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Nucleophilic alkylations of 3-nitropyridines

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3-Nitropyridine and 4-substituted-3-nitropyridines were reacted with chloroform, methyl chloroacetate and ethyl 2-chloropropionate under vicarious nucleophilic substitution (VNS) conditions. Substitution was obtained in the *ortho* or *para* position to the nitro group with acceptable to good yields and regioselectivity. With potassium 5-nitropyridine-2-sulfonate the substitution took place in the 4-position. Further substitution of the sulfonate group proved to be possible.

Nucleophilic substitution reactions of both nitroaromatic and nitroheteroaromatic compounds are important synthetic reactions. Typically, a leaving group, for instance a halide or an alkoxy group, is substituted. The nitro group in the *ortho* or *para* positions acts as an electron withdrawing, activating agent.[1] It is also possible to have substitution of hydrogen in these compounds. The vicarious nucleophilic substitution (VNS) protocol has been particularly effective for the substitution reactions of a large number of nitroaromatic and nitroheteroaromatic compounds.[2] We have reported the amination of 3-nitropyridine and 4- and 5-substituted-3-nitropyridines by both the VNS and the oxidative nucleophilic substitution method.[3,4] Substitution with carbon nucleophiles is an important part of the VNS methodology. Makosza *et al.* have substituted a number of nitropyridines by this method.[5] Nitration of pyridines has been restricted to those containing electron releasing substituents on the pyridine ring. The number of nitropyridine compounds available for further reactions has therefore been limited.

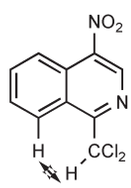
We have reported a general method for nitration of pyridine compounds which does not proceed by the electrophilic aromatic substitution mechanism and which therefore does not depend upon electron donating substituents for a successful result. A number of substituted 3-nitropyridines has been made available by this method.[6] We now wish to report the alkylations of some of these nitropyridines with different carbon nucleophiles.

Results and discussion

The alkylating agents used in the VNS reactions contain a leaving group and a hydrogen atom made acidic by an electron withdrawing group.[2] An example with the accepted mechanism for the reaction[2] is shown in Scheme 1 which also gives the scope of the present report. The precursor to the nucleophile reacts with base to produce a carbanion which attacks the electrophilic compound and gives an adduct. The attack may take place in the *para* position to the nitro group as shown in Scheme 1 or in an analogous manner in the *ortho* position. Reaction of the adduct with base eliminates HCl to give an anion which on protonation gives the product.

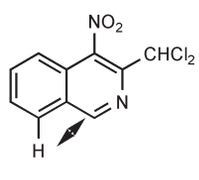
In their series of alkylation reactions with nitropyridines Makosza *et al.* also reacted 3-nitropyridine with chloroform. We chose this simple system as a starting point and obtained the same product, 4-(dichloromethyl)-3-nitropyridine in 80% yield.[5] We then carried out a series of reactions of chloroform with substituted nitropyridines. The results are given in Table 1.

For **1a** and **1b** the regioselectivity was low. However, the regioisomers could be separated by flash chromatography. Compounds **2a**–**d** and **3a**–**b** are new compounds. Their structures were derived from their ^{1}H and ^{13}C NMR spectra. For the product from the reaction of 4-nitroisoquinoline, two structures from addition to the pyridine ring are possible, 1- or 3-(dichloromethyl)-4-nitroisoquinoline, **4a** or **4b**.



