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Reactions of 3-([(Trifluoromethyl)sulfonyl]oxy)-1*H*-indole Derivatives With Diamines and Carbon Nucleophiles. Synthesis of 6*H*-Indolo[2,3-*b*]quinoxaline Derivatives

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Abstract Indolic triflate reacted with 1,2-diamines to afford pyrazino[2,3-b]indole or indolo[2,3-b] quinoxaline. Carbon nucleophiles such as malonate derivatives also reacted with indolic triflate in absence of palladium catalyst to afford 2-($3-\infty - 2$, 3-dihydro-1H-2-indolyliden) malonate derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

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Quinoxaline derivatives possess antiviral¹ and antibacterial properties.² In particular 6*H*-indolo[2,3*b*]quinoxaline derivatives with a basic side-chain at position 6 have been found to show significant anti-HSVI activity, by way of the inhibition of the viral decapsidation process.^{13,4} In addition 5*H*-Pyrazino[2,3-*b*]indole derivatives have been synthesized as antiviral agents and have shown to interact with the minor groove of DNA.⁵ Bergman *et al.* had described derivatives of type **1b-c** and **2b-c** obtained by the condensation of indole-2,3-diones^{3,6,7} (isatin) with 1,2-diamines.

Since the original report of Schunk, ⁸ the reactivity of isatins with amines or alcohols has been extensively studied.⁹ However, it was interesting for us to develop a new access to this class of compounds, because of their pharmacological properties and structural analogy with ellipticine derivatives.



We have recently ^{10,11} reported the unusual reactivity of indolic triflate **3** towards allylic alcohols giving *inter alia* the allyloxy compound **4**. In order to enhance the reactivity of triflate **3** towards other nucleophilic reagents, we treated it with allylamine in the presence of palladium acetate (6%), triphenylphosphine (3%), triethylamine (2 eq), in DMF and obtained the unexpected compound **5** in 57% yield accompanied with ethyl E-mail jean-yves.merour@univ-orleans.fr

3-hydroxy-1-methyl-2-oxo-3-indolinecarboxylate 6 in 24% yield; compound 6 was also obtained during the reaction of allyl alcohol with triflate 3.^{10,11}



A mechanism that could explain the formation of 5 is shown in figure 1. It involves the formation of an acyliminium species, stabilized by the polar aprotic solvent DMF, as reported by Edstrom *et al.*¹² for pyrido[3,4-*b*]pyrrolizidine triflate; this intermediate is attacked at the C-2 carbon atom by the nucleophilic nitrogen atom of the allylamine (NuH).



Figure 1

Apparently the formation of the acyliminium species did not require the presence of palladium but we observed that yields and rate were improved in the *presence of palladium acetate*. During the course of the reaction, a keto group is generated in position 3 and we anticipated that a nucleophile with two nucleophilic centers would be able to interact with both electrophilic sites to generate a ring. Thus compound **3** was treated with ethylenediamine in presence of palladium acetate (6%), triphenylphosphine, triethylamine (2 eq) in DMF (100°C) or in acetonitrile at reflux, to afford the pyrazino[2,3-*b*]indole **2a** in 40% yield (Scheme 1).



Scheme 1

The reaction of N,N'-disubstituted ethylenediamine with triflate 3, under the same experimental conditions, gave however the spiroderivatives 7 and 8 in 83% and 86% yields respectively (Scheme 1).



Scheme 2

The formation of spiro compounds 7 or 8 is explained by the reaction of the second amino group directly with the ester function in the intermediate A. The 3-keto group is not subject to the attack by secondary 1,2-diamines since water elimination yielding an imino intermediate is not possible. The formation of 2a could result from a decarboxylative process at the stage of the imino intermediate B, which is generated by the addition of the amine onto the ketone in position 3 of intermediate A, as indicated in Scheme 2. All attempts to reduce the lactam of 8 were unsuccessful.

We have treated the triflate 3 with 1,2-diaminobenzene (o-phenylenediamine) in the presence of palladium acetate (6%)/triphenyl phosphine/triethylamine in DMF at 100°C to obtain the 6-methyl-6*H*-indolo[2,3-b] quinoxaline $1a^{13}$ in 60% yield accompanied by a second product 9 in 27% yield. The structure of this product could be that of the *N*-oxide of 1a.



An authentic sample of **1a** was obtained in 95% yield by the reaction of 6H-indolo[2,3-*b*]quinoxaline¹⁴ **1c** with iodomethane in the presence of sodium hydride in DMF. We have observed a regioselective alkylation at the 6-nitrogen atom of the indole moiety and not at position 5, a behaviour that had been noted by Bergman¹⁵ with 2-chloroethyl dimethylamine as the electrophile.

The structure identification of 9 was established by NMR and mass spectroscopy; the 13 C NMR and IR spectra did not reveal the presence of any carbonyl or carboxyl group. To support the structural assignment of 9, the following chemical transformations were performed. On one hand, treatment of 9 with triphenyl phosphine, which is known to reduce *N*-oxides to amines, in refluxing xylene, for 2 days, afforded compound

1a in 70% yield. On the other hand, the reaction of 1a with an oxidant like *meta*-chloroperbenzoic acid (1.1 eq) afforded 9 in 57% yield. An excess of *m*-CPBA gave the dioxide 10^{16} which could be reduced back to 1a by triphenylphosphine (32% yield) or more efficiently by sodium dithionite (76% yield); however we could not totally exclude the isomeric structure 9a since HMBC, HMQC NMR (400 MHz) experiments in pyridined₅ or indirect ¹⁵N NMR data were not conclusive.



2,3-Diaminopyridine was also reacted with triflate 3 to afford a 1:6 mixture of regioisomeric 10-methyl-10*H*-pyrido[3',2': 5,6]pyrazino[2,3-*b*]indole **11** and 6-methyl-6*H*-pyrido [2',3': 5,6] pyrazino[2,3-*b*]indole **12** in a total yield of 84%.



We did not observe the formation of by-products such as *N*-oxides of compounds 11 or 12. To establish the structure of regioisomer 11, we performed the synthesis of 10*H*-pyrido[3',2': 5,6]pyrazino[2,3-*b*]indole 13 according to the recently published procedure of Bergman.³ The regioselective methylation at the indolic nitrogen atom of 13 was achieved with iodomethane/NaH to afford 11 in 71% yield.



