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Efficient Generation and [3+2] Cycloaddition of Cyclic Azomethine Ylides: A General Synthetic Route to X-Azabicyclo (m.2.1) Alkane Framework.

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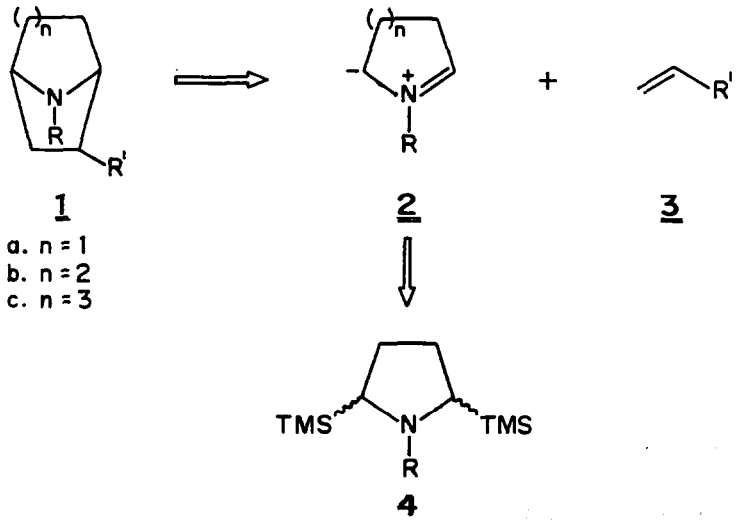
Abstract: *An efficient method of cyclic azomethine ylide generation and their application in synthesizing x-azabicyclo (m.2.1) alkanes has been described.*

Due to the wide variety of biological activities exhibited by compounds possessing x-azabicyclo (m.2.1) alkane skeleton (**1**, x=7, 8 and 9), their syntheses have occupied a prominent position as targets for organic chemists[1-3]. In recent years, a resurgence of interest has also surfaced in the synthesis of structural derivatives of **1b** owing to the recognition of their utility in probing the study of the neurochemistry of cocaine abuse[4]. Therefore, an expeditious and general route to compounds **1** having functionalities amenable to derivatisation would be highly desirable. As these compounds possess a bridged pyrrolidine ring system, a promising synthetic approach can be envisaged through the [3+2]-cycloaddition of the corresponding cyclic azomethine

SCHEME-I



ylide[5] **2** with dipolarophile **3** as shown in **SCHEME-I**. However, the major impediment in exploiting this strategy had been the inaccessibility[6] of the ylide **2**.

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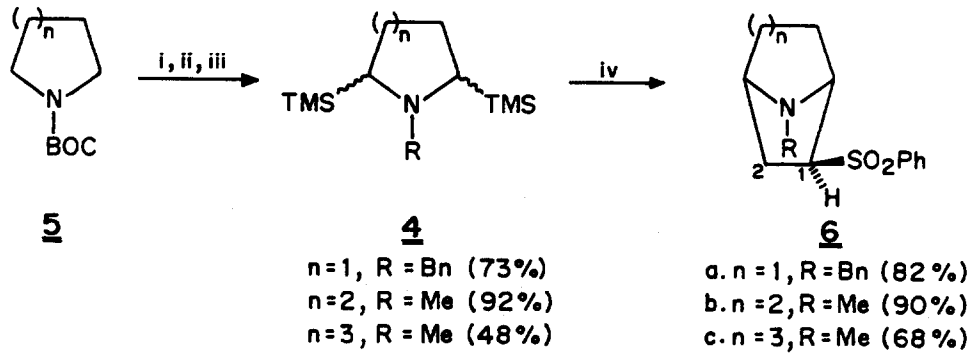
Encouraged by our recent success[7] of non-stabilized azomethine ylide generation by a sequential double desilylation strategy, we envisioned the same approach for the generation of **2**, from **4**,by an analogous reaction with Ag(I)F. We are pleased to disclose our success in this communication.

The desired precursors **4** were easily prepared in good yield (48-92%) from corresponding amines **5** as shown in **SCHEME-II**. The general experimental procedure for the generation and cycloaddition of **2** consists of the addition of **4** (1 equiv) to a stirred mixture of Ag(I)F (2 equiv) and phenylvinylsulfone (1.2 equiv) in dry acetonitrile under an argon atmosphere at room temperature. Instant precipitation of Ag(0) metal was noticed and after an additional 15-20 minutes of stirring, the contents were decanted and filtered through a pad of celite. Evaporation of CH_3CN gave cycloadducts **6** in 68-90% yield.These were further purified by column chromatography and characterised by ^1H NMR, ^{13}C NMR and mass spectral data[8].

