ETHYL α-AMINO-β,β-DIETHOXYPROPIONATE, A USEFUL SYNTHON FOR THE PREPARATION OF 3,4-FUSED PYRIDINE-6-CARBOXYLATES FROM AROMATIC ALDEHYDES

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Abstract - An efficient synthesis of ethyl α-amino-β,β-diethoxypropionate (**1**), *via* a titanium tetrachloride-catalyzed coupling reaction of ethyl nitroacetate and triethyl orthoformate, is described. Condensation of **1** with various aldehydes followed by reduction and titanium tetrachloride-promoted cyclization of the products afforded 3,4-fused pyridine-6-carboxylates belonging to the azaindole, γ-carboline and isoquinoline families of heterocycles.

In connection with our ongoing studies of novel central nervous system agents, we recently described the use of ethyl α-amino-β,β-diethoxypropionate (**1**) as a building block for the synthesis of ethyl 6-azaindole-5-carboxylate (**3a**)[1] and ethyl β-carboline-3-carboxylate (**3b**),[2] both prototypic ligands of the benzodiazepine receptor.[3,4] The procedure involves condensation of **1** with an *N*-tosylpyrrole-2-carboxaldehyde (**2a**) or indole-2-carboxaldehyde (**2b**), reduction of the resulting imine bond with sodium cyanoborohydride followed by titanium tetrachloride-catalyzed cyclization of the product to give **3a** or **3b**, respectively. Because this methodology makes use of starting materials different from those generally employed for the preparation of compounds of type **3a** and **3b** (pyrroles and indoles, respectively, instead of pyridine[5,6] and tryptophan[7] derivatives), the

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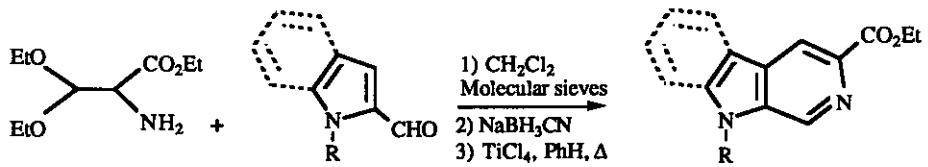
Dedicated to Professor Shigeru Oae on the occasion of his 77th birthday.

incorporation of a wider variety of substituents on the final products can be envisaged. Moreover, the reaction sequences of Scheme 1 can be conducted without isolation of the intermediates, overall yields for the three steps being of the order of 50-60%.



Scheme 1

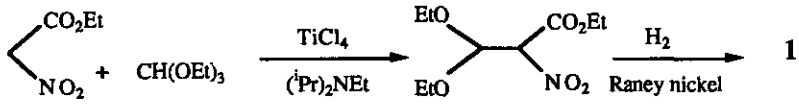
In order to better appreciate the generality of this novel and efficient method of preparing 3,4-fused pyridine-6-carboxylates, we have applied it to a number of 4-substituted pyrrole-2-carboxaldehyde derivatives as well as to other types of aromatic substrates. We present in this paper the results of these studies as well as an improved and more convenient procedure for the preparation of the important starting amino acetal (1).

Preparation of ethyl α-amino-β,β-diethoxypropionate (1).

Amino acetal 1 was originally prepared by Doyle and coworkers[8] by reacting the anion of formamidoglycine ethyl ester with ethyl formate to give the corresponding α-formylglycine derivative. By careful treatment of the latter with ethanolic hydrochloric acid, the formyl group was transformed into its diethyl acetal and the formamido group was cleaved giving **1**. Although 1 could effectively be obtained in large quantities by this method, the procedure is tedious and time-consuming and the final product is sometimes impure due to incomplete reaction at any of the three steps involved.