The versatility of these reactions was limited by the use of an indolic triflate in which the nitrogen atom is substituted by a methyl group which is difficult to remove.

The reaction of triflate 14 having an unsubstituted nitrogen atom gave only decomposition products; we also synthesized triflate 15 having a N-benzyl substituent (see preceding paper) which can be used in palladium-catalysed coupling reactions, followed by mild debenzylation of the indolic nitrogen atom; this last procedure was tedious. So we were pleased to observe that



indolic triflate 17, obtained from 1-acetyl-1*H*-indol-3(2*H*)-one 16 (LDA/-78°C/*N*,*N*-phenyltriflimide, 95%), unsubstituted at position 2, was sensitive to nucleophilic attack during attempts of carbopalladation in the presence of methoxyallene and dimethylmalonate anion.¹¹ So we decided to examine the reactivity of triflate 17 towards 1,2-diamines. Gribble *et al.* had described the synthesis of an analogous triflate with a *N*-benzenesulfonyl group ^{17,18} from the corresponding 1-benzenesulfonyl-1*H*-indole-3(2*H*)-one.



Reaction of triflate 17 with ethylenediamine in the presence of palladium tetrakis (triphenylphosphine) (5%) in DMF afforded directly in 71% yield, the pyrazino[2,3-*b*]indole $2c^{13,14}$ with an unsubstituted indolic nitrogen atom. In the absence of palladium catalyst the yield was much lower (31%) and the reaction time was longer (15h). Alkylation of compound 2c using iodomethane (potassium carbonate/acetonitrile/reflux) afforded 2a in 70% yield. The reaction of *ortho*-phenylenediamine with 17 afforded the indolo[2,3-*b*] quinoxaline compound $1c^{13,14}$ in 71% yield without any detectable presence of *N*-oxide derivative 9; finally the use of 2,3-diaminopyridine gave in 41% yield, a 1:1 mixture of regioisomers 13 and 18.³



The behaviour of nucleophiles towards triflate 17 was initiated by the study of the reactivity of sodium dimethyl malonate in an attempted carbopalladation reaction; the ethylenic ketone 19 was obtained in 94% yield and not the compound resulting from a nucleophilic attack on the intermediate π -allyl complex. It is interesting to note that by performing the same reaction in the absence of methoxyallene and *even in the absence of palladium catalyst*, compound 19¹⁹ was still obtained in the same yield.



When triflate 17 was treated with sodium diethylmalonate or sodium cyanomethylmalonate (2.5 eq) in THF, in the absence of palladium salt, we isolated products 20 (55%, yield) or 21 (46% yield) respectively. The reaction of ethyl nitroacetate anion with triflate 17 gave 22 in 56% yield with loss of the nitro group. We

have already described ketones 20 and 22 obtained respectively by an aldolisation reaction of diethyl ketomalonate or methyl glyoxylate with 1-acetyl-1*H*-indol-3(2*H*)-one 16. 20,21



The reaction of the sodium anion of monosubstituted diethyl malonate derivatives ($R = CH_3$, allyl, phenyl) with triflate 17 afforded the C-2 alkylated indoles 23-25 with concomitant *O*-acetylation (31-63% yield). The use of diethyl 2-nitrophenyl malonate or diethyl acetamidomalonate was unsuccessful; similarly the reaction of nitromethane with 17 was unproductive.



We have synthesized an authentic sample of compound 23 by a selective C-methylation of compound 26 with iodomethane, under an atmosphere of hydrogen. The yield of the reaction was low since compound 20 was also formed. The starting material 26 was obtained by hydrogenation (Pd/C) of product 20 in acetic anhydride.²⁰



We explain these results as follows: cleavage of the labile acetyl group, under basic condition, of triflate 17 is followed by the generation of the acyliminium intermediate C which is attacked by the nucleophilic carbon atom of the malonate derivative; then, depending on the presence or absence of a hydrogen atom on the nucleophilic carbon, the outcome of the reaction is slightly different. For R =H, the resulting saturated ketone D is unstable²⁰ and immediately loses H₂ to give 20. For R \neq H, the ethylenic ketone cannot be generated and thus, the enol form undergoes acetylation to give 23-25. (Scheme 3)

The use of other nucleophilic species like sodium methoxide or the sodium allyloxide resulted in the opening of the pyrrole ring of compound 17, at room temperature, to give anthranilate derivatives.



Carbon nucleophiles also reacted with triflate 3 under the same conditions as triflate 17. Sodium diethyl malonate in THF gave the C-2 alkylated indole 27 in 50% yield. Methylation (ICH₃/NaH/DMF/62%) of compound 27 afforded compound 28. The reaction of sodium dimethyl methylmalonate with triflate 3, which should have led to 28 was unsuccessful.



In summary, we were able to introduce nucleophilic reagents at position 2 of indolic structure; ²² this is unusual since electrophilic reagents are usually used to perform substitution at position 2 or 3 of indole derivatives.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were recorded on Perkin Elmer FT Paragon 1000 PC spectrometer. NMR spectra were obtained on a Bruker advance DPX 250 using TMS as internal standard. Mass spectra were obtained on a Nermag R 10C instrument (chemical ionisation with ammonia) or a Perkin Elmer API 300 instrument.

6-Methyl-6H-indolo[2,3-b]quinoxaline (1a).¹³

Compound 1a was obtained according the following procedures:

Condensation of ortho-phenylenediamine with 1-methylisatin¹³

A mixture of 1-methylisatin (200 mg, 1.24 mmol), ortho-phenylenediamine (200 mg, 1.86 mmol), acetic acid (0.5 mL) and ethanol (5 mL) were stirred at 60°C for 3h. The volatile materials were removed *in vacuo*, water

(5 mL) was added; the aqueous layer was neutralised with 5% NaOH and extracted with ethyl acetate (3x15 mL). Organic layers were dried over MgSO₄ and evaporated. The residue was chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether: 2/8), **1a** was first eluted (m = 143 mg; yield 50%) followed by **9**; m = 85 mg; yield 27%.