SCHEME-II



5 **4** **6**

n=1, R = Bn (73%) a. n = 1, R = Bn (82 %)
n=2, R = Me (92%) b. n = 2, R = Me (90%)
n=3, R = Me (48%) c. n = 3, R = Me (68 %)

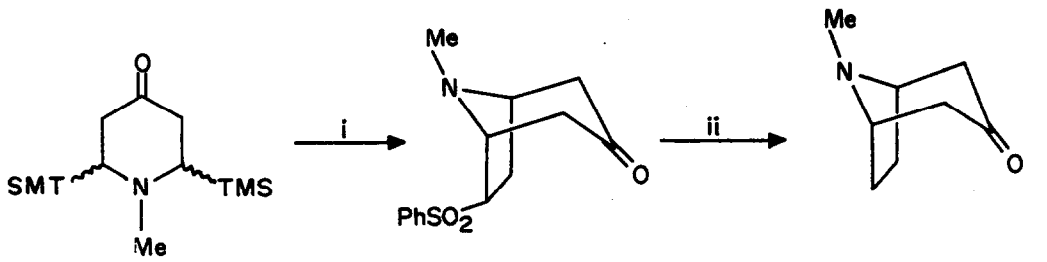
(i) Ether, TMEDA, Sec-BuLi, -78°C, TMSCl, 3h, Repeat of Sequence; (ii) TFA, DCM, 5°C, 30 min.; (iii) Benzylation or Methylation; (iv) Acetonitrile, Ag(I)F, Phenylvinylsulphone, R.T., 15-20 min.

The *exo*-position of the phenyl sulphonyl group in adduct **6a** was elucidated by extensive proton decoupling experiments between H-1, H-2 and the bridgehead protons. H-1 is found to couple only with H-2 (*exo* and *endo*) but not with the bridgehead protons, which is in agreement with the reported[1b] ^1H NMR pattern of an analogous compound. The stereochemistry of **6b** was suggested by its similar ^1H NMR pattern. However, the ^1H NMR spectrum of **6c** indicated it to be a mixture of two diastereomers (*exo*:*endo* = 3:1), which is likely due to the relative stabilities of *exo*- and *endo*- transition states of conformationally flexible hexamethyleneimine ring system.

These successes led us to apply this strategy for the synthesis of tropinone[9] **9**, an important member of the tropane class of alkaloids. To this end, compound **8** was first synthesized (92%) by the reaction (**SCHEME-III**) of Ag(I)F with **7** and phenylvinylsulphone in an identical way as described for **4**. Compound **7** was easily obtained by following the methodology as described earlier, from commercially available 4-hydroxy piperidine. A typical desulphonylation reaction[10] of **8** was performed by stirring with Raney nickel

in ethyl acetate and gave **9** (90%). Compound **9** gave satisfactory ^{1}H NMR, ^{13}C NMR and mass spectral data.

SCHEME-III



7 8 (92%) 9 (90%)

(i) Acetonitrile, Ag(I)F, Phenylvinylsulphone, R.T., 20 min.; (ii) Raney Ni, Ethylacetate, R.T. 4 h.

In conclusion, we have demonstrated an efficient and unprecedented strategy for cyclic azomethine ylide generation and its utilization in the synthesis of biologically important compounds having the x-azabicyclo(m.2.1) alkane skeleton. Further application of this methodology for the synthesis of (±)-Ferruginine[11] and (±)-Anatoxin[12] is in progress and will be presented in full paper.

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(8) **6a**: ^{1}H NMR($CDCl_3$, 200 MHz): δ1.35-1.45 (m,1H), 1.72-1.85 (dd,1H,J=9.40 & 14.30 Hz), 1.85-2.15 (m,3H), 2.18-2.28 (m,1H), 3.18 (dd,1H,J=4.75 & 9.40 Hz), 3.26-3.38 (m,1H), 3.45 (AB quartet,2H), 3.76 (d,1H,J=4.76 Hz), 7.02- 7.15 (m,2H), 7.22-7.35 (m,3H), 7.47- 7.72 (m,3H), 7.83-8.02 (m,2H). ^{13}CNMR($CDCl_3$, 50.4 MHz): δ25.85, 27.26, 33.83, 51.28, 58.80, 61.39, 68.78, 127.12, 128.36, 128.57, 129.18, 129.42, 133.10, 139.36, 139.46. MS m/e: 327(M^+), 186(100%), 158, 91.

6b: ^{1}H NMR($CDCl_3$, 200 MHz): δ1.46-1.76 (m,3H), 1.82-2.10 (m,4H), 2.55 (s,3H), 2.55-2.65 (dd,1H,J=7.3 & 12.18 Hz), 3.32-3.40 (m,1H), 3.55-3.66 (dd,1H,J=7.3 & 9.74 Hz), 3.75 (bs,1H), 7.55-7.75 (m,3H), 7.79-8.20 (m,2H). ^{13}CNMR($CDCl_3$, 50.4 MHz): δ16.88, 27.01, 28.19, 30.79, 38.37, 61.63, 62.32, 69.02, 128.54, 129.34, 133.55, 139.63. MS m/e: 265(M^+), 124(100%), 97, 84.

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