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Iminophosphorane-Mediated Synthesis of the Genotoxic Heterocyclic Amine Trp-P-2.

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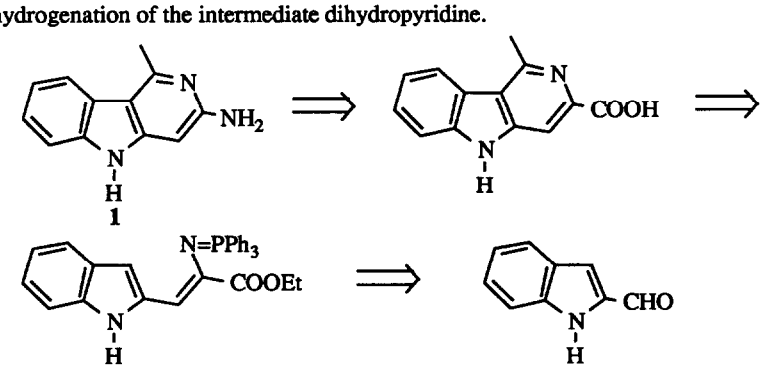
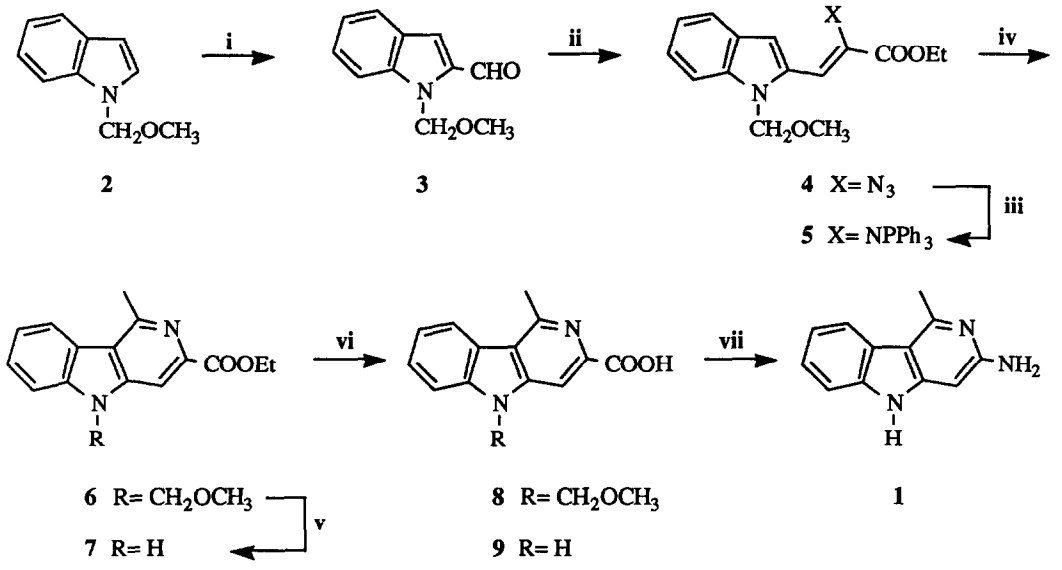
Abstract. A new eight-step synthesis of the genotoxic amine Trp-P-2 in an overall yield of 14.4% is described. The key step, formation of the γ-carboline ring, involves a tandem aza Wittig/electrocyclic ring closure process.

Research on environmental mutagens and carcinogens has led to the identification of many of these compounds in food, water an air.[1] One series of such environmental agents, heterocyclic amines, are known to be formed when aminoacids are pyrolyzed or protein-containing foods are cooked at high temperature.[2] Among these amines, the highly potent mutagen γ-carboline derivative Trp-P-2 was isolated from tryptophan pyrolysate.[3] Its structure was determined by X-ray analysis as 3-amino-1-methyl-5H-pyrido [3,4-b] indole.[4] Two synthetic routes to Trp-P-2 have been previously reported, the first one involves as key step acid-catalyzed cyclization of 2-acetamido-3-(2-indolyl)alkanoic acids to 1,2-dihydro-γ-carbolines followed by dehydrogenation.[5] The key reaction step in the second approach is based on the thermal electrocyclic ring-closure of an 1-azahexa-1,3,5-triene system involving the indole [b] bond derived from 2-vinylindoles.[6]

