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Reactions of substituted 2,3-dihydro-1*H*-indol-3-ones and pyrrolo[2,3-*b*]pyridin-3-ones with Wittig and Horner–Emmons reagents: synthesis of 7-azatryptamine

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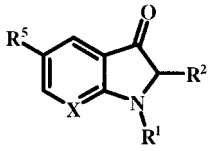
Abstract—The reactivity of indolinone **1** towards Wittig and Horner–Emmons reactions was reported; the influence of the nature of substituent on the nitrogen atom was examined. 7-Azaindolinone **2** reacted with diethyl cyanomethanephosphonate for giving the corresponding (7-azaindol-3-yl)acetonitrile or more unexpectedly, a C-2 alkylated product; this behavior has been extended to another nucleophilic reagent. Finally the synthesis of 7-azatryptamine was reported. © 2001 Elsevier Science Ltd. All rights reserved.

For many years now, our interest of the behavior of the 2,3-dihydro-1*H*-indol-3-one **1**[1] (Fig. 1) is driven by different aspects of the molecule. This framework is not only found in different natural products like Austamide[2] or Brevianamide,[3] but **1** has also been used as synthon for the preparation of biological compounds[4] such as tryptamine,[5–7] δ-carboline[8] and cryptoline.[9] In framework **1**, the carbonyl in 3-position possesses different properties depending on the nature of substituents in 1, 2 and 5-position. This paper summarizes the new results we have recently obtained on 7-azaindolinone **2**[10–13] (pyrrolo[2,3-*b*]-pyridin-3-one), after we have tried to complete the tremendous work already described by Sakamoto and his coworkers on the behavior of **1** in Wittig reaction,[14–16] Claisen rearrangement,[17,18] or Michael addition.[19]



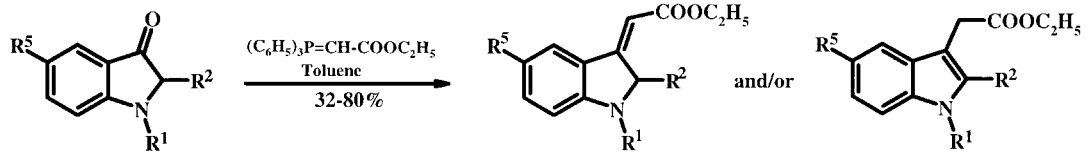
1 X = CH
2 X = N

Figure 1.

To start with, we have considered the nature of the substituent on the nitrogen atom in 1-position and the substitution in 2-position of indolinone **1** in the Wittig reactions with stabilized ylide, ethoxycarbonylmethylenetriphenylphosphorane (Chart 1).

Table 1, where we gather Sakamoto[14,15] and own results highlights, once again gives the great importance of the substituents in 1- and 2-position.

Upon reaction with ethoxycarbonylmethylenetriphenylphosphorane (2 equiv.) in refluxing toluene, indolinone **1** afforded either the α,β-ethylenic ester **3** or the ethyl indoleacetate **4**. If the nitrogen atom of **1** is protected with an acetyl group (**1a**–**f**) we generated compounds **3b**–**d**, with the exception for the 2-unsubstituted indolinone **1a** and the 2-benzylsubstituted indolinone **1e** which gave respectively,



1 3 4

Chart 1.

Keywords: 2,3-dihydro-1*H*-indol-3-one; pyrrolo[2,3-*b*]pyridin-3-one; Horner–Emmons reactions; 7-azatryptamine.
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Table 1.

Compound	R^1	R^2	R^5	Compound	Yield (%)	Compound	Yield (%)
1a	Ac	H	H			**4a**[a]	86
1b	Ac	CH_3	H	**3b**	72		
1c	Ac	C_6H_5	H	**3c**	75		
1d	Ac	4-CH_3Bn	OCH_3	**3d**	72		
1e	Ac	Bn	H			**4e**[15]	86[b]
1f	Ac	OCH_3	H	**3f**[14]	99[b]		
1g	$SO_2C_6H_5$	H	H			**4g**	32
1h	$SO_2C_6H_5$	4-CH_3Bn	H	**3h**	0	**4h**	0

Bn=Benzyl
[a] Methyl ester of **4a** was also described by Sakamoto.[15]
[b] **4e** in refluxing toluene and **3f** were obtained by Sakamoto[14] as methyl ester, in refluxing benzene.

the ethyl indoleacetates **4a** or **4e**.[15] Formation of **4e** was explained by isomerization of **3e** to the more stable structure **4e**. Compounds **3** were obtained as *Z* isomers predominantly due to the steric demand of the transition states to form the oxaphosphetane.[14]

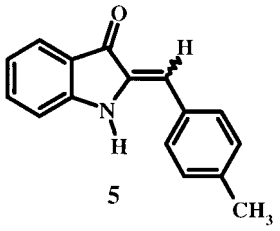

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Figure 2.

