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2-Phenyl-*N*-tosylazetidine as a formal 1,4 dipole precursor†‡

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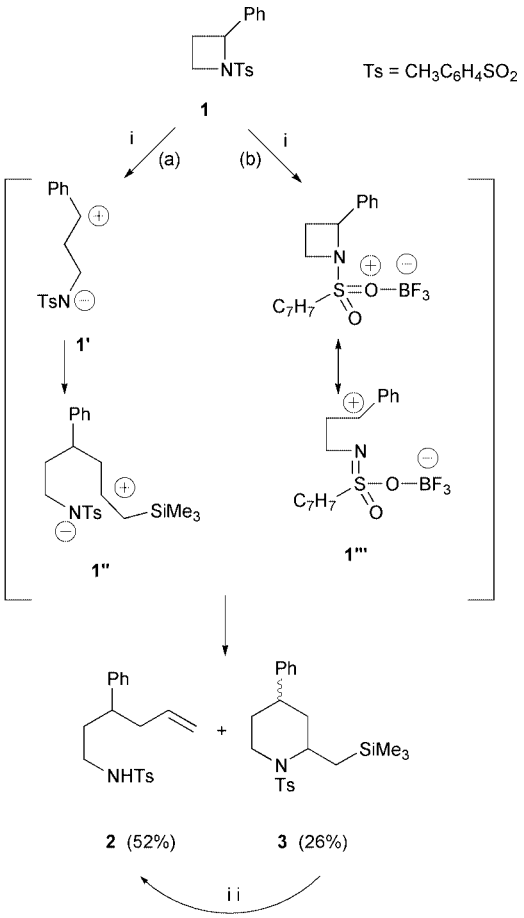
_N_-Tosyl-2-phenylazetidine 1 in the presence of $BF_3{\cdot}Et_2O$ reacts as a formal 1,4 dipole with various activated or non activated alkenes.

Recently we reported that phenyl-*N*-tosylaziridines, in the presence of Lewis acids generate a double *exo* stabilized 1,3 dipole, suitable for [3 + 2] dipolar cycloadditions.[1] If the concept of dipole with *exo* stabilisation could be extended to phenyl-*N*-tosylazetidine **1**,[2,3] a zwitterionic or 1,4 dipole **1′** would be produced. Herein we present evidences for the existence of **1′** and several examples of its utilisation in [4 + 2] cycloaddition reactions (Scheme 1).

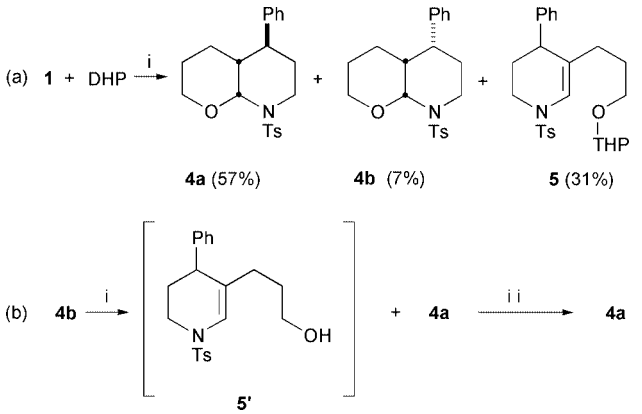
If azetidin-2-ones have received considerable attention, activity on the related azetidines has been less fevered.[4–6] As the benzylic C–N bond in **1** can be regioselectively broken,[7] we speculated that conditions might be found to open the azetidine ring and to realize complete charge separation, producing a transient dipole **1′**. This putative 1,4 dipole **1′** can be described as follows:[8] **1′** is a dipole of zwitterionic type according to the Huisgen's classification[3] with the two charges stabilized in an *exo* manner by the benzyl and tosyl groups. Indeed 1,4 dipole **1′**, if opposed to olefins, could represent a device to realise a formal *carboamination* for the rapid construction of azaheterocycles (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) allyltrimethylsilane $BF_3{\cdot}Et_2O$, −78 °C, CH_2Cl_2; (ii) TBAF, THF (95%).

