INTRAMOLECULAR [2+2] CYCLOADDITIONS OF KETENIMINIUM SALTS DERIVED FROM α- AND β-AMINO ACIDS. A ROUTE TO AZABICYCLIC KETONES.‡

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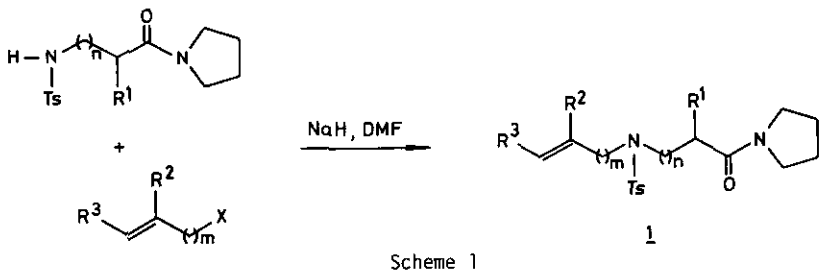
Abstract - Unsaturated N-tosylaminoketeniminium salts generated in situ from α- and β-aminoamides readily underwent intramolecular [2+2] cycloadditions to give azabicyclic ketones in good yields.

Intramolecular [2+2] cycloadditions of ketenes and keteniminium salts have recently been shown to be valuable reactions for the stereocontrolled synthesis of polycyclic molecules[1]. The preparation of 3-azabicyclo[3.2.0]heptenones from ω-unsaturated iminoketenes is an illustration of the potential of the method for the synthesis of heterocyclic compounds[2]. Keteniminium salts represent an attractive alternative to ketenes for cycloaddition with alkenes[3] because they are more electrophilic and also offer easy access to chiral cyclobutanones[4]. However nothing was known about the generation and fate of keteniminium salts bearing protected α- or β-amino substituents. These were of interest to us for the synthesis of α-aminocylobutanones as analogs of β-lactam antibiotics. We have found that keteniminium salts derived from α and β-N-tosylaminoamides can be generated and effectively trapped intramolecularly by double bonds.

Unsaturated N-tosylaminoamides 1 were prepared by alkylation of N-tosylaminoamides[5,6] with an appropriate bromide or mesylate 2 in the presence of NaH in DMF at 90-100°C (Scheme 1).

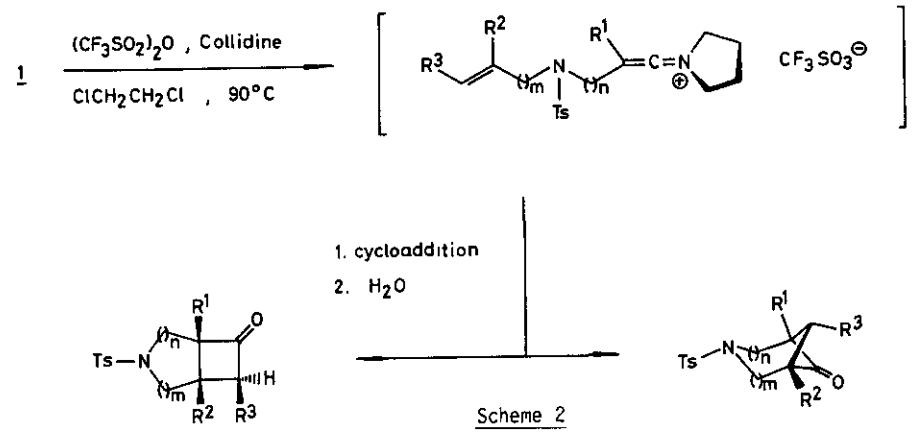


2 1

Scheme 1

Treatment of 1 with triflic anhydride[7] in 1,2-dichloroethane followed by slow addition of collidine yielded a solution of the iminium salt which was then heated at 90°C for 90 min. Hydrolysis yielded ketonic products which were purified by chromatography on silica gel (AcOEt - cyclohexane 1:1 to 1:3)[8] (Scheme 2).

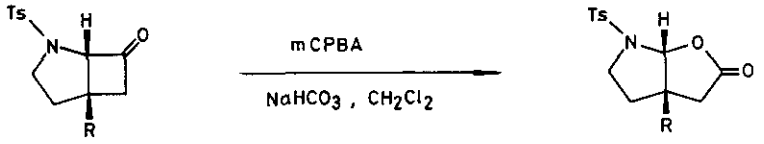
‡ Dedicated to Professor Sir Derek Barton on the occasion of his seventieth birthday.