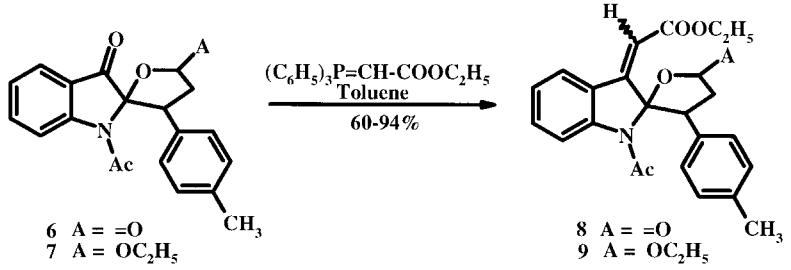
The protection of the nitrogen atom with a sulfonyl group dramatically modifies the reactivity; so compound **1g** afforded only in 32% yield the indolic compound **4g**; the 2-substituted indolinone **1h**, obtained by catalytic hydrogenation of 2-[(1-(4-methylphenyl)methylidene]-1-phenylsulfonyl-1*H*-indol-3-one, did not give condensation product but rather, the formation of the desulfonylated α,β-ethylenic ketone **5**[20] in 64% yield (Fig. 2).

The relative inertness of 1-acetyl-2-methoxy-2-benzyl-1*H*-indol-3-one **1f** towards Wittig reagents has already been reported;[14] nevertheless, spiroindolinones **6** and **7** (single diastereomers), obtained from the oxidation of pyrano-[2,3-*b*]indole,[12] cleanly reacted with the ethoxycarbonylmethylenephosphorane to give the ethylenic esters **8** and **9**, respectively, in 60 and 94% yield, as a *E*/*Z* mixture (ratio 4:7 for **8**, 7:3 for **9**) (Chart 2).

Using the allyl substituted ylide, ($[(C_6H_5)_3]P{=}C(CH_2CH{=}CH_2)COOC_2H_5$), with the more reactive indolinone **1a** afforded only decomposition of the mixture, after extending heating in toluene; no Cope rearrangement was observed.

The reactivity of the carbonyl group of indolinone **1** is obviously dependant on the substituent of the nitrogen atom; the phenylsulfonyl group decreased the reactivity of indolinone **1** towards Wittig reagent. The electron withdrawing effect of this substituent might stabilize the enol form of **1** compared to the acetyl group.

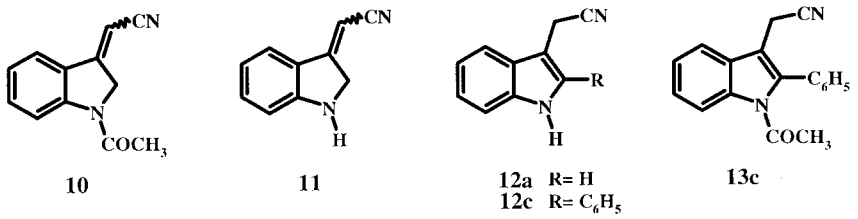
These studies should be compared with our previous works to synthetize tryptamine derivatives.[5–7] If diethyl cyanomethanephosphonate was used to perform Horner–Emmons



6 A = =O
7 A = OC_2H_5

8 A = =O
9 A = OC_2H_5

Chart 2.



10 **11** **12a** R= H, **12c** R= C_6H_5 **13c**

Figure 3.

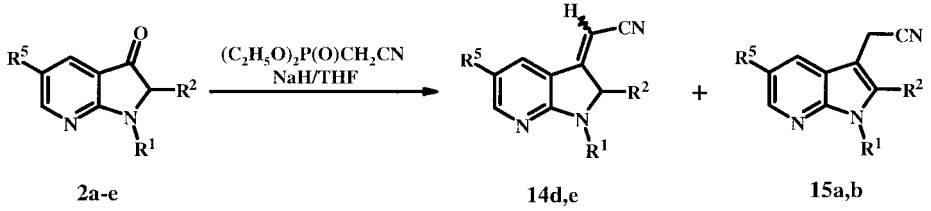


Chart 3.

Table 2.

Compound	R^1	R^2	R^5	Compound	Yield (%)	Compound	Yield (%)
2a	Ac	H	H	**14a**	0	**15a**	25
2b	$SO_2C_6H_5$	H	H	**14b**	0	**15b**	60
2c	$SO_2C_6H_5$	4-CH_3OBn	H	**14c**	0	**15c**	0
2d	CO*t*-Bu	OCH_3	H	**14d**	69	**15d**	0
2e	CO*t*-Bu	OCH_3	Br	**14e**	55	**15e**	0

reaction in the presence of indolinone **1a**, a mixture of α,β-ethylenic nitriles **10**, **11** and indolacetonitrile **12a** has been isolated. The α,β-ethylenic nitriles **10** and **11** were always the minor isomers and could be quickly isomerized in basic medium into compound **12a** (Fig. 3). Indolinone **1c** gave exclusively the indolic structures **12c** and **13c** in a ratio 62:38 (Among all the indolinones **1** used, only **1c** gave the acetylated indolic product **13c**).

In order to prepare more tryptamine derivatives, 7-azaindolinone **2** has been considered to be an excellent synthon; we started this program few years ago considering the rather poor investigation[21–25] done on this moiety, despite the biological potential of 7-azaindoles: NADH models,[26] mimics of adenosine base[27] and dopaminergic ligands.[28]

We discovered that the 7-azaindolinones **2a**–**e** behaved differently in the presence of phosphonate derivatives compared to the indole counterparts (Chart 3); the unsubstituted azaindolinones in 2-position, **2a** and **b**, afforded the 7-azaindoleacetonitriles **15a** and **b** in 25 and 60% yield, respectively; but if a pivaloyl group is used as a protecting group on the nitrogen atom, the ketones **2d** and **e** afforded the ethylenic nitriles **14d** and **e** in 69 and 55% yield (Table 2).

