The search for aliphatic nitrenium ions from solvolysis of *N*-2,2,6,6-tetramethylpiperidinyl *p*-nitrobenzoate

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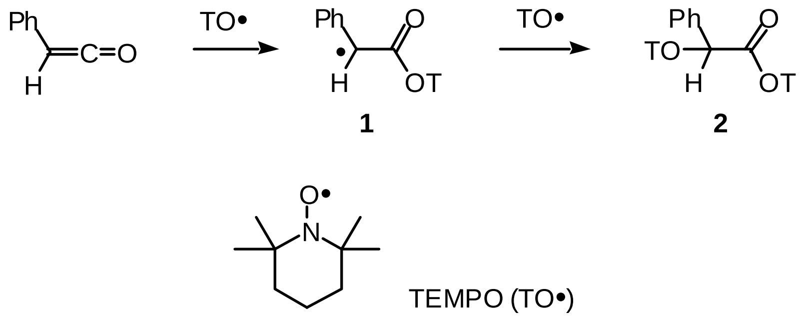
Abstract

The *N*-4-nitrobenzoate of 1-hydroxy-2,2,6,6-tetramethylpiperidine undergoes solvolysis in methanol, trifluoroethanol, and hexafluoroisopropanol forming salts of 2,2,6,6-tetramethylpiperidine (**4**) and the rearranged iminium ion **19** which yields 2,2-dimethylpyrrolidine (**26**) on hydrolysis. In trifluoroacetic acid only the rearranged iminium ion **19b** which forms **26** is observed, and the formation of this product is interpreted as involving ionization with rearrangement through an incipient nitrenium ion. The *N*-toluenesulfonate ester of 1-hydroxy-2,2,6,6-tetramethylpiperidine **24** was prepared as an unstable solid from 4-toluenesulfonyl chloride and *N*-hydroxy-2,2,6,6-tetramethylpiperidine, but upon chromatography rearranged to the cleavage product *N*-**4**-toluenesulfonyl-2,2-dimethylpyrrolidine (**25**).

Keywords: Nitrenium ions, 2,2-dimethylpyrrolidine, cationic rearrangement, hydroxylamine esters, *N*-hydroxy-2,2,6,6-tetramethylpiperidine.

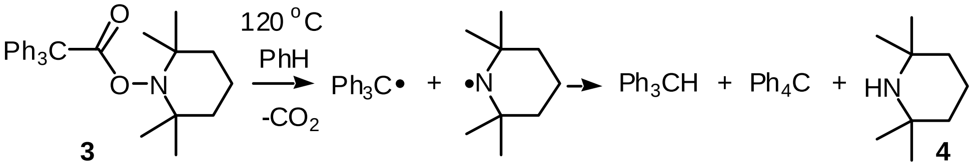
Introduction

The aminoxyl radical 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO, TO•) is widely used for the trapping of free radicals,[1,2] and has been extensively utilized in controlling living free radical polymerization.[3] The chemistry of the resulting adducts from reactions with TEMPO have consequently also assumed increasing importance, especially because of their tendency to undergo homolytic fission generating a radical pair.[1-3] We have been carrying out studies of the reactions of ketenes with aminoxyl radicals,[4] as exemplified by the addition of TEMPO to phenylketene, which is found to proceed by radical attack at the carbonyl carbon forming α-acyl radical **1** which is then trapped by a second TEMPO giving the 1,2-diaddition product **2** (Scheme 1).