Based on Evans' studies[9] of the coupling reactions of titanium enolates with various electrophiles, including ortho esters, we have developed an improved preparative route to **1** starting from ethyl nitroacetate (**4**, Scheme 2). Thus, treatment of the latter with titanium tetrachloride, *N,N*-diisopropylethylamine and triethyl orthoformate afforded the diethyl acetal derivative (5) in almost quantitative yield. Hydrogenation of 5 in the presence of Raney nickel then produced the desired amine (1), again in almost quantitative yield. Compound (1), isolated by filtration of the catalyst and removal of the solvents *in vacuo*, was greater than 95% pure by ^{1}H-nmr and was used as such

for all subsequent reactions. It was identical in all respects to that prepared by the method of Doyle and coworkers.[8]



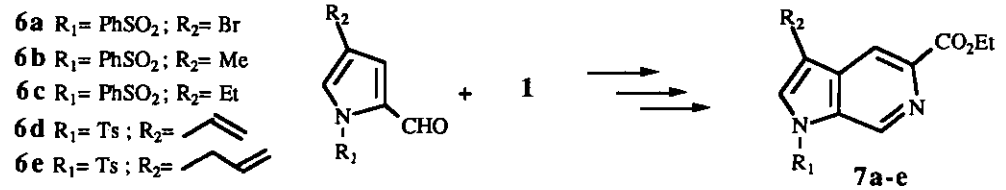
4 5

Scheme 2

Reaction of 1 with 4-substituted pyrrole-2-carboxaldehydes

In preparing the 6-azaindole-5-carboxylate derivative (**3a**) from **1**, we had observed that protection of the amine function of the starting pyrrole-2-carboxaldehyde (i.e., **2a**) was necessary in order to *a* - ensure efficient Schiff base formation with **1** and *b* - avoid intramolecular attack of the diethyl acetal function by the pyrrole nitrogen function after Schiff base formation, which would give pyrrolopyrazines instead of azaindoles.

The *N*-arylsulfonyl derivatives of the starting 4-substituted pyrrole-2-carboxaldehydes (4-bromo, 4-methyl, 4-ethyl, 4-allyl)[10,11] used in this study were thus prepared by treatment of the pyrroles with sodium hydride and benzenesulfonyl chloride (**6a-c**) or *p*-toluenesulfonyl chloride (**6e**) in THF (Scheme 3).[12] Each of these compounds was then reacted with **1** in dichloromethane in the presence of 4 Å molecular sieves to give an intermediate imine condensation product. The latter was reduced with sodium cyanoborohydride in ethanol and the resulting amine, after rudimentary purification by extractive procedures, was subjected to titanium tetrachloride-catalyzed cyclization in refluxing benzene. In the case of the 4-bromo derivative (**6a**) and the 4-alkyl derivatives (**6b**) and (**6c**), the expected 6-azaindole products (**7a-c**) were obtained in good yields (52 to 65% overall for three steps). In contrast, the 4-vinyl derivative (**6d**) failed to give the azaindole product (**7d**) under these reaction conditions. The problem in this case no doubt arises during the cyclization step since isolation and ^{1}H-nmr analysis of the intermediate imine condensation product and its subsequent reduction product showed that these had indeed been formed. It can be surmised that the additional

