00	63[c]
23.	4-Chloroacetophenone	A	1:1.0	5.00	77[b]
24.	4-Nitroacetophenone	A	1:1.0	8.00	52[c]
25.	4-Nitroacetophenone	A	1:1.5	4.00	64[c]
26.	4-Nitroacetophenone	A	1:2.0	0.50	97[c]
27.	4-Nitroacetophenone	D	1:1.1	3.00	50[c]
28.	Ethyl 4-acetylphenoxy-acetate	A	1:1.1	3.0	80[b,d]
29.	Ethyl 4-acetylphenoxy-acetate	B	1:1.1	1.00	89[b,d]
30.	Ethyl 4-acetylphenoxy-acetate	C	1:1.1	3.0	59[b]
31.	4-Allyloxyacetophenone	A	1:1.1	1.25	91[d]
32.	Benzophenone	A	1:1.1	1.50	35[d]
33.	Benzophenone	B	1:2.0	6.00[c]	77[d]
34.	Benzophenone	C	1:2.0	1.50	85[d]
35.	4-Nitrobenzophenone	A	1:1.1	4.00	94[c]
36.	Cyclohexanone	A	1:1.0	4.50	43[d]

Continued...

Table 1 Continued

Entry	Oxime/Sodium Oximate/ Benzoyloxime (1) of	Mode[a]	Molar Ratio (1) : (2)	Reaction Time Refluxing (h)	Yield(%)
37.	Cyclohexanone	B	1:1.1	0.08[f]	15[d]
38.	Cyclohexanone	C	1:1.1	0.25	67[d]
39.	Cyclohexanone	D	1:1.1	1.50	34[d]
40.	Camphor	A	1:1.2	2.50	44[b]

(a) A: Reaction of oxime with (2) in CH_3CN
B: Reaction of oxime with (2) in CH_3CN/H_2O[22]
C: Reaction of sodium oximate with (2) in CH_3CN
D: Reaction of benzoyloxime with (2) in CH_3CN;

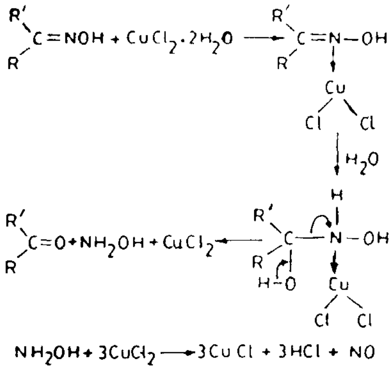
(b) Yield of semicarbazone;

(c) Yield of isolated pure carbonyl compound;

(d) Yield of DNP derivative;

(e) The longer reaction time may be attributed to the insolubility of the oxime in the reaction medium;

(f) In this case reaction mixture was warmed only. carbon double bond, phenolic group and ether linkages could survive under the present conditions. The alcoholic group also appears to survive under these reaction conditions as shown by the recovery of benzyl alcohol even on prolonged heating under reflux with (2) in acetonitrile. The proposed mechanism of the reaction is shown in Scheme I.



Scheme - 1

This mechanism is supported by the fact that transition metal ions are known to form complexes with oximes[19]. Hydroxylamine is known to get oxidised to the oxides of nitrogen by transition metal ions[20]. The role of metal ion in the reaction appears to be two fold. First it activates the oxime group towards hydrolysis by coordination with the nitrogen, and second, it shifts the equilibrium to the right by oxidising the hydroxylamine liberated from the oxime. the oxidation of the liberated hydroxylamine was evidenced by the evolution of nitric oxide gas during the course of the reaction. It was also supported by the evolution of nitric oxide when hydroxylamine was heated under reflux with (2) in acetonitrile in a separate experiment. However, the possibility of direct oxidation of the oxime is not ruled out.

Under similar conditions hydrated copper (II) acetate and anhydrous iron (III) chloride were also found to be effective. However, hydrated copper (II) nitrate failed to accomplish the deoximation. A significant feature of this methodology is that oxime ethers and DNP derivatives are not cleaved under these conditions.

Deoximation of Oximes (1) in Acetonitrile (Method B). From the Scheme-1, it is evident that water is participating in the second step of the reaction. In order to find out the role of water in the reaction, experiments were carried out in aqueous acetonitrile. The percentage of water in each reaction was varied depending upon the solubility of oxime in water so as to get a homogeneous reaction mixture. In case of aromatic compounds the reaction proceeded faster and gave enhanced yield as compared to the reaction in acetonitrile alone.

