Inexpensive and Environmentally Friendly Oxidation of Hydroxylamines to Nitrones with Bleach

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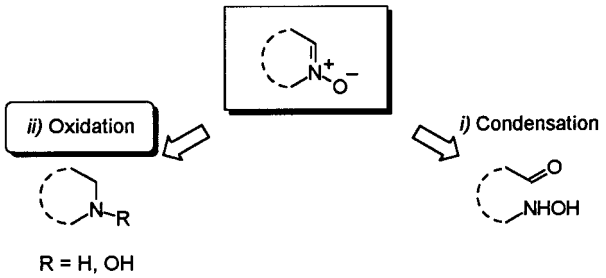
Nitrones proved to be very useful tools in the construction of structurally complex molecules, usually allowing a high degree of diastereocontrol. In this context, either the nitrone [3 + 2] cycloaddition to alkenes[1] and the alkylation of nitrones by organometallic reagents[2] have been extensively developed and have become extremely reliable synthetic procedures. In addition, nitrones are useful spin trap reagents, widely employed in biological systems.[3]

Among the synthetic methods for obtaining nitrones,[4] two procedures are by far the most useful and utilized (Scheme 1): (i) the condensation of *N*-monosubstituted hydroxylamines with carbonyl compounds, and (ii) the oxidation of secondary amines or *N*,*N*-disubstituted hydroxylamines. These latter compounds can be in turn produced as intermediate oxidation products from secondary amines, or by nucleophilic attack of *N*-monosubstituted hydroxylamines to different substrates.[5] Recently, a new double nucleophilic displacement of ditosylates, dimesylates, or dibromides with NH_2OH developed in our group allowed an easy access to cyclic hydroxylamines.[6] However, the most successful and popular method for the subsequent oxidation of hydroxylamines to nitrones requires the use of highly toxic mercury salts in large amounts, the use of different oxidants being less universal and satisfactory.[4] Other methods involve the use of metal salts or oxides (copper, lead, silver), or the use of complex organic oxidants (oxaziridines, quinones).

Scheme 1



In the last years we have been involved in the search for alternative and more practical oxidation methodologies to nitrones,[7] and we have recently reported an oxidation of hydroxylamines catalyzed by (salen)Mn(III) complexes.[8] During the latter study, the observation that sodium hypochlorite is sufficient by itself to promote the oxidation of hydroxylamines to nitrones has prompted us to evaluate the use of commercial bleach as an inexpensive, convenient, safe, and environmentally benign (the only byproduct being sodium chloride) alternative to the use of the currently employed oxidants. In this paper we report the results of oxidation of various *N*,*N*-disubstituted hydroxylamines to the corresponding nitrones with only the use of common, commercial bleach.

Hydroxylamines **1**−**10**, synthesized according to literature methods (see Experimental Section), have been subjected to sodium hypochlorite oxidation at 0 °C or room temperature (Table 1). Commercial bleach was able to give quantitative conversion of all the studied hydroxylamines in 2−28 h (Table 1, entries a). Workup of the reaction mixtures followed by column chromatography purification afforded the desired nitrones **11**−**20** in good yields (50−85%), most of which compare well with those obtained by the known oxidation methods.

The acyclic nitrones **11** and **12** were obtained with opposite stereochemistry. *C*-Phenyl nitrone **11** was isolated as the *Z* isomer exclusively, as usual.[11] A scale-up of the reaction on 5 mmol of **1** allowed an almost

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(9) We have reported throughout the text the titer of NaClO solutions as stated by the companies on the samples, i.e., ≤5% for bleach and 13% for the concentrated sodium hypochlorite commercially available from Fluka. However, we have determined the exact titer by titration of the solutions with 0.89 M sodium thiosulfate.[10] While the titer of bleach remained always in the range 3.5−4% during all the time of this study, we observed a dramatic decrease in the NaClO concentration of the 13% solution. Then, all the reactions with the more concentrated solution have been carried out at the same time with a 10.2% solution, immediately after titration. In our experience, the use of bleach is much more practical, requiring no titration providing that a 1.5−2-fold excess is used. On the other hand, it is advisable to titrate the 13% NaClO solution before its use: we are indebted to one referee for warning us about the rapid decline of its titer.

