The Intramolecular Nitrile Oxide Cycloaddition Route to Spirocyclic Alkaloids. A Total Synthesis of Isonitramine and Sibirine

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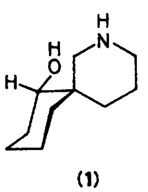
The intramolecular nitrile oxide cycloaddition reaction has been found to accommodate the construction of spirocycles in modest yield as revealed by a synthesis of the title alkaloids.

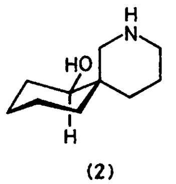
Nitramine (**1**), isonitramine (**2**), and sibirine (**3**), isolated from plants of the genus Nitraria, represent structurally new alkaloid systems.[1] All three of these substances possess the 2-azaspiro[5.5]undecane skeleton. Their structures resemble closely that of histrionicotoxin, a product which possesses the 1-azaspiro[5.5]undecane skeleton and which has been the subject of intensive synthetic studies.[2]

We now report a regio- and stereo-controlled entry to these molecules which is based on the ability of the intramolecular nitrile oxide cycloaddition, INOC, reaction[3] to generate spirocycles. The known cyclohex-1-enylmethylamine (**4**)[4] was treated with methyl acrylate in a Michael fashion[5] and the nitrogen atom of the intermediate disubstituted amine was protected as its benzyloxycarbonyl (Cbz) derivative. After borohydride reduction of ester to alcohol,[6] Swern oxidation[7] of alcohol to aldehyde, and oxime formation [(5) → (6)], we were ready to attempt the key INOC reaction.† Treatment of this oxime with aqueous sodium hypochlorite in methylene chloride[8]‡ gave the desired isoxazoline-bridged spirocycle (**8**) in 30% yield (Scheme 1). Attempts to improve this reaction have not been favourable; indeed it is surprising that the reaction proceeds at all. The trisubstituted nature of the double bond undergoing addition, the unfavourable regio-directing character of this double bond,[9] and the serious non-bonded interactions present in the transition state [see (**7**)] should together make this a relatively unfavourable cycloaddition. To confirm the structure of the INOC product, (**8**) was further converted into the title compounds. Such conversions require that the isoxazoline ring functions as a simple alcohol equivalent. Upon hydrogenation, the newly released carbonyl group was converted into its dithiolane derivative (**9**),[10] and a standard tri-n-butyltin hydride reduction was carried out to produce (**10**).[11] Lastly, hydrogenolytic removal of the Cbz group[12] yielded (**1**). By carrying out the hydrogenolysis of the Cbz group with Raney nickel in methanol, the *N*-methyl derivative of (**1**) was produced,[13] which is the natural product sibirine (**3**).

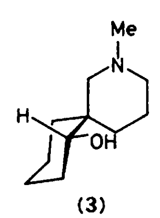
In conclusion, these reactions substantiate the use of the INOC reaction in the preparation of spirocycles. Furthermore, the reactions reveal the use of the isoxazoline unit as an alcohol equivalent in the synthesis of (**1**) and (**3**) (Scheme 2).



(1)



(2)



(3)

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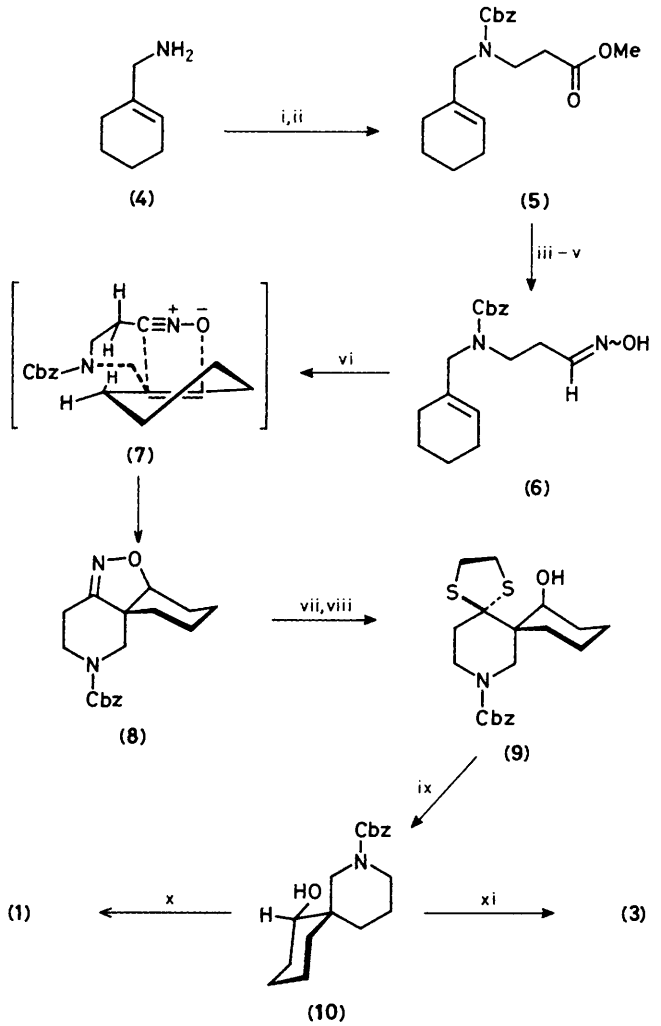
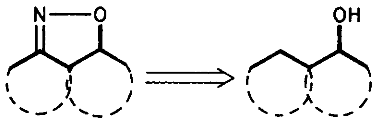
† Satisfactory i.r., n.m.r., and high resolution mass spectral data were obtained for all new compounds. (**5**): R_f 0.16 (silica gel, 35% ethyl acetate–hexane); i.r. (thin film) 2941, 1706, 1408, 1290, 1267, 1239, 1111, 979, 885, 790, 765, 738, and 698 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$, 300 MHz, 323 K) δ 7.3 (m, 5H), 5.16 (ABq, 2H, J_{AB} 11.25 Hz, w_{AB} 27.8 Hz), 4.47 (m, 2H), 3.93 (s, 1H), 2.75 (dt, 1H, *J* 15.0, 3.8 Hz), 2.5—2.7 (m, 2H), 2.27—2.40 (m, 1H), 2.15 (m, 1H), 1.4—1.7 (m, 5H), 1.1—1.3 (m, 2H); mass spectrum (15 eV) m/z 314 (M^+).

‡ Triethylamine was not used in this reaction. The sodium hypochlorite solution was obtained from Fisher Scientific and was diluted with an equal amount of water prior to use.



Scheme 1. *Reagents and conditions:* i, $CH_2{=}CHCO_2Me$, MeOH, H_2O (*ca.* 100% yield); ii, CbzCl, K_2CO_3, Et_2O (100%); iii, $NaBH_4$, Bu^tOH, MeOH, reflux (72%); iv, ClCOCOCl, dimethylsulphoxide, CH_2Cl_2, Et_3N (97%); v, $H_2NOH{\cdot}HCl$, pyridine (100%); vi, NaOCl (30%); vii, H_2, Raney Ni, MeOH, HOAc (86%); viii, $HS[CH_2]_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (72%); ix, $Bu^n{}_3SnH$, azoisobutyronitrile, C_6H_6, reflux (60%); x, H_2, Pd–C, HCl (96%); xi, H_2, Raney Ni, MeOH (50%).



Scheme 2

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