Compounds **14d** and **e** were obtained as a mixture of *E*/*Z* isomers in ratio 50:50 and 42:58, respectively. Compound **14d** heated in toluene in the presence of a catalytic amount of sodium hydroxide gave the isomeric compound **15d**; but purification of **15d** on a silica gel column gave back **14d**, so compound **15d** was only obtained as trace amount. The 1-sulfonyl-2-[(4-methoxyphenyl)methyl]-7-azaindolinone **2c** did not afforded neither **14c** nor **15c**, but rather the unexpected compound **17** (Chart 4).

The catalytic hydrogenation conditions over palladium, usually used in the indolinone series, for preparing the 2-benzylindolinones **1d** and **e** from the corresponding α,β-ethylenic ketone[6,7] were unfruitful in the 7-azaindolinone series. Therefore, **2c** was prepared in 72% yield by ionic reduction (triethylsilane/trifluoroacetic acid) of the double bond of compound **16**[10,11] (Chart 4).

The diethyl cyanomethanephosphonate anion did not react with the keto group in 3-position of the 7-azaindolinone **2c** as indicated *supra* but afforded unexpectedly, the 7-azaindolinone **17** (76% yield) substituted in 2-position, as a result of the alkylation of the methylene group of the diethyl cyanomethanephosphonate. Compound **17** was obtained as a mixture of diastereomers in the ratio 47:53.

The formation of **17** can be explained as shown in Chart 5; first a desulfonylation reaction in basic medium which generates an imine intermediate (A), then followed by an addition of the nucleophilic phosphonate on the C-2 carbon atom. The spectroscopic data of **17** were compatible with the presence of a carbonyl and a cyano group; in the ^1H NMR spectrum, a coupling constant of 22.8 Hz (J_{P-CH}) indicates a connection P–CH–CN. The molecular peak in mass spectra is observed at 429.

In order to check this hypothesis of a nucleophilic attack on the C-2 carbon atom of **2c**, we reacted the dimethyl malonate anion with **2c**; the substituted malonate **18** was obtained (Fig. 4) in 94% yield, as the result of a nucleophilic

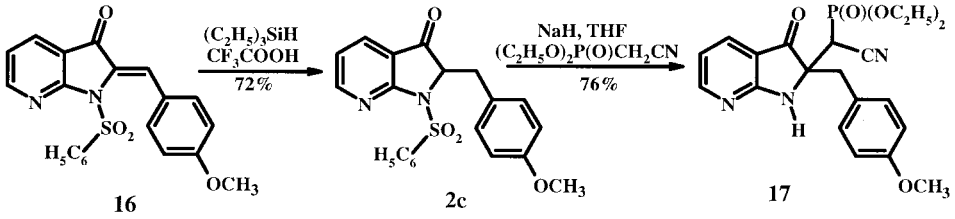


Chart 4.

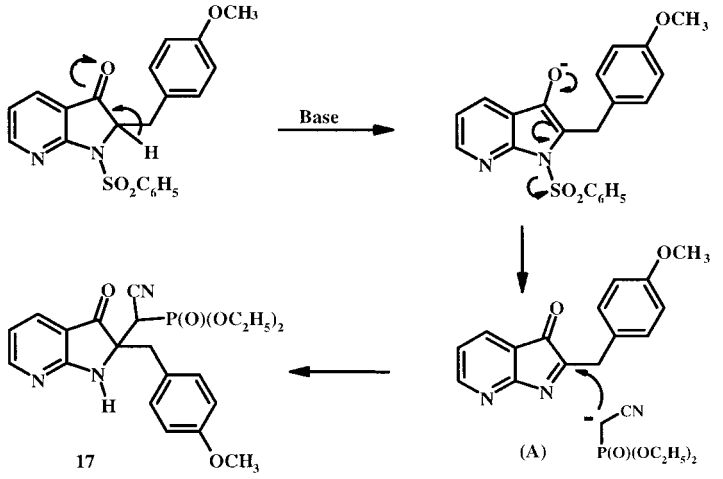


Chart 5.

attack on the C-2 carbon atom. The structure of **18** is in agreement *inter alia* with its ^{13}C NMR spectrum: a quaternary carbon atom C_2 at 68.4 ppm, a CH at 57.1 ppm, two CO at 166.2 and 168.2 ppm and finally a CO at 199.3 ppm; the molecular mass is equal to 384.

The formation of an imine intermediate with indolic structure, postulated in Chart 5 is frequently observed.[14b] For instance, we have recently described nucleophilic alkylation in 2-position of 3-indolic triflate via an iminium intermediate.[29,30]

We have precedently[5,7] shown that the mixture of indolic nitriles **10**, **11** and **12** upon hydrogenation with Raney nickel gave a sole tryptamine **19** (Fig. 4). The reduction of the nitrile function of the 7-azaderivative **15b** was not so easy as for the corresponding indolic nitrile **12a**. Hydrogenation over Raney nickel afforded the desulfonylated nitrile compound **20**[31] in 60% yield; the use of lithium aluminium hydride gave a mixture of the tryptamine **21** (30%) and starting material **15b** (35%). Using Adams' catalyst (PtO_2) in hydrogenation, at atmospheric pressure, in ethanol/THF afforded the desired 7-azatryptamine **21**[32] in 51% yield (Chart 6).