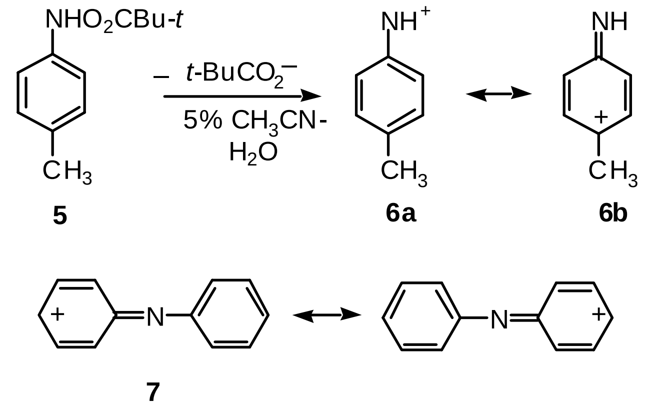
Scheme 1

Because of the importance of these TEMPO adducts we have been further examining their reactivity, as well as the thermal reactivity of TEMPO esters including Ph_3CCO_2T (**3**).[4j] This was found to undergo homolytic cleavage in benzene forming triphenylmethyl radical and 2,2,6,6-tetramethylpiperidinyl radicals T•, which lead to the formation of 2,2,6,6-tetramethylpiperidine (**4**, 91%), triphenylmethane (84%), and tetraphenylmethane (8%, Scheme 2).[4j] The reactivity of **3** in homolysis was greatly accelerated over that of $PhCH_2CO_2T$, which indicated there was concerted 2-bond scission in the initial step, forming the trityl radical Ph_3C• (Scheme 2).[4j]



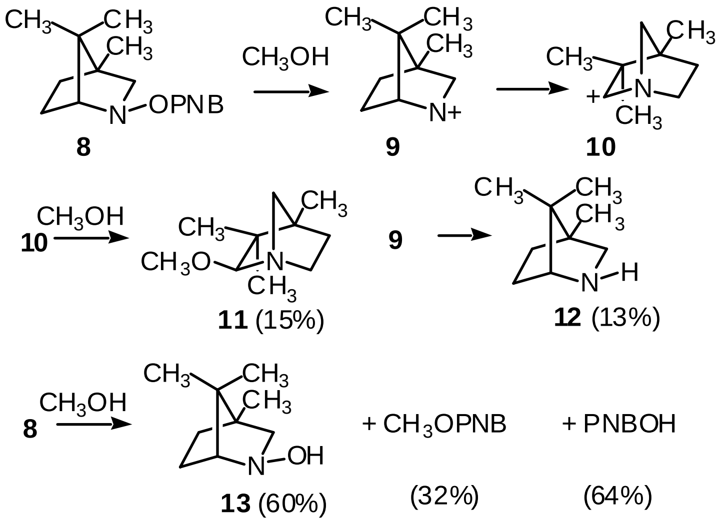
Scheme 2

The ionic chemistry of *N*-substituted amines has long been studied, and is implicated in the Stieglitz, Curtius, Hoffman, Lossen, and Schmidt rearrangements.[5] These reactions have been considered to involve putative divalent positively charged nitrogen species, or nitrenium ions. However even in ionic processes free nitrenium ions are not necessarily formed, as rearrangement may be synchronous with ionization. Arylnitrenium ions[6,7] have been of major recent interest because they have been implicated as cancer causing agents, and their reactions have been well studied, including time resolved study by UV and by IR. These species are readily prepared in ionizing solvents from a variety of precursors such as the *N*-pivalyl 4-toluidine **5** (Scheme 3) bearing good leaving groups on nitrogen, but the nitrenium ions formed are quite reactive.[6,7,10] In the product **6** the positive charge is largely delocalized away from nitrogen into the aryl ring in these species as shown in **6b**, as evidenced by the formation of products of nucleophilic attack on the aryl ring.[6,7,10] This structure is confirmed by the analysis of the time-resolved IR spectrum of Ph_2N^+ (**7**), shown to have a linear singlet structure (Scheme 3).[7e]



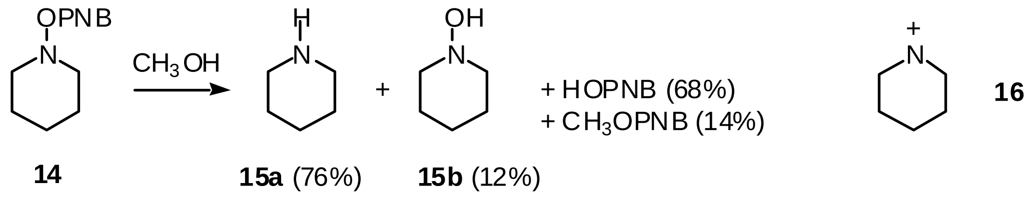
Scheme 3

Alkylnitrenium ions have been the subject of considerable mechanistic and synthetic study,[8] as in the reaction of *N*-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptyl *p*-nitrobenzoate (**8**) (Scheme 4).[8a] This was proposed to form the nitrenium ion **9**, which in the singlet state rearranged to a carbocation **10** which was captured by solvent to give **11**, and in the triplet state abstracted a hydrogen atom from CH_3OH forming **12**. Methyl *p*-nitrobenzoate and **13** were proposed to result from transesterification of **8** by methanol (Scheme 4).