For the generation of the dipole **1′** we expected that a Lewis acid might cause the desired charge separation.[1] To trap both the benzylic carbocation and the amide function in the elusive dipole **1**, we chose allyltrimethylsilane as a 'probe'.[9] Indeed, azetidine **1** reacts with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$. The obtained allylated product **2** and silylated piperidine **3** may have a common intermediate, a 1,6 zwitterion **1″**. If desired, the conversion of piperidine **3** to allylamine **2** can be performed in refluxing THF with TBAF [pathway (a) in Scheme 1]. However, a slightly different mechanism can also be proposed: BF_3 activates the oxygen (or nitrogen atom) of the sulfonamide function, the formed intermediate **1‴** is then ready for a nucleophilic attack at the benzylic cation operated by allylsilane and subsequent intramolecular capture or desilylation of the newly formed cation can then produce either **2** or **3** [pathway (b) in Scheme 1]. If from a theoretical point of view there is a great difference between a naked dipole such as **1′** and a more conventional zwitterion such as **1‴**, in practice the observed reactivity of **1** is best explained using the simplified intermediate **1′**.

According to our previous experience, dihydropyran (DHP) seems to be a better reagent than allylsilane for a dipole 'capture'.[1,10] Indeed in the presence of $BF_3{\cdot}Et_2O$ and a threefold excess of DHP, **1** is quantitatively transformed into three adducts **4a**, **4b** and **5**, but the chemical events are more complex than expected. A [4 + 2] cycloaddition takes place. The formation of the adducts **4a** (*exo*), **4b** (*endo*) and **5**, a di-substituted tetrahydropyridine with a pyranyl appendage, are accounted for by Scheme 2a. The structure of **4a** was obtained by a single crystal X-ray analysis.[11]



Scheme 2 *Reagents and conditions*: DHP, $BF_3{\cdot}Et_2O$, −78 °C, CH_2Cl_2; (ii) pTSA, toluene, reflux.

† This paper is dedicated to Professor Camille-Georges Wermuth.

‡ Electronic supplementary information (ESI) available: experimental details and characterization for key intermediates, including the ORTEP figures of the X-ray structures for compounds **4a** and **10**. See http://www.rsc.org/suppdata/cc/b1/b101168p/

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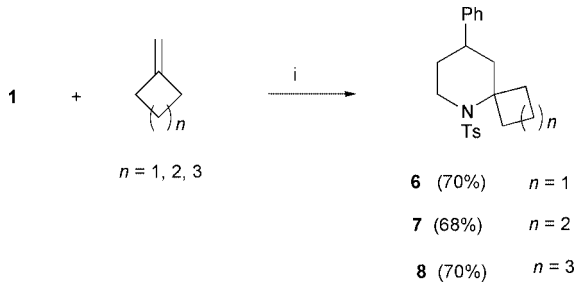
The formation of **5** is best explained in the following way: under the reaction conditions the pyranyl ring in **4a** and/or **4b** is opened through an immonium/enamine acid catalysed process and the transiently formed alcohol **5′** is trapped by the excess of DHP present in the reaction mixture. In fact we suspect that the major pathway which produces **5** is the transformation of **4b**. Indeed in complementary experiments, we verified the stability of the two cycloadducts **4a** and **4b** in presence of $BF_3{\cdot}Et_2O$ at −78 °C. After 30 min **4a** was recovered unchanged, while **4b** was completely transformed into **4a** and **5′**, as shown by the analysis of the crude reaction mixture by NMR. Now if heated in toluene in the presence of pTSA, the mixture of **4a** and **5′** is totally converted to **4a** (Scheme 2b). Therefore it can be concluded that the reaction between **1** and DHP is a sequence of equilibria, the thermodynamic bicycle **4a** surviving under the reaction conditions, whereas **4b** evolves to **5** *via* **5′**. It should be noted that only the *cis* aza, oxo [4.4.0] bicycle was observed because the geometrical condition required for a maximal anomeric effect is accomplished only in a *cis* aza, oxo [4.4.0] bicycle.[12] Finally, it has to be emphasized that the chemical potentialities of **4a** as N,O acetal are considerable.[13]

Another question which was addressed: does **1′** react with simple non-activated double bonds? We selected commercially available exomethylene cycloalkanes (cyclobutane, pentane, and cyclohexane) as partners for **1**. In this case the formation of spiropiperidines was precisely anticipated. Indeed the adducts isolated and characterised were respectively the spiro compounds **6**, **7** and **8** (Scheme 3). These results confirm nicely the reactivity of **1** as a formal 1,4 dipole in [4 + 2] cycloaddition to olefins and are in line with the results obtained with the corresponding aziridine.[1] This sequence constitutes a new and rapid entry to spiropiperidine rings.