In this paper, we have shown the importance of the nature of substituents on the nitrogen and carbon C-2 atoms in indolinones **1** and **2** towards the reactivity with Wittig and Horner–Emmons reagents. A different behavior was observed between indolinone **1** and 7-azaindolinone **2**, notably in the susceptibility of nucleophilic attack on the C-2 carbon atom.

1. Experimental

1.1. General

^1H and ^{13}C NMR spectra were obtained with a Brüker instrument Avance DPX250 (250 MHz); for samples in $CDCl_3$ solution with TMS as internal standard, chemical shifts (δ values) were reported in ppm and coupling constants (J values) in Hz. IR were recorded as a thin film on NaCl plates for the oils and in KBr pellet for the solids on a Perkin Elmer spectrometer FT Paragon 1000PC. Mass spectra were recorded on a Perkin Elmer mass spectrometer SCIEX API 300 (ion spray). Mps were measured using a Kofler hot stage apparatus and are uncorrected. Flash chromatography was performed on silica gel Merck 60,

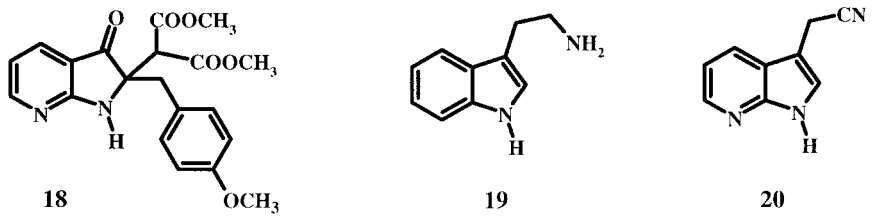


Figure 4.

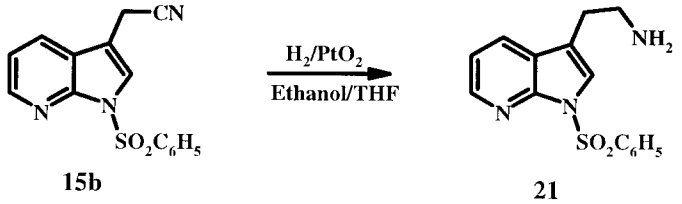


Chart 6.

230–400 mesh). Compounds **2a**,[10] **2b**,[12] **2d**,[11] **2e**[11] and **16**[10] have been previously described.

1.1.1. 2-(4-Methoxyphenyl)methyl-1-phenylsulfonyl-1,2-dihydropyrrolo[2,3-*b*]pyridin-3-one (2c). Under nitrogen atmosphere, trifluoroacetic acid is added dropwise (0.423 ml, 5.50 mmol) to a solution of **16** (276 mg, 0.55 mmol), triethylsilane (0.01 ml, 0.61 mmol) in dichloroethane (10 ml) at rt. The mixture was refluxed for 7 h. After cooling, water (15 ml) was added and after neutralisation, the mixture was twice extracted with CH_2Cl_2 (2×10 ml); drying over $MgSO_4$, evaporation under vacuum and purification on a silica gel column (elution CH_2Cl_2) afforded **2c**; m 156 mg; yield 72%. Mp 171–173°C (Ethanol). IR (film): 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.45 (1H, dd, J=3.0, 14.0 Hz, CH_2), 3.60 (1H, dd, J=5.9, 14.0 Hz, CH_2), 3.65 (3H, s, OCH_3), 4.62 (1H, dd, J=3.0, 5.9 Hz, H_2), 6.61 (2H, d, J=8.8 Hz, H_{arom}), 6.93 (1H, dd, J=5.2, 7.4 Hz, H_5), 7.05 (2H, d, J=8.8 Hz, H_{arom}), 7.46–7.52 (2H, m, H_{arom}), 7.56–7.62 (1H, m, H_{arom}), 7.71 (1H, dd, J=2.2, 7.4 Hz, H_4), 8.09 (2H, d, J=7.4 Hz, H_{arom}), 8.48 (1H, dd, J=2.2, 5.2 Hz, H_6). MS (NH_3) m/z: 395 (MH^+). Anal. calcd for $C_{21}H_{18}N_2O_4S$: C, 63.95; H, 4.60; N, 7.10. Found: C, 64.31; H, 4.43; N, 7.27.

1.2. Reaction of indolinones 1 with ethoxycarbonylmethylenetriphenylphosphorane: general procedure

A solution of indolinone **1** (2 mmol), ethoxycarbonylmethylenetriphenylphosphorane (4.5 mmol) in toluene (20 ml) was refluxed for 24 h. Water (20 ml) was added, the toluene layer was decanted and the aqueous layer was twice extracted with CH_2Cl_2 (2×15 ml); after drying over $MgSO_4$ and evaporation, the residue was chromatographed on a silica gel column using ethyl acetate: petroleum ether 1:9 (v/v) as eluent.