Reaction of triflate 3 (200 mg, 0.57 mmol), $Pd(OAc)_2$ (7 mg, 0.031 mmol) and orthophenylenediamine (185 mg, 1.70 mmol 3 eq) according to the general procedure described for compound 5 afforded 1a; time reaction 48h; elution ethyl acetate/petroleum ether: 2/8; two products were obtained: 1a (yield: 60%), which was eluted first, followed by *N*-oxide 9 (yield 27%).

Methylation of 6H-indolo[2,3-b]quinoxaline (1c)¹³

6*H*-Indolo[2,3-*b*]quinoxaline $1c^{14,15}$ (45 mg, 0.20 mmol) was added under argon to a suspension of sodium hydride (6 mg, 0.25 mmol) in THF (3 mL). After 30 min, iodomethane (0.01 mL, 0.24 mmol) was added and the mixture was stirred at room temperature for 18h. The solvent was evaporated, water (10 mL) was added and the aqueous layer neutralised with 10% HCl; extraction with ethyl acetate (5 mL), drying over MgSO₄ and evaporation afforded a residue which was chromatographed on a silica gel column (eluent: ethyl acetate/ petroleum ether 2/8); m = 47 mg; yield 95%.

Reduction of N-oxide 9.

A solution of *N*-oxide **9** (200 mg, 0.8 mmol) and triphenylphosphine (216 mg, 0.82 mmol) in xylene (10 mL) was refluxed for 48 h. After evaporation of the solvent the residue was chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether 2/8) to give 6-methyl-6*H*-indolo[2,3-*b*]quinoxaline **1a**; m = 130 mg; yield 70%.

Reduction of 6-methyl-6H-indolo[2,3-b]quinoxaline-5,11-diium-5,11-diolate (10):

To a solution of dioxide **10** (80 mg, 0.30 mmol) in acetic acid (10 mL) was added a warm solution of sodium dithionite (157 mg, 0.90 mmol) in water (3 mL). The mixture was refluxed for 30 min; water was added, then few drops of 5% NaOH were added till a precipitate was formed. The solid was chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether 3/7) to give **1a**; m = 53 mg; yield 76%; mp 146-148°C; (Lit.¹³ 148-149°C). ¹H NMR (CDCl₃) δ = 3.99 (s, 3H, NCH₃); 7.41-7.49 (m, 2H, Harom); 7.69-7.78 (m, 3H, Harom); 8.14 (d, 1H, Harom, J = 8.2 Hz); 8.31 (d, 1H, Harom, J = 8.2 Hz); 8.49 (d, 1H, Harom, J = 7.8 Hz).¹³C NMR (CDCl₃) δ = 26.4 (NCH₃); 108.0 (CH); 118.2 (C)119.8 (CH); 121.4 (CH); 124.8 (CH); 126.6 (CH); 127.7 (CH); 128.3 (CH); 129.9 (CH); 138.1 (C); 139.0 (C); 139.5 (C); 143.8 (C); 144.7 (C). MS (CI/ NH₃): m/z = 234 (M⁺+1). Anal. Calcd for C₁₅H₁₁N₃: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.11; H, 4.93; N, 17.87.

6H-Indolo[2,3-b]quinoxaline (1c).^{13,14}

Starting from triflate **17** (100 mg, 0.32 mmol), Pd(PPh₃)₄ (0.05 eq) and *ortho*-phenylenediamine (104 mg, 0.96 mmol, 3 eq) according to the general procedure; reaction time 36h; m = 50 mg; yield 71%; solid; mp > 250°C; mp (Lit.¹³ 295-296 °C). IR (KBr): v = 3142 (NH) cm⁻¹. ¹H NMR (DMSO-d6) $\delta = 7.35$ (t, 1H, Harom, J = 8.2 Hz); 7.57 (d, 1H, Harom, J = 8.2 Hz); 7.64-7.82 (m, 3H, Harom); 8.06 (d, 1H, Harom; J = 7.7 Hz); 8.27 (d, 1H, Harom, J = 7.7 Hz); 8.33 (d, 1H, Harom, J = 7.7 Hz); 12.01 (m, 1H, NH, exchangeable with D₂O).¹³C NMR (DMSO-d6) $\delta = 112.8$ (CH); 117.8 (C); 120.9 (CH); 123.1 (CH); 126.2 (CH); 127.4 (CH); 127.7 (CH); 130.3 (CH) 135.8 (CH); 137.3 (C); 138.5 (C); 138.8 (C); 142.7 (C); 144.7 (C). Anal. Calcd for C₁₄H₉N₃: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.53; H, 4.02; N, 19.31.

5-Methyl-5*H*-pyrazino[2,3-*b*]indole (2a).

Same procedure as for 5 starting from ethylenediamine (99 mg, 1.65 mmol) and triflate 3 (200 mg, 0.57 mmol); time reaction 7h; elution: ethyl acetate/petroleum ether 2/8; m = 42 mg; yield 40%; mp 78-80°C. ¹H NMR (CDCl₃) δ = 3.98 (s, 3H, NCH₃); 7.32 (t, 1H, Harom, J = 8.2 Hz); 7.52 (d, 1H, Harom; J = 8.2 Hz); 7.68 (t, 1H, Harom, J = 8.2 Hz); 8.38 (d, 1H, Harom, J = 8.2 Hz); 8.42 (d, 1H, N=CH, J = 3.5 Hz); 8.49 (d, 1H, N=CH; J = 3.5 Hz). ¹³C NMR (CDCl₃) δ = 27.9 (CH₃); 109.8 (CH); 119.9 (C); 121.3 (CH); 122.1 (CH); 129.6 (CH); 136.6 (C); 136.7 (CH); 139.9 (CH); 142.0 (C); 146.1 (C). MS (CI/NH₃): m/z = 184 (M⁺+1). Anal. Calcd for C₁₁H₉N₃: C, 72.11; H, 4.95; N, 22.93. Found: C, 72.38; H, 4.83; N, 22.87.