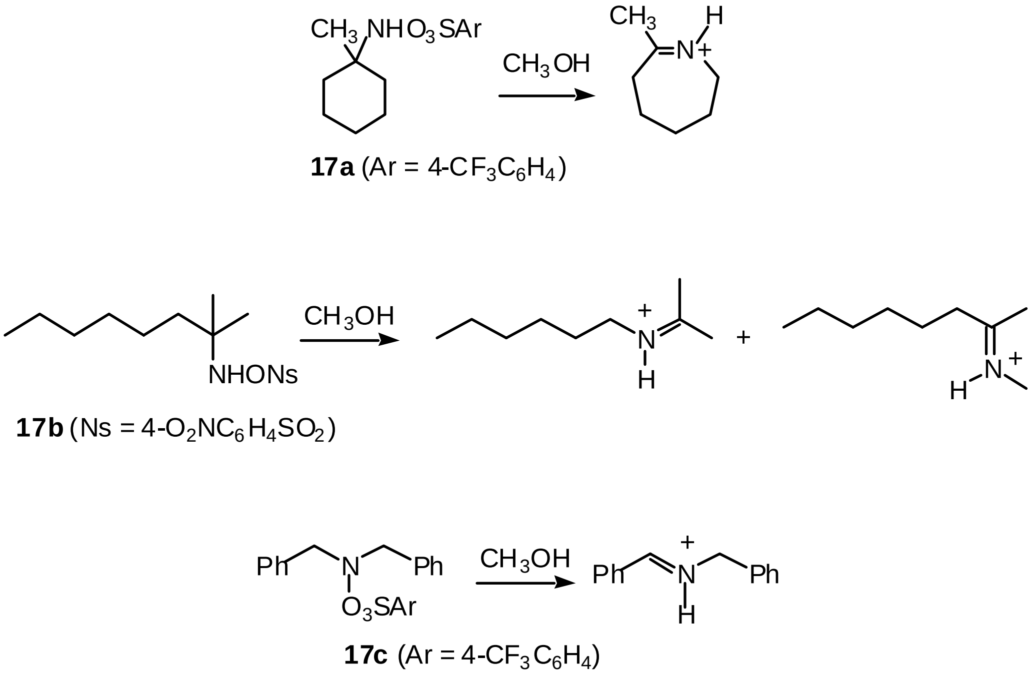
Scheme 4

Similarly the reaction of *N*-piperidinyl *p*-nitrobenzoate (**14**) in CH_3OH gave piperidine (**15a**, 76%), *N*-hydroxypiperidine (**15b**, 12%), *p*-nitrobenzoic acid (68%), and methyl *p*-nitrobenzoate (14%) (Scheme 5).[8b] The formation of piperidine and *p*-nitrobenzoic acid was attributed to the formation of the triplet nitrenium ion **16** which abstracted a hydrogen atom from methanol.[8a]



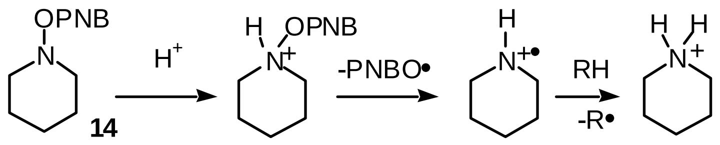
Scheme 5

A different interpretation of these results was proposed by Hoffman, *et al*, who studied the reactions of the *N*-substituted arenesulfonate esters **17** and found only products attributable to rearrangements following departure of sulfonate leaving groups (Scheme 6).[8c-e] They suggested rearrangement was concerted with leaving group departure so that discrete nitrenium ions were not formed.