1.2.1. Ethyl 2-(1-acetyl-2-methyl-2,3-dihydro-1*H*-3-indolyliden)acetate (3b). Yield 72%. Mp 97–99°C (ethanol). IR (KBr): 1694, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.2 Hz, CH_3), 1.52 (3H, d, J=6.2 Hz, CH_3), 2.35 (3H, s, $COCH_3$), 4.20 (2H, q, J=7.2 Hz, OCH_2), 5.62–5.64 (1H, m, CH), 6.16 (1H, brs, CH=), 7.11 (1H, t, J=7.8 Hz, H_{arom}), 7.42 (1H, t, J=7.8 Hz, H_{arom}), 7.53 (1H, d, J=7.8 Hz, H_{arom}), 8.32 (d, 1H, J=7.8 Hz, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 14.7 (CH_3), 21.3 (CH_3), 23.8 (CH_3), 60.7 (CH_2), 61.1 (CH), 106.3 (CH), 118.9 (CH), 122.0 (CH), 124.6 (CH), 126.3 (C), 133.4 (CH), 144.5 (C), 157.2 (C), 165.5 (CO), 167.4 (CO). Anal. calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.18; H, 6.40; N, 5.59.

1.2.2. Ethyl 2-(1-acetyl-2-phenyl-2,3-dihydro-1*H*-3-indolyliden)acetate (3c). Yield 75%. Mp 111–113°C (ethanol). IR (film): 1704, 1673 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.2 Hz, CH_3), 2.12 (3H, s, $COCH_3$), 4.16 (2H, m, OCH_2), 6.16 (1H, d, J=1.9 Hz, CH=); 6.61 (1H, d, J=1.9 Hz, CH), 7.15–7.32 (6H, m, H_{arom}), 7.47 (1H, t, J=7.8 Hz, H_{arom}), 7.56 (1H, d, J=7.8 Hz, H_{arom}), 8.44 (1H, d, J=7.8 Hz, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 14.2 (CH_3), 24.4 ($COCH_3$), 60.2 (CH_2), 66.9 (CH), 107.4 (CH), 117.8 (CH), 121.6 (CH), 124.3 (CH), 124.3 (C), 127.4 (2×CH), 128.2 (CH), 128.4 (2 CH), 133.1 (CH), 138.9 (C), 146.6 (C), 155.7 (C), 165.8 (CO), 168.8 (CO). Anal. calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 75.07; H, 6.12; N, 4.20.

1.2.3. Ethyl 2-[1-acetyl-2-(4-methylbenzyl)-5-methoxy-2,3-dihydro-1*H*-3-indolyliden]acetate (3d). Yield 72%. Oil. IR (film): 1705, 1670 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.2 Hz, CH_3), 1.69 (3H, s, CH_3), 2.23 (3H, s, $COCH_3$), 2.81 (1H, dd, J=7.5, 13.5 Hz, CH_2), 3.20 (1H, dd, J=3.5, 13.5 Hz, CH_2), 3.75 (3H, s, OCH_3), 4.26 (2H, q, J=7.2 Hz, OCH_2), 5.75 (1H, brd, J=4.1 Hz, CH), 6.16 (1H, d, J=1.7 Hz, CH=), 6.80–7.05 (6H, m, H_{arom}), 8.12 (1H, d, J=8.9 Hz, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 14.2 (CH_3), 21.0 (CH_3), 22.8 (CH_3), 41.3 (CH_2), 55.6 (OCH_3), 60.3 (OCH_2), 66.2 (CH), 104.7 (CH), 106.3 (CH), 119.5 (CH), 119.8 (CH), 127.6 (C), 129.0 (2×CH), 129.8 (2×CH), 133.3(C), 136.5 (C), 139.8 (C), 156.4 (C), 157.9 (C), 166.2 (CO), 168.3 (CO). Anal. calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.59; H, 6.47; N, 3.83.

1.2.4. Ethyl 2-(1-phenylsulfonyl-2,3-dihydro-1*H*-indol-3-yl)acetate (4g). Yield 32%. Oil. ^1H NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.5 Hz, CH_3), 3.67 (2H, s, CH_2), 4.13 (2H, q, J=7.5 Hz, OCH_2), 7.20–7.51 (6H, m, H_{arom}), 7.57 (1H, s, CH=), 7.86–7.89 (2H, m, H_{arom}), 7.98 (1H, d, J=7.9 Hz, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 14.1 (CH_3), 31.0 (CH_2), 61.0 (OCH_2), 113.6 (CH), 115.3 (C), 119.5 (CH), 123.3 (CH), 124.6 (CH), 124.9 (CH), 126.7 (2×CH), 129.2 (2×CH), 130.4 (C), 133.7 (CH), 135.0 (C), 138.2 (C), 170.4 (CO). Anal. calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.64; H, 4.77; N, 3.95.