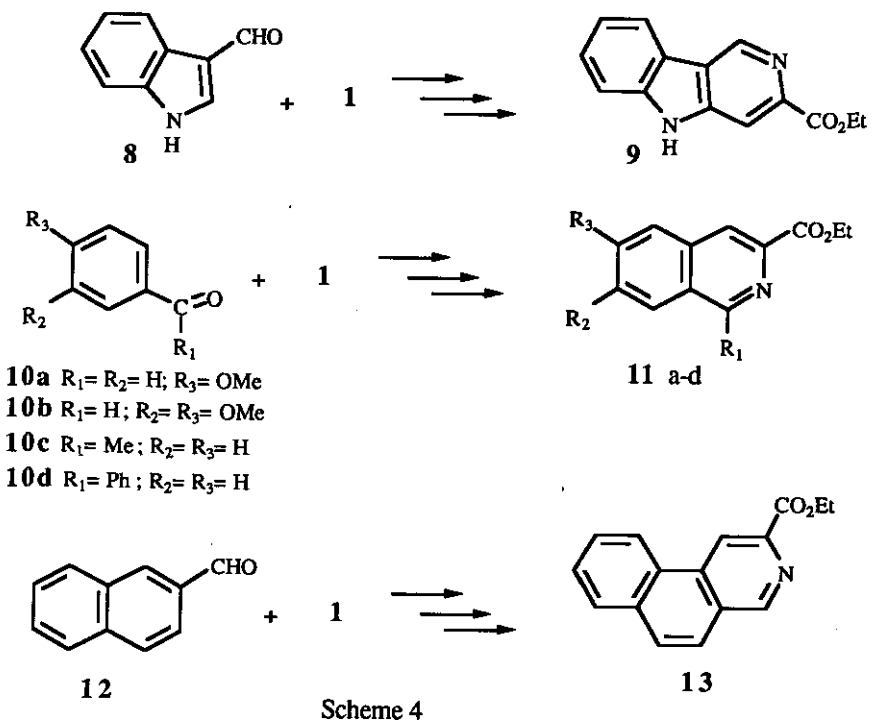


Scheme 3

delocalization of the nitrogen lone pair provided by the vinyl group inhibits or retards the titanium tetrachloride-catalyzed cyclization, leading to decomposition products instead. This hypothesis was substantiated by the observation that the 4-allylpyrrole-2-carboxaldehyde derivative (**6e**), in which the exocyclic double bond is no longer in conjugation with the pyrrole ring, does provide the azaindole product (**7e**) when reacted with **1** using the same reaction sequences. However, yields were low (~ 28%), probably due to isomerization of the allylic 2,3 double bond to the conjugated 1,2-position *via* a 1,3-proton shift.

Reaction of 1 with other types of aromatic aldehydes

We next turned our attention to the synthesis, using this technique, of other types of heterocycles containing a 3,4-fused pyridine-6-carboxylate motif. Thus, applied to indole-3-carboxaldehyde (**8**), the sequence of reactions consisting of condensation with **1**, imine reduction and titanium tetrachloride-catalyzed cyclization afforded ethyl γ-carboline-2-carboxylate (**9**) (Scheme 4) in 59%



Scheme 4

yield. In comparison, the methyl ester analogue of **9** has previously been prepared in low overall yield by a multistep procedure based on an Ullmann reaction.[13] The spectral properties of **9**, all

compatible with the proposed structure, were also similar to the published values for the methyl ester derivative. It is interesting to note, moreover, that, as in the case of indole-2-carboxaldehyde (**2b**) (giving β-carboline **3b**) and unlike when pyrrole-2-carboxaldehyde derivatives are used, protection of the nitrogen function is not necesssary in the case of **8**.

Titanium tetrachloride-catalyzed cyclization of the acetal function of **1** can also be effected on aryl-type substrates (i.e., in the absence of a ring nitrogen or other electron-donating heteroatom) as the following examples demonstrate. Thus, reaction of 4-methoxy- and 3,4-dimethoxybenzaldehyde (**10a, 10b**) with **1** gave the corresponding ethyl isoquinoline-3-carboxylates (**11a**) and (**11b**), respectively. Both **11a**[14] and the methyl ester analogue[15] of **11b** have been prepared by Pictet-Spengler reactions using the appropriate phenylalanine derivatives as starting materials. The physical and spectral characteristics of the compounds prepared by our method were identical (**11a**) or similar (**11b**) to the published values. Similarly, reaction of **1** with acetophenone (**10c**) provided the 1-methylisoquinoline derivative (**11c**), identical to that prepared via another route.[16] The use of benzophenone (**10d**) as starting material did not allow synthesis of the 1-phenylisoquinoline derivative (**11d**) ; this failure can be attributed to the inability to form the initial imine intermediate from **1** and **10d**, perhaps due to steric factors. The reaction route also failed when electron-withdrawing substituents were present on the aromatic ring (e.g., 4-nitro- and 2-bromobenzaldehyde).

Finally, naphthalene-2-carboxaldehyde (**12**) proved to be a satisfactory substrate, reacting with **1** to afford the benzoisoquinoline compound (**13**). That cyclization had occurred at the C-1 position of naphthalene instead of the C-3 position was clearly indicated by the ^{1}H-nmr spectrum of **13**, in which H-5 was observed as a doublet, coupled to H-6. Electrophilic reactions at C-1 of naphthalenes are the most commonly observed.

In conclusion, the present results demonstrate that ethyl α-amino-β,β-diethoxypropionate (**1**) is an easily prepared and very useful building block for the preparation of a variety of fused pyridinecarboxylate heterocycles, including 6-azaindoles, β- and γ-carbolines and isoquinolines, starting from the appropriate aromatic aldehydes (or ketones).