NOE 3.6 %

4a

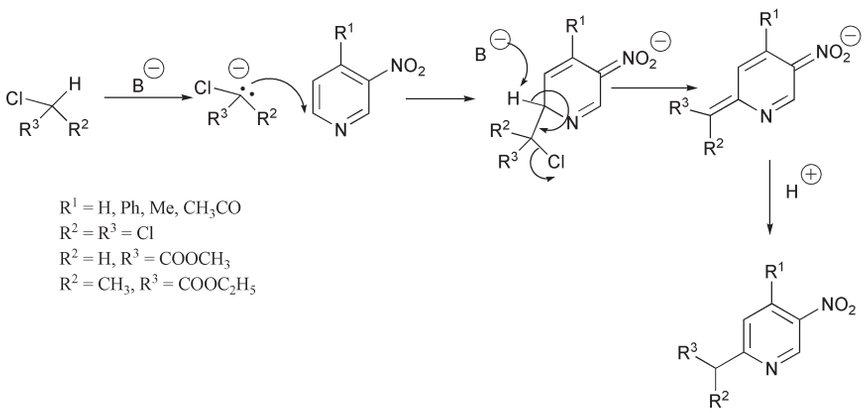


J ~ 5 Hz

4b

For the product from the reaction we observed an NOE at H^{8} from irradiation of **H**CCl$_2$ which would not have been possible for structure **4b**. Furthermore, a gated decoupling NMR experiment showed the signal from the unsubstituted carbon atom in the pyridine ring to be a doublet with a $^{2}J_{CH}$ of 190 Hz. If this had been C^{1}, a *dd* system would have been expected as a similar system, 3-chloro-4-aminoisoquinoline, showed a $^{3}J_{CH}$ of 5 Hz for H^{8}–C^{1}.[7]

We then reacted 3-nitropyridine with methyl chloroacetate and ethyl 2-chloropropionate. With 3-nitropyridine three isomers appeared possible, with substitution in the 2-, 4- and 6-positions. However, when reacted with methyl chloroacetate in THF at room temperature and *t*-BuOK as base, 3-nitropyridine gave an 80% yield of the 4-isomer, 4-methoxycarbomethyl-3-nitropyridine (**6a**).

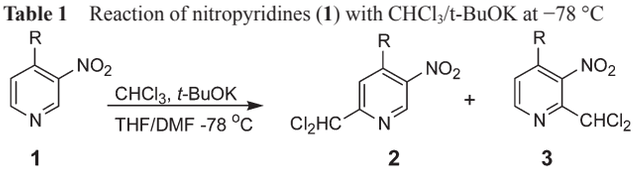


R^1 = H, Ph, Me, CH_3CO
$R^2 = R^3$ = Cl
R^2 = H, R^3 = $COOCH_3$
R^2 = CH_3, R^3 = $COOC_2H_5$

Scheme 1

DOI: 10.1039/b408840a

Table 1 Reaction of nitropyridines (**1**) with $CHCl_3$/t-BuOK at −78 °C

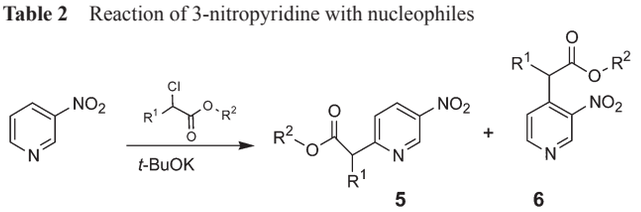


1 **2** **3**

Substrate	Yields/%[a] **2**	**3**
1a, R = Ph	27 (**2a**)	63 (**3a**)
1b, R = CH_3	51 (**2b**)	21 (**3b**)
1c, R = $C(OCH_2CH_2O)CH_3$[b]	83 (**2c**)	—
1d, R = CH_3CO	60 (**2d**)	—
4-Nitroisoquinoline	1-(Dichloromethyl)-4-nitroisoquinoline (**4a**) 69%	

[a] Isolated yields. [b] From ^1H NMR spectroscopy.

Table 2 Reaction of 3-nitropyridine with nucleophiles

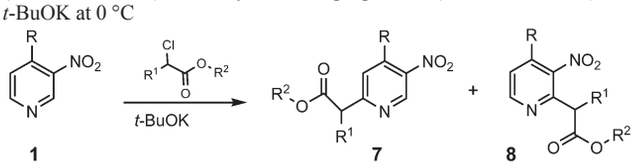


5 **6**

R^1	R^2	Solvent	*T*/°C	Base	Yields/% **5**	**6**
H	CH_3	THF	20	*t*-BuOK	—	80 (**6a**)
CH_3	C_2H_5	DMF	0	*t*-BuOK	29 (**5b**)	32 (**6b**)
CH_3	C_2H_5	DMF	0	NaH	68 (**5b**)	—
CH_3CO	C_2H_5	DMF[a]	0	*t*-BuOK	Complex mixture	

[a] In addition, THF and mixtures of this and DMF were tried.