5H-Pyrazino[2,3-b]indole (2c).¹⁴

Starting from triflate **17** (100 mg, 0.33 mmol), Pd(PPh₃)₄ (0.05 eq) and ethylenediamine (58 mg, 0.97 mmol) according to the general procedure; time reaction 40 min; elution: ethyl acetate/petroleum ether 3/7; m = 40 mg; yield: 71%; mp 246-248°C; (Lit.¹⁴ 241-243°C). IR (KBr) v = 3312 (NH) cm⁻¹. ¹H NMR (DMSO-d6) $\delta = 7.28-7.34$ (m, 1H, Harom); 7.55-7.59 (m, 2H, Harom); 8.20 (d, 1H, Harom, J = 7.7 Hz); 8.40 (d, 1H, Harom, J = 2.8 Hz); 8.48 (d, 1H, Harom, J = 2.8 Hz); 12.12 (br s, 1H, NH). ¹³C NMR (DMSO-d6) $\delta = 113.7$ (CH); 120.9 (C); 122.1 (CH); 122.6 (CH); 130.6 (CH-N); 136.8 (C); 138.1 (CH-N); 141.6 (CH); 141.8 (C-N); 147.1 (C-N). MS (CI / NH₃): m/z = 170 (M⁺+1). Anal. Calcd for C₁₀H₇N₃: C, 70.99; H, 4.71; N, 24.84. Found: C, 71.15; H, 4.62; N, 24.77.

Ethyl 2-(Allylamino)-1-methyl-3-oxo-2-indolinecarboxylate (5).

Typical procedure reaction between indolic triflate 3 and allylamine: To $Pd(OAc)_2$ (7 mg, 0.031 mmol) and PPh_3 (4.5 mg, 0.017 mmol) were added under argon a solution of triflate 3 (200 mg, 0.57 mmol), allylamine (3 eq) and triethylamine (2 eq) in DMF (10 mL). The solution was stirred at 100°C and monitored by TLC. When all the starting material has disappeared (12h), water (20 mL) was added and the aqueous layer was neutralised with a 10% HCl solution and twice extracted with ethyl acetate (2x10 mL). The organic layers were washed with water, brine and dried (MgSO₄). After filtration and evaporation the residue was purified on a silica gel

column using dichloromethane/petroleum ether 75/25 as eluent; m = 89 mg; yield 57%; oil. IR (film): v = 3356 (NH), 1746 (CO), 1713 (CO) cm^{-1.1}H NMR (CDCl₃) δ = 1.17 (t, 3H, CH₃, J = 7.3 Hz); 2.84-3.10 (m, 2H, CH₂); 2.91 (s, 3H, NCH₃); 4.07-4.62 (m, 2H, OCH₂); 5.00-5.06 (m, 2H, CH=CH₂); 5.75-5.89 (m, 1H, CH=CH₂); 6.71-6.77 (m; 2H, Harom); 7.46-7.53 (m; 2H, Harom).¹³C NMR (CDCl₃) δ =14.5 (CH₃); 28.0 (NCH₃); 45.2 (NCH₂); 62.9 (OCH₂); 85.7 (C-2); 108.9 (CH=); 116.1 (=CH₂); 119.2 (C); 119.4 (CH); 125.2 (CH); 136.3 (CH); 138.8 (CH); 161.9 (C); 167.0 (CO); 198.0 (CO). Anal. Calcd for C₁₅H₁₈N₂O₃: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.42; H, 6.73; N, 10.36.

Spiro [2-(2-oxo-3,6-dimethylpiperazine)]-1-methyl-3-oxo-1H-2-indoline (7).

Same procedure as for compound **5** starting from *N-N*-dimethylethylenediamine (75 mg, 0.85 mmol) and triflate **3** (100 mg, 0.285 mmol); time reaction 6h; elution: ethyl acetate/petroleum ether 2/8; m = 61mg; yield 83%; oil. IR (film): v = 1704 (CO), 1666 (CO) cm⁻¹. ¹H NMR (CDCl₃) $\delta = 2.29$ (s, 3H, NCH₃); 2.79-2.84 (m, 1H, CH₂); 2.85 (s, 3H. NCH₃); 3.01 (s, 3H, NCH₃); 3.23-3.29 (m, 1H, CH₂); 3.62-3.64 (m, 1H, CH₂); 4.05-4.19 (m, 1H, CH₂); 6.66-6.76 (m, 2H, Harom); 7.42-7.49 (m, 2H, Harom). ¹³C NMR (CDCl₃) $\delta = 26.9$ (NCH₃); 33.9 (NCH₃); 36.7 (NCH₃); 41.9 (CH₂); 56.8 (CH₂); 86.4 (C-2); 108.7 (CH); 117.9 (CH); 118.0 (C); 119.6 (C); 126.3 (CH); 138.6 (CH); 171.6 (CO); 201.2 (CO); MS (CI/NH₃) 260 (M⁺+1). Anal. Calcd for C₁₄H₁₇N₃O₂: C, 64.85; H, 6.61; N, 16.20. Found: C, 65.02; H, 6.53; N, 16.39.

Spiro[2-(2-Oxo-3,6-dibenzylpiperazine)]-1-methyl-3-oxo-1H-2-indoline (8).

Same procedure as for **5** starting from *N*-*N*^{*}-dibenzylethylenediamine (205 mg, 0.85 mmol) and triflate **3** (100 mg, 0.285 mmol); time reaction 24h; elution: ethyl acetate/petroleum ether 2/8; m =103 mg; yield 86%; oil. IR (film) v = 1700 (CO), 1656 (CO) cm^{-1.1}H NMR (CDCl₃) δ = 2.75-2.80 (m, 1H, CH₂); 2.94 (s, 3H, NCH₃); 3.10-3.16 (m, 1H, CH₂); 3.38-3.46 (m, 2H, CH₂N); 3.75-3.80 (d, 1H, CH₂C₆H₅, J = 13.5 Hz); 3.97-4.17(m, 1H, CH₂); 4.60 (d, 1H, CH₂C₆H₅, J = 14.6 Hz); 4.70 (d, 1H, CH₂C₆H₅, J = 14.6 Hz); 6.74-6.82 (m, 2H, Harom); 7.26-7.35 (m, 10H, Harom); 7.49 (t, 1H, Harom; J = 8.2 Hz); 7.82 (d, 1H, Harom, J = 8.2 Hz).¹³C NMR (CDCl₃) δ = 27.1 (NCH₃); 40.2 (CH₂); 44.6 (CH₂); 49.7 (CH₂); 52.6 (CH₂); 85.3 (C-2); 107.4 (CH); 116.8 (CH); 123.5 (CH); 127.1 (CH); 128.2 (CH); 135.2 (C); 137.2 (CH); 161.7 (C); 161.9 (CO); 199.4 (CO). Anal. Calcd for C₂₆H₂₅N₃O₂: C, 75.89; H, 6.12; N, 10.21. Found: C, 75.62; H, 6.23; N, 10.39.