Table I. Reactions of **1** with **6a-e, 6e, 8, 10a-d** and **12**

	Reaction Time (h)		
Product	Imine formation	Cyclization	Yield(%)*
7a	12	3	52
7b	10	0.5	65
7c	12	3	55
7d	10	3	0**
7e	8	1	28
9	40	2	59
11a	30	1.5	65
11b	40	2	83
11c	40	1.5	54
11d	60	-	0***
13	48	2	69

* Isolated overall yields for the 3 steps. ** Only decomposition products were observed after $TiCl_4$ treatment. *** Imine formation was not observed.

EXPERIMENTAL

General - Melting points were determined on a Büchi apparatus and are uncorrected. Ir spectra of samples were obtained either as KBr pellets, as films, or in solution with a Nicolet 205 FT-IR spectrometer. ^{1}H-Nmr and ^{13}C-nmr spectra were determined on a Bruker 250 MHz instrument. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High resolution mass spectra were obtained using a Kratos MS-80 spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with uv light (254 nm) and with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230-400 mesh) at medium pressure (200 mbar). All reagents were purchased from the Aldrich Chemical Co. and were

used without further purification. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

Ethyl α-nitro-β,β-diethoxypropionate (5) - To a solution of ethyl nitroacetate (**4**) (1 g, 7.5 mmol) in anhydrous dichloromethane (25 ml) held at - 10°C under an argon atmosphere was slowly added by syringe titanium tetrachloride (0.92 ml, 8.4 mmol). The solution was stirred for 10 min and *N,N*-diisopropylethylamine (1.44 ml, 8.4 mmol) was added over 30 min. The solution was then stirred for 1 h, triethyl orthoformate (3.12 ml, 18.9 mmol) was slowly added and stirring was continued for 2 h at - 10°C. The reaction mixture was diluted with a 20% solution of ethanol in saturated aqueous $NaHCO_3$ (100 ml) and after 10 min of vigorous stirring, the dichloromethane was removed under reduced pressure. Water (200 ml) was added to the concentrated reaction mixture and the pH of the solution was adjusted to 5-6 by addition of saturated aqueous $NaHCO_3$. The solution was extracted successively with ether (3 x 200 ml) and with ethyl acetate (3 x 50 ml), and the combined organic extracts were washed with water (2 x 250 ml) and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure afforded compound (5) as an oil (1.7 g, 96%) which was used without further purification in the following step. Ir (CH_2Cl_2) : 1760, 1568 cm^{-1}. CIms m/z 236 $(MH)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 1.08-1.15 (m, 6H, 2 x $OCH_2C\underline{H}_3$), 1.24 (t, 3H, J = 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 3.52-3.75 (m, 4H, 2 x $OC\underline{H}_2CH_3$), 4.22 (q, 2H, J = 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 5.10 (d, 1H, J = 8.1 Hz, $C\underline{H}OCH_2CH_3$), 5.17 (d, 1H, J = 8.1 Hz, $CHNO_2$). ^{13}C-Nmr ($CDCl_3$) δ : 14.1, 15.2, 15.3, 63.4, 64.8, 65.0, 88.8, 100.3. Anal. Calcd for $C_9H_{17}NO_6$: C, 45.96 ; H, 7.23 ; N, 5.96. Found : C, 45.61 ; H, 6.96 ; N, 6.24.

Ethyl α-amino-β,β-diethoxypropionate (1) - A mixture of the nitro derivative (5) (200 mg, 0.85 mmol) and active Raney nickel (50 mg) in absolute ethanol (8 ml) was hydrogenated at atmospheric pressure for 1.5 h. The reaction mixture was filtered through celite and the filter pad was washed copiously with ethanol. The combined filtrate and washings were concentrated under reduced pressure, leaving compound (1) as a reddish oil (171 mg, 98%) identical in all respects with that prepared by another route.[8] CIms m/z 206 $(MH)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 1.15-1.23 (m, 6H, 2 x $OCH_2C\underline{H}_3$), 1.28 (t, 3H, J = 7.4 Hz, $CO_2CH_2C\underline{H}_3$), 1.71 (br s, 2H, exchangeable with D_2O, NH_2),

3.48-3.61 (m, 3H, $OC\underline{H}_2CH_3$ + $C\underline{H}NH_2$), 3.68-3.80 (m, 2H, $OC\underline{H}_2CH_3$), 4.22 (q, 2H, J = 7.4 Hz, $CO_2C\underline{H}_2CH_3$), 4.58 (d, 1H, J = 7.9 Hz, $C\underline{H}OCH_2CH_3$).