Table 3 Reaction of 3-nitropyridines (**1**) with methyl chloroacetate (R^1 = H, R^2 = Me) and ethyl 2-chloropropionate (R^1 = Me, R^2 = Et) and *t*-BuOK at 0 °C



1 **7** **8**

Substrate	R^1	R^2	Solvent	Yield (**7**)/%
1a, R = Ph	H	CH_3	THF	Complex mixture
1a	CH_3	C_2H_5	DMF	78 (**7a**)
1b, R = CH_3	H	CH_3	THF	Complex mixture
1b	CH_3CO	C_2H_5	DMF	Complex mixture
1b	CH_3	C_2H_5	DMF	54 (**7b**)
1c, R = CH_3CO	H	CH_3	THF	Complex mixture
1c	CH_3	C_2H_5	DMF	90 (**7c**)

In neither of the examples given in Table 2 was substitution in the α-position, *ortho* to the nitro group, observed. The reaction with ethyl 2-chloropropionate shows the importance of the reaction conditions for its regioselectivity. With *t*-BuO^-K^+ in DMF, presumably forming the very reactive *t*-BuO^- as base, attack both in the *ortho* and *para* positions to the nitro group was observed. With NaH as base in DMF, the abstraction of the proton in the last step (Scheme 1) takes place on the surface of the NaH particles, making this a slow, rate determining step with the possibility of establishment of the thermodynamic equilibrium between the two intermediates. This would most likely favour the formation of the sterically less hindered *para* isomer **5**. The reaction with ethyl 2-chloroacetoacetate gave complex mixtures under a variety of reaction conditions (Table 2, entry 4).

We then tried this reaction with a number of 4-substituted-3-nitropyridines. With these substrates two products were expected from substitution *ortho* or *para* to the nitro group (**7** and **8**, Table 3). This was however, not the case. With ethyl 2-chloropropionate, only one product was observed, compounds **7** with substitution *para* to the nitro group. This may be explained by the steric demand of the carbanion attacking the nitropyridine, the available *ortho* position being more crowded than the *para* position. More surprisingly, the reactions with methyl chloroacetate gave complex mixtures with the three substrates **1a**, **1b** and **1d** tested, even though the same compound gave a good yield with 3-nitropyridine itself (Table 2).

Some time ago we reported the preparation of 5-nitro-2-pyridinesulfonic acid and its potassium salt (**9**) from 3-nitropyridine.[8] We have also reported the substitution of the sulfonate group by chloro, alkoxy and amino groups.[9]

We have now reacted the potassium sulfonate **9** with the carbanion of methyl chloroacetate. Two reaction paths appeared possible, a substitution of the sulfonate group to give compound **11** (Scheme 2) or a VNS attack at compound **9** *ortho* to the nitro group. In both cases the product would be of interest, especially as a starting material for ring formations on the *a* or *c* face of the pyridine ring.

The product from the reaction was potassium 4-methoxycarbomethyl-5-nitro-2-pyridinesulfonate (**10**), obtained in 43% yield from a VNS reaction in the 4-position. This outcome is in accordance with the results reported by Makosza *et al.*, the VNS reaction is usually faster than a competing S_NAr reaction.[10]

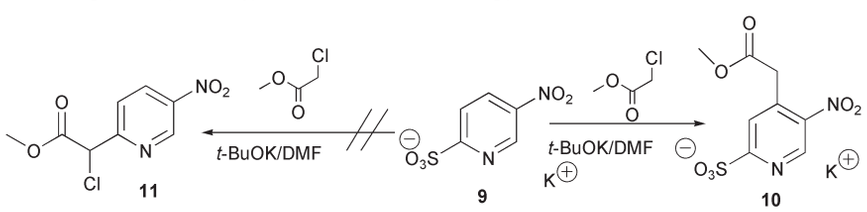
Compound **10** contains the *para* relationship between the sulfonate group and the nitro group. The sulfonate group might therefore be substituted by suitable nucleophiles by analogy with the reactions of the starting compound **9**.[9] From a few introductory experiments, this appears to be the case as shown in Table 4.