6-Methyl-6*H*-indolo[2,3-*b*]quinoxaline-5-ium-5-olate (9) or 6-Methyl-6*H*-indolo[2,3-*b*]quinoxaline-11ium-11-olate (9a).

Compound 9 was obtained either during the formation of 6-methyl-6*H*-indolo[2,3-b]quinoxaline 1a or by direct oxidation of 1a.

To a 0°C solution of **1a** (100 mg, 0.43 mmol) in chloroform (2 mL) was added *meta*-chloroperbenzoic acid (82 mg, 0.48 mmol). The mixture was stirred at room temperature for 5 h. The volatile materials were

removed *in vacuo* and the residue was chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether 2/8) to give 9; m = 61 mg; yield 57%; mp 150-152°C. IR(KBr): v = 1252 (NO) cm^{-1.1}H NMR (CDCl₃) δ = 3.85 (s, 3H, NCH₃); 7,40-7.55 (m, 4H, Harom); 7.13 (t, 1H, Harom, J = 8.2 Hz); 7.92 (d, 1H, Harom, J = 8.2 Hz); 8.53 (d, 1H, Harom, J = 7.7 Hz); 8.61 (d, 1H, Harom, J = 7.7 Hz).¹³C NMR (CDCl₃) δ = 30.3 (NCH₃); 113.0 (C); 114.2 (CH); 115.3 (CH); 119.2 (CH); 123.6 (CH); 124.0 (CH); 125.3 (2xCH); 131.1 (C); 132.0 (CH); 137.6 (C); 143.6 (C); 146.5 (C); 146.7 (C). MS (CI / NH₃): m/z = 250 (M⁺+1).

6-Methyl-6H-indolo[2,3-b]quinoxaline-5,11-diium-5,11-diolate (10).

Action of hydrogen peroxide:

To a stirred solution of **1a** (250 mg, 1.07 mmol) in acetic acid (5 mL) was added H₂O₂ (37% solution, 2.5 mL); the mixture was heated at 60°C for 16 h. After evaporation, the residue was chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether 3/7) to give **10**; m = 125 mg; yield: 45%; mp > 250°C. IR (KBr) v = 1254 (NO) cm^{-1.1}H NMR (CDCl₃) δ = 3.97 (s, 3H, NCH₃); 7.38-7.45 (m, 2H, Harom); 7.62-7.70 (m, 2H, Harom); 7.76-7.83 (t, 1H, Harom, J = 7.2 Hz); 8.14 (d, 1H, Harom), J = 7.2 Hz); 8.81 (t, 2H, Harom, J = 7.2 Hz). ¹³C NMR (CDCl₃) δ = 28.3 (NCH₃); 109.1 (CH); 115.4 (C); 118.8 (CH); 121.9 (CH); 125.1 (CH); 126.4 (CH); 130.1 (CH); 130.6 (C); 133.9 (CH); 134.9 (CH); 142.4 (C); 142.9 (C); 149.4 (C); 149.8 (C). MS (CI / NH₃): m/z = 266 (M⁺+1).

Methylation of 6H-indolo[2,3-b]quinoxaline-5,11-diium-5,11-diolate;

A mixture of 6*H*-indolo[2,3-*b*]quinoxaline-5,11-diium-5,11-diolate¹⁶ (500 mg, 2 mmol), acetonitrile (25 mL) DMF (0.2 mL), potassium carbonate (330 mg, 2.39 mmol) and iodomethane (0.37 mL, 5.97 mmol) were stirred at refluxed for 5h. The volatile materials were removed *in vacuo*, water (15 mL) and ethyl acetate (20 mL) were added; the aqueous layer was neutralised with 10% HCl and extracted with ethyl acetate (3x15 mL). The organic layers were dried over MgSO₄ and evaporated. The residue was chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether 3/7); m = 367 mg; yield: 70%.

10-Methyl-10H-pyrido[3',2':5,6]pyrazino[2,3-b]indole (11).

Compound 13³ (100 mg, 0.45 mmol) dissolved in THF (5 mL) /DMF (3 mL) was added at 0°C to a suspension of sodium hydride (60% weight, 18 mg, 0.45 mmol) in THF (5 mL). The mixture was stirred for 15 min and iodomethane (0.07 mL, 1.12 mmol) was added followed by stirring at room temperature for 2h; water (5 mL) was added, the aqueous layer was neutralised with 10% HCl and extracted with ethyl acetate (2x10 mL). After drying over MgSO₄ and evaporation, the residue was chromatographed on a silica gel column (eluent dichloromethane); m = 75 mg; yield 71%; mp 222-224°C; ¹H NMR (CDCl₃) δ = 4.03 (s, 3H, NCH₃); 7.42 (t, 1H, Harom, J = 8.2 Hz); 7.51 (d, 1H, Harom, J = 8.2 Hz); 7.61-7.65 (m, 1H, Harom); 7.69-7.79 (m, 1H,

Harom); 8.44 (d, 1H, Harom, J = 8.2 Hz); 8.63 (dd, 1H, Harom, J = 8.2 Hz, J = 1.8 Hz); 9.10 (dd, 1H, Harom, J = 4Hz, J = 1.8Hz).¹³C NMR (CDCl₃) δ = 28.2 (NCH₃); 110.1 (CH); 119.4 (C); 122.0 (CH); 122.1 (CH); 123.3 (CH); 132.2 (CH); 134.2 (C); 135.2 (C); 138.6 (CH); 146.1 (C); 148.0 (C); 149.9 (C); 152.7 (CH). MS (CI / NH₃): m/z = 235 (M⁺+1). Anal. Calcd for C₁₄H₁₀N₄: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.60; H, 4.46; N, 24.08.