Scheme 6

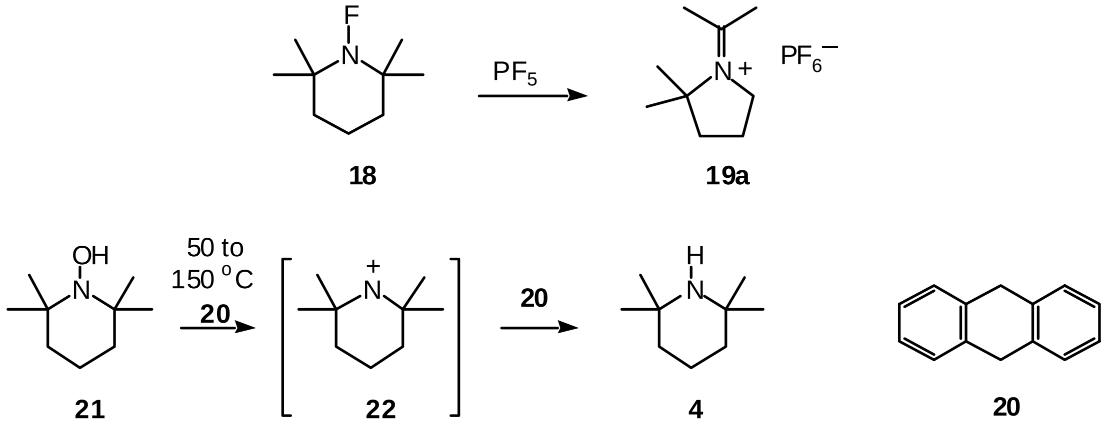
These authors also proposed that in the examples where amine formation was reported that the hydrogen abstraction did not involve a triplet nitrenium ion but rather resulted from protonation on nitrogen in the *N*-substituted ester, followed by homolysis forming a radical cation which abstracted hydrogen.[8d] In the example of **14** this would imply the reaction mechanism of Scheme 7. However no direct evidence for the formation of carboxylic radicals $RCO_2\bullet$ in these reactions has apparently been reported.



Scheme 7

Sulfonate esters of hydroxylamines are often highly reactive and difficult to isolate and purify, and evidence for the efficient generation of cationic intermediates from carboxylate esters of hydroxylamines has been lacking. It appeared however that *N*-carboxylate esters of 2,2,6,6-tetramethylpiperidine in highly ionizing and non-nucleophilic solvents could provide an effective route to cationic intermediates, and would eliminate the diversion of material by solvent attack on the ester moiety.

There is a report regarding possible cation generation from 2,2,6,6-tetramethylpiperidine. It was reported that *N*-fluoro-2,2,6,6-tetramethylpiperidine (**18**) on treatment with PF_5 gave the stable iminium salt **19a**, but the characterization of the product did not include measurement of the ^{13}C NMR spectrum (Scheme 8).[9a] Heating of TEMPO from 50 to 150 °C in hydrogen donor solvents such as 9,10-dihydroanthracene (**20**) was reported to form 2,2,6,6-tetramethylpiperidine,[1e] and this was proposed to involve formation of *N*-hydroxy-2,2,6,6-tetramethylpiperidine (**21**) which was converted to the 2,2,6,6-tetramethylpiperidinyl nitrenium ion **22**, which abstracted hydride from **20** (Scheme 8).[1e] Based on the reported formation of **19a** and the low ionizing power of **20** as a solvent it appears this latter process instead followed some other path, possibly a radical reaction.

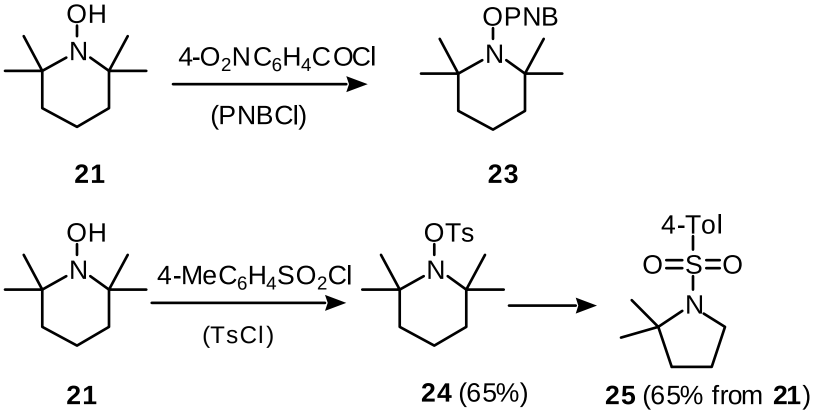


Scheme 8

This study was therefore undertaken to clarify the cationic reactivity and possible synthetic utility of the 2,2-6,6-tetramethylpiperidinyl system.