General procedure for the *N*-arylsulfonylation of the 4-substituted pyrrole-2-carboxaldehydes - A solution of the pyrrole-2-carboxaldehyde derivative (1-2 mmol) in anhydrous THF (20-30 ml) was treated at 0°C under a nitrogen atmosphere with sodium hydride (1.5 eq ; 50% dispersion in oil). The mixture was stirred for 1 h at 0°C at which point a solution of benzenesulfonyl chloride (**6a-c**) or *p*-toluenesulfonyl chloride (**6e**) (1 eq in all cases) in THF (5 ml) was slowly added. After completion of the addition, the reaction mixture was allowed to come to room temperature and stirring was maintained for 10 h. At the end of the reaction period, the solution was diluted with water (3 volumes) and extracted with dichloromethane (3 x). The combined organic extracts were dried over Na_2SO_4 and the solvents were removed under reduced pressure leaving the crude product which was purified as described below.

1-Benzenesulfonyl-4-bromopyrrole-2-carboxaldehyde (6a) - The title compound, prepared as described above using 4-bromopyrrole-2-carboxaldehyde[10] as starting material, was obtained as an amorphous solid in 86% yield after purification of the crude material by chromatography on silica gel (ethyl acetate-heptane 1:1). Ir (KBr) : 1700 cm^{-1}. EIms m/z 315 (M^+ with ^{81}Br), 313 (M^+ with ^{79}Br). ^{1}H-Nmr ($CDCl_3$) δ : 7.17 (d, 1H, J = 2.0 Hz, H-3), 7.60 (d, 1H, J = 2.0 Hz, H-5), 7.62 (d, 2H, J = 8.0 Hz, ArH), 7.69 (t, 1H, J = 8.0 Hz, ArH), 7.96 (d, 2H, J = 8.0 Hz, ArH), 9.93 (s, 1H, CHO). ^{13}C-Nmr ($CDCl_3$) δ: 101.7, 125.6, 127.6, 127.8, 129.9, 133.4, 134.4, 135.0, 137.6, 178.1. Anal. Calcd for $C_{11}H_8NO_3BrS$: C, 42.03 ; H, 2.55 ; N, 4.45 ; S, 10.19. Found: C, 41.65; H, 3.05 ; N, 4.34 ; S, 10.59.

1-Benzenesulfonyl-4-methylpyrrole-2-carboxaldehyde (6b) - The title compound, prepared as described above using 4-methylpyrrole-2-carboxaldehyde[11] as starting material, was obtained as a solid in 40% yield after purification of the crude material by chromatography on silica gel (ethyl acetate-heptane 1:2 followed by 1:1), mp 62-64°C (dichloromethane-cyclohexane). Ir (film) : 1670, 1186 cm^{-1}. EIms m/z 249 $(M)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 2.10 (s, 3H, CH_3), 7.00 (s, 1H, H-3), 7.38 (s, 1H, H-5), 7.52 (t, 2H, J = 8.0Hz, ArH), 7.62 (m, 1H, ArH), 7.89 (d, 2H, J = 8.0 Hz, ArH), 9.95 (s, 1H, CHO). ^{13}C-Nmr ($CDCl_3$) δ : 11.5, 123.2, 127.2, 127.3, 127.4, 129.5, 133.5, 134.5, 138.3, 179.0.

Anal. Calcd for $C_{12}H_{11}NO_3S$. 1/8 H_2O : C, 57.31 ; H, 4.47 ; N, 5.57 ; S, 12.73. Found : C, 57.26 ; H, 4.50 ; N, 5.63 ; S, 12.82.