10-Methyl-10H-pyrido[3',2':5,6]pyrazino[2,3-b]indole (11) and 6-methyl-6H-

pyrido[2',3':5,6]pyrazino[2,3-b]indole (12).

Same procedure as for compound 5 starting from triflate 3 (200 mg, 0.57 mmol) and 2,3-diaminopyridine (186 mg, 1.71 mmol, 3 eq); time reaction 4h; elution: dichloromethane; m = 112 mg; yield: 84%. The two regioisomers 11 and 12 were obtained respectively in the ratio 1:6. ¹H NMR (CDCl₃) δ = 3.98 (s, 3H, NCH₃ 12); 4.03 (s, 3H, NCH_{3 11}); 7.40-7.51 (m, 4H, Harom); 7.64-7.80 (m, 4H, Harom); 8.44 (d, 1H, Harom 11, J = 8.2 Hz); 8.46 (dd, 1H, Harom₁₂, J=7.6Hz, J = 1.8Hz); 8.55(d, 1H, Harom 12, J=7.1Hz); 8.63(dd, 1H, Harom 11, J = 8.2 Hz, J = 1.8 Hz); 9.08 (dd, 1H, Harom 12 J = 4Hz, J = 1.8Hz); 9.10 (dd, 1H, Harom 11, J = 4Hz, J = 1.8Hz).

General procedure for the reaction of triflate 17 with 1,2-diamines :

To Pd(PPh₃)₄ (0.05 eq) were successively added DMF (1 mL), 1,2-diamine (3 eq) and triflate 17^{11} (100 mg, 0.326 mmol, 1 eq) dissolved in DMF (2 mL). The solution was heated at 65°C till the disappearance of triflate 17 (TLC monitoring). Water (5 mL) was added and the solution was neutralised and extracted with ethyl acetate (3x10 mL). The organic layers were washed (3x5 mL) and dried over MgSO₄. After evaporation the residue was chromatographed on a silica gel column.

10H-pyrido[3',2':5,6]pyrazino[2,3-b]indole (13) and 6H-pyrido[2',3':5,6]pyrazino[2,3-b]indole (18).

Starting from triflate **17** (100 mg, 0.33 mmol), $Pd(PPh_3)_4$ (0.05 eq) and 2,3-diaminopyridine (110 mg, 0.98 mmol, 3 eq); reaction time 20h; m = 30 mg; yield 41%; mixture 1:1 of the 2 regioisomers.³

General procedure for the reaction of triflate 17 (or triflate 3) with carbon nucleophiles:

The malonate derivative (1.95 mmol) was added dropwise to a suspension of sodium hydride (1.62 mmol) in DMF (2 ml); the solution was stirred at room temperature for 30 min. 1-Acetyl-1*H*-3-indolyl trifluoromethanesulfonate 17 (200 mg, 0.65 mmol) (or triflate 3) in DMF (3 mL) was added dropwise to the solution followed by heating at 65°C till disappearance of 17 (TLC monitoring). After cooling, water (10 mL) was added and the mixture extracted with ethyl acetate (3x10 mL). The organic layers were washed with water (3x10 mL) and dried over MgSO₄. Evaporation provided a residue which was chromatographed on a silica gel column.

Dimethyl 2-(3-Oxo-2,3-dihydro-1H-2-indolyliden)malonate (19).

To a NaH suspension (39 mg, 1.62 mmol) in DMF (2 mL), dimethylmalonate (258 mg, 1.95 mmol, 3 eq) was added dropwise at room temperature followed by stirring at room temperature for 15 min. Triflate **17** (200 mg, 0.65 mmol) dissolved in DMF (3 mL) was dropwise added and the stirring continued at 65°C for 1h. After cooling, water (10 mL) was added and the mixture extracted with ethyl acetate (3x10 mL); the organic extracts were washed with water (3x10mL) and dried over MgSO₄. After evaporation, the residue was chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether 2/8); m = 160 mg; yield 94%; mp = 190-192 C; (Lit.¹⁹ 215°C). IR (KBr) v = 3383 (NH), 1745 (CO), 1687 (CO) cm⁻¹.¹H NMR (CDCl₃) δ = 3.83 (s, 3H, OCH₃); 3.92 (s, 3H, OCH₃); 6.93 (t, 1H, Harom, J=8.2 Hz); 6.99 (d, 1H, Harom, J=8.2 Hz); 7.49 (t, 1H, Harom, J=8.2 Hz); 7.62 (d, 1H, Harom, J=8.2 Hz); 9.15 (br s, 1H, NH).¹³C NMR (CDCl₃) δ = 48.0 (CH₃); 51.7 (CH₃); 100.2 (C); 110.9 (CH); 118.8 (C); 121.3 (CH); 124.6 (CH); 136.7 (CH); 141.8 (C); 151.1 (C); 164.3 (CO); 165.3 (CO); 184.6 (CO). MS (CI / NH₃): m/z = 262 (M⁺+1). Anal. Calcd for C₁₃H₁₁NO₅: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.83; H, 4.19; N, 5.45.

Diethyl 2-(3-Oxo-2,3-dihydro-1H-2-indolyliden)malonate (20).^{20,21}

Starting from diethyl malonate (0.31g, 1.95 mmol, 3 eq), triflate **17** (200 mg, 0.65 mmol) and sodium hydride (60% weight, 65 mg, 1.62 mmol); time reaction: 1h; elution: ethyl acetate/petroleum ether 2/8; m = 102 mg; yield 55%; mp 116-118°C; (Lit.^{20,21} 117-118°C). IR (KBr) v = 3382 (NH), 1722 (CO), 1696 (CO) cm^{-1.1}H NMR (CDCl₃) $\delta = 1.24$ -1.39 (m, 6H, CH₃); 4.28 (q, 2H, OCH₂, J = 7.1 Hz,); 4.40 (q, 2H, OCH₂, J = 7.1 Hz); 6.93 (t, 1H, Harom, J = 7.1 Hz); 6.99 (d, 1H, Harom; J = 7.1 Hz); 7.48 (t, 1H, Harom, J = 8.2 Hz); 7.62 (d, 1H, Harom, J = 8.2 Hz); 9.15 (br s, 1H, NH). ¹³C NMR (CDCl₃) $\delta = 13.4$ (CH₃); 13.7 (CH₃); 61.2 (CH₂); 61.6 (CH₂); 101.8 (=C(COOC₂H₅)₂); 111.4 (CH); 119.5 (C); 121.7 (CH); 125.2 (CH); 137.1 (CH); 142.0 (C₂=); 151.7 (C); 164.3 (CO); 167.7 (CO); 185.2 (CO). Anal. Calcd for C₁₅H₁₅NO₅: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.51; H, 5.12; N, 4.67.