1.2.5. Spiro[(3-{4-methylphenyl}-tetrahydro-5-furanone)-2,2′(ethyl{1′-acetyl-2′,3′-dihydro-1*H*-3′-indolyliden}acetate)] (8). Compound **6**[12] (65 mg. 0.194 mmol) was dissolved in toluene (2 ml), and carbethoxymethylene triphenylphosphorane (236 mg, 0.679 mmol) was added; the mixture was refluxed for 24 h. After evaporation, the residue was purified by silica gel column chromatography using CH_2Cl_2/petroleum ether 1:1 (v/v) as eluent; two isomers *E* and *Z* were obtained (ratio 36:64); m=40 mg. Yield 60%. Mp 60–62°C (mixture of isomers *E* and *Z*). IR (KBr): 1800, 1715, 1670 cm^{-1}. *E* isomer: ^1H NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.0 Hz, CH_3), 2.15 (3H, s, CH_3), 2.48 (3H, s, $COCH_3$), 3.12 (1H, dd, J=8.7, 18.2 Hz, CH_2), 3.28 (1H, dd, J=10.3, 18.2 Hz, CH_2,), 4.09 (2H, q, J=7.0 Hz, OCH_2), 4.48 (1H, dd, J=8.7, 10.3 Hz, CH), 5.57 (1H, s, CH=), 6.70 (2H, d, J=8.1 Hz, H_{arom}), 6.85 (2H, d, J=8.1 Hz, H_{arom}), 6.94 (1H, t, J=7.7 Hz, H_{arom}), 7.28–7.37 (2H, m, H_{arom}), 8.29 (1H, d, J=7.7 Hz, H_{arom}). *Z* isomer: ^1H NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.1 Hz, CH_3), 2.15 (3H, s, CH_3), 2.49 (3H, s, $COCH_3$), 3.16 (1H, dd, J=11.1, 17.4 Hz, CH_2), 3.57 (1H, dd, J=7.9, 17.4 Hz, CH_2), 4.08 (2H, q, J=7.1 Hz, OCH_2), 4.60 (1H, dd, J=7.9, 11.1 Hz, CH), 5.96 (1H, s, CH=), 6.75 (2H, d, J=7.9 Hz, H_{arom}), 6.79 (2H, d, J=7.9 Hz, H_{arom}), 6.98 (1H, t, J=7.7 Hz, H_{arom}), 7.25 (1H, d, J=7.7 Hz, H_{arom}), 7.28–7.37 (2H, m, H_{arom}). MS (NH_3) m/z: 406 (MH^+).

1.2.6. Spiro[(3-{4-methylphenyl}-5-ethoxytetrahydrofurane)-2,2′(ethyl{1′-acetyl-2′,3′-dihydro-1*H*-3′-indolyliden}acetate)] (9). Similarly obtained as for **8** starting from compound **7**. Two isomers *E* and *Z* were obtained (ratio 7:3). Yield 94%. Mp 126–128°C (mixture of isomers *E* and *Z*). IR (KBr): 1710, 1670 cm^{-1}. *E* isomer: ^1H RMN

($CDCl_3$) δ: 1.16–1.32 (6H, m, $COOCH_2CH_3$ and OCH_2CH_3), 2.04 (3H, s, CH_3), 2.18 (1H, dd, J=7.0, 13.8 Hz, CH_2), 2.63 (3H, s, $COCH_3$), 2.91 (1H, ddd, J= 6.3, 13.5, 13.8 Hz, CH_2), 3.52–4.25 (4H, m, $COOCH_2$ and OCH_2), 4.04 (1H, dd, J=7.0, 13.5 Hz, CH), 5.65 (1H, d, J=6.3 Hz, HCO), 5.69 (1H, s, CH═), 6.60–6.85 (5H, m, H_{arom}), 7.10–7.19 (1H, m, H_{arom}), 7.95 (1H, d, J=7.9 Hz, H_{arom}), 8.15 (1H, d, J=7.9 Hz, H_{arom}). *Z* isomer: ^{1}H RMN ($CDCl_3$) δ: 1.16–1.32 (6H, m, $COOCH_2CH_3$ and OCH_2CH_3), 2.06 (3H, s, CH_3), 2.18 (1H, dd, J=7.0, 13.8 Hz, CH_2), 2.64 (3H, s, $COCH_3$), 3.31 (1H, ddd, J= 6.3, 13.5, 13.8 Hz, CH_2), 3.52–4.25 (4H, m, $COOCH_2$ and OCH_2), 4.09 (1H, dd, J=7.0, 13.5 Hz, CH), 5.55 (1H, d, J=6.3 Hz, HCO), 6.04 (1H, s, CH═), 6.60–6.85 (6H, m, H_{arom}), 7.10–7.19 (1H, m, H_{arom}), 8.07 (1H, d, J=7.9 Hz, H_{arom}). Anal. calcd for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 72.03; H, 6.55; N, 3.37.

1.3. General procedure for Horner–Emmons reactions with indolinones 1 or 7-azaindolinones 2

To a suspension of sodium hydride (0.46 mmol) in THF (2 ml) at 0°C, the diethyl cyanomethane phosphonate (0.46 mmol) was added dropwise; after disappearance of the sodium hydride, the 7-azaindolinone (0.23 mmol) in THF (2 ml) was added dropwise to the solution; the mixture was stirred for 2 h at 0°C then for 1 h at rt. Water (4 ml) and CH_2Cl_2 (4 ml) were added; the aqueous layer was made neutral with addition of diluted HCl and twice extracted with CH_2Cl_2 (2×5 ml). After drying of the organic layers over $MgSO_4$ and evaporation, the residue was purified by column chromatography on a silica gel column using CH_2Cl_2 as eluent.