1-Benzenesulfonyl-4-ethylpyrrole-2-carboxaldehyde (6c) - The title compound, prepared as described above using 4-ethylpyrrole-2-carboxaldehyde[11] as starting material, was obtained as a foam in 40% yield after purification of the crude material by chromatography on silica gel (ethyl acetate-heptane 1:1). Ir(KBr) : 1680 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 1.23 (t, 3H, J = 7.2 Hz, CH_3), 2.53 (q, 2H, J = 7.2 Hz, CH_2), 7.08 (d, 1H, J = 2.0 Hz, H-3), 7.42 (d, 2H, J = 2.0 Hz, H-5), 7.57 (t, 2H, J = 8.0 Hz, ArH), 7.65 (m, 1H, ArH), 7.92 (d, 2H, J = 8.0 Hz, ArH), 9.98 (s, 1H, CHO). HREIms calcd for $C_{13}H_{13}NO_3S$ m/z 263.0616, found 263.0632.

4-Allyl-1-(*p*-toluenesulfonyl)pyrrole-2-carboxaldehyde (6e) - The title compound, prepared as described above using 4-allylpyrrole-2-carboxaldehyde[11] as starting material, was obtained as a solid in 30% yield after purification of the crude material on silica gel (ethyl acetate-heptane 1:1), mp 56-58°C (ethyl acetate-heptane). Ir (film) : 1672, 1173 cm^{-1}. CIms m/z 290 $(MH)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 2.26 (s, 3H, CH_3), 3.07 (d, 2H, J = 3.5 Hz, $CHC\underline{H}_2$), 4.95 (m, 2H, H_2C=), 5.75 (m, 1H, H_2C=C<u>H</u>), 7.20 (d, 2H, J = 9.0 Hz, ArH), 7.30 (s, 1H, H-3), .42 (s, 1H, H-5), 7.69 (d, 2H, J = 9.0 Hz, ArH), 10.04 (s, 1H, CHO). ^{13}C-Nmr ($CDCl_3$) δ : 21.7, 116.7, 124.6, 126.2, 126.8, 127.4, 127.7, 130.1, 130.4, 133.6, 135.4, 145.7, 179.0. Anal. Calcd for $C_{15}H_{15}NO_3S$.0.4 H_2O : C, 60.76 ; H, 5.33 ; N, 4.72. Found: C, 60.56 ; H, 5.18 ; N, 4.98.

General procedure for the preparation of 3,4-fused pyridine-6-carboxylate heterocycles from aromatic aldehydes and ketones - A solution of the aromatic aldehyde (**6a-e, 8, 10a,b**, 12) (1-2 mmol) or ketone (**10c**) (2 mmol) in anhydrous dichloromethane (10-20 ml) containing freshly activated 4 Å molecular sieves (0.5 g) was treated with amine (1) (3 eq) for 8-48 h at room temperature under an argon atmosphere. At the end of the reaction period (as indicated by tlc), the mixture was filtered through celite and the filtrate was washed with water (2x). The aqueous washings were combined and extracted with dichloromethane (2x) after which the organic phases were in turn combined, dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was then dissolved in ethanol (20 ml), the solution was cooled to 0°C and sodium

cyanoborohydride (2 eq) was added, the reaction mixture being maintained at pH 4 by intermittent addition of HCl-saturated ethanol. After 1 h, water was added to the solution and the latter was made basic by addition of saturated aqueous $NaHCO_3$. The mixture was then extracted with dichloromethane (3x), the combined organic extracts were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was in turn dissolved in anhydrous benzene (25 ml), the solution was cooled to 0°C and titanium tetrachloride (4 eq) was added under an argon atmosphere. The reaction mixture was refluxed for 0.5-3 h, cooled and made basic by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (3x), the combined organic extracts were dried over Na_2SO_4 and the solvents were removed under reduced pressure leaving the crude product (**7a-c, 7e, 9, 11a-c** or **13**) which was purified by chromatography on silica gel using ethyl acetate-heptane (1:1) as eluent. Reaction times and product yields are given in Table I.

