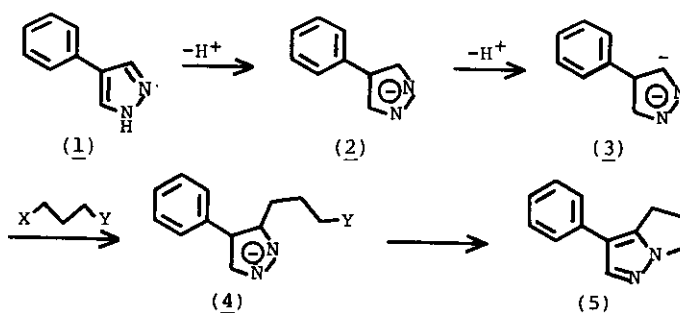


A SYNTHESIS OF WITHASOMNINE FROM 4-PHENYLPYRAZOLE

Seiichi Takano*, Yoko Imamura, and Kunio Ogasawara
 Pharmaceutical Institute, Tohoku University, Aobayama
 Sendai 980, Japan

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

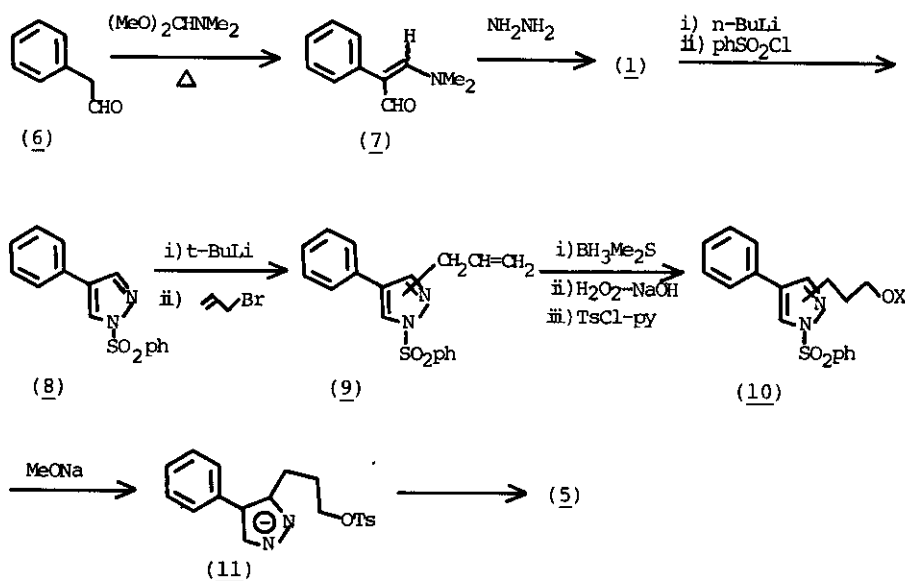
Construction of organic molecules is sometimes greatly facilitated by utilizing a symmetric substrate as a starting material, especially in controlling regio- and stereochemistry. In this direction, we have been employing the strategy using a symmetric starting material in the syntheses of a variety of natural products¹. 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 recovered starting material was 29.6%. We assumed the alkylated product to be 5-allyl-4-phenyl-1-phenylsulfonyl-pyrazole based on a comparison of ¹H-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

REFERENCES AND NOTES

- (a) S. Takano, K. Tanigawa, and K. Ogasawara, *J. Chem. Soc., Chem. Comm.*, 189(1976). (b) S. Takano, H. Iwata, and K. Ogasawara, *Heterocycles*, 9, 845, 1249(1978). (c) S. Takano, S. Hatakeyama, and K. Ogasawara, *Tetrahedron Lett.*, 2519(1978). (d) S. Takano, S. Hatakeyama, Y. Takahashi, and K. Ogasawara, *Heterocycles*, 12, 765(1979); 17, 263(1982) and references cited therein. (e) S. Takano, C. Kasahara, and K. Ogasawara, *J. Chem. Soc., Chem. Comm.*, 635(1981). (f) S. Takano, C. Murakata, and K. Ogasawara, *Heterocycles*, 16, 247(1981). (g) S. Takano, Y. Imamura, and K. Ogasawara, *Chemistry Lett.*, 1385(1981). (h) S. Takano, N. Ogawa, and K. Ogasawara, *Heterocycles*, 16, 915(1981). (i) S. Takano, C. Murakata, Y. Imamura, N. Tamura, and K. Ogasawara, *Heterocycles*, 16, 1291(1981).
- Isolation: H. -B. Schroter, D. Neumann, A.R. Katritzky, and F.J. Swinbourne, *Tetrahedron*, 22, 2895(1966).
- Former syntheses: (a) A. Morimoto, K. Noda, T. Watanabe, and H. Takasugi, *Tetrahedron Lett.*, 5707(1968). (b) T. Onaka, *Tetrahedron Lett.*, 5711(1968).
- Biosynthesis: D.G. O'Donovan and T.J. Forde, *Tetrahedron Lett.*, 3637(1970).
- There were some precedent reactions intervening a dianion intermediate from a pyrazole precursor: R. Huttel and M.E. Schon, *Ann. Chem.*, 625, 55(1959).
- K. von Auwers and O. Ungemach, *Ber.*, 66, 1198(1933).
- The present report also consisted a simple synthesis of 4-phenylpyrazole(1).
- Satisfactory spectroscopic and analytical data were obtained for all new compounds: NMR((CDCl₃) ppm), MS(m/e): (7X δ 2.78(6H, s), 6.84(1H, s), 9.05(1H, s)); (1X δ 7.90(2H, s), (144(M⁺), 117); (8X δ 7.94(1H, s), 8.27(1H, s)), (248(M⁺), 220); (9X δ 3.46(2H, dd, J=6 and 2 Hz), 8.11(1H, s)), (324(M⁺)); (10X X=HX 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=TsX 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)
- A minor amount of the secondary alcohol was also obtained.

Received, 5th March, 1982