A SYNTHESIS OF WITHASOMNINE FROM 4-PHENYLPYRAZOLE

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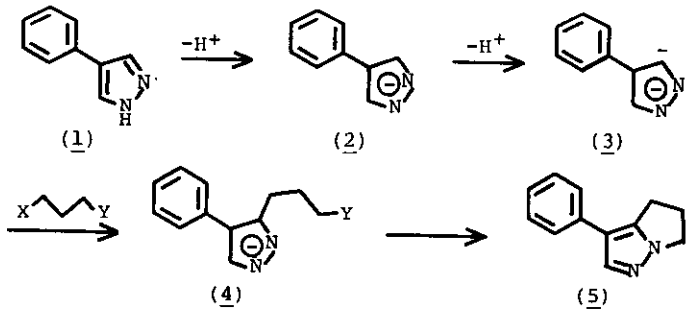
Abstract-----Withasomnine(5), a pyrazole alkaloid isolated from Withania somnifera Dun.(Solanaceae), has been synthesized from 4-phenylpyrazole(1), a compound with potential symmetry.

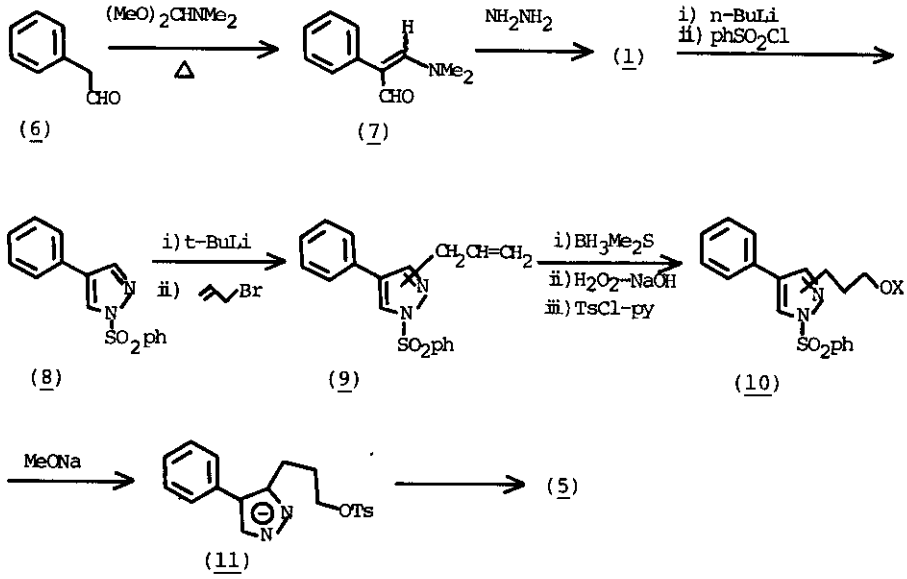
Construction of organic molecules is sometimes greatly facillitated by utilizing a symmetric substrate as a starting material, especially in controlling regio- and stereochemistry. In this direction, we have been employing the strategy using a symmetric starting material in the syntheses of a variety of natural products[1]. We report here a synthesis of a unique pyrazole alkaloid withasomnine(5),[2,3,4] isolated from Withania somnifera Dun.(Solanaceae), along this line using a starting material with potential symmetry. The present starting material, 4-phenylpyrazole(1), being unsymmetric itself, can be transformed into a symmetric intermediate(2) by deprotonation from which we expected to obtain withasomnine(5) through consecutive one-pot operations, viz., formation of highly reactive dianion(3) and alkylation with an appropriate three-carbon unit(Scheme 1).



Scheme 1

In practice, as all attempts to trap the dianion intermediate(3)[5] with alkyl halides were failed, an alternative sequence was employed. Thus, 4-phenylpyrazole(1),[6,7] mp 235°C(lit.[6] 149.5-150°C) prepared in 25.6% yield by treating phenylacetaldehyde with dimethylformamide dimethylacetal, followed by hydrazine hydrate in ethanol, was converted into the phenylsulfonamide(8),[8] mp 89°C, employing standard procedure.

Upon alkylation using allyl bromide in the presence of tert-butyllithium in tetrahydrofuran at 0°C, the sulfonamide(8) furnished the mono-allyl compound(9), mp 74-75°C, as a single isomer accompanied by (1) which was competitively formed in the deprotonation stage. Overall yield from (1) based on the recoverd starting material was 29.6%. We assumed the alkylated product to be 5-allyl-4-phenyl-1-phenylsulfonyl-pyrazole based on a comparison of ^{1}H-NMR spectra between (8)(8.27(5-H) and 7.94(3-H) ppm) and (9)(8.11(3-H) ppm). However, the position of the alkyl group was not important from the synthetic point of view as the common anionic intermediate(11) could be generated from either 3- or 5-alkylated precursor in the later stage. Hydroboration-oxidation procedure converted (9) into the primary alcohol(10)[9] which was then transformed to the tosylate(10). Treatment of (10) with sodium methoxide in methanol initiated concomitant desulfonylation and intramolecular cyclization to give withasomnine(5), mp 116-116.5°C (lit.[2] mp 117-118°C), in 70.8% yield, whose IR, NMR, and mass spectra were completely identical with those reported.[2]



Scheme 2

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2. Isolation: H. -B. Schroter, D. Neumann, A.R. Katritzky, and F.J. Swinbourne, Tetrahedron, 22, 2895(1966).
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4. Biosynthesis: D.G. O'Donovan and T.J. Forde, Tetrahedron Lett., 3637(1970).
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7. The present report also consisted a simple synthesis of 4-phenylpyrazole(1).
8. Satisfactory spectroscopic and analytical data were obtained for all new compounds: NMR($(CDCl_3)$ ppm), MS(m/e): (7) δ 2.78(6H, s), 6.84(1H, s), 9.05(1H, s)); (1) δ 7.90(2H, s), (144(M^+), 117); (8) δ 7.94(1H, s), 8.27(1H, s)), (248(M^+), 220); (9) δ 3.46(2H, dd, J=6 and 2 Hz), 8.11(1H, s)), (324(M^+)); (10) (X=H) δ 2.85(2H, t, J=7 Hz), 3.58(2H, t, J=6 Hz),8.19(1H, s)), (342(M^+), 324, 297,201), (X=Ts) δ 2.75(2H, t, J=7 Hz), 4.03(2H, t, J=6 Hz), 8.04(1H, s)), (496(M^+)); (5) (δ 4.14(2H, t, J=7 Hz), 7.78(1H, s)), (184(M^+), 169, 156, 140, 128)
9. A minor amount of the scondary alcohol was also obtained.

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