Pergamon

Tetrahedron Letters, Vol. 35, No. 11, pp. 1715-1718, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0112-B

Intramolecular Quenching of Iminium Ions Generated by Photooxidation of Aminoalcohols with Ketones. A New Synthesis of Oxazines and Oxazoles

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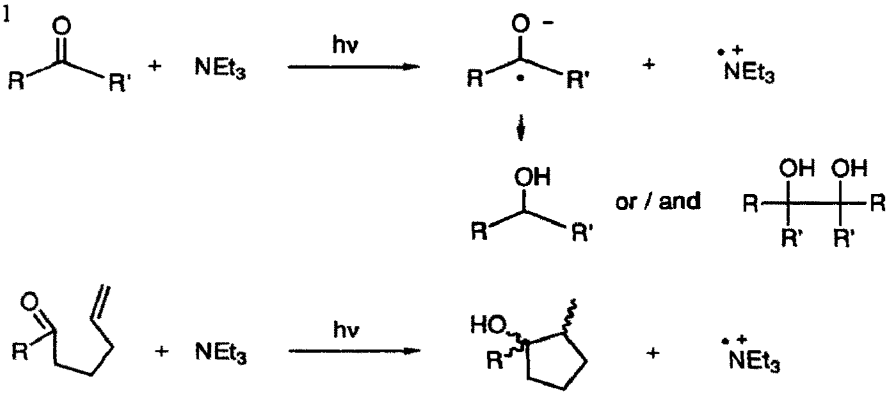
Key words *Ammoniumyl ions, iminium ions, electron transfer, amines, ketones, tetrahydro[1,3]oxazine tetrahydrooxazoles.*

Abstract: *The irradiation of tertiary amines in the presence of ketones leads to a regioselective and stereoselective formation of iminium salts which then react to afford the corresponding oxazines or oxazoles.*

Recently, photoinduced electron transfer reactions have attracted considerable attention [1] and have been used in the synthesis of natural products [2]. In these transformations, the key reactive intermediates are radical ions rather than the initially populated excited states. In polar solvents such as acetonitrile (CH_3CN), the solvated ions are separated to form free radical pairs [3]. Furthermore, the radical anion is less reactive in such polar solvents with the radical cation and *vice versa* [4]. The electron transfer between a ketone and a tertiary amine such as triethylamine produces a radical anion and an ammoniumyl ion. The ketyl radical anion can lead to the alcohol and/or duplicate to produce pinacol [5]. On the other hand, the ketyl radical anion formed from an unsaturated ketone may cyclize intramolecularly and lead to a 5- or a 6- membered ring

Scheme 1



If the behaviour of the ketyl radical anion is well known, the behaviour of the amino radical cation is still obscure. We would like to show herein that the ammoniumyl radical cation obtained by irradiation of a tertiary amine in the presence of a ketone is transformed into an iminium intermediate, which can react with an internal nucleophile such as an alcohol to produce an oxazine or an oxazole.

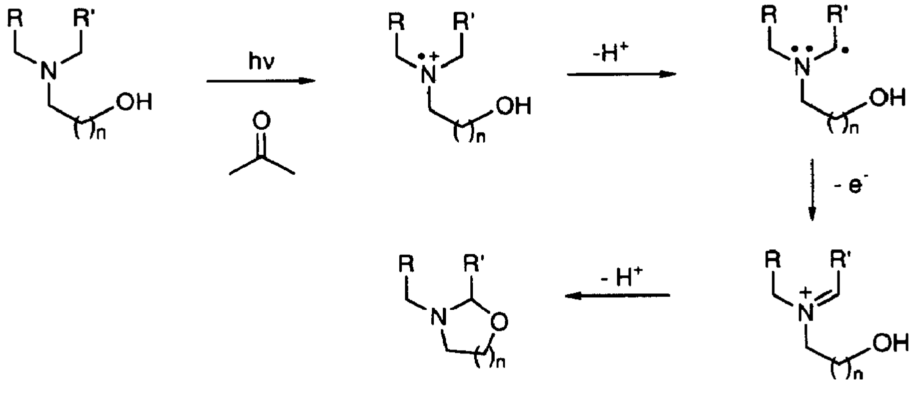
The amino alcohols **1** - **7** were prepared from the corresponding ω-chloroalcohols by heating under reflux with the appropriate secondary amines in dry acetonitrile containing anhydrous potassium carbonate

The irradiation of **1** was realized in the presence of different ketones. When **1** was irradiated (254 nm, quartz vessel) in acetonitrile (5 x 10^{-2} M) in the presence of one equivalent of benzophenone, the oxazine **8** was formed in 41% yield after a conversion of 63%. In the presence of two equivalents of benzophenone, the yield of **8** was increased to 60% for a 73% conversion. As the purification of **8** was not easy due to the formation of benzhydrol, the benzophenone was replaced by acetone. In the presence of twenty equivalents of acetone, the oxazine **8** was isolated in 88% yield for a 50% conversion [7]. This reaction is general (Table)

Substrates **2** - **6** led to the formation of tetrahydro[1,3]oxazines with yields ranging from 40% to 88% In the case of **7**, its irradiation led to the formation of the oxazole derivative **14** in 50% yield for a conversion of 94%