Scheme 2

Table 1 summarizes our results to date. In all cases the [2+2] cycloadducts are the major products and are obtained in good yields. In one case (entry b) we isolated a small amount of a monocyclic ketone resulting from Friedel-Crafts acylation. The position of the nitrogen atom has little effect upon the reaction. Elimination of N-alkyltosylamide from β-aminoamides or the corresponding iminium salts (entries d to h) is obviously not an important side-reaction. Alkene substitution plays a significant role in the regiochemistry of the reaction as previously shown for other intramolecular cycloadditions[1]. Substrates with no substituent on the double bond (entries a,c,d,g,h) or in which the internal alkene carbon bears a methyl group (entries b,e) gave the adducts resulting from attack of the more nucleophilic terminal carbon atom on the C-1 atom of the keteniminium salt. Small amounts of the regioisomeric adducts were isolated in three cases (entries c, d and g). On the other hand, compound 1f, in which the terminal olefinic carbon atom bears a methyl group, gave 7-methyl-3-azabicyclo[3.1.1.]heptan-6-one as the major adduct. This compound results from attack of the internal alkene carbon on the C-1 atom of the keteniminium salt. Thus, when there is no directing electronic effect, a six-membered transition state is preferred over a seven-membered transition state. α-Substitution does not affect product distribution but significantly lowers the reaction rate.

Compounds 3a,b were submitted to standard Bayer-Villiger conditions (Scheme 3). In spite of the presence of the strongly electron-withdrawing tosyl group on the nitrogen, ring expansion took place regiospecifically with migration of the C-C bond α to the nitrogen atom.



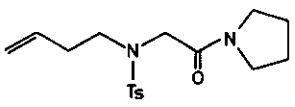
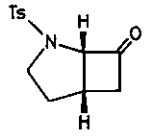
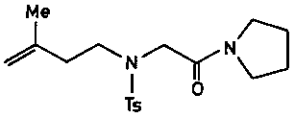
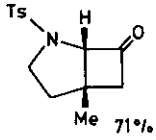
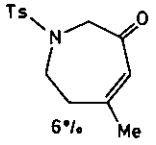
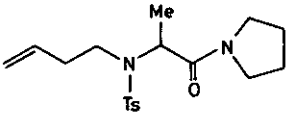
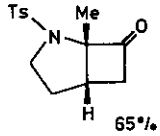
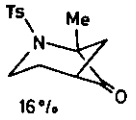
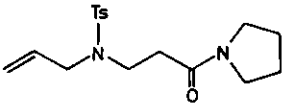
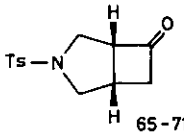
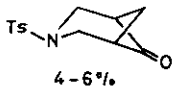
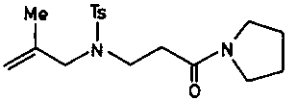
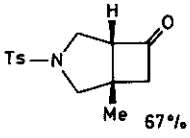
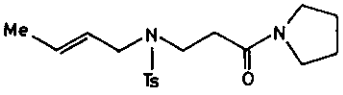
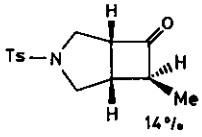
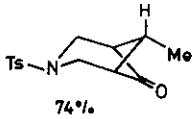
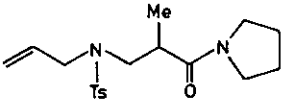
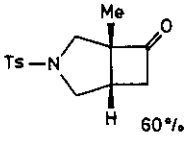
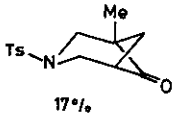
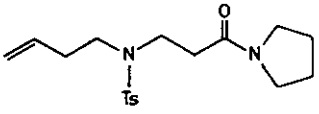
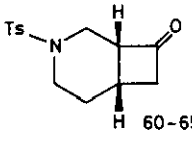
3 4

a. R = H 92%

b. R = Me 90%

Scheme 3

Table I : Intramolecular cycloadditions of keteniminium salts derived from α- and β-amino amides

Entry	Amide 1	Product
a		 56%
b		 71%  6%
c		 65%  16%
d		 65-71%  4-6%
e		 67%
f		 14%  74%
g		 60%  17%
h		 60-65%

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6. The N-tosylaminoacid (5) in methanol is treated with thionyl chloride and the reaction mixture is heated, if necessary, to complete the esterification. The ester obtained is dissolved in pyrrolidine (7 equivalents) and the mixture is heated to reflux for several hours. The N-tosylaminoamide is obtained in an overall yield of 80-90%.
7. Typical procedure in a dried vessel and under dried nitrogen : A solution of amide 1e (596 mg, 1.7 mM) in 1,2-dichloroethane (17 ml) is added over 20 min to a solution of triflic anhydride (2.55 mM, 719 mg) in 17 ml of 1,2-dichloroethane. A solution of collidine (1.87 mM, 227 mg) in 1,2-dichloroethane (17 ml) is then added slowly over 30 min. After addition is completed the reaction mixture is heated at 90°C for 2 h. After cooling to room temperature, the reaction mixture is concentrated under vacuum. The residue is hydrolyzed in a two phases system H_2O-CCl_4 (20 ml/20 ml) at reflux for 2 h. The reaction mixture is decanted and the aqueous layer is extracted with 3x20ml of CCl_4. The organic layers are dried over magnesium sulfate and concentrated under vacuum. The residue is chromatographied on silica gel (AcOEt : cyclohexane, 1:2) to give 329 mg (69% yield) of pure 1-methyl-3-azabicyclo[3.2.0]heptan-6-one.
8. All new compounds have been fully characterized by ir, ^1H nmr (200 MHz), ^{13}C nmr, mass spectroscopy and elemental analysis.

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