Novel α-Carboline Synthesis Using Tandem aza-Wittig–Electrocyclization Reaction of Indol-2-yl Phosphorane with Enone

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Abstract: Mild thermal reaction of indol-2-yl triphenyl- and methyldiphenyl-phosphorane derived from 2-azido-1-methylindole with enones provides a novel entry to 9-methyl-9*H*-pyrido[2,3-*b*]indoles through a tandem aza-Wittig–electrocyclization process.

Key words: indolyl phosphoranes, enones, aza-Wittig, electrocyclization, α-carbolines

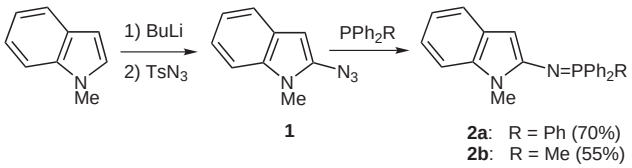
In the past thirty years iminophosphoranes, first prepared at the beginning of the last century by Staudinger in the reaction of organic azides with triphenylphosphine, have become a powerful tool in synthetic methods for the construction of nitrogen-containing heterocycles.[1] In particular, the aza-Wittig reaction of suitable iminophosphoranes with (unsaturated) carbonyl compounds followed by 6π-electrocyclization of resultant azahexatrienes has found important applications in the synthesis of simple as well as *c*-fused pyridines.[2]

Our recent studies have discovered that iminophosphoranes derived from 2-azido- and 3-azido-benzothiophene can be efficiently employed in the tandem aza-Wittig–electrocyclization strategy for the synthesis of *b*-fused pyridines such as benzothieno[2,3-*b*]pyridines and benzothieno[3,2-*b*]pyridines.[3]

In this communication we report that such strategy can successfully be extended to iminophosphoranes derived from 2-azido-1-methylindole (**1**) for the construction of pyrido[2,3-*b*]indoles (α-carbolines). The use of *N*-(indol-2-yl)iminophosphoranes in α-carboline synthesis is unprecedented; indeed, these heteroaryl phosphoranes are to date unknown compounds, despite the fact that a synthetic route to a potential precursor such as azide **1** has been available since 1989.[4] Iminophosphoranes derived from β-(indol-3-yl)vinyl azides have found previous use in the production of β-carbolines via analogous aza-Wittig–electrocyclization process.[1c]

The biological importance of α-carboline ring system is well known. This ring is found in several alkaloids[5] and in carcinogenic metabolites.[6] Moreover, some synthetic α-carboline derivatives are anxiolytic or neuroprotectant agents.[7] The best known synthetic approaches for this class of compounds involve construction of either pyridine ring from 2-amino-3-substituted indole derivatives[5,8] or synthesis of pyrrole (B ring) ring via cross-coupling between an appropriately substituted pyridine and aniline derivative.[9] Other approaches involve intramolecular Diels–Alder reaction of 2(1*H*)-pyrazinones[10] and conjugated carbodiimides,[11] reaction of 1-methyl-2-oxyindole enolate with α-oxoketene dithioacetals,[7a] condensation of 2-amidinylindole-3-carbaldehydes with arylmethylketones[12] as well as reaction of indol-2(3*H*)-one derivatives with enamines.[13] Very recently, α-carbolines have also been prepared by copper-catalyzed radical cyclization of β-(3-indolyl)ketone *O*-pentafluorobenzoyloximes.[14] However, the existing methods often suffer from limitations such as not easily accessible starting materials, overall poor yields or inflexibility for substituent introduction.

2-Azido-1-methylindole (**1**) was prepared by azidation of commercial 1-methylindole by 'azido group transfer' from tosyl azide, following the previously reported procedure.[4] The crude azido compound was directly treated with triphenylphosphine and methyldiphenylphosphine in diethyl ether at 0 °C furnishing *N*-(1-methylindol-2-yl)iminotriphenylphosphorane (**2a**) and *N*-(1-methylindol-2-yl)iminomethyldiphenylphosphorane (**2b**) in 70% and 55% yield, respectively, based on the starting indole (Scheme 1).[15] The triphenylphosphorane (**2a**) was isolated as a fairly stable solid compound, whereas the methyldiphenyl analogue **2b** was obtained as a crude viscous oil which showed a tendency to decompose and thence was directly used without purification.



