IMINOPHOSPHORANE-MEDIATED SYNTHESIS OF OXAZOLE ALKALOIDS: ONE-STEP PREPARATION OF *O*-METHYLHALFORDINOL AND ANNULOLINE

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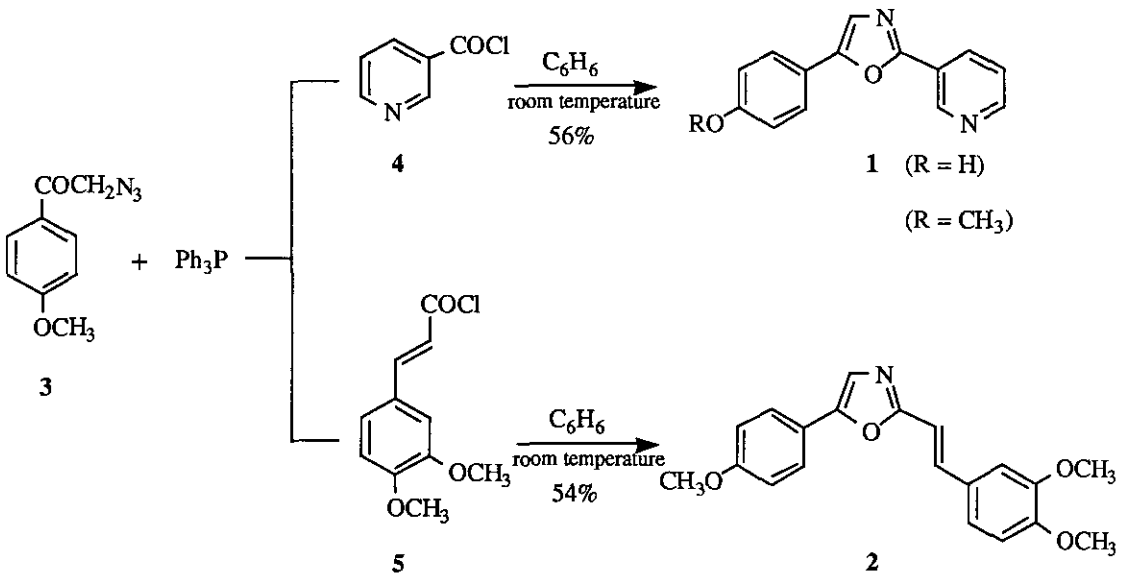
Abstract- The three-component reaction between triphenylphosphine, 4-methoxyphenacyl azide and nicotinoyl chloride or 3,4-dimethoxycinnamoyl chloride leads directly in good yields to *O*-methylhalfordinol or annuloline respectively.

Only five naturally occurring bases with an oxazole ring have been isolated to date,[1] all of them are 2,5-disubstituted oxazoles. Worthy of note among these are halfordinol (**1**)(R=H), the mother compound of oxazole alkaloids of *Halfordia screroxyla*[2] and *Aegle marmelos*;[3] annuloline (**2**), a brilliant blue fluorescent pigment isolated from the roots of the annual rye grass *Lolium multiflorum*;[4] and pimprinine, a mold metabolite isolated from *Streptomices pimprina*.[5] Halfordinol (**1**)(R=H) has been synthesized either by using the Robinson-Gabriel synthesis in 0.62% overall yield after five steps of troublesome elaboration[6] or by a modification of the Fischer synthesis in 16.5% overall yield from 4-hydroxymandelonitrile, nicotinaldehyde and thionyl chloride.[7] Annuloline (**2**) has been prepared by reaction of the 3,4-dimethoxycinnamoyl chloride with 4-methoxyphenacylamine, followed by cyclodehydration of the resulting amide with phosphorus oxychloride,[8] or by condensation of the 2-methyl-5-(4-methoxyphenyl)oxazole with 3,4-dimethoxybenzaldehyde.[6] Another method[9] which allows the isolation of (**2**) in yield higher (48% as picrate salt) than that achieved with the above mentioned is based on the reaction of α-diazo-4-methoxyacetophenone with 3,4-dimethoxycinnamonitrile in the presence of boron trifluoride dimethyl etherate. We have recently reported[10] the preparation of pimprinine, 2-(3-indolyl)-5-methyloxazole, by aza -Wittig reaction

of the iminophosphorane derived from 3-azidoacetyl-1-methylindole and acetyl chloride.

