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A New Modified "Montanari Oxidation Process" by Means of Chlorine Dissolved in the Reaction Solvent as Oxidant and TEMPO as Catalyst: Oxidation of 3-*S*-Quinuclidinol to 3-Quinuclidinone

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Abstract:

Results from a process improvement project for preparation of 3-*R*-quinuclidinol, a highly valuable intermediate for several muscarine-active compounds are described. The studied process was based on the kinetic resolution of racemic 3-quinuclidinol and thus involved a large side-stream production. Our outline for process improvement is based on that this side stream can be recycled by a two-step sequence of oxidation and reduction processes. Findings concerning the conversion of 3-*S*-quinuclidinol into 3-quinuclidinone by using an improved oxidation process based on TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl radical) and molecular chlorine are discussed in detail. The developed oxidation procedure affords nearly quantitatively yield in the conversion of 3-*S*-quinuclidinol into 3-quinuclidinone.

Introduction

3-*R*-Quinuclidinol (*R*-1-azabicyclo[2.2.2]octan-3-ol) **1** is used as a building block in the synthesis of muscarine M1 and M3 agonists as well as for muscarine M3 antagonists. See for example the recent review by Broadley and Kelly[1] concerning muscarinic receptor agonist and antagonist. Talsaclidine fumarate (WAL 2014 FU),[2−4] cevimeline HCl,[5,6] and YM 905[7] are all examples of products where 3-*R*-quinuclidinol constitutes an integral part of the molecular entity. These products have shown potential in the treatment of Alzheimer's disease, Sjögren syndrome, and urinary incontinence, respectively. 3-*R*-Quinuclidinol **1** constitutes therefore a highly valuable building block for the synthetic production of several important pharmaceutical chemicals.

3-*R*-Quinuclidinol **1** can be obtained by kinetic resolution of racemic mixtures of *R*- and *S*-3-quinuclidinol. Borregaard Synthesis, Norway (BSY), operates such a process, and it was this that was the subject of a process improvement project with focus on (1) decreasing the side streams, that constitute 50% of the raw materials, (2) reducing the variable costs, (3) increasing exploitation of the raw materials, (4) improving the throughput of the process, and (5) general process development and optimisation.

Thus, in this context, we have outlined a process involving the recycling of the side-stream of 3-*S*-quinuclidinol **2** in a two step-sequence oxidation and reduction process. The first step is constituted of the current BSY kinetic resolution process of *R*- and *S*-3-quinuclidinol indicated as pathway *(a)* in Scheme 1. The side stream of 3-*S*-quinuclidinol **2** is according to our process sketch submitted for oxidation following pathway (*b*) to give 3-quinuclidinone **3**. In the subsequent step, the ketone **3** can either undergo a simple reduction, following pathway *(c)* or a stereoselective reduction following pathway *(d)*, thus providing a racemic mixture of *R*- and *S*-3-quinuclidinol and 3-*R*-quinuclidinol **1**, respectively. The net process constituted by the pathways *(a)*, *(b)*, and *(c)* ideally converts all of the racemic material via the achiral ketone **3** into the desired *R* form **1**, and can be considered as a dynamic kinetic resolution process. However, an alternative to the sketched process is to follow the pathways (*e*) and (*d*), where pathway (*e*) is exactly the same oxidation procedure as applied in the pathway (*b*), while pathway (*d*) requires a new efficient enantioselective reduction process that affords 3-*R*-quinuclidinol only, eventually in a high enantiomeric excess.

Methods and Results

The chemical literature reports several methods to be generally applicable for oxidising secondary alcohols into their corresponding ketones.[8] A number of these were tested for the oxidation step, pathway (*b*) of the outlined process in Scheme 1. Nevertheless, most of the methods tried afforded only low yields, did not operate at all, and ultimately proved to be unsuitable for large-scale applications. In the screening phase for oxidation methods and processes, organic nitroxyl radicals also attracted our attention as potential oxidants for our process, since such species are reported[9,10] to be good oxidants for oxidising primary and secondary alcohols.