Scheme 1 Synthesis of indolylphosphoranes

The triphenylphosphorane (**2a**) underwent smooth reaction with equimolar amounts of acrylaldehyde, *trans*-crotonaldehyde, *trans*-cinnamaldehyde, and methyl *trans*-4-oxo-2-pentenoate in toluene solution at 70 °C over 18–24 h to give directly the corresponding α-carbolines **3a–d**

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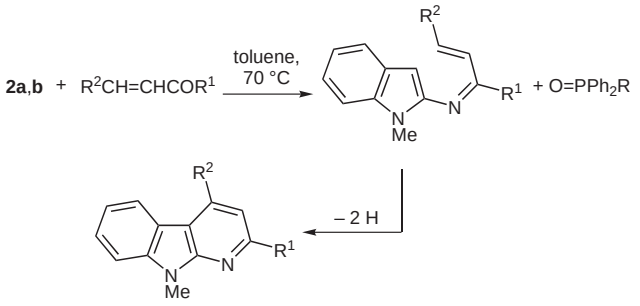
which were isolated by column chromatography in satisfactory to excellent yields (Scheme 2 and Table 1, entries 1–4).[16] Our additional reaction of **2a** with but-3-en-2-one also furnished a useful yield of the respective carboline **3e** (Scheme 2 and Table 1, entry 5); this finding was especially rewarding in light of the relative inertness previously displayed by this ketone with benzothiophenyl phosphoranes.[3a–c]



3a: $R^1 = R^2 = H$
3b: $R^1 = H$, $R^2 = Me$
3c: $R^1 = H$, $R^2 = Ph$
3d: $R^1 = Me$, $R^2 = COOMe$
3e: $R^1 = Me$, $R^2 = H$

Scheme 2 Synthesis of α-carbolines

Table 1 α-Carbolines **3a**–**e** Prepared from Iminophosphoranes **2a**,**b** and Enones

Entry	Iminophosphorane	Enone	Carboline (yield, %)[a]
1	**2a**	$R^1 = R^2 = H$	**3a** (70)
2	**2a**	$R^1 = H$, $R^2 = Me$	**3b** (80)
3	**2a**	$R^1 = H$, $R^2 = Ph$	**3c** (45)
4	**2a**	$R^1 = Me$, $R^2 = COOMe$	**3d** (90)
5	**2a**	$R^1 = Me$, $R^2 = H$	**3e** (38)
6	**2b**	$R^1 = R^2 = H$	**3a** (50)
7	**2b**	$R^1 = H$, $R^2 = Me$	**3b** (43)
8	**2b**	$R^1 = H$, $R^2 = Ph$	**3c** (35)
9	**2b**	$R^1 = Me$, $R^2 = COOMe$	**3d** (48)

[a] Yields isolated by column chromatography.

The carboline **3a** was a well-known compound which had been prepared in several instances, but in modest to poor yields, through multistep processes;[17] the 4-methyl derivative **3b** had been produced in poor yield by reaction of 2-amino-1-methylindole with 3-buten-2-one;[18] the 2-methyl derivative **3e** was very recently prepared in fairly good yield by radical cyclization of the *O*-pentafluorobenzoyl derivative of 4-(1-methyl-3-indolyl)butan-2-one oxime;[14] the remaining two carbolines **3c**,**d** were previously unknown.

Under analogous conditions the methyldiphenylphosphorane (**2b**) with the above unsaturated aldehydes and oxopentenoate similarly furnished the carbolines **3a**–**d**, but in these cases the resultant yields always were markedly lower (Scheme 2 and Table 1, entries 6–9).[16] Thus, our original expectation that replacement of phenyl with electron-donating methyl P-substituent might improve reaction of indolyl phosphorane with enone[19] was unfortunately frustrated as a probable consequence of significant decomposition of the hardly stable phosphorane **2b** under the reaction conditions.

Evidently, the phosphoranes **2b** and, especially, **2a** with our enones could initially form formal aza-Wittig azahexa-1,3,5-triene intermediates. These intermediates then underwent thermal electrocyclization eventually leading to the isolated pyridines **3a**–**e** after further dehydrogenation of the cyclized dihydropyridines (Scheme 2). With both phosphoranes **2a**,**b** the exclusive occurrence of the tandem aza-Wittig–electrocyclization process was dictated by the fact that with crotonaldehyde, cinnamaldehyde, methyl 4-oxo-2-pentenoate as well as butenone the outcoming substituted carbolines **3b**–**e** were always produced as single compounds in the expected regiochemistry.[3] Under these circumstances replacement of phenyl with methyl substituent did not affect the reaction mode of indol-2-yl phosphorane with the enone reagent. In this respect, the phosphoranes **2a**,**b** were consistent with their benzothiophen-2-yl counterparts which, irrespective of phenyl or methyl P-substituent, similarly furnished only aza-Wittig–electrocyclization benzothienopyridines in their reactions with enones.[3a,3c,19] The benzothiophen-3-yl phosphoranes, instead, were found to exhibit a different trend since progressive replacement of phenyl with methyl group(s) on phosphorus caused an increasing propensity of the phosphorane itself for addition to the enone carbonyl moiety by adopting the β-(α-thienyl)carbon instead of the imino nitrogen; this fact then caused progressive suppression of the *b*-fused pyridines due to aza-Wittig–electrocyclization in favor of those due to opposite regiochemistry.[3a,b,19]

