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Ag(I)F as One Electron Oxidant for Promoting Sequential Double Desilylation : An Ideal Approach to Non-Stabilized Azomethine Ylides for the Rapid Construction of 1-Azabicyclo (m:3:0) Alkanes

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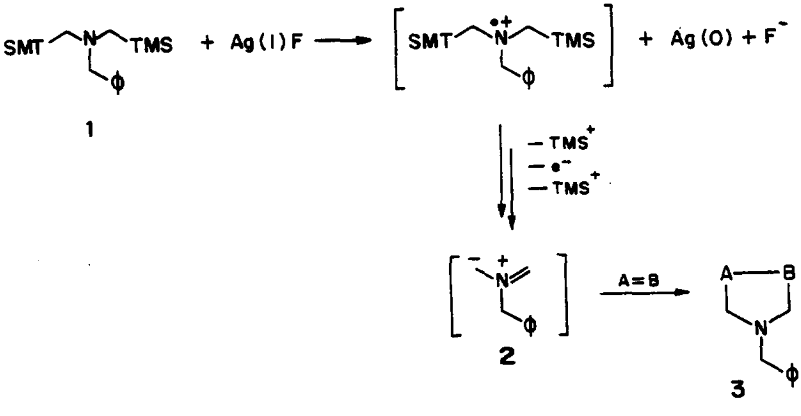
Abstract: *A novel methodology for effecting sequential double desilylation by Ag(I)F for the generation of non-stabilized azomethine ylide and its application for the synthesis of 1-azabicyclo(m.3.0) alkane systems are described.*

Construction of stereospecifically substituted pyrrolidine[1] ring system by 1,3-dipolar cycloaddition of non-stabilised azomethine ylide[2] has been recognised as elegant approach. Considerable efforts have been devoted to developing simpler and more efficient routes for generating these intermediates[3]. While the fluoride ion mediated desilylation strategy of Vedejs[4] and Padwa[5] are significant, they lack convenience due to the inefficient process[4] or the requirement of toxic KCN for precursor synthesis[5]. Moreover, these approaches are restricted and lack flexibility for application to a diverse range of alkaloid syntheses. Our photoinduced electron transfer (PET) strategy[6] suffers from the limitation of scale-up and through-put. We report herein an alternative strategy to effect sequential double desilylation to generate **2** from **1** using Ag(I)F as a one electron oxidant which is extremely efficient, provides quantitative yield of cycloadducts upon trapping with dipolarophiles, and can be performed on a multigram scale. To the best of our knowledge, this is the first report of Ag(I)F mediated one electron oxidation of silylated amines as shown in **SCHEME-I.**

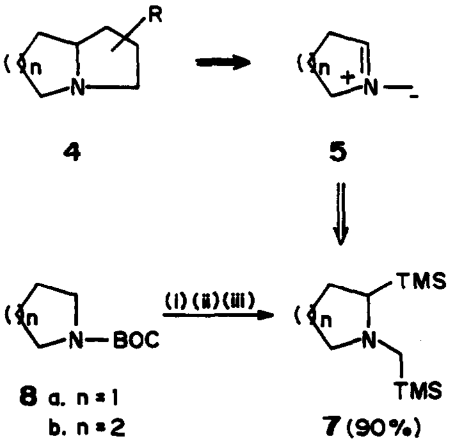
SCHEME - I



A typical reaction procedure consists of the addition of **1** (1 equiv) to a stirring solution of Ag(I)F (2 equiv) containing the appropriate dipolarophile (1.2 equiv)[7] in dry acetonitrile under an argon atmosphere. Instant reaction commences with concomitant deposition of Ag(0) metal on the walls of the reaction flask and the reaction is completed within 10-15 minutes. The corresponding cycloadducts **3** are obtained in quantitative yield simply by decanting and filtering the reaction mixture through a plug of celite followed by evaporation of acetonitrile under reduced pressure.

Encouraged by these results, we envisioned generating ylide **5** from the disilylated amine **7** in order to synthesize the indolizidine[8,9] and pyrrolizidine[10] skeletons **4**, which are endowed with an array of biological activities. Although the efforts of Vedejs[11], Roussi[12] and Achiwa[13] are important in this context, their methodologies often leads to poor yields of cycloadducts **4**. Starting amines **7a-b** are synthesized in >90% yield in three steps starting from corresponding Boc-protected amine **8a-b** as illustrated in **SCHEME-II**.

