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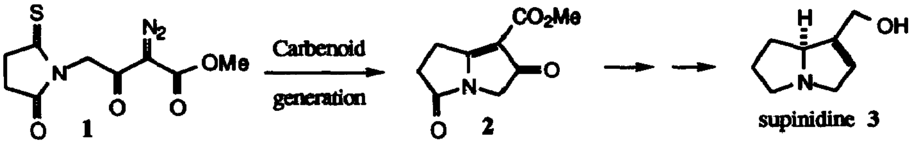
A Synthesis of (±)-Supinidine *via* an Intramolecular Carbenoid-Thioimide Coupling Reaction

Guncheol Kim*, Sunwha Kang and Gyochang Keum

Hanhyo Institutes of Technology, San 6, Daeyadong, Siheungshi, Kyunggido, S.Korea, 429-010

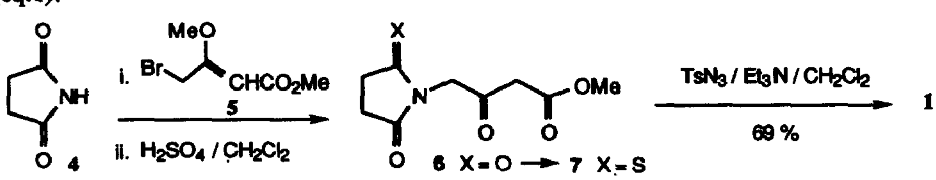
Abstract: *Intramolecular diazoketoester-thioimide annulation reaction in the presence of rhodium(II) acetate dimer provided a new way to pyrrolizidine skeletones. (±)-Supinidine was synthesized by subsequent manipulations.*

The chemistry of sulfur ylides which can be easily formed from the reaction of cabenoids and divalent sulfurs and rearrange to various structures has been increasingly investigated.[1,2] Recently, thiocarbonyl ylides have shown their potential as useful intermediates for the synthesis of a variety of alkaloids.[3] In the synthesis using these intermediates the desired structures are furnished by subsequent rearrangements of ylides followed by Raney Ni reduction or thermal extrusion of sulfur atom. In this letter we describe a new route to pyrrolizidines by exploiting diazoketoester-thioimide cyclization through its ylide intermediate and an application to the synthesis of (±)-supinidine 3.



(1)

Pyrrolizidine alkaloids which exhibit a wide range of pharmacological activities[4] have been unabating targets for synthesis.[5] For the synthesis of pyrrolizidines many routes for the skeletones have been developed, and appropriate functionalities in the skeletons have facilitated their ways to final products. In this design we suggest monothioimide 1 having a diazoketoester group as a key intermediate. Upon cyclization it would afford the properly functionalized 1-carbomethoxy-$\Delta^{1,8}$-dehydro-2,5-dioxo-pyrrolizidine 2. Then the allylic alcohol group of 3, a common subunit of the necine bases, should be easily installed by the subsequent manipulation of 2 (eq.1).

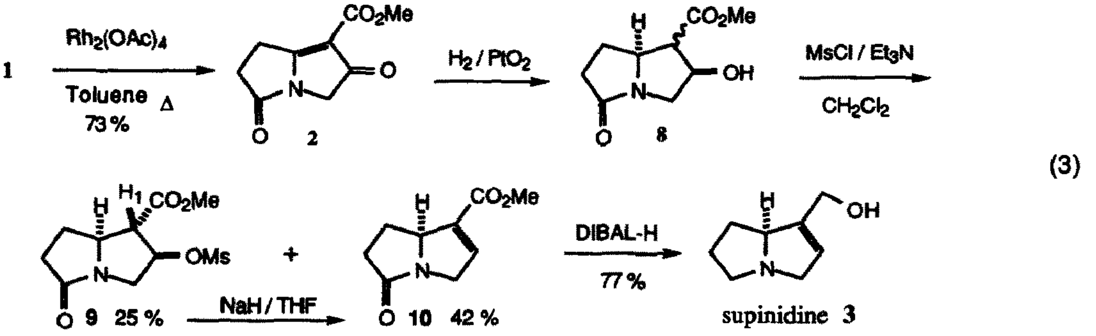


(2)

For this purpose diazoketoester 1 was prepared from ketoester 7 using p-toluenesulfonyl azide[6] as a diazo transfer reagent (69%), and 7 was obtained by three step sequence from succinimide 4 as follows. Treatment of 4 with 4-bromo-3-methoxy-2-butenoate 5[7] using NaH in DMF (88%) and hydrolysis with 2 eqv. of H_2SO_4 in CH_2Cl_2 afforded ketoimide 6 (94%). Practically the starting material succinimide was made as a byproduct in the preparation of 5 from methyl acetoacetate. Reaction of 6 with Lawesson's reagent[8] in toluene at 90° C provided 7 (44% with 38% of starting material recovered) (eq. 2).

Treatment of compound 1 in refluxing toluene containing a catalytic amount of $Rh_2(OAc)_4$ led to complete consumption of the starting material, with formation of 2[9] in 73% yield. Catalytic hydrogenation of 2 with platinum dioxide in MeOH/AcOH[10] afforded an inseparable mixture of stereoisomers **8** quantitatively. The relative stereochemistry of pyrrolizidine hydroxy esters **8** was assigned on the assumption[11] that reduction of the double bond of **2** followed by facial selective reduction of the enol form of ketoester intermediate, and epimerization of α-proton of hydroxy ester yield the epimeric mixture. When **8** was subjected to mesylation followed by elimination, compounds **9** (25%) and **10**[9] (42%) were obtained, and **9** could be converted to **10** quantitatively by using NaH in THF.[12] Finally, DIBAL-H reduction of **10** provided (±)-supinidine **3** in 77% yield; Spectral data of synthetic **3** were identical with those reported.[13]

In summary, diazoketoester-thioimide coupling reaction has made a concise route to the pyrrolizidine skeletone. By subsequent simple manipulations, (±)-supinidine was readily prepared. Further application of this method directed to the synthesis of more complicated pyrrolizidines is in progress and will be described in due course.



(3)

Acknowledgements: We thank professor Eun Lee for his helpful suggestions.

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9. Spectral data **2**; IR (film) 2952, 1734, 1698, 1582, 1463, 1357, 1312, 1167, 1041 Cm^{-1} : ^{1}H NMR (300 MHz, CDCl$_3$): δ= 2.85 (ddd, J= 5.0 Hz, 4.5 Hz, 1.5 Hz, 2H); 3.45 (ddd, J= 4.7 Hz, 4.5 Hz, 1.2 Hz, 2H); 3.85 (s, 3H); 4.10 (s, 2H): MS m/e 196 (M+1). **10**; ^{1}H NMR (300 MHz, CDCl$_3$): δ= 1.97 (m, 1H); 2.34 (dd, J= 15.7 Hz, 8.9 Hz, 1H); 2.6 ~ 2.8 (m, 2H); 3.79 (s, 3H); 3.85 (ddd, J=17.9 Hz, 4.5 Hz, 1.5 Hz, 1H); 4.58 (ddd, J=18.0 Hz, 4.2 Hz, 2.4 Hz, 1H); 4.86 (m, 1H); 6.81 (q, J=2.0 Hz, 1H).
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