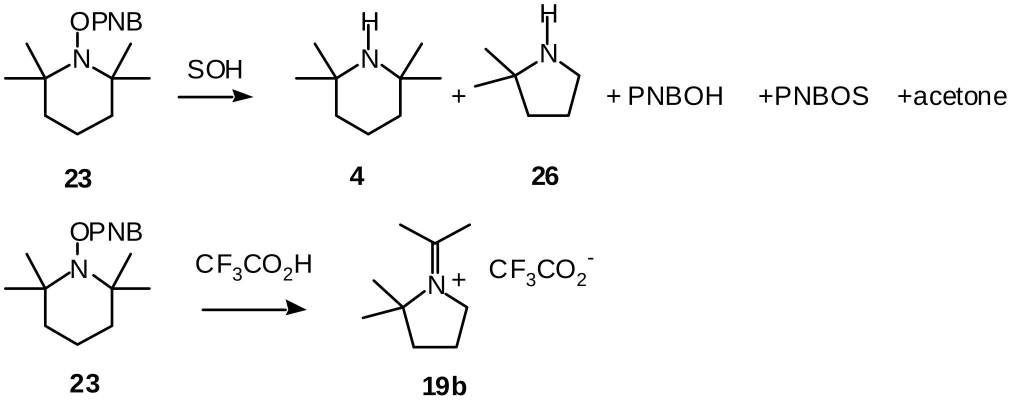
Results and Discussion

N-2,2,6,6-Tetramethylpiperidinyl *p*-nitrobenzoate (**23**) was prepared by the reaction of *N*-hydroxy-2,2,6,6-tetramethylpiperidine (**21**) with 4-nitrobenzoyl chloride (Scheme 9). A similar reaction of **21** and 4-toluenesulfonyl chloride in one trial gave *N*-2,2,6,6-tetramethylpiperidinyl *p*-toluenesulfonate (**24**), which was obtained in 65% yield after recrystallization from hexane, and was characterized by spectroscopic methods. However in a subsequent preparation upon chromatography the product rearranged to give the cleaved sulfonamide **25**, isolated in 65% yield (Scheme 9). The structure of the sulfonamide **25** was confirmed by preparation of an authentic sample from 2,2-dimethylpyrrolidine and TsCl. Sulfonate esters of other dialkyl hydroxyl amines have been prepared by Hoffman, Gassman, and others,[8] and typically show a high propensity for cleavage of the N-O bond, and rearrangement.



Scheme 9

The reaction of **23** in the solvents CH_3OH, CF_3CH_2OH (TFE), and $(CF_3)_2CHOH$ (HFIP) was carried out by heating the solutions in sealed tubes. After evaporation of the solvent the residual salt was dissolved in $CDCl_3$ and analysis by ^1H NMR indicated the formation of 2,2,6,6-tetramethylpiperidine (**4**) and the 2,2-dimethylpyrrolidinium salt (**19b**). The product was partitioned between KOH solution and ether and the yield of **4** was determined by quantitative gas chromatography. The yield of *p*-nitrobenzoic acid was determined by acidification of the KOH layer and isolation, and the solvent derived *p*-nitrobenzoate ester MeOPNB was isolated by chromatography (Scheme 10). The reaction of **23** in CF_3CO_2D gave the salt **19b** and *p*-nitrobenzoic acid as the only observable products after evaporation of the solvent, as established by the ^1H, ^{13}C, and ^{19}F NMR spectra, and by comparison to the spectra of the corresponding salt from the unsubstituted pyrrolidine (Scheme 10). Hydrolysis of the product gave 2,2-dimethylpyrrolidine (**26**), which was identified by comparison to the reported spectral data.[9c] Product yields are given in Table 1.