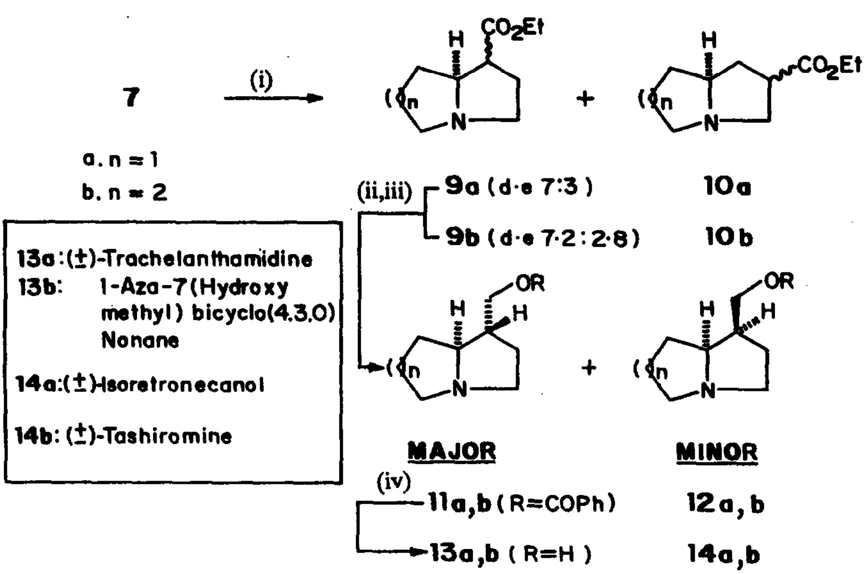
SCHEME-II



i) ether, TMEDA, Sec-BuLi, -78°C, Me_3SiCl, 3h. ii) TFA, CH_2Cl_2, 5°C, 30 min. iii) Me_3SiCH_2Cl, K_2CO_3, CH_3CN, reflux, 4h.

An analogous reaction of Ag(I)F on a mixture of **7** (exemplified with **7a**) and ethyl acrylate provided two regioisomeric pyrrolizidines **9** and **10** in 17:3 ratio, determined by capillary GC (methyl silicone, fused silica, 10mts) analysis, in 98% combined yield. The ^{13}C NMR of major isomer **9**, isolated by careful chromatography over silica gel, suggested it was a mixture of two diastereomers due to the observation of two pairs of carbon signals for C_1 (at δ 68.3 and 65.9) and C_8 (at δ 50.5 and 47.5). Comparison of these values with the reported[13] spectral data of **9**, indicated it to be the mixture of cis-(*endo*) and trans-(*exo*) adducts. The diastereomer ratio of these adducts was established by resolving on a long capillary GC column (methyl silicone, fused silica, 50 mts). Since the isolation of pure diastereomers proved difficult the mixture was reduced by lithium aluminium hydride to corresponding alcohols, which upon derivatization with benzoyl chloride were separated to give pure diastereomers **11** (major) and **12** (minor) by column chromatography using pet.ether:acetone (93:7) as eluant. The stereochemical assignments of **11** and **12** is suggested on the basis of the comparision of spectral characteristics of debenzoylated products **13** and **14** with the literature[14] values of (±)-trachelanthamidine (**13a**) and (±)-isoretronecenol (**14a**). A similar sequence from **7b** provided a short synthesis of the indolizidine natural products, 1-aza-7-(hydroxy) bicyclo [4:3:0] nonane[15a] (**13b**) and (±)-tashiromine[15b] (**14b**) as shown in SCHEME-III.

SCHEME-III



i) Ag(I)F, ethyl acrylate, CH_3CN, r.t. 15 min. ii) LAH, THF, r.t. 3h. iii) Et_3N, THF, PhCOCl, r.t. 8h. iv) 1% NaOH, MeOH.

The mechanism of ylide generation involves sequential electron-TMS^+- electron transfer processes from amines 1 and 7 to Ag(I)F in a similar manner to that reported[6] by us previously. The instant reduction of Ag(I)F to Ag(0) metal during the reaction, similar to Koser's[16] observation of strained hydrocarbon oxidation promoted by Ag(I) salts, supports the electron transfer (ET) mechanism for these transformations. Initiation of desilylation processes from 1 with $Ag(I)ClO_4$[17] and the failure of CsF to start the reaction rules out the possibility of fluoride ion mediation in these reactions. The ET mechanism is further substantiated by observing no reaction with disilylated amine carbamates[18]. The evalution of thermodynamic parameters utilizing the oxidation potentials of amines 1 and 7 and reduction potential of Ag(I)F, to confirm the mechanism, is in progress and will be reported in a full paper.

Several advantages of this methodology are worthy of mention. The reaction is efficient and the ylides gave high yields of cycloadducts. The cost of Ag(I)F should not be considered a limitation of the strategy, as the expensive Ag(0) metal is recovered after the reaction.

In conclusion, a practical and efficient methodology for the generation of non-stabilized azomethine ylides has been developed. The process is versatile and useful for the large scale[19] preparation of isolated and fused pyrrolidine moieties. Our effort continues to find a cheaper oxidant to initiate these reactions and apply the chemistry to the synthesis of structurally complex alkaloids.

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19. Trapping of **2** with ethyl acrylate to give corresponding pyrrolidine have been performed successfully by using upto 10g of 1.

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