Methyl 2-Cyano-2-(3-oxo-2,3-dihydro-1H-2-indolilyden) acetate (21).

Starting from methyl cyanoacetate (193 mg, 1.95 mmol, 3 eq), triflate **17** (200 mg, 0.65 mmol) and sodium hydride (60% weight, 65 mg, 1.62 mmol); time reaction 40 min; elution: ethyl acetate/petroleum ether 2/8; m = 68mg; yield 46%; mp>260°C. IR (KBr) v = 3335 (NH), 2207 (CN), 1680 (CO) cm⁻¹. ¹H NMR (DMSO-d6) δ = 3.85 (s, 3H, OCH₃); 7.13 (t, 1H, Harom, J = 7.5 Hz); 7.34 (d, 1H, Harom, J = 7.5 Hz); 7.60-7.68 (m, 2H, Harom); 11.4 (br s, 1H, NH). ¹³C NMR (DMSO-d6) δ = 54.8 (OCH₃); 77.5 (=C-CN); 116.1 (CH); 116.8 (C);121.2 (C); 125.6 (CH); 127.5 (CH); 140.1 (CH); 151.6 (C); 153.6 (C); 167.1 (CO); 186.8 (CO). MS (CI/NH₃): m/z = 229 (M⁺+1). Anal. Calcd for C₁₂H₈N₂O₃: C, 63.16; H, 3.53; N, 12.28. Found: C, 62.85; H, 3.67; N, 12.33.

Ethyl 2-(3-Oxo-2,3-dihydro-1H-2-indolyliden) acetate (22).²⁰

Starting from ethyl nitroacetate (131 mg, 0.99 mmol, 3 eq), triflate **17** (100 mg, 0.33 mmol) and sodium hydride (60% weight, 33 mg, 0.82 mmol); time reaction 3h30; elution: ethyl acetate/ petroleum ether 2/8; m = 40 mg; yield 56%; mp 128-130°C; (Lit.²⁰ 131°C). IR (KBr) v = 3362 (NH), 1719 (CO), 1670 (CO) cm⁻¹. ¹H NMR (CDCl₃) $\delta = 1.33$ (t, 3H, CH₃, J = 7.6 Hz); 4.27 (q, 2H, OCH₂, J = 7.6 Hz); 5.86 (s, 1H, CH=); 6.92 (t, 1H, Harom, J = 8.2 Hz); 6.98 (d, 1H, Harom, J = 8.2 Hz); 7.48 (t, 1H, Harom, J = 8.2 Hz); 7.67 (d, 1H, Harom); 8.84 (br s, 1H, NH). ¹³C NMR (DMSO-d6) $\delta = 15.4$ (CH₃); 61.1 (OCH₂); 92.5 (=CH); 114.1 (CH); 120.2 (C); 122.3 (CH); 125.8 (CH); 138.9 (CH); 145.1 (C=); 155.4 (C); 167.9 (CO); 188.3 (CO). MS(IS): m/z = 218 (M⁺+1). Anal. Calcd for C₁₂H₁₁NO₃: C, 66.35; H, 5.10; N, 6.45. Found: C. 65,98; H, 5.41; N, 6.01.

Diethyl 2-[3-(Acetyloxy)-1H-2-indolyl]-2-methylmalonate (23).

Starting from diethyl methylmalonate (238 mg, 1.36 mmol, 3 eq), triflate **17** (140 mg, 0.45 mmol) and sodium hydride (60% weight, 45mg, 1.13 mmol); reaction time 1h; elution: ethyl acetate/petroleum ether 2/8; m = 100 mg; yield 63%. IR (film) v = 3408 (NH), 1738 (CO) large cm⁻¹. ¹H NMR (CDCl₃) δ = 1.23-1.30 (m, 6H, CH₃); 1.86 (s, 3H, CH₃); 2.34 (s, 3H, COCH₃); 4.19-4.31 (m, 4H, OCH₂); 7.05-7.22 (m, 2H, Harom); 7.32-7.37 (m, 2H, Harom); 9.54 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ = 13.5 (CH₃); 20.0 (CH₃); 21.1 (CH₃); 22.4 (CH₃); 52.2 (C); 61.8 (OCH₂); 62.0 (OCH₂); 111.3 (CH); 116.9 (CH); 119.6 (CH); 120,5 (C); 122.3 (CH); 123.1 (C); 126.3 (C); 132.1 (C); 168,6 (CO); 169.6 (CO); 170.5 (CO). MS (CI/NH₃): m/z = 348 (M⁺+1). Anal. Calcd for C₁₈H₂₁NO₆: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.45; H, 5.84; N, 4.19.

Diethyl 2-[3-(Acetyloxy)-1H-2-indolyl]-2-allylmalonate (24).