In the course of our studies directed towards the synthesis of nitrogen heterocyclic compounds based on heterocyclization reactions of azahexatriene systems, we have developed the so-called tandem aza Wittig/electrocyclic ring-closure strategy for the synthesis of pyridines,[7] isoquinolines[8] and quinoline[9] derivatives. This methodology has been applied to prepare the carbon skeleton of the alkaloids olivacine[10] and lavendamycin.[11] In all cases a formal 2-aza or 3-azahexa-1,3,5-triene is generated by aza Wittig reaction of vinyl iminophosphoranes with aldehydes which by thermal treatment leads to fused pyridines through a 6π-eletrocyclic ring-closure process followed by dehydrogenation of the intermediate dihydropyridine.



We wish to report here a short and improved synthesis of Trp-P-2 by an application of this methodology. According to our retrosynthetic analysis of **1** the amino group at C-3 position could be derived from a carboxylic acid at this position of the γ-carboline ring, by the same manner achieved in the Hibino synthesis,[6] and this ring system could be formed by electrocyclic ring-closure of a formal 2-azahexa-1,3,5-triene readily available from aza Wittig reaction of an iminophosphorane, derived from 2-formylindole, and the appropriate aldehyde.



Reagents and conditions: i) t-BuLi, Ph-N(CH_3)CHO, Et_2O (53%); ii) N_3CH_2COOEt, NaEtO, EtOH, -15°C, (70%); iii) Ph_3P, CH_2Cl_2, r.t. (85%); iv) CH_3CHO, toluene, 160°C, sealed tube (85%); v) HCOOH, reflux, (70%); vi) LiOH, H_2O/THF, r.t. (98%); vii) a: Ph_2PON_3, Et_3N, t-BuOH (98%); b: AcOH, H_2O (80%).

Thus, we initially required a N-protected 2-formylindole and the protecting group of choice was the methoxymethyl group. To this end the N-methoxymethyl 2-formylindole **3** was prepared from **2** by sequence lithiation/formylation in somewhat higher yields (53%) than the reported in the literature.[12] Conversion of **3** into the azide **4** was perfomed by reaction with ethyl azidoacetate under standard conditions.[13] Staundinger reaction of the azide **4** with triphenylphosphine in dichloromethane at room temperature provided the iminophosphorane[14] **5** in excellent yield (85%). Compound **5** reacted with acetaldehyde in toluene at 160°C in a sealed tube to give the 1-methyl-γ-carboline **6** in 85% yield[15] and thus completing the assembly of the carbon skeleton of Trp-P-2. The conversion **5**→**6** involves initial aza Wittig reaction to give a 2-azahexa-1,3,5-triene involving the indole [b] bond

as a 2π-component, which subsequently undergoes electrocyclic ring-closure.[16] Further dehydrogenation under the reaction conditions leads to the γ-carboline **6**. When compound **6** was treated with formic acid at reflux temperature deprotection took place and the N-unprotected indole **7** was obtained in good yield (70%). Hydrolysis of the esters **6** and **7** was carried out by the action of LiOH at room temperature to give the known γ-carboline carboxilic acids[5] **8** (96%) and **9** (98%) respectively. Conversion of the carboxylic acid functions at C-3 position in compounds **8** and **9** to amino group was achieved by a modified Curtius rearrangement following the Hibino's protocol[6] using the Shioiri-Yamada reagent, diphenylphosphoryl azide.[17] Limited success was met upon treatment of **8** with this reagent in t-butanol, this gave 3-t-butoxycarbonylamino-1-methyl-5-methoxymethyl-γ-carboline in a disappointing yield of 30%. Better result was obtained when **9** was used, in this instance N-t-Boc-Trp-P-2 was isolated in near quantitative yield. Finally, hydrolysis with aqueous acetic acid provived Trp-P-2 **1** as its acetate (80%, mp 245-247°C, lit[4,6] 242-250°C).