However, the present indolyl triphenylphosphorane **2a**, unlike the rather disappointing methyldiphenyl analogue **2b**, proved to be superior to both previous phenyl/methyl-substituted benzothiophen-2-yl and benzothiophen-3-yl congeners as it was usually able to provide enhanced amounts of (single) *b*-fused pyridines with the same unsaturated aldehydes and ketones.

In conclusion, we have shown that the mild thermal reaction of enones with the readily accessible 1-methylindol-2-yl phosphoranes **2a**,**b** can offer a novel synthesis of 9-methyl-9*H*-pyrido[2,3-*b*]indoles **3**, which is especially appealing when using triphenylphosphorane **2a** instead of hardly stable methyldiphenylphosphorane **2b**. The practical procedure is very simple since, at the end of the reaction, the crude reaction mixture just requires evaporation of the toluene solvent under reduced pressure and eventual chromatographic purification. It is presumable that the present protocol might be of wide utility for the

preparation of other variously substituted 9*H*-pyrido[2,3-*b*]indole compounds from appropriate enones and simple indole precursors. Studies are in progress to explore the actual scope of our protocol.

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References and Notes

(1) (a) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197. (b) Wamhoff, H.; Richardt, G.; Stolben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 125. (c) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1.

(2) (a) Molina, P.; Pastor, A.; Vilaplana, M. J. *J. Org. Chem.* **1996**, *61*, 8094. (b) Kobayashi, T.; Nitta, M. *Chem. Lett.* **1981**, 1459. (c) Iino, Y.; Nitta, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2235. (d) Molina, P.; Pastor, A.; Vilaplana, M. J. *Tetrahedron Lett.* **1993**, *34*, 3773. (e) Molina, P.; Pastor, A.; Vilaplana, M. J.; Foces-Foces, C. *Tetrahedron* **1995**, *51*, 1265.

(3) (a) Degl'Innocenti, A.; Funicello, M.; Scafato, P.; Spagnolo, P.; Zanirato, P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2561. (b) Bonini, C.; Chiummiento, M.; Funicello, M.; Spagnolo, P. *Tetrahedron* **2000**, *56*, 1517. (c) Bonini, C.; D'Auria, M.; Funicello, M.; Romaniello, G. *Tetrahedron* **2002**, *58*, 3507. (d) Bonini, C.; Funicello, M.; Scialpi, R.; Spagnolo, P. *Tetrahedron* **2003**, *59*, 7515.

(4) (a) Foresti, E.; Spagnolo, P.; Zanirato, P. *J. Chem Soc., Perkin Trans. 1* **1989**, 1354. (b) Foresti, E.; Di Gioia, M. T.; Nanni, D.; Zanirato, P. *Gazz. Chim. Ital.* **1995**, *125*, 151.

(5) Molina, P.; Fresneda, P. M.; Sanza, M. A.; Foces-Foces, C.; De Arellano, M. C. R. *Tetrahedron* **1998**, *54*, 9623.

(6) (a) Bhatti, I. A.; Busby, R. E.; Binmohamed, M.; Parrick, J.; Shaw, C. J. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3581. (b) Kazerani, S.; Novak, S. *J. Org. Chem.* **1998**, *63*, 895.

(7) (a) Barun, O.; Patra, P. K.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1999**, *40*, 3797. (b) Stolc, S. *Life Sci.* **1999**, *65*, 1943.

(8) (a) Meyer, M.; Guyot, M. *Tetrahedron Lett.* **1996**, *37*, 4931. (b) Molina, P.; Fresneda, P. M.; Sanz, M. A. *Tetrahedron Lett.* **1997**, *38*, 6909.

(9) (a) Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 2615. (b) Rocca, P.; Marsais, S.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49.

(10) Tahri, A.; Buysens, K. J.; Van der Eycken, E. V.; Vandenberghe, D. M.; Hoornaen, G. J. *Tetrahedron* **1998**, *54*, 13211.

(11) (a) Molina, P.; Alajarin, M.; Vidal, A.; Sanchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929. (b) Molina, P.; Fresneda, P. M. *Synthesis* **1989**, 878.