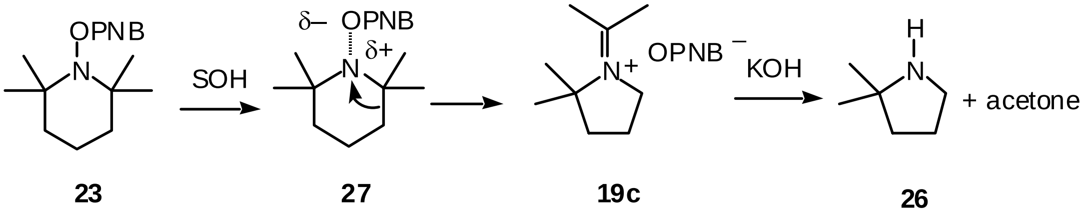


Scheme 10

Table 1. Product yields (%) from solvolysis of **23**

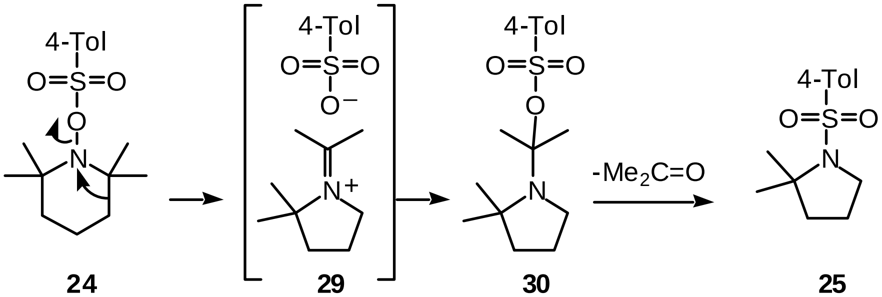
Solvent	T °C	t (h)	4	26	PNBOS	PNBOH
MeOH	130	16	60	30	15	80
CF_3CH_2OH	130	2	36	48	0	82
$(CF_3)_2CHOH$	130	1.5	40	56	0	90
CF_3CO_2H	130	0.5	0	70	0	80

The formation of 2,2-dimethylpyrrolidine (**26**) and acetone from **23** provides evidence for rearrangement of an incipient nitrenium ion **27** with formation of the ion pair **19c** which is hydrolyzed to the **26** (Scheme 11). The formation of a discrete nitrenium ion is not required. The facile rearrangement of the incipient nitrenium ion suggests that a nitrenium ion **22** is not involved in the reported reduction of TEMPO to tetramethylpiperidine (Scheme 8).[1e]



Scheme 11

The formation of the sulfonamide **25** during the attempted preparation of **24** is unusual, but can formally be depicted as occurring in a one step process through a transition structure **28** (Scheme 12). An alternative stepwise process can be imagined with initial formation of the ion pair **29** which could recombine to form the transient tosylate **30** which cleaves with rearrangement to acetone and the observed product **25** (Scheme 12). These seem to be improbable reactions to occur in solution, but may be promoted during silica gel chromatography.



24 **29** **30** **25**

Scheme 12

In summary the value of the use of highly ionizing, non-nucleophilic solvents to promote ionic reactions of *N*-acyl amines is demonstrated, and the formation of the iminium ion **19** of 2,2-dimethylpyrrolidine is established. An unusual fragmentation-rearrangement of *N*-sulfonyloxy amines has apparently been observed. Discrete nitrenium ions need not occur in these reactions, as the products can arise from concerted reactions forming iminium ions.

Experimental Section

General Procedures. Chromatography was carried out on silica gel. Solutions for reactions of TEMPO products were degassed and handled under argon or nitrogen. Gas chromatography (GC) was carried out with a PE Autosystem XL instrument with a flame ionization detector and programmable split-splitless capillary injector and a Supelco Simplicity 5 (5% phenyl 95% methylpolysiloxane) column. *N*-hydroxy-2,2,6,6-tetramethylpiperidine (**21**) was prepared as described previously.[4j]