Ethyl 1-benzenesulfonyl-3-bromopyrrolo[2,3-*c*]pyridine-5-carboxylate (7a) - The title compound, prepared as described above using 1-benzenesulfonyl-4-bromopyrrole-2-carboxaldehyde (**6a**) as starting material, was obtained as a foam : Ir (KBr) : 1715, 1127 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 1.46 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$), 4.52 (q, 2H, J = 7.0 Hz, $C\underline{H}_2CH_3$), 7.51 (t, 2H, J = 7.5 Hz, ArH), 7.64 (d, 1H, J = 7.5 Hz, ArH), 7.82 (s, 1H, H-2), 7.95 (d, 2H, J = 7.5 Hz, ArH), 8.34 (s, 1H, H-4), 9.41 (s, 1H, H-7). HRms calcd for $C_{16}H_{31}N_2O_4$ ^{79}BrS m/z 408.9858, found 408.9857 ; calcd for $C_{16}H_{31}N_2O_4$ ^{81}BrS m/z 410.9839, found 410.9879.

Ethyl 1-benzenesulfonyl-3-methylpyrrolo[2,3-*c*]pyridine-5-carboxylate (7b) - The title compound, prepared as described above using 1-benzenesulfonyl-4-methylpyrrole-2-carboxaldehyde (**6b**) as starting material, was obtained as a pale yellow powder after crystallization in dichloromethane-cyclohexane ; mp 157-160°C. Ir (film) 1715, 1187 cm^{-1}. EIms m/z 344 $(M)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 1.46 (t, 3H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 2.30 (s, 3H, CH_3), 4.20 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 7.44-7.64 (m, 4H, ArH, H-2), 7.91 (d, 2H, J = 7.5 Hz, ArH), 8.23 (s, 1H, H-4), 9.36 (s, 1H, H-7). ^{13}C-Nmr ($CDCl_3$) δ : 9.4, 14.4, 61.9, 117.0, 118.7, 127.0, 127.3, 129.6, 133.3, 134.5, 135.5, 137.6, 141.4, 165.6. Anal. Calcd for $C_{17}H_{16}N_2O_4S$. 0.5 H_2O : C, : 57.79 ; H, 4.81 ; N, 7.93 ; S, 9.06. Found : C, 57.96 ; H, 4.79 ; N, 7.83 ; S, 9.11.

Ethyl 1-benzenesulfonyl-3-ethylpyrrolo[2,3-*c*]pyridine-5-carboxylate (7c) – The title compound, prepared as described above using 1-benzenesulfonyl-4-ethylpyrrole-2-carboxaldehyde (**6c**) as starting material, was obtained as an amorphous white powder : Ir (film) : 1716, 1142 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 1.33 (t, 3H, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.45 (t, 3H, J = 7.5 Hz, $OCH_2C\underline{H}_3$), 2.75 (q, 2H, J = 7.5 Hz, $C\underline{H}_2CH_3$), 4.50 (q, 2H, J= 7.5 Hz, $OC\underline{H}_2CH_3$), 7.46 (t, 2H, J = 7.0 Hz, ArH), 7.50 (s, 1H, H-2), 7.58 (d, 1H, J = 7.0 Hz, ArH), 7.90 (d, 2H, J = 7.0 Hz, ArH), 8.34 (s, 1H, H-4), 9.37 (s, 1H, H-7). HRms calcd for $C_{18}H_{18}N_2O_4S$ m/z 358.0987, found 358.0978.

Ethyl 3-allyl-1-(*p*-toluenesulfonyl)pyrrolo[2,3-*c*]pyridine-5-carboxylate (7e) – The title compound, prepared as described above using 4-allyl-1-(*p*-toluenesulfonyl)pyrrole-2-carboxaldehyde (**6e**) as starting material, was obtained as an unstable oil. ^{1}H-Nmr ($CDCl_3$) δ : 1.45 (t, 3H, J = 7.5 Hz, $CH_2C\underline{H}_3$), 2.45 (s, 3H, CH_3), 3.14 (d, 2H, J = 3.5 Hz, $CHC\underline{H}_2$), 4.48 (q, 2H, J = 7.5 Hz, $C\underline{H}_2CH_3$), 5.17 (m, 2H, $\underline{H}_2C$=CH), 6.00 (m, 1H, H_2C=C$\underline{H}$), 7.25 (d, 2H, J = 7.0 Hz, ArH), 7.52 (s, 1H, H-2), 7.79 (d, 2H, J = 7.0 Hz, ArH), 8.32 (s, 1H, H-4), 9.36 (s, 1H, H-7). HRms calcd for $C_{20}H_{20}N_2O_4S$ m/z 384.1084, found 384.1140.