(12) Erba, E.; Gelmi, M. L.; Pocar, D. *Tetrahedron* **2000**, *56*, 9991.

(13) Beccalli, E. M.; Clerici, F.; Marchesini, A. *Tetrahedron* **2001**, *57*, 4787.

(14) Tanaka, K.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1659.

(15) **Preparation of the 1-Methylindol-2-yl Phosphoranes 2a,b.**
2-Azido-1-methylindole (**1**), freshly obtained after filtration through a Florisil® pad of the crude product from azido transfer reaction of 1-methylindole (1 mmol) with tosyl azide,[4] was dissolved in dry Et_2O (2 mL) and then slowly added to an anhyd Et_2O solution (2 mL) of PPh_3 (1 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for ca. 1 h after which the separated solid material was filtered off to give the triphenylphosphorane (**2a**, 0.7 mmol, 70%) as a dark-yellow powder, mp 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.33 (m, 15 H), 7.20–7.15 (m, 1 H), 7.10–6.95 (m, 1 H), 6.90–6.80 (m, 2 H), 5.15 (s, 1 H), 3.87 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.5, 144.4, 137.0, 134.5, 132.4, 132.0, 131.1, 130.0, 129.3, 127.8, 127.0, 125.5, 125.0, 124.3, 121.5, 118.7, 117.5, 117.0, 114.0, 113.7, 111.0, 109.3, 39.0.
The methyldiphenylphosphorane (**2b**) was similarly prepared in 55% yield by azidation of 1-methylindole (1 mmol) followed by direct treatment with methyldiphenylphosphine (1 mmol). The compound **2b** was obtained as a viscous oil which showed a tendency to decompose under work-up conditions and was thus employed without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.65 (m, 5 H), 7.58–7.40 (m, 5 H), 7.21–7.18 (m, 1 H), 7.15–7.10 (m, 1 H), 6.90–6.80 (m, 2 H), 5.20 (s, 1 H), 3.87 (s, 3 H), 2.23 (d, 3 H, $^2J_{PH}$ = 12.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.6, 141.0, 134.6, 133.0, 132.3, 131.6, 131.5, 130.7, 129.5, 129.2, 129.2, 128.2, 126.1, 125.9, 118.8, 117.0, 116.5, 107.5, 37.0, 14.88.

(16) **Synthesis of the Carbolines 3a–e. Typical Procedure.**
A mixture of the triphenylphosphorane (**2a**, 1 mmol) and *trans*-crotonaldehyde (1 mmol) in dry toluene (5 mL) was stirred at 70 °C for ca. 20 h under a stream of nitrogen. After cooling, the solvent was removed in vacuo and the resultant residue chromatographed on a silica gel column by progressive elution with PE–EtOAc mixtures to give 4,9-dimethyl-9*H*-pyrido[2,3-*b*]indole (**3b**,[18] 80%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.36 (m, 1 H), 8.20–8.15 (m, 1 H), 7.60–7.55 (m, 1 H), 7.40–7.35 (m, 1 H), 7.23 (s, 1 H), 7.15–7.00 (m, 1 H), 4.10 (s, 3 H), 2.94 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.3, 150.6, 145.8,143.0, 129.4, 125.8, 125.0, 123.1, 117.3, 116.6, 108.3, 30.0, 27.8.
The carbolines **3a**[17b,17c] and **3e**[14] had physical and/or spectral data consistent with those previously reported. The hitherto unknown carbolines **3c**,**d** were identified on the basis of NMR and MS data as well as elemental analysis.

(17) (a) Zhestkov, V. P.; Druzhinina, V. V.; Rudnitskikh, A. V. *Khim. Geterotsikl. Soedin.* **1995**, 1507; *Chem. Abstr.* **1996**, *125*, 33513x. (b) Clark, V. M.; Cox, A.; Herbert, E. J. *J. Chem. Soc. C* **1968**, 831. (c) Eiter, K.; Nagy, M. *Monatsh. Chem.* **1949**, *80*, 607. (d) Eiter, K. *Monatsh. Chem.* **1948**, *79*, 17.

(18) Abramenko, P. I. *Zhurnal Vses. Khim. Obshch. im. D.I. Mendeleeva* **1973**, *18*, 715; *Chem. Abstr.* **1974**, *80*, 95788b.

(19) Replacement of phenyl with methyl group(s) on phosphorus could enhance the reactivity of our previous benzothiophen-2-yl and, especially, benzothiophen-3-yl phosphoranes with enones, see ref. 3b,3c.