The formation of oxazines and oxazoles can be explained in terms of ammoniumyl radical cation intermediates that can be deprotonated rapidly at the site adjacent to the nitrogen center. One electron oxidation of the resulting α-amino radicals produces the corresponding iminium ions, since the latter oxidation is expected to be an easy process due to the low ionisation energy of the radical

Scheme 2

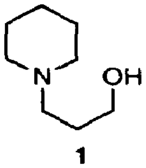
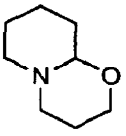
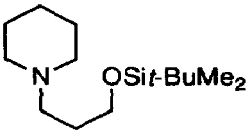
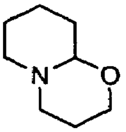
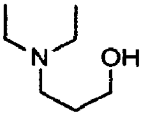
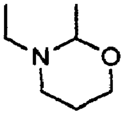
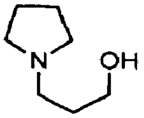
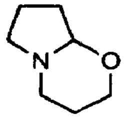
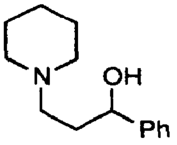
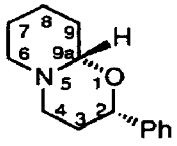
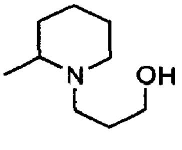
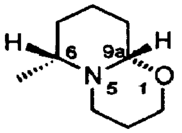
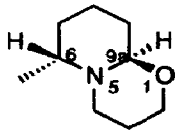
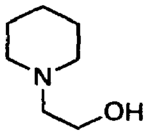
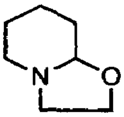


When the alcohol was protected as a silyl ether, as in **3**, the formation of the corresponding heterocyclic system was also observed Interestingly the irradiation of substrate **5** led exclusively to a single isomer **11**. The relative configuration of the phenyl group at C-(2) and the hydrogen atom at C-(9a) was established by nOe experiments in the ^{1}H NMR spectrum of **11**. Irradiation of the hydrogen atom signal H-(9a) (δH = 3 7 ppm) led to a 11% increase in the integration of the signal attributed to H-(2) (δH = 4 4 ppm)

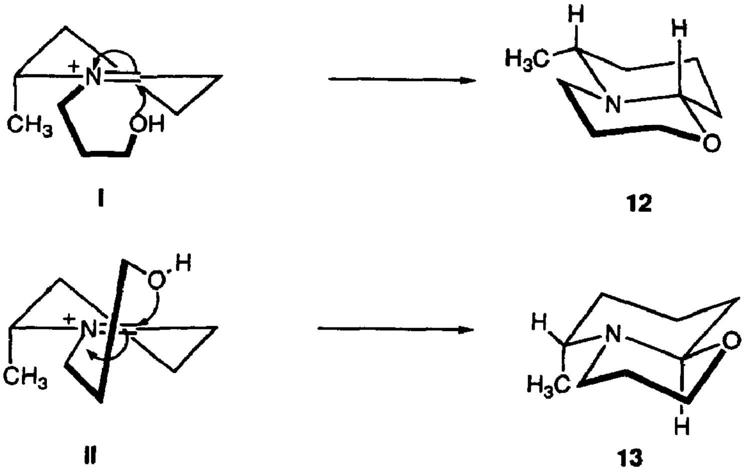
In the case of substrate **6**, where the two ring CH protons were different, the α-deprotonation occurred on the less substituted α-carbon atom of the cyclic amine. Two diastereoisomers **12** and **13** were formed in a 3 1 ratio with an overall yield of 50%. The analysis of the ^{1}H NMR spectra did not show the presence of the oxazine that corresponds to the trapping of the more substituted iminium ion. The reaction is regioselective and suggests that the α-deprotonation generates the less substituted α-amino radical.

The relative configuration of the cyclized products **12** and **13** was determined by comparison of the chemical shift of the bridgehead proton H-(9a) with those reported for the related system [8]. The signal of H-(9a) in **12** (the major isomer) appeared at 3 98 ppm, J_{ax} = J_{eq} = 3 7 Hz (the *cis* isomer) whereas the signal of H-(9a) in **13** (the minor isomer) appeared at 4 10 ppm, J_{ax} = 5 1 Hz, J_{eq} = 1 9 Hz and was the

TABLE: Irradiation of Aminoalcohols in the Presence of Acetone

Starting Material	Time (h)	Conversion (%)	Product (Yield %)
 **1**	2	48	 **8** (88)
 **2**	3	83	 **8** (50)
 **3**	3	95	 **9** (50)
 **4**	1	96	 **10** (41)
 **5**	2	67	 **11** (65)
 **6**	2	81	 **12** (36)  **13** (12)
 **7**	2	94	 **14** (50)

trans isomer. The formation of the major *cis* compound can be explained by the transition structure **I** in which steric hindrance is less important than in the alternative transition structure **II**.



Applications to the preparation of natural products using this new synthesis of oxazines and oxazoles are currently being explored in our laboratory.

References and Notes

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7. To a solution of aminoalcohol in acetonitrile (5 x 10^{-2} M) was added acetone (20 equiv). The reaction mixture was then irradiated at 254 nm (merry-go-round system equipped with 12 TUV 15 Philips lamps) for one to three hours depending on the aminoalcohol.

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(*Received in France* 6 *December* 1993; *accepted* 8 *January* 1994)