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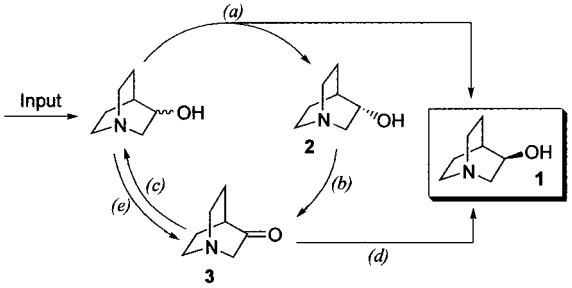
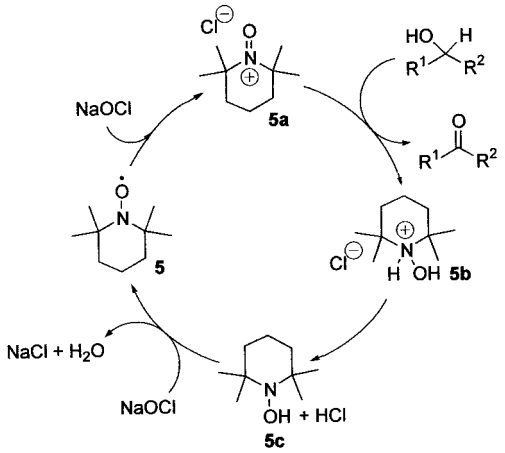
Scheme 1[a]



[a] *(a)* Kinetic resolution, *(b)* oxidation, *(c)* reduction, *(d)* stereoselective reduction, *(e)* oxidation

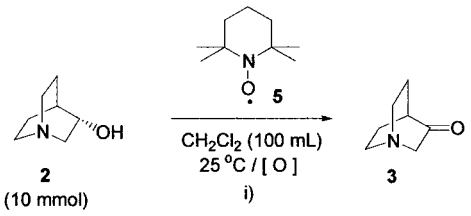
Scheme 2



A particularly convenient method, involving a two-phase system constituted by methylene chloride and water, using hypochlorite as oxidant and 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO) **5** as catalyst, was reported by Montanari and co-workers.[11−13] The mechanism for this oxidation reaction is given in Scheme 2. It is worth noting that the real oxidant for the alcohol in this cycle is the oxo-piperidinium compound **5a** (2,2,6,6-tetramethyl-1-oxo-piperidinium). While hypochlorite is indicated as the oxidant for 2,2,6,6-tetramethyl-piperidin-1-ol **5c** and TEMPO **5**, several other oxidants may also be used.

However, our trials using the "Montanari procedure" revealed rather unsatisfactory results when utilised for the alcohol **1**: conversion and selectivity where low. In our opinion this is due to the presence of the basic nitrogen, which strongly increases the solubility of the alcohol **1** in the aqueous phase. Other oxidative systems used in combination with TEMPO **5**, such as molecular oxygen and aldehydes (acetaldehyde, benzaldehyde) in combination with Cu salts, and peracids generated in situ from acetic anhydride and hydrogenperoxide, gave only trivial results. We believe that all of these poor results were due to the presence of the basic nitrogen in the alcohol **2**. However, when *m*-chloroperbenzoic acid (MCPBA) was used as oxidant for **5c** and **5** (entry 3 Table 1) a quite satisfactory result was achieved. This procedure has however the disadvantages of defective atom economy, as equivalents of *m*-chlorbenzoic acid are produced as side product.

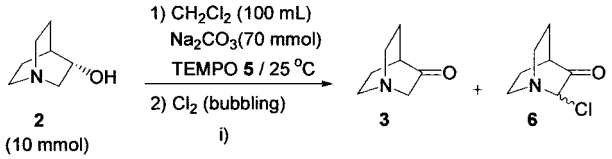
Table 1. Experimental results from oxidation experiments in attempts to oxidise 1-aza-bicyclo [2.2.2] octan-3-ol to 1-aza-bicyclo [2.2.2] octan-3-one[a]



	oxidising system [O]	solvents	yield of **3** (%) (gc)
1	NaOCl/TEMPO	CH_2Cl_2/H_2O	16
2	$Ca(OCl)_2$/TEMPO	CH_2Cl_2	10
3	MCPBA/TEMPO	CH_2Cl_2	78
4	$O_2/CH_3(CH_2)_2CHO$/TEMPO	CH_2Cl_2	traces
5	O_2/*t*-Bu(OOCO)$_2$/TEMPO	CH_2Cl_2	2
6	O_2 (6 bar)/CuCl/TEMPO	CH_3CN	traces
7	C_6H_5CHO/Air (25 bar)/TEMPO	EtOAc	5
8	H_2O_2/Br_2	EtOAc	traces

[a] i) The reactions were carried out at 25 °C in 100 mL scale starting with 1.27 g (10 mmol) of the substrate.