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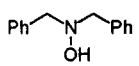
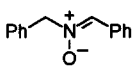
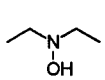
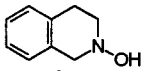
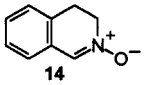
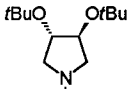
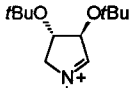
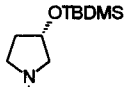
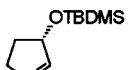
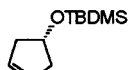
Table 1. Sodium Hypochlorite Oxidations of Hydroxylamines 1-10 to Nitrones 11-20[a]

Hydroxylamine	Nitrone(s)	Entry	% NaClO	Time (h)	% Yield	Regioisomeric ratio
 **1**	 **11**	1a	5	20	85 (94[b])	
		1b	13	20	84	
		1c	5 (pH 2.8[c])	1.5	92	
 **2**	 **12**	2a	5	5	50[d]	
 **3**	 **13**	3a	5	3	68	
		3b	5 (pH 2.8[c])	0.2	50	
 **4**	 **14**	4a	5	7	78	
 **5**	 **15**	5a	5	21	82	
 **6**	 **16**	6a	5	5	40	
		6b	5 (pH 2.8[c])	0.3[e]	50	
 **7**	 **17a**  **17b**	7a	5	25	73	72:28
		7b	13	4	75	60:40
		7c	5 (pH 7.5[f])	8	57	81:19
		7d	5 (pH 2.8[c])	0.3[e]	57	83:17
 **8**	 **18a**  **18b**	8a	5	8	82	66:34
		8b	5 (pH 2.8[c])	2[e]	82	70:30
 **9**	 **19a**  **19b**	9a	5	5	68	65:35
		9b	13	3	73	56:44
		9c	5 (pH 2.8[c])	0.25[e]	60	50:50
 **10**	 **20a**  **20b**	10a	5	2	62	100:0
		10b	13	2	73	100:0

[a]Reactions carried out on 0.5 mmol of hydroxylamine by addition of a 5% or a 13% NaClO aqueous solution (ca. 1.3 equiv)[9] at 0 °C and then reacted at rt (see Experimental Section). [b]On 5 mmol of **1**. [c]By addition of 0.5 M $KHSO_4$. [d]On 4 mmol of **2**. [e]Reaction carried out at 0 °C. [f]By addition of 0.1 M CH_3COOH.

quantitative recovery of nitrone **11**. On the contrary, oxidation of diethylhydroxylamine (**2**) furnished exclusively the less stable *E* nitrone **12**. The issue of stereoselectivity in the synthesis of acyclic *C*-alkyl nitrones by oxidation methods is often not addressed. Nitrone **12** has been obtained previously from hydroxylamine **2** as a 9:1 mixture of a *E*/*Z* isomers by oxidation with silver oxide[12] and as a diastereomeric mixture whose ratio depended upon the reaction time by oxidation with TPAP/NMO.[7a]

Enantiomerically pure nitrones **15**, **17**, and **18**, useful intermediates for the synthesis of valuable polyhydroxypyrrolizidines, indolizidines, and pyrrolidines,[1g,13] were obtained in yields comparable with those given by HgO oxidation. However, the nonsymmetric hydroxylamines **7** and **8** afforded a mixture of regioisomeric nitrones with

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very scarce selectivity (2−3:1, entries 7a and 8a) compared to the high ratios (9−12:1) obtained with HgO or other oxidants.[6b,d] This difference might imply that a different mechanism is involved in the oxidation with NaClO, since the supposed mechanism through nitrosonium cations should favor nitrones **a** over their regioisomers **b**.[6b,d] Finally, the 2-methyl-substituted hydroxylamines **9** and **10** have been considered in order to address the issue of regioselectivity in the formation of ketonitrones **a** vs aldonitrones **b**. While the regioselectivity in the oxidation of **9** (entry 9a) is slightly lower than with HgO (3:1),[14] the oxidation of **10** gave exclusively the ketonitrone **20a** (entry 10a), compared to the same 3:1 **20a/20b** ratio obtained with HgO.[15]

The effect of the concentration of sodium hypochlorite on the reaction has also been studied with the use of commercially available 13% NaClO (entries 1b, 7b, 9b, 10b).[9] The results show no substantial difference from the use of bleach, apart from minor variations in reaction time and/or regioisomeric ratios in some cases (entries 7b, 9b). However, the use of 13% NaClO proved to be less practical, due to rapid loss of strength of the solution.[9]

We examined then the effect of the variation of pH of the solution on the reaction. An oxidation of **7** at a lower pH (7.5, obtained by adding a 0.1 M solution of CH_3CO-OH) gave effectively a complete conversion after only 8 h (entry 7c). The reaction rate for the oxidation dramatically increased when the reactions were performed at pH 2.8, adjusted by addition of a 0.5 M solution of $KHSO_4$. All the hydroxylamines tested under these conditions were consumed after times as short as 10 min to 1.5 h (entries 1c, 3b, 6b, 7d, 8b, 9c)! The reaction yields remained in the range of those obtained with bleach, albeit in some cases a slight decrease was observed. The observed results are consistent with the much higher standard reduction potentials of HClO ($E° = 1.63$ V) and Cl_2 ($E° = 1.36$ V) compared to ClO^- ($E° = 0.89$ V).[16] At acidic pH values, HClO ($K_a = 3.4 \times 10^{-8}$) and Cl_2, formed by initial reduction, must be therefore the actual oxidants.