Compound characterization

***N*-2,2,6,6-Tetramethylpiperidinyl 4-nitrobenzoate (23).** 4-Nitrobenzoyl chloride (0.84 g, 5 mmol,) in CH_2Cl_2 (2 mL) was added to a stirred mixture of *N*-hydroxy-2,2,6,6-tetramethylpiperidine[4j] (**21**, 0.84 g, 5 mmol) and Et_3N (0.69 mL, 5 mmol) in CH_2Cl_2 (35 mL) and stirred 20 min, and 10% HCl (25 mL) was added. The organic layer was washed with $NaHCO_3$ (3 x 15 mL) and brine, and dried over $MgSO_4$, and concentrated. Chromatography (silica gel, CH_2Cl_2) gave **23** (1.2 g, 78%) as white crystals, mp 129-132 ^oC. ^1H NMR (400 mHz, $CDCl_3$) δ 1.10 (s, 6), 1.27 (s, 6), 1.48-1.76 (m, 6), 8.21-8.32 (m, 4). ^{13}C NMR (100 mHz, $CDCl_3$) δ 16.9, 20.9, 31.9, 39.1, 42.8, 60.7, 123.6, 130.6, 135.2, 150.5, 164.6. IR ($CDCl_3$) 1745, 1528 cm^{-1}. EIMS *m/z* 306 (M^+), 291 (M^+ - CH_3), 156 (TO^+), 150 (M^+ -TO), 123, 83, 69, 55. HREIMS *m/z* calcd for $C_{16}H_{22}N_2O_4$ 306.1570, found 306.1580.

***N*-4-Toluenesulfonyl-2,2-dimethylpyrrolidine (25).** 4-Toluenesulfonyl chloride (1.2 g, 6 mmol) in CH_2Cl_2 (2 mL) was added to a stirred mixture of *N*-hydroxy-2,2,6,6-tetramethylpiperidine[4j] (1 g, 6 mmol) and Et_3N (0.88 mL, 6 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC and stirred 20 min, and 10% HCl (30 mL) was added. The organic layer was washed with $NaHCO_3$ (3 x 15 mL) and brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, CH_2Cl_2) gave **25** (0.1 g, 6%) as white crystals, recrystallized from hexane, mp 82-85 ^oC. ^1H NMR (400 mHz, $CDCl_3$) δ 1.47 (s, 6), 1.79-1.86 (m, 4), 2.44 (s, 3), 3.42 (t, 2, J = 6.4 Hz) 7.30 (d, 2, J = 8.4 Hz), 7.75 (d, 2, J = 8.2 Hz). ^{13}C NMR (100 mHz, $CDCl_3$) δ 21.5, 22.5, 28.3, 42.9, 49.3, 65.1, 127.1, 129.3, 142.5, 147.0. IR ($CDCl_3$) 1330, 1154, 1092 $cm^{-1.}$ EIMS *m/z* 253 (M^+), 238 (M^+ - CH_3), 156 (TO^+), 150 (M^+ -TO), 212, 155, 91 (Ts^+). HREIMS *m/z* calcd for $C_{13}H_{19}NO_2S$, 253.1142, found 253.1137. When the preparation was repeated with 2 equivalents of *N*-hydroxy-2,2,6,6-tetramethylpiperidine **25** was obtained in 65% yield.

***N*-2,2,6,6-Tetramethylpiperidinyl 4-toluenesulfonate (24).** In one experiment recrystallization of the crude product from the preparation as for **25** gave **24** as pale orange crystals (65%). ^1H NMR (400 mHz, $CDCl_3$) δ 1.41 (s, 6), 1.57 (s, 6), 1.80-1.92 (m, 6), 2.37 (s, 3), 3.42 (t, 2, J = 6.4 Hz) 7.22 (d, 2, J = 7.9 Hz), 7.79 (d, 2, J = 8.2 Hz). ^{13}C NMR (100 mHz, $CDCl_3$) δ 15.7, 20.0, 21.4, 28.3, 37.1, 68.1, 126.1, 129.1, 140.8, 141.1. IR ($CDCl_3$) 1389, 1232, 1122 $cm^{-1.}$ HRESMS *m/z* calcd for $C_{13}H_{19}NO_2NaS$ (M^+ + Na -C_2H_6O), 276.1034, found 276.1028.