Table 2. Experimental results from oxidation experiments in attempts to oxidise 1-aza-bicyclo [2.2.2]octan-3-ol to 1-aza-bicyclo[2.2.2]octan-3-one using TEMPO and chlorine[a]



	w/w **5**	time for bubbling Cl_2 (min)	reaction time	amounts (%) (gc) **3**	**2**	**6**
1	10%	30	1 h 45 min	88.0	<1	9.2
2	5%	35	2 h 40 min	73.8	<1	26.1
3	1%	60	2 h	60.0	<1	37.5

[a] i) The reactions were carried out at a temperature of 25 °C in 100 mL methylene chloride using 1.27 g (10 mmol) of the alcohol **2**.

We thus investigated a modification of the Montanari procedure[11−13] developed by Yamaguchi et al.[14] involving TEMPO **5**, using anhydrous sodium carbonate in methylene chloride through which is passed a stream of chlorine gas. We have found that this procedure works moderately satisfactory with the alcohol **1**. In these experiments, relatively high yields of the ketone **3** were achieved even without rigorous optimisation of the oxidation process (Table 2). A chlorinated product was also formed during the reaction. GC−MS analysis suggested a monochlorinated derivative of the ketone **3**, most probably formed due to a subsequent electrophilic chlorination of the formed ketone **3** to give 2-chloro-1-azabicyclo[2.2.2]octan-3-one **6**. In addition to the formation of the side product, several other concerns were also present for the use of such an oxidation process for large-scale process, namely, the handling of chlorine gas during the oxidation process and the relative

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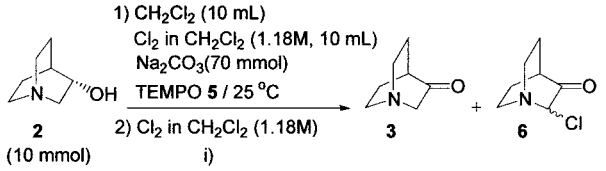
Table 3. **Experimental results from oxidation experiments in attempts to oxidise 1-aza-bicyclo[2.2.2] octan-3-ol to 1-aza-bicyclo[2.2.2]octan-3-one using TEMPO and chlorine[a]**



			amount of Cl_2		amounts (%) (gc)		
	w/w **5** (%)	t [min]	$n^{1stAdd}_{chlorine}$	$n^{2ndAdd}_{chlorine}$	**3**	**2**	**6**
1	10	30	11.8	11.8	∼99	<1	-
2	5	30	11.8	-	69	28	-
3	5	30	11.8	17.7	∼99	<1	-
4	1	30	11.8	18.0	78	<1	15

[a] i) At the start of the reaction 11.8 mmol of chlorine ($n^{1stAdd}_{chlorine}$) was added to the reaction mixture. A second dropwise addition ($n^{2ndAdd}_{chlorine}$) of chlorine to the reaction mixture was carried out over a period of 30 min.

high quantity of TEMPO **5** (10%) that was required. The experiments utilising bubbling chlorine gas as oxidant with TEMPO **5** as catalyst, revealed, however, that an oxidation system based on using the oxo-piperidinium compound **5a** as the oxidant for the alcohol **2** is a promising direction in which to develop the process.

In this context, our idea was to utilize the same solvent as carrier for the chlorine gas as for preparing the solution of the alcohol **2**, TEMPO **5**, and anhydrous sodium carbonate to which the gas solution would be added. Thus, a solution (∼1.2 M) of molecular chlorine in methylene chloride was prepared and used in the series of experiments reported in Table 3.

Entry 1 of Table 3 shows the result when 10% w/w of TEMPO **5**, the alcohol **2** and 2.36 equiv of chlorine are used. This experiment affords quantitative transformation of the alcohol **2**, into desired product, the ketone **3**, without formation of chloroketone **6**. When the quantity of TEMPO **5** is reduced to 5% w/w, a somewhat higher amount of chlorine was necessary (totally 2.95 equiv) to achieve a quantitatively transformation of the alcohol **2** (entry 3 of Table 3). Without the following-up dropwise addition of chlorine, a partial conversion of the alcohol is achieved (entry 2 of Table 3). Entry 4 of Table 3 gives the result from a experiment using only 1% w/w of TEMPO. In this experiment there was also formed the chlorinated side product **6** in the same way as for the experiment where chlorine gas was bubbled through the reaction mixture; at higher concentrations of TEMPO **5** (entries 1 and 3) no detectable quantities of **6** (2-chloro-1-azabicyclo[2.2.2]octan-3-one) were observed.