1.3.1. (2-Phenyl-1*H*-3-indolyl)acetonitrile (12c) and (1-acetyl-2-phenyl-1*H*-3-indolyl)acetonitrile (13c). Obtained as a mixture: 62:38. Yield 48%. Oil. IR (film): 3250, 2250, 1710 cm^{-1}. **12c**: ^{1}H NMR ($CDCl_3$) δ: 3.88 (2H, s, CH_2), 7.25–7.75 (9H, m, H_{arom}), 8.37 (1H, brs, NH). Characteristic signals for ^{13}C NMR ($CDCl_3$) δ: 13.9 (CH_2), CH and C signals for the mixture of **12c** and **13c** can be attributed to **12c** and/or **13c**. MS (NH_3) *m/z*: 233 (MH^+). **13c**: ^{1}H NMR ($CDCl_3$) δ: 1.98 (3H, s, $COCH_3$), 3.56 (2H, s, CH_2), 7.25–7.75 (8H, m, H_{arom}), 8.45 (1H, dd, J=1.3, 7.5 Hz, H_7arom). Characteristic signals for ^{13}C NMR ($CDCl_3$) δ: 13.8 (CH_2), 29.4 (CH_3), 171.1 (CO). MS (NH_3) *m/z*: 275 (MH^+).

1.3.2. 2-[1-(2,2-Dimethylpropanoyl)-2-methoxy-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yliden]acetonitrile (14d). Elution CH_2Cl_2. Yield 69%. Mixture *E*/*Z* 50:50. Oil. IR (film): 2200, 1660 cm^{-1}. *E* isomer ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s, 3×CH_3), 3.32 (3H, s, OCH_3), 5.67 (1H, d, J= 1.5 Hz, CH), 6.33 (1H, d, J=1.5 Hz, CH═), 7.06 (1H, dd, J=5.2, 8.1 Hz, H_5), 8.35–8.38 (1H, m, H_6), 8.45 (1H, dd, J=1.5, 8.1 Hz, H_4). *Z* isomer:1.49 (9H, s, 3×CH_3), 3.62 (3H, s, OCH_3), 5.84 (1H, d, J=2.2 Hz, CH), 6.47 (1H, d, J= 2.2 Hz, CH═), 6.99 (1H, dd, J=5.2, 8.1 Hz, H_5), 7.72 (1H, dd, J=1.5, 8.1 Hz, H_4), 8.35–8.38 (1H, m, H_6). Anal. calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.02; H, 6.44; N, 15.37.

1.3.3. 2-[5-Bromo-1-(2,2-dimethylpropanoyl)-2-methoxy-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yliden]acetonitrile (14e). Elution CH_2Cl_2. Yield 55%. Mixture *E*/*Z* 42:58. Mp 214–216°C. IR (film): 2200, 1660 cm^{-1}. *E* isomer: ^{1}H NMR ($CDCl_3$) δ: 1.44 (9H, s, 3×CH_3), 3.34 (3H, s, OCH_3), 5.73 (1H, d, J=1.5 Hz, CH), 6.33 (1H, d, J=1.5 Hz, CH═), 8.43 (1H, d, J=2.2 Hz, H_6), 8.52 (1H, d, J=2.2 Hz, H_4). *Z* isomer: 1.44 (9H, s, 3×CH_3), 3.69 (3H, s, OCH_3), 5.85 (1H, d, J=2.2 Hz, CH_2), 6.46 (1H, d, J=2.2 Hz, CH═), 7.82 (1H, d, J=2.2 Hz, H_4), 8.41 (1H, d, J=2.2 Hz, H_6,). Anal. calcd for $C_{15}H_{16}BrN_3O_2$: C, 51.44; H, 4.60; N, 12.00. Found: C, 51.81; H, 4.40; N, 12.16.

1.3.4. 2-(1-Acetyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetonitrile (15a). Mp 127–129°C (ethanol/petroleum ether). Yield 25%. IR (KBr): 2240, 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.06 (3H, s, CH_3), 3.78 (2H, s, CH_2), 7.28 (1H, dd, J=5.2, 8.1 Hz, H_5), 7.94 (1H, dd, J=1.5, 8.1 Hz, H_4), 8.09 (1H, s, H_2), 8.45 (1H, dd, J=1.5, 5.2 Hz, H_6). MS (NH_3) *m/z*: 200 (MH^+). Anal. calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.11; H, 4.35; N, 20.94.

1.3.5. 2-(1-Phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) acetonitrile (15b). Mp 187–189°C (ethanol). IR (KBr): 2250 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.77 (2H, s, CH_2), 7.25 (1H, dd, J=5.2, 8.1 Hz, H_5), 7.48–7.52 (2H, m, H_{arom}), 7.58–7.62 (1H, m, H_{arom}), 7.78 (1H, s, H_2), 7.89 (1H, dd, J=1.5, 8.1 Hz, H_4), 8.19–8.23 (2H, m, H_{arom}), 8.50 (1H, dd, J=1.5, 5.2 Hz, H_6). MS (NH_3) *m/z*: 298 (MH^+). Anal. calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.41; H, 3.88; N, 14.30.

1.3.6. 2-[1-(2,2-Dimethylpropanoyl)-2-methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]acetonitrile (15d). Obtained as trace compound after purification on a silica gel column chromatography (CH_2Cl_2) of the products resulting of the isomerization of **14d** (heating in toluene at reflux for 24 h in presence of a catalytic amount of sodium hydroxide). ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s, CH_3), 3.72 (2H, s, CH_2), 4.04 (3H, s, OCH_3), 7.13 (1H, dd, J=5.2, 7.9 Hz, H_5), 7.81 (1H, d, J=7.9 Hz, H_4), 8.29 (1H, d, J=5.2 Hz, H_6).

