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AN EASY ENTRY TO ISOQUINOLINE ALKALOIDS BY AZA-WITTIG ELECTROCYCLIC RING-CLOSURE

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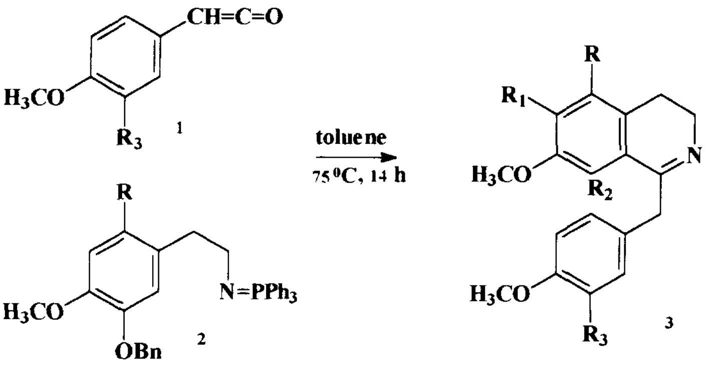
Abstract: The reaction of phenethyliminophosphorane with arylketenes gave 1-benzyl-3,4-dihydroisoquinolines in good yields. An aza-Wittig type reaction of vinyliminophosphorane with *p*-toluenesulfonylisocyanate furnished 1-aminoisoquinoline **6** in high yield.

We report new methods to obtain isoquinolines and 1-substituted-3,4-dihydroisoquinolines through an aza-Wittig reaction that are apparently a general procedure for pyrido-annulation under completely neutral conditions and therefore are important alternatives to the classical methods. The literature mentions that some 3,4-dihydroisoquinolines are labile and that a preparation under mild conditions is essential for their isolation. Also, the Bichler-Napieralski procedure requires an electron-donating group *para* to the cyclized position which is not necessary in the case of aza-Wittig cyclization.

Normally, dihydro- or tetrahydroisoquinoline alkaloids are prepared by the classical Bischler-Napieralski, Pictet-Spengler or Pomeranz-Fritsch reactions,[1] and the aromatic isoquinolines by the dehydrogenation of the corresponding dihydro- or tetrahydroisoquinolines. Recently, we have developed a new and efficient route to rutecarpine derivatives *via* an intramolecular aza-Wittig reaction.[2] As part of our work on the total synthesis of (+)-cularine alkaloids,[3] we now describe our results on the preparation of 1-benzyl-3,4-dihydroisoquinolines that are necessary, not only for the synthesis of these alkaloids, but for isoquinoline alkaloids in general.[4] We also report an example of the application of an aza-Wittig reaction for the preparation of 1-aminoisoquinoline derivative.

In essence, our synthetic approach to the aza-Wittig reaction consists of treating iminophosphoranes with easily accessible heterocumulenes such as ketenes that undergo electrocyclic ring closure to give 1-benzyl-3,4-dihydroisoquinolines in high yields. The necessary arylketenes were prepared by dehydration of homoveratric acids with dicylohexylcarbodiimide and triethylamine in THF at 0°C in yields around 80%.[5]

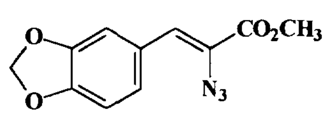


a R=Br, R_1=H, R_2=OBn, R_3=OCH_3, 76 %
b R=Br, R_1=H, R_2=OBn, R_3=NO_2, 78 %
c R=Br, R_1=H, R_2=OBn, R_3=N_3, 30 %
d R=R_1=H, R_2=R_3=OBn, 60 %
e R=R_2=H, R_1=R_3=OBn, 24 %

These homoveratric acids were prepared in two steps: firstly hyppuric acid was condensed with aromatic aldehydes in the presence of sodium acetate in a microwave oven[6] (household, 1.58 kw, Teflon bomb for 5 min) in nearly quantitative yields (the literature[7] procedure gave yields around 50%), and then the oxazolone intermediates were hydrolyzed with sodium hydroxide at 90°C and finally with H_2O_2.[8] The iminophosphoranes were obtained in a sequence of four steps beginning with the reaction of aryl aldehydes with $CrCl_2$-$CHCl_3$[9] under reflux in THF to give chlorostyrene intermediates that were treated with $LiAlH_4$ in boiling THF[10] to give styrenes. Hydroboration with $SnCl_4$-$NaBH_4$ in THF and then H_2O_2 gave the phenethyl alcohols[11] in high yield that underwent a Mitsunobu reaction with HN_3-PPh_3 and then DEAD to give the iminophosphoranes in yields over 95%.[12]

Alternatively, the iminophosphoranes **2a** and **2b** were also prepared from phenethylamine with PPh_3-CCl_4 giving the phosphinimino salts in 79% yield that were converted to the iminophosphoranes in the presence of sodium amide in boiling toluene in 95% yield.

The aza-Wittig reactions were carried out by adding the ketenes **1** to a solution of the iminophosphoranes **2** at 0°C. After 2 h, the temperature was increased to 75°C and maintained for 14 h. The isolated yields of dihydroisoquinolines varied from 76 to 84% and only with the azide derivative **3a,** the yield was much lower (30%). We used R=Br to protect that position during the cyclization. When R=H the cyclization gave two compounds, **3d** in 60% and **3e** in 24% yields. To our knowledge, this is the first report of an aza-Wittig reaction between iminophosphoranes and ketenes. In general, the thermal cyclization of isocyanates,[13] isothiocyanates,[14] aldehydes,[15] ketones,[16] carbon dioxide and carbon disulfide[17] has been mentioned.



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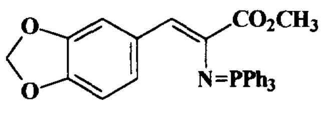

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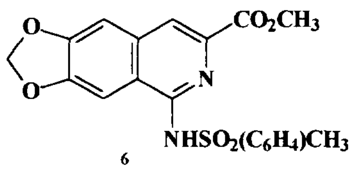

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The versatility of the aza-Wittig reaction for the preparation of isoquinolines is illustrated in a further example. Piperonal was condensed with ethyl azidoacetate in the presence of sodium methoxide at -10°C for 6 h to give methyl 2-azido-1-(3,4-methylenedioxybenzene)propen-2-ate **4** as a yellow solid in 96% yield. The preparation of the iminophosphorane was easily accomplished by a Staudinger's reaction with triphenylphosphine in dry dichloromethane at 0°C for 30 minutes and then 12 h at room temperature to give **5** (97%). An aza-Wittig reaction of the iminophosphorane and *para*-toluenesulfonyl isocyanate in boiling dry toluene for 12 h gave 1-(*p*-tolunensulfonilamide)-3-methoxycarbonyl-6,7-methylenedioxyisoquinoline **6** in (95%) as a yellow solid. This short and simple route involves three steps and gives the 1-aminoisoquinoline in 88% overall yield.

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