Conclusions

Our modification of the Montanari procedure[11−13] using a saturated solution of Cl_2 in methylene chloride shows important advantages for large-scale production: (1) it avoids the handling of chlorine as gas during the oxidation process, (2) it affords excellent yields even with a reduced quantity of catalyst, (3) the reaction rate is also increased using the modified procedure, with the consequence of a shorter residence time with possibility of higher througput in plant scale.

Interestingly, when a reduced quantity of TEMPO **5** is used under otherwise similar condition, the ketone **3** is in a subsequent process chlorinated to give the chloroketone **6** in quite high yields. Especially when the chlorine gas is bubbled through the reaction mixture, high yields are afforded (Table 2). Further optimising by using response surface methodology[15] of this process may provide a method for preparation for exactly this compound.

Experimental Section

Reaction Procedure Bubbling Cl_2 through the Oxidation Mixture. 1-Azabicyclo[2.2.2]octan-3-ol (10 mmol, 1.27 g), sodium carbonate (70 mmol, 7.4 g), and 2,2,6,6-tetramethylpiperidin-1-oxyl (1−10% w/w) was mixed in CH_2Cl_2 (100 mL). Chlorine gas was then bubbled through the reaction mixture, approximately one bubble per each 2 s through a Pasteur pipet for a reaction time of 105−160 min.

Reaction Procedure Using Cl_2 Dissolved in CH_2Cl_2. The solution of dissolved chlorine in methylene chloride was prepared by bubbling chlorine gas through CH_2Cl_2 (50 mL) for 30 min. The concentration of absorbed chlorine gas was determined by adding KI (200 mg) in concentrated CH_3COOH (5 mL) and water (5 dr) to a sample of 10 mL of the CH_2Cl_2/Cl_2 solution. This solution was then titrated with $Na_2S_2O_3$ (0.1 N; 59 mL were used). The chlorine content in CH_2Cl_2 was determined to be 1.18 M.

The oxidation reaction was carried out by dissolving 3-quinuclidinol (1.27 g, 10 mmol) in CH_2Cl_2 (10 mL) to which anhydrous Na_2CO_3 (7.40 g, 70 mmol) and TEMPO (1−10% w/w) were added. The CH_2Cl_2/Cl_2 solution (0.0118 mol, 10 mL of 1.18 M) was added in one portion followed by another ($n^{2ndAdd}_{chlorine}$) mol of chlorine (see Table 3) dropwise over a period of 30 min.

Work-up and Purification. The white solid was filtered off, and the solvent was evaporated. Solvent system used for TLC: CH_2Cl_2:MeOH/1:1. The ketone was isolated by flash chromatography (CH_2Cl_2:MeOH/8:2) and characterised by ^1H and ^{13}C NMR.

^1H NMR (MeOD): 3.38−2.82 δ (m, 5H), 2.46−1.62 δ (m, 6H).

^{13}C NMR (MeOD): δ 219.4 (C═O), 57.64 (N−C−CO), 40.56 (CH_2−N), 35.96 (C−CO), 27.62 (CH_2).

Crystallisation Procedure 1. The red crude product (1.3 gram) was dissolved in a solvent mixture (1:1) of CH_2Cl_2 and CH_3OH (10 mL). However, the crude product was not completely soluble due to the presence of tars. The obtained solution (orange-coloured) was filtered using a glass sinter filter to remove the tars. Then, the solvent was removed under vacuum to obtain about 150 mg of orange solid, which was crystallised using 2-propanol (5 mL). The crystallised product appeared as a white powder (isolated yield about 100 mg). The product was analysed on GC−MS, which showed only the desired product.

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Crystallisation Procedure 2. The red crude product (760 mg) was dissolved in 2-propanol (15 mL). Charcoal (200 mg) was added to this solution, and the mixture was stirred for 1.5 h at 100 °C. The solution was then filtered on a glass sinter filter. A brown solid was precipitated from the filtrate. Hence, a second filtration was performed to obtain a pale-orange solution. The solvent was then removed under vacuum. The residue was recrystallised by dissolving the solid in ethanol (2 mL). Petroleum ether bp 30−60 °C (1 mL) was added to this solution to lower the solubility of the ketone and hence initiate crystallisation. Isolated yield of the ketone was 170 mg. The product was analysed on GC−MS, which showed only the desired product.

It should be noted that experience indicates that an immediate work-up with recrystallisation after oxidation gives a higher isolated yield as well as a simpler work-up.

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