Solvolysis of 23 in CF_3CO_2D. A solution of **23** (10 mg, 0.03 mmol) in CF_3CO_2D (1 mL) was degassed by bubbling N_2 through the solution for 5 min (the results were the same when the sample was not degassed) and was heated at 130 ^oC for 1 h in a sealed tube. The precipitated *p*-nitrobenzoic acid was filtered off, and the ^1H NMR spectrum in CF_3CO_2D indicated the presence of iminium salt **19b**. The solvent was evaporated, and the residue dissolved in $CDCl_3$, and identified as **19b**: ^1H NMR (400 mHz, $CDCl_3$) δ 1.63 (s, 6, 2 $C\underline{\mathbf{H}}_3C$), 2.16 (s, 4, $2C\underline{\mathbf{H}}_2$), 2.48 (s, 3, $C\underline{\mathbf{H}}_3CN$), 2.65 (s, 3, $C\underline{\mathbf{H}}_3CN$), 4.04 (s, 2, $C\underline{\mathbf{H}}_2CN$). ^{13}C NMR (100 mHz, $CDCl_3$) δ 21.4, 26.3, 287.9, 42.7, 57.9, 73.4 ($N(CH_3)_2\underline{\mathbf{C}}^+$), 123.9 (q, J_{CF} = 287.6 Hz,$\underline{\mathbf{C}}F_3$), 160.3 (m, $\underline{\mathbf{C}}OCF_3$), 187.0 ($N\underline{\mathbf{C}}(CH_3)_2$). ^{19}F NMR (CF_3CO_2D) δ -75.6. The NMR assignments were confirmed by COSY and CIGAR experiments. IR ($CDCl_3$) 1778 cm^{-1}. HRESIMS (*m/z*) calc for $C_9H_{18}N$ (M^+) 140.1441; found 140.1433. HRESIMS (*m/z*) calc for $C_2O_2F_3^-$ (M^-) 112.9860; found 112.9855.

2,2-Dimethylpyrrolidine (26). The solvent from the NMR experiments was evaporated and Et_2O (2 mL) was added. The solution was extracted with aq. KOH to remove traces of *p*-nitrobenzoic acid and to hydrolyze **19b** to **26**. Further extractions with Et_2O (3 mL in total) and short path distillation afforded **26** (70%). The structure of 2,2-dimethylpyrrolidine **26** gave spectral data in agreement with those reported:[9b] ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H, $2C\underline{\mathbf{H}}_3$), 1.53 (t, 2H, J = 7.5 Hz, $Me_2CC\underline{\mathbf{H}}_2$), 1.76-1.86 (m, 2H, $CH_2C\underline{\mathbf{H}}_2CH_2$), 2.97 (t, 2H, J = 6.9 Hz, $-NHC\underline{\mathbf{H}}_2-$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 25.3, 35.3, 43.5, 55.9. EIMS (*mz*) 99 (M^+), 84 (M^+-CH_3), 72, 55, 42. HREIMS (*mz*) calc for $C_6H_{12}N$ (M^+-H) 98.0965; found 98.0970. HRESIMS (*mz*) calc for $C_6H_{14}N$ (MH^+) 100.1125; found 100.1120.

The yield of acetone was obtained from a second run under the same conditions. After filtration of the *p*-nitrobenzoic acid the solvent CF_3CO_2D was evaporated, and the crude product was dissolved in $CDCl_3$ (1 mL), and was extracted with aq. KOH as before. The ^1H NMR of the hydrolyzed product was measured and the yield of acetone was calculated from the ^1H NMR integration compared with that of 2,2-dimethylpyrrolidine (**26**).

Solvolysis of 23 in $(CF_3)_2CHOH$, CF_3CH_2OD, and in CH_3OH. A solution of **23** (20 mg) in solvent (1 mL) was degassed by bubbling in N_2 for 5 min (without degassing the same results were obtained) and heated as shown in Table 1. The solvent was evaporated and the residual salt dissolved in $CDCl_3$, and the relative yields of 2,2-dimethylpyrrolidine (**26**) and tetramethylpiperidine (**4**) were obtained using ^1H NMR. The solution was partitioned between KOH solution and ether, and the ether layer was quantitatively analyzed by gas chromotography for tetramethylpiperidine (**4**). Methyl 4-nitrobenzoate was separated by chromatography and weighed.

Acknowledgements

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