2-Methoxy-5-nitropyridine is available by a substitution reaction with **9**[9] or with 2-chloro-5-nitropyridine[11] or by direct nitration of 2-methoxypyridine.[12] One might therefore think that compound **12a** might be easily made by the reaction of 2-methoxy-5-nitropyridine with *t*-BuOK/$ClCH_2COOCH_3$ in analogy with the reactions in Table 3. However, an introductory experiment showed that this reaction did not give **12a** but a mixture of 2-(methoxycarbomethyl)-3-nitro-6-*tert*-butoxypyridine (**13**, 38%) and 2-(1-tert-butyloxycarbomethyl)-3-nitro-6-tert-butoxypyridine (**14**, 12%):

This indicates that the procedure in Table 4 may be the only way to compounds of type **12**.

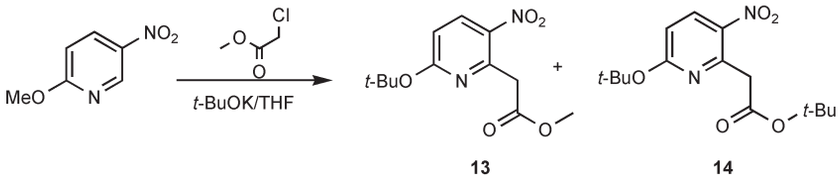
Conclusion

We have demonstrated syntheses of two sets of alkyl substituted β-nitropyridines. One is with dichloromethyl groups in the 2- or 4-position in the pyridine ring (compounds **2**, **3** and **4a**), the other with carbalkoxyalkyl groups in the same positions (compounds **5**, **6**, **7** and **10**). The dichloromethyl group can be hydrolysed to the corresponding aldehyde group[13] and also has the potential for transformation to copper carbenoids.[14] Compounds **5** to **10** may take part in ring forming reactions. We believe that these new compounds may be of some value as materials for further synthetic development in the pyridine field.



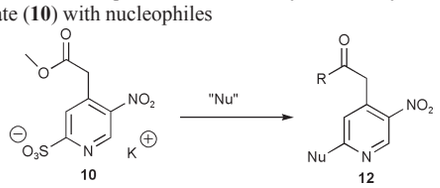
11 **9** **10**

Scheme 2



13 14

Table 4 Reactions of potassium 4-methoxycarbomethyl-5-nitro-2-pyridinesulfonate (**10**) with nucleophiles



10 12

Nucleophile ("Nu")	Product, Nu/R	Yield (%)
CH_3O	**12a**, CH_3O/CH_3O	63
NH_3	**12b**, NH_2/NH_2	68
$BuNH_2$	**12c**, BuNH/BuNH and **12d**, BuNH/OH	29 and 45

Experimental

NMR spectra were recorded on Bruker Avance DPX 300, DPX 400 or DRX 600 instruments with chemical shifts referenced to tetramethylsilane for deuteriochloroform, sodium 3-(trimethylsilyl)-propionate-2,2,3,3-d_4 for deuteriowater or the residual ^1H or ^{13}C resonances of the deuteriomethanol or deuteriodimethylsulfoxide solvent employed. Coupling constants are given in Hz. Sodium acetate was used as an internal standard when ^1H NMR spectroscopy was used to determine purity. IR spectra were recorded on a Thermo Nicolet FT-IR Nexus spectrometer. EI-MS spectra were obtained on a Finnigan MAT 95XL spectrometer. UV-Vis spectra were recorded on a Varian Cary 50 UV-Vis spectrophotometer. Melting points are uncorrected. Elemental analyses were determined by the Laboratory of Organic Elemental Analysis, Institute of Chemical Technology, Prague, Czech Republic. Solvents were purified by standard methods.[15] Silica gel SDS 60A, 43–60 mesh was used for flash column chromatography. The substitution pattern of the products were deduced from the coupling constants ^3J and ^4J of the pyridine protons.[16]

General procedure of chloromethylation of 4-substituted-3-nitropyridines

The appropriate 3-nitropyridine (3.0 mmol) and chloroform (0.4 ml, 5.0 mmol) was dissolved in dry DMF (3.0 ml) and added dropwise to a solution of potassium *tert*-butoxide (1.35 g, 12.0 mmol) in a mixture of dry DMF (2.0 ml) and dry THF (5.0 ml) at −78 °C. After 2 min the reaction was quenched by addition of conc. HCl (2.0 ml) dissolved in methanol (4.0 ml) and allowed to reach room temperature. Addition of water (100 ml), extraction with Et_2O (4 × 50 ml), washing with brine and drying (Na_2SO_4) gave the product which was purified by flash chromatography.