1.3.7. Diethyl cyano-[2-(4-methoxybenzyl-3-oxo-2,3-dihydro-1*H*-2-pyrrolo[2,3-*b*]pyridin-2-yl]methylphosphonate (17). Mixture of diasteromers A and B, 47:53. Yield 76%. Oil. IR (film): 3240–3140 (NH), 2200 (CN), 1705 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$+D_2O) δ: 1.15–1.45 (6H, m, CH_{3A+B}), 3.06 (1H, d, J=14.0 Hz, CH_{2A}), 3.19 (1H, d, J= 14.0 Hz, CH_{2B}), 3.30 (1H, d, J=14.0 Hz, CH_{2B}), 3.42 (1H, d, J=14.0 Hz, CH_{2A}), 3.61 (3H, s, OCH_{3B}), 3.63 (3H, s, OCH_{3A}), 3.67 (1H, d, J=22.8 Hz, P–CH_A), 3.70 (1H, d, J=22.8 Hz, P–CH_B), 4.00–4.45 (4H, m, OCH_{2A+B}), 6.55–6.62 (3H, m, $2H_{aromA+B}$+H_{5A+B}), 6.95–7.05 (2H, m, $H_{aromA+B}$), 7.63 (1H, dd, J=1.5, 7.4 Hz, H_{4A+B}), 8.21 (1H, dd, J=1.4, 5.2 Hz, H_{6B}), 8.27 (dd, J=1.4, 5.2 Hz, 1H, H_{6A}). MS (NH_3) *m/z*: 430 (MH^+). Anal. calcd for $C_{21}H_{24}N_3O_5P$: C, 58.74; H, 5.63; N, 9.79. Found: C, 58.37; H, 5.46; N, 9.93.

1.3.8. Dimethyl 2-[(4-methoxybenzyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo-[2,3-*b*]pyridin-2-yl)]malonate (18). Dimethyl malonate (50 mg, 0.38 mmol) were added to a cooled (0°C) suspension of NaH (9 mg, 0.38 mmol) in THF (5 ml); after disappearance of NaH, compound **2c** (100 mg, 0.25 mmol) in THF (5 ml) was added dropwise; the mixture was stirred

for 1 h at 0°C then for 3 h at rt. Water (10 ml) was added and the solution was made neutral; extraction with CH_2Cl_2 (3×15 ml), drying over $MgSO_4$ and evaporation in vacuo leave a yellow solid which was purified by column chromatography using CH_2Cl_2 as eluent; *m*=90 mg. Yield 94%. Mp 215–217°C (ethanol/petroleum ether). IR (KBr): 3180 (NH), 1730, 1700 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.97 (1H, d, *J*=14 Hz, CH_2), 3.05 (1H, d, *J*=14 Hz, CH_2), 3.53 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.13 (1H, s, CH), 6.40 (1H, brs, NH), 6.56 (1H, dd, *J*=5.2, 8.1 Hz, H_5), 6.61 (2H, d, *J*=8.8 Hz, H_{arom}), 7.00 (2H, d, *J*=8.8 Hz, H_{arom}), 7.62 (1H, d, *J*=8.1 Hz, H_4), 8.18 (1H, d, *J*=5.2 Hz, H_6). ^{13}C NMR ($CDCl_3$) δ: 40.8 (CH_2), 52.9 (2×$COOCH_3$), 55.1 (OCH_3), 57.1 (CH), 68.4 (C_2), 113.3 (2×CH), 114.4 (CH), 114.6 (C), 124.9 (C), 131.4 (2×CH), 132.3 (C), 132.7 (CH), 156.5 (CH), 158.6 (C), 166.2 (CO), 168.2 (CO), 199.3 (CO). MS (NH_3) *m/z*: 385 (MH^+). Anal. calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.35; H, 5.36; N, 7.38.

1.3.9. 2-(1-Phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethylamine (21). Compound **15b** (0.060 g, 0.2 mmol) was dissolved in a mixture of THF/ethanol (4 ml/4 ml) and PtO_2 (0.025 g) was added. The suspension was stirred under 1 atm. of hydrogen for 24 h at rt. After filtration and evaporation of the solvent, the residue was treated with ethanol containing a few drops of concentrated HCl; evaporation of the alcoholic solution left a residue which was treated with water, neutralized and extracted with CH_2Cl_2 (2×5 ml); drying over $MgSO_4$ and evaporation afforded **21**. Yield 51%. Mp 167–169°C (ethanol). IR (KBr): 3450–3250 (NH_2) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.60 (2H, brs, NH_2), 3.15 (2H, t, *J*=7.4 Hz, CH_2), 3.37 (2H, t, *J*=7.4 Hz, NCH_2), 7.42 (1H, dd, *J*=5.2, 8.1 Hz, H_5), 7.56–7.60 (2H, m, H_{arom}), 7.68–7.74 (1H, m, H_{arom}), 7.83 (1H, s, H_2), 8.01–8.05 (2H, m, H_{arom}), 8.11 (1H, d, *J*=8.1 Hz, H_4), 8.36 (1H, d, *J*=5.2 Hz, H_6). MS (NH_3) *m/z*: 302 (MH^+). Anal. calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 60.02; H, 5.17; N, 14.11.

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