In this context, we wish to report a significantly improved procedure for the preparation of *O*-methylhalfordinol (**1**)(R=CH_3) and annuloline (**2**) under mild and neutral reaction conditions. This one-step route is based on the aza-Wittig reaction of iminophosphoranes derived from α-azidocarbonyl compounds with acyl chlorides. Thus, the reaction of 4-methoxyphenacyl azide (**3**),[11] prepared from 4-methoxyphenacyl bromide and polymeric quaternary ammonium azide,[12] with nicotinoyl chloride (**4**) in the presence of triphenylphosphine at room temperature directly leads to *O*-methylhalfordinol (**1**)(R=CH_3) in 56% yield.



In a similar way, α-azidoketone (**3**) by treatment with 3,4-dimethoxycinnamoyl chloride (**5**)[13] and triphenyl phosphine under the same conditions furnishes after chromatographic separation annuloline (**2**) in 54% yield.[14] It should be mentioned that similar results were obtained when tributylphosphine was used instead of triphenyl phosphine. The formation of compounds (**1**) and (**2**) takes place through an initially formed iminophosphorane, which undergoes acylation and further elimination of triphenylphosphine oxide to give an imidoyl chloride as intermediate which undergoes cyclization to give the five-membered ring.[15]

These results clearly indicate the utility of the aza-Wittig reaction for the synthesis of oxazole alkaloids. Due to the easy access of the starting materials, the good yields, mild reactions conditions, and due to the simplicity of the one-step procedure this synthetic approach appears to be highly competitive with the other methods reported in the literature.

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14. **General Procedure:** To a stirred solution of Ph_3P (0.58 g, 2.23 mmol) in anhyd. C_6H_6 (30 ml) at room temperature was added dropwise a solution of 4-methoxyphenacyl azide (**3**) (0.25 g, 1.3 mmol) and the appropriate acyl chloride (1.3 mmol) in the same solvent (30 ml). The resultant mixture was stirred at room temperature for 12 h and then filtered. The filtrate was washed with a 5% solution of $NaHCO_3$ (2 x 15 ml), H_2O (2 x 15 ml) and dried on anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was chromatographed on a silica gel column (40 cm x 3.5 cm, 70-230 mesh) using Et_2O/EtOAc (2:3) (compound **1**, R=CH_3) or CH_2Cl_2/EtOAc (4:1) (compound **2**) as eluent, further recrystallization from Et_2O/n-hexane (1:1) gave (**1**) or (**2**).

   ***O*-Methylhalfordinol (1)**(R=CH_3): colorless prisms; yield 0.18 g (56%); mp 103-104°C. Ir (Nujol) : υ= 1614, 1498, 1377, 1298, 1019, 841 cm^{-1}.^{1}H Nmr ($CDCl_3$) : δ= 3.84 (s, 3H, CH_3O), 6.96 (dt, J= 8.8 Hz, 1.8, 2H, H_{ortho}),

7.34 (s,1H, H-4), 7.39 (dd, J= 7.9, 4.9 Hz, 1H, H_{arom}), 7.63 (dt, J= 8.8, 1.8 Hz, 2H, H_{meta}), 8.32 (dt, J= 8.0, 1.8 Hz, 1H, H_{arom}), 8.66 (dd, J= 4.5, 1.3 Hz, 1H, H_{arom}), 9.30 (d, J=1.5 Hz, 1H, H_{arom}).^{13}C Nmr ($CDCl_3$): δ=55.3 (CH_3O), 114.4 (C_{ortho}), 120.3 (C_{ipso}), 122.1 (C-4), 123.5 (CH), 123.8 (q), 125.8 (C_{meta}), 133.2 (CH), 147.2 (CH), 150.6 (CH), 152.0 (C_{para}), 158.0 (C-5), 160.1 (C-2). Ms: m/z= 252 (M^+, 10), 77 (100).

Annuloline (2): yield 0.24 g (54%); mp 108-109°C (lit.,[6] 107-108°C).

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