In conclusion, a new method for the oxidation of *N*,*N*-disubstituted hydroxylamines to the corresponding nitrones has been developed. This method employs inexpensive bleach as the reagent and is very simple to perform, requiring only a separation of the biphasic mixture before purification of the products. More importantly, it is a safe method which avoids the use of toxic reagents and is ecologically friendly, the byproduct consisting of an aqueous NaCl solution. These features might make it the method of choice for this useful transformation, especially on a large scale. Moreover, the reaction can be speeded up enormously if carried out at acidic pH. At the present level of study, the only limitation appears to be the low regioselectivity in the oxidation of 3-substituted hydroxypyrrolidines.

Experimental Section

Bleach, whose concentration is reported as ≤5%, has been purchased from a general store. 13% Sodium hypochlorite has been purchased from Fluka.

Hydroxylamines. Hydroxylamines **1** and **2** have been purchased from Aldrich and used without further purification. Hydroxylamines **3** and **9** have been synthesized according to ref 6e, **5** according to ref 6a, **6** according to ref 8, **7** according to ref 6d, and **8** according to ref 6b. Hydroxylamine **4** has been synthesized by $NaBH_4$ reduction of nitrone **14**[17] and **10** by H_2O_2 oxidation of 2-methylpiperidine.[18]

1-Hydroxy-2-methylpyrrolidine (9).[14] A two-necked round-bottomed 250 mL flask equipped with a condenser and a dropping funnel was charged with $NH_2OH·HCl$ (3.13 g, 45 mmol) and dry NEt_3 (60 mL). A solution of 1,4-dibromopentane (2.1 mL, 15 mmol) in dry NEt_3 (10 mL) was added dropwise to the stirred solution maintained under reflux during 4 h. The reaction mixture was then cooled to room temperature and the solution separated from the insoluble salts, which were washed with Et_2O (3 × 20 mL). The collected organic phases were dried over Na_2SO_4, filtered, and concentrated to give a crude, which afforded the title product (1.07 g, 70% yield) as an oil by purification on a short pad of silica gel, eluting with Et_2O (R_f 0.29).

General Procedure for the Oxidation of Hydroxylamines 1−10 with Bleach. A 0.5 M solution of hydroxylamine **1**−**10** (0.5 mmol) in CH_2Cl_2 was cooled at 0 °C and bleach (5% NaClO, actual titer 3.5−4%,[9] 1.3 mL, 0.6−0.7 mmol) was added slowly. After 0.5 h, the mixture was warmed to room temperature and reacted for the appropriate time (see Table 1) as indicated by TLC control. The crude mixture was then diluted with CH_2Cl_2 (2 mL) and the organic phase separated. The aqueous layer was extracted with more CH_2Cl_2, and the collected organic phases were dried over Na_2SO_4, filtered, and concentrated. The obtained crude products were purified on silica gel, eluent CH_2Cl_2/CH_3OH 15:1.

General Procedure for the Oxidation of Hydroxylamines with 13% NaClO. The same procedure used in the oxidations with bleach was followed, but using 380 μL of 13% NaClO (actual titer 10.2%,[9] 0.65 mmol).

General Procedure for the Oxidation of Hydroxylamines at pH 2.8. A 0.25 M solution of hydroxylamine (0.5 mmol) in CH_2Cl_2 was cooled to 0 °C and bleach (5% NaClO, actual titer 3.5−4%,[9] 1.3 mL, 0.6−0.7 mmol) was added. After 5 min, a 0.5 M solution of $KHSO_4$ (1.2 mL) was added, bringing the pH of the solution to ca. 2.8. The reaction was carried out at 0 °C or at room temperature until completion by TLC control (see Table 1). The mixture was then worked up and the product purified as in the reactions with bleach alone.

Oxidation of Hydroxylamine 7 at pH 7.5. A 0.25 M solution of hydroxylamine **7** (0.5 mmol) in CH_2Cl_2 was cooled to 0 °C and bleach (5% NaClO, actual titer 3.5−4%,[9] 1.3 mL, 0.6−0.7 mmol) was added. After 5 min, a 0.1 M solution of CH_3COOH (1.7 mL) was added, bringing the pH of the solution to ca. 7.5. The reaction was carried out at room temperature until completion by TLC control (8 h). The mixture was then worked up and the product purified as in the reactions with bleach alone.

Nitrones 11−20. All the nitrones have been obtained as pure compounds (for the yields see Table 1) and have been identified by comparison of their spectral and physical data with those reported in the literature (see ref 11 for nitrones **11**, **13**, and **14**, ref 12 for **12**, ref 6a for **15**, ref 13a for **16**, ref 6d for **17**, ref 6b for **18**, refs 14 and 19 for **19**, and refs 11 and 15 for **20**).

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