Deoximation of Sodium Oximate (1) in Acetonitrile (Method C). The concept of deoximation using sodium salt of the oxime was exploited for the first time. The oximate anion is expected to be more reactive in the oxidative deoximation because (i) it should be more susceptible to oxidation due to its raised HOMO, and (ii) the attack by the oppositely charged oxidising reagent on the oximate anion should be facilitated due to electrostatic attraction. As expected all the reactions using this method proceeded much faster than either of the preceding reactions (methods A/B) and also gave higher yields of the products in some cases. Moreover, benzophenone oxime, which gave a mixture of benzophenone and benzanilide by Method A, gave exclusively the parent carbonyl compound in high yield (85%) by this method.

Cyclohexanone oxime which did not give cyclohexanone in satisfactory yields, by other methods, afforded the product in good yield by this method. The experimental procedure was so manipulated that the hydrolytically labile groups, such as ester and acetamido, were safely tolerated.

Deoximation of O-Benzoyloximes (1) in Acetonitrile (Method D). Like the semicarbazones, O-benzoyloximes can also act as bidentate ligands and their complexation with (2) may activate the oximino group towards hydrolysis as was observed in the case of semicarbazones[18]. The reaction proceeded much faster by this method than that of the oximes under similar conditions.

CONCLUSION

The methodology described here for regeneration of carbonyl compound from their oximes is manipulatively simple, selective, mild and economical. It affords good yield of the carbonyl compounds and avoids many disadvantages of the existing methods. Methods A and B are particularly valuable for the regeneration of aromatic aldehydes. Method C, involving sodium salts of the oximes is conceptually attractive and appears to incorporate aliphatic oximes also in its scope, which do not give satisfactory results by the methods A and B. Thus, wherever the methodology works, it appears to be superior to the existing ones in many respects mentioned above.

EXPERIMENTAL SECTION

Melting points were taken in an electrical melting point apparatus (Adair Dutt and Co. Calcutta, India) and are uncorrected. For comparison, IR spectra were recorded on a 5DX Nicolet FT-IR spectrometer either as KBr pellet or as liquid film. ^{1}H NMR were recorded in $CDCl_3$ on JEOL JNM FX100 FT-NMR (99.55 MHz) with TMS as internal standard.

Oximes were prepared according to standard methods[21]. O-Benzoyloximes were prepared by Schotten-Baumann reaction with benzoyl chloride. The oxime and a slight excess of benzoyl chloride were stirred at rt in 10% NaOH solution for 15 min. Ice was added to the reaction mixture and the solid thus obtained was filtered, washed, recrystallized and characterized.

General Procedure for Regeneration of Carbonyl Compounds from their Oximes/O-benzoyloximes (Methods A, B, D). Oximes were deoximated in CH_3CN (Method A) and CH_3CN-H_2O (Method B)[22], and O-benzoyloximes were deoximated in CH_3CN (Method D). A suspension of the oxime/O-benzoyloxime (0.01 mol) and $CuCl_2.2H_2O$ (0.011

mol) was heated under reflux with stirring in CH_3CN or CH_3CN-H_2O (25ml). The progress of the reaction was monitored by TLC. The reaction mixture was cooled after completion, filtered and the residue washed with ether. If any solid precipitated on addition of ether to the filtrate then the solution was again filtered, and extracted with ether (3x25ml). The ether extract was washed with brine (3x20ml), dried over anhyd. Na_2SO_4 filtered, concentrated and either recrystallized to give the pure carbonyl compound or derivatized. The resulting compound was identified by comparisons of its ^1H NMR and FT-IR spectra, melting points and mixture melting points with those of the authentic sample.

General Procedure for Regeneration of Carbonyl Compounds from Sodium Oximate (Method C). To a solution of the oxime (0.01 mol) in CH_3CN, was added an equimolar amount of powdered NaOH and the resulting suspension was stirred at rt for 0.50h. The sodium salt formation could be observed by following the change in the texture of the reaction mixture. $CuCl_2,2H_2O$ (0.011 mol) was then added to the reaction mixture followed by CH_3CN (total volume of CH_3CN = 25ml). The reaction mixture was then heated under reflux with stirring. The progress of the reaction was monitored by TLC. The reaction mixture was cooled after completion of the reaction and filtered. The filtrate was extracted with ether (3x25 ml), washed with brine (3x20ml), dried over anhyd. Na_2SO_4, filtered, evaporated and either recrystallized to get the pure carbonyl compound or derivatized. The product was identified as in the Methods A/B/D.

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22. Under the conditions of Method B, the % CH_3CN used in the reaction. Entries corresponding to 13, 16, 18, 29, 33, 37 of the Table I were 0, 50, 50, 50, 60, 36% respectively.

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