Ethyl 5*H*-pyrido[4,3-*b*]indole-3-carboxylate (9) – The title compound, prepared as described above using indole-3-carboxaldehyde (**8**) as starting material, was obtained as a white powder, mp 260°C. Ir (CH_2Cl_2) : 3139, 1723 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 1.49 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$), 4.54 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$), 7.34-7.42 (m, 1H, ArH), 7.56 (d, 2H, J = 7.2 Hz, ArH), 8.22 (d, 1H, J = 7.9 Hz, ArH), 8.30 (s, 1H, H-4), 8.70 (br s, 1H, exchangeable with D_2O, NH), 9.41 (s, 1H, H-1). HRCIms calcd for $C_{14}H_{13}N_2O_2$ m/z 241.0977, found 241.0951.

Ethyl 6-methoxyisoquinoline-3-carboxylate (11a) – The title compound, prepared as described above using *p*-methoxybenzaldehyde (**10a**) as starting material, was obtained as a pale yellow solid, mp 105-106°C (lit.,[14] mp 104-105°C). CIms m/z 232 $(MH)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 1.48 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$), 3.97 (s, 3H, $OC\underline{H}_3$), 4.52 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$), 7.19 (d, 1H, J = 2.2 Hz, H-5), 7.35 (dd, 1H, J = 2.2 Hz and 8.9 Hz, H-7), 7.93 (d, 1H, J = 8.9 Hz, H-8), 8.49 (s, 1H, H-4), 9.19 (s, 1H, H-1).

Ethyl 6,7-dimethoxyisoquinoline-3-carboxylate (11b) – The title compound, prepared as described above using 3,4-dimethoxybenzaldehyde **(10b)** as starting material, was obtained as a yellowish solid, mp 162°C. Ir (CH_2Cl_2) : 1707 cm^{-1}. CIms m/z 262 $(MH)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 1.48 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$), 4.06 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 4.52 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$), 7.20 (s, 1H, H-5), 7.28 (s, 1H, H-8), 8.46 (s, 1H, H-4), 9.13 (s, 1H, H-1). Anal. Calcd for $C_{14}H_{15}NO_4$. 1/3 H_2O : C, 62.92 ; H, 5.86 ; N, 5.24. Found : C, 62.97 ; H, 5.88 ; N, 5.29.

Ethyl 1-methylisoquinoline-3-carboxylate (11c) – The title compound, prepared as described above from acetophenone **(10c)**, was obtained as an off-white solid, mp 101-103°C (lit.,[16] mp 104°C). CIms m/z 216 $(MH)^+$. ^{1}H-Nmr ($CDCl_3$) δ : 1.48 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$), 3.06 (s, 3H, CH_3), 4.51 (q, 2H, J = 7.1Hz, $C\underline{H}_2CH_3$), 7.75 (m, 2H, ArH), 7.95 (m, 1H, ArH), 8.20 (m, 1H, ArH), 8.46 (1H, s, H-4).

Ethyl benz[*f*]isoquinoline-2-carboxylate (13) – The title compound, prepared as described above using 2-naphthaldehyde (12) as starting material, was obtained as an off-white solid, mp 88°C. Ir (CH_2Cl_2) : 1735 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ : 1.52 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$), 4.57 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$), 7.68-7.77 (m, 3H, ArH), 7.85-7.91 (m, 2H, ArH), 8.63 (d, 1H, J = 7.5 Hz, ArH), 9.20 (s, 1H, H-4), 9.24 (s, 1H, H-1). ^{13}C-Nmr ($CDCl_3$) δ : 14.5, 61.9, 118.8, 123.4, 124.1, 127.7, 127.9, 128.6, 129.1, 130.7, 133.4, 134.7, 143.4, 151.6, 165.8. HRCIms calcd for $C_{16}H_{14}NO_2$ m/z 252.1024, found 252.1010.

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