Starting from diethyl allylmalonate (196 mg, 0.98 mmol, 3 eq), triflate **17** (100 mg, 0.33 mmol) and sodium hydride (60% weight, 33 mg, 0.82 mmol); time reaction 2h30; elution: ethyl acetate/petroleum ether 2/8; m = 51 mg; yield 42%. IR (film) v = 3416 (NH), 1740 (CO) large cm⁻¹. ¹H NMR (CDCl₃) δ = 1.21-1.31 (m, 6H, CH₃); 2.33 (s, 3H, COCH₃); 3.07 (d, 2H, CH₂, J = 7.3 Hz); 4.14-4.32 (m, 4H, OCH₂); 5.01 (m, 2H, CH₂=CH); 5.47-5.57 (m, 1H, CH₂=CH); 7.05-7.12 (m, 1H, Harom); 7.15-7.24 (m, 1H, Harom); 7.31-7.36 (m, 2H, Harom); 9.83 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ = 14.5 (2CH₃); 21.1 (CH₃); 41.0 (CH₂); 57.3 (C); 62.7 (OCH₂); 63.1 (OCH₂); 112.3 (CH); 117.9 (CH); 119.9 (CH₂); 120.6 (CH); 121.3 (C); 122.5 (C); 123.2 (CH); 127.3 (C); 130.1 (CH); 132.4 (C); 169.4 (2CO); 169.7 (CO). MS (CI / NH₃): m/z = 374 (M⁺+1). Anal. Calcd for C₂₀H₂₃NO₆: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.47; H, 6.33; N, 3.88.

Diethyl 2-[3-(Acetyloxy)-1H-2-indolyl]-2-phenylmalonate (25).

Starting from diethyl phenylmalonate (231 mg, 0.98 mmol, 3 eq), triflate **17** (100 mg, 0.33 mmol), and sodium hydride (60% weight, 33 mg, 0.82 mmol); time reaction 1h30; elution: ethyl acetate /petroleum ether 2/8; m = 42mg; yield 31%. IR (film) v = 3418 (NH), 1733 (CO) large cm⁻¹. ¹H NMR (CDCl₃) δ = 1.23-1.35 (m, 6H, CH₃); 2.08 (s, 3H, COCH₃); 4.22-4.40 (m, 4H, OCH₂); 7.22-7.62 (m, 8H, Harom); 7.75 (d, 1H, Harom, J = 8.2

Hz); 9.79 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ = 14.5 (CH₃); 14.7 (CH₃); 21.1 (COCH₃); 57.3 (C); 62.7 (OCH₂); 63.1 (OCH₂); 112.7 (C); 117.9 (CH); 119.9 (CH); 120.2 (CH); 120.6 (CH); 121.0 (CH); 121.3 (C); 122.5 (C); 123.2 (CH); 124.1 (CH); 125.2 (CH); 127.3 (C); 130.1 (CH); 132.4 (C); 169.4 (CO); 169.7 (CO); 169.9 (CO). MS (CI / NH₃): m/z = 410 (M⁺+1). Anal. Calcd for C₂₃H₂₃NO₆: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.19; H, 5.83; N, 3.59.

Dimethyl 2-[2-(Ethoxycarbonyl)-1-methyl-3-oxo-2,3-dihydro-1H-2-indolyl] malonate (27).

Starting from triflate 3 (200 mg, 0.57 mmol), dimethyl malonate (225 mg, 1.71 mmol) and sodium hydride (60% weight, 57mg, 1.42 mmol); time reaction: 4h; elution: dichloromethane /petroleum ether 80/20; m= 99 mg; yield 50%. IR (film): v = 1760 (CO) large cm⁻¹. ¹H NMR (CDCl₃) $\delta = 1.20$ (t, 3H, CH₃, J = 7.2 Hz); 3.25 (s, 3H, OCH₃); 3.37 (s, 3H, OCH₃); 3.82 (s, 3H, NCH₃); 4.16 (q, 2H, OCH₂, J = 7.2 Hz); 4.72 (s, 1H, CH); 6.79-6.86 (m, 2H, Harom); 7.50 (t, 1H, Harom, J = 7.8 Hz); 7.61 (d, 1H, Harom, J = 7.8 Hz). ¹³C NMR (CDCl₃) $\delta = 13.9$ (CH₃); 31.2 (NCH₃); 51.0 (OCH₃); 52.4 (OCH₃); 57.5 (CH); 62.7 (OCH₂); 109.1 (CH); 118.5 (CH); 125.3 (CH); 138.1 (CH); 162.2 (C); 164.8 (C); 166.2 (C); 168.5 (CO); 192.1 (CO). MS (CI / NH₃): m/z = 350 (M⁺+1). Anal. Calcd for C₁₇H₁₉NO₇: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.62; H, 5.59; N, 4.16.

Dimethyl 2-[2-(Ethoxycarbonyl)-1-methyl-3-oxo-2,3-dihydro-1H-2-indolyl]-2-methylmalonate (28).

Compound **27** (100 mg, 0.29 mmol) was added at 0°C to a suspension of sodium hydride (60% weight, 15 mg, 0.37 mmol) in DMF (5 mL). After 15 min, iodomethane (0.09 mL, 1.43 mmol) was added followed by stirring at 40°C for 3 h; water (10 mL) was added. Extraction with ethyl acetate (3x10 mL), washing with water (10mL) followed by drying over MgSO₄ and concentration provided a crude residue which was chromatographed on a silica gel column (eluent ethyl acetate/petroleum ether 1/9); m = 65 mg; yield: 62%; oil. IR (film) v = 1750 large (CO) cm⁻¹. ¹H NMR (CDCl₃) δ = 1.21 (t, 3H, CH₃, J = 7.3 Hz); 1.86 (s, 3H, CH₃); 3.15 (s, 3H, OCH₃); 3.34 (s, 3H, OCH₃); 3.81 (s, 3H, NCH₃); 4.10-4.25 (m, 2H, OCH₂); 6.74-6.80 (m, 2H, Harom); 7.46 (t, 1H, Harom, J = 8.2 Hz); 7.55 (d, 1H, Harom, J = 8.2 Hz). ¹³C NMR (CDCl₃) δ =13.9 (CH₃); 17.8 (CH₃); 32.1 (NCH₃); 52.2 (CH₃); 52.9 (CH₃); 61.8 (C); 62.2 (CH₂); 76.7 (C); 109.2 (CH); 118.4 (CH); 119.7 (C); 124.8 (CH); 137.7 (CH); 161.9 (C); 165.7 (CO); 169.6 (CO); 171.0 (CO); 192.6 (CO). MS (IS): m/z = 364 (M⁺+1). Anal. Calcd for C₁₈H₂₁NO₇: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.84; H, 5.63; N, 3.73.

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