2-(Dichloromethyl)-5-nitro-4-phenylpyridine (2a) and 2-(dichloromethyl)-3-nitro-4-phenylpyridine (3a). The crude product was purified by flash chromatography (EtOAc : pet. ether = 1 : 9) to give **2a** as a light yellow solid, 300 mg (42%); mp 64–65 °C; Found: C, 50.9; H, 2.9; N, 9.9. $C_{12}H_8Cl_2N_2O_2$ requires: C, 50.5; H, 2.9; N, 9.6%; IR (KBr) ν_{max}/cm^{-1}: 1605 (s), 1547 (s), 1531 (s), 1517 (s), 1493 (s), 1461 (s), 1354 (s), 1301 (s); ^1H NMR (300 MHz, $CDCl_3$): 9.00 (1H, s, H-6), 8.15 (1H, s, H-3), 7.59–7.34 (5H, m, ph), 6.79 (1H, s, C**H**Cl_2); ^{13}C NMR (100 MHz, $CDCl_3$): 160.9 (d), 145.9 (s), 145.5 (s), 144.4 (d), 133.9 (s), 130.1 (s), 129.2 (d), 127.6 (d), 123.5 (d), 70.0 (d); *m*/*z* (EI) 281.99625 (M^+, $C_{12}H_8{}^{35}Cl_2N_2O_2$ requires 281.99628), 286 (M + 4, 1%), 284 (M + 2, 6%), 282 (M, 9%), 254 (47), 247 (29), 221 (35), 219 (100), 191 (35), 139 (71), 127 (31), 36 (39). Also obtained from the flash chromatography was **3a** as a light yellow solid, 140 mg (20%); mp 83–85 °C; IR (KBr) ν_{max}/cm^{-1}: 3447 (br), 3022 (m), 1590 (s), 1533 (s), 1498 (s), 1458 (s), 1448 (s), 1357 (s); ^1H NMR (300 MHz, $CDCl_3$): 8.89 (1H, d, *J* = 4.9, H-6), 7.52–7.34 (6H, m, H-5, Ph), 6.92 (1H, s, C**H**Cl_2); ^{13}C NMR (100 MHz, $CDCl_3$): 151.4 (s), 147.7 (d), 143.8 (d), 143.2 (s), 133.2 (d), 130.2 (d), 129.3 (d), 127.5 (d), 126.7 (s), 65.7 (d); *m*/*z* (EI): 281.99584 (M^+, $C_{12}H_8Cl_2N_2O_2$ requires 281.99628), 286 (M + 4, 3%), 284 (M + 2, 14%), 282 (M, %21), 256 (65), 254 (100), 237 (35), 219 (78), 155 (61), 145 (52), 140 (70), 139 (68), 127 (49), 126 (52).

2-(Dichloromethyl)-4-methyl-5-nitropyridine (2b) and 2-(dichloromethyl)-4-methyl-3-nitropyridine (3b). The crude product was purified by flash chromatography (EtOAc : pet. ether = 1 : 4) to give **2b** as a light yellow oil, 720 mg (45%); Found: C, 37.9; H, 3.0; N, 12.1. $C_7H_6Cl_2N_2O_2$ requires: C, 38.0; H, 2.7; N, 12.7%; IR (neat) ν_{max}/cm^{-1}: 2998 (w), 1609(m), 1559 (w), 1525 (s), 1444 (m), 1351 (s), 1302 (m), 1215 (w), 1173 (w), 1095 (w); ^1H NMR (400 MHz, $CDCl_3$): 9.10 (1H, s, H-6), 7.80 (1H, s, H-3), 6.75 (1H, s, C**H**Cl_2), 2.74 (3H, s, Me); ^{13}C NMR (100 MHz, $CDCl_3$): 161.0 (s), 145.6 (s), 145.1 (d), 145.0 (s), 124.6 (d), 69.9 (d), 20.2 (q); *m*/*z* (EI) 224 (M + 4, 1%), 222 (M + 2, 7%), 220 (M, 11%), 205 (39), 203 (60), 187 (33), 185 (100), 139 (30), 112 (38), 111(37). Also obtained from the flash chromatography was **3b** as a light yellow solid, 240 mg (15%); mp 49–51 °C; Found: C, 38.1; H, 2.7; N, 12.3. $C_7H_6Cl_2N_2O_2$ requires: C, 38.0; H, 2.7; N, 12.7%; IR (KBr) ν_{max}/cm^{-1}: 3032 (m), 1595 (m), 1536 (s), 1436 (m), 1357 (s), 1299 (m); ^1H NMR (400 MHz, $CDCl_3$): 8.72 (1H, d, *J* = 4.9, H-6), 7.38 (1H, dd, *J* = 4.9; 0.6, H-5), 6.90 (1H, s, C**H**Cl_2), 2.44 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 151.1 (d), 147, 8 (s), 141.3 (s), 127.6 (d), 125.9 (s), 65.9 (d), 17.8 (q); *m*/*z* (EI) 224 (M + 4, 1%), 222 (M + 2, 3%), 220 (M, 5%), 185 (36), 155 (48), 149 (100), 127 (51), 111 (119), 104 (23), 102 (28).