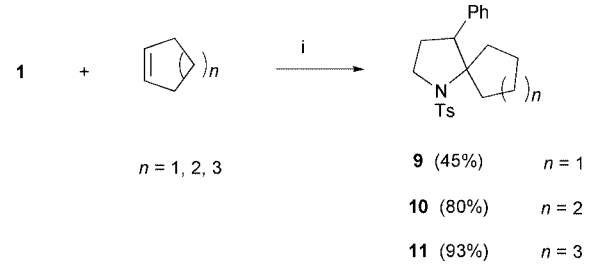


Scheme 3 *Reagents and conditions*: $BF_3{\cdot}Et_2O$, −78 °C, CH_2Cl_2.

The results from using cycloalkenes (cyclopentene, cyclohexene, cycloheptene) as 'dipolarophiles' were a surprise: cycloalkenes reacted with azetidine **1** in the presence of $BF_3{\cdot}Et_2O$, but no trace of the expected [4 + 2] cycloaddition products was observed. A complete NMR analysis of the obtained products showed the exclusive formation of spiro-pyrrolidines **9**–**11**. The single crystal X-ray analysis of **10**[14] confirmed the structural assignment made by NMR (Scheme 4). These unexpected results are best explained if the two following arguments are considered: hydride shift is assumed to provide the intermediate with the more stable tertiary (carbocation in respect to the secondary) and the formation of **9**–**11** is accounted for by the preferential formation of five over six-membered rings. These results are in sharp contrast with those for the corresponding aziridine where [3 + 2] cycloaddition was always the major pathway.[1]

Finally the formation of spiro-pyrrolidines results from a formal [4 + 1] cycloaddition of dipole **1′**. The hydride shift can be seen as additional proof for a stepwise, not concerted, mechanism of cycloaddition reactions of **1** on non-activated 1,2 disubstituted double bonds. *To the best of our knowledge no examples of such a reaction have been reported.* This sequence is a new entry to spiro-pyrrolidines, which constitute the core of some natural products.[15]

In summary, in this work we demonstrate that the 1,4 dipole **1′** with double *exo* stabilisation is accessible from azetidine **1**; **1′** reacts under mild conditions with several olefins to produce spiro-pyrrolidines or -piperidines by [4 + 2] or formal [4 + 1] cycloadditions; **1′** reacts with DHP to produce aza oxo [4.4.0] bicycles which are valuable intermediates. Finally, azetidine **1** allows, in one chemical step, a new and unique entry to azaheterocycles.



Scheme 4 *Reagents and conditions*: $BF_3{\cdot}Et_2O$, −78 °C, CH_2Cl_2.

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11 The X-ray structure and coordinates for compound **4a** have been deposited at the Cambridge Crystallographic Database, CCDC 142897. See http://www.rsc.org/suppdata/cc/b1/b101168p/ for crystallographic files in .cif format. *Crystal data* for **4a**: $C_{21}H_{25}NO_3S$, M = 371.50, triclinic, space group: $P\bar{1}$, a = 7.6170 (4), b = 11.0840 (6), c = 12.3600 (6) Å, U = 982.9 Å^3, T = 294 K, Z = 2, μ(Mo-K) = 0.184 mm^{-1}, 8028 measured reflections, 2079 unique (R_{int} = 0.04). The final $wR(F2)$ was 0.057 (all data).

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14 The X-ray structure and coordinates for compound **10** have been deposited at the Cambridge Crystallographic Database, CCDC 142898. See http://www.rsc.org/suppdata/cc/b101168p/ for crystallographic files in .cif format. *Crystal data for* **10**: $C_{22}H_{27}NO_2S$, M = 369.59, monoclinic, space group P 1 21/n 1, a = 9.4881 (3), b = 18.6503 (8), c = 11.1767 (5) Å, U = 1937.2 Å^3, T = 293 K, Z = 4, μ(Mo-Kα) = 0.184 mm^{-1}, 10796 measured reflections, 3037 unique (R_{int} = 0.04). The final $wR(F2)$ was 0.067 (all data).

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