In conclusion, we have developed a new and efficient eight-step synthesis[18] of the genotoxic heterocyclic amine 3-amino-1-methyl-5H-pyrido [3,4-b] indole (Trp-P-2) in an overall yield of 14.4%. This synthesis, which involves as key step an aza Wittig/electrocyclic ring-closure process, shows to be an useful alternative to those previously reported (Hibino's synthesis involves a nine-steps sequence in 3.8% overall yield).

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14. Compound **5**. m.p. 127-129°C (from benzene/n-hexane) yellow prisms. ^{1}H n.m.r.(200 MHz, $CDCl_3$) δ 0.98 (t, 3H, J= 7.2 Hz, CH_3CH_2OCO), 3.30 (s, 3H, CH_3O), 3.88 (q, 2H, J= 7.2 Hz, CH_3CH_2OCO), 5.75 (s, 2H, CH_3OCH_2N), 6.96 (d, 1H, J= 6.9 Hz, H-β), 7.04 (td, 1H, J= 7.1, 1.4 Hz, H-5), 7.14 (td, 1H, J= 6.9, 1.5 Hz, H-6), 7.34 (s, 1H, H-3), 7.40-7.52 (m, 9H, $6H_m + 3H_p$), 7.70-7.81 (m, 8H, H-4 + H-7 + $6H_o$); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.1 (CH_3), 55.8 (CH_3), 60.8 (CH_2), 73.5 (CH_2), 104.3 (d, $^3J_{P-C}$= 20.7 Hz, C-β), 105.7 (C-3), 108.8 (C-7), 119.9 (C-6), 120.3 (C-4), 121.6 (C-5), 128.0 (C-2), 128.2 (d, $^3J_{P-C}$= 12.1Hz, C_m), 129.3 (C-3a), 131.1 (d, $^4J_{P-C}$= 2.9 Hz, C_p), 132.5 (d, $^2J_{P-C}$= 9.7 Hz, C_o), 132.7 (d, $^1J_{P-C}$= 103.4 Hz, C_i), 137.6 (C-7a), 138.2 (C-α), 167.1 (d, $^3J_{P-C}$= 6.9 Hz, C=O), m/z (%) 534 (M^+, 11).

15. *Typical Procedure*: A mixture of iminophosphorane **5** (0.48g, 0.9 mmol), acetaldehyde (0.044g, 1mmol) and dry toluene (50 ml) was heated at 160°C in a sealed tube for 12 h. After cooling, the solvent was removed under reduced pressure at 35°C and the residual material was chromatographed on a silica gel column eluting with CH_2Cl_2:EtAcO (9:1) to **6** which after recrystallization from EtAcO/n-Hexane (1:1) was isolated in 85% yield as brown prisms, m.p. 170-171°C. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.50 (t, 3H, J= 7.2Hz, CH_3CH_2OCO), 3.13 (s, 3H, CH_3), 3.30 (s, 3H, CH_3OCH_2), 4.54 (q, 2H, J= 7.2 Hz, CH_3CH_2OCO), 5.71 (s, 2H, CH_3OCH_2), 7.42 (td, 1H, J= 8.1, 1.2 Hz, H-8), 7.58 (td, 1H, J= 8.4, 0.9 Hz, H-7), 7.65 (d, 1H, J= 8.4 Hz, H-6), 8.19 (d, 1H, J= 8.1 Hz, H-9), 8.24 (s, 1H, H-4); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.4 (CH_3), 24.2 (CH_3), 56.4 (CH_2), 74.1 (CH_2), 105.2 (C-4), 110.0 (C-6), 120.3 (C-1), 121.8 (C-7), 122.0 (C-9a), 123.0 (C-9), 127.4 (C-8), 141.2 (C-3), 143.2 (C-9b), 144.9 (C-5a), 153.6 (C-4a), 166.1 (C=O); m/z (%) 298 (M^+, 7).

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18. Satisfactory ^{1}H, ^{13}C n.m.r. (values assigned by decoupling methods and 2D ^{1}H-^{13}C correlation techniques), mass spectra and elemental analyses were obtained for all new compounds.

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