2-(Dichloromethyl)-4-(2-methyl-1,3-dioxolan-2-yl)-5-nitropyridine (2c). The crude product was recrystallized from methanol/water to give a light brown solid (83%). mp 111.0–112.0 °C; IR (KBr) ν_{max}/cm^{-1}: 3101, 2905, 1600, 1562, 1540, 1375, 1366, 1277, 1231, 1200; ^1H NMR (400 MHz, $CDCl_3$): 8.64 (1H, s, H-6), 8.05 (1H, s, H-3), 6.75 (1H, s, C**H**Cl_2), 4.08 (2H, m, OC**H**$_2$), 3.72 (2H, m, OC**H**$_2$), 1.87 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 161.0 (s), 148.0 (s), 146.0 (d), 144.0 (d), 120.0 (s), 108.0 (s), 70.0 (d), 65.0 (t,2 × –OCH_2), 27.0 (q); *m*/*z* (EI): 281 (6%), 279 (45), 277 (68), 235 (7), 233 (15), 124 (7), 43 (52).

4-Acetyl-2-(dichloromethyl)-5-nitropyridine (2d). The crude product was purified by flash chromatography (EtOAc : pet. ether = 1 : 4) or crystallized from cyclohexane to give **2d.** mp 50.0–50.5 °C; Found: C, 38.6; H, 2.4; N, 10.7. $C_8H_6Cl_2N_2O_3$ requires: C, 38.6; H, 2.4; N, 11.3%; IR (neat) ν_{max}/cm^{-1}: 1719 (s), 1557 (s), 1533 (s), 1352 (s), 1235 (s); ^1H NMR (300 MHz, $CDCl_3$): 9.27 (d, 1H, *J* = 0.5, H-6), 7.81 (s, 1H, *J* = 0.5, H-3), 6.78 (s, 1H, C**H**Cl_2), 2.65 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 196.9 (s), 163.4 (s), 146.8 (s), 145.1 (d), 140.8 (s), 118.8 (d), 69.5 (d), 30.0 (q); *m*/*z* (EI): 252 (M + 4, 0.2%), 250 (M + 2, 1.2), 248 (M, 1.9), 235 (22), 233 (34), 43 (100).

1-(Dichloromethyl)-4-nitroisoquinoline (4a). The crude product was dissolved in a pentane/dichloromethane solution (15 : 1) and cooled overnight at −25 °C. The solution was filtered and the filtrate concentrated to give the product as a light yellow solid (69%). mp 144.0–145.5 °C; IR (KBr) ν_{max}/cm^{-1}: 3022 (w), 1616 (w), 1552 (w), 1519 (s), 1502 (m), 1356 (w), 1323 (s), 1290 (w),

1241 (m); ^{1}H NMR (300 MHz, $CDCl_3$): 9.13 (1H, s, H-3), 8.83 (1H, d, J = 8.6, H-8), 8.63 (1H, d, J = 8.0 H-5), 8.04 (1H, dd, J = 8.6; 6.9, H-7), 7.91 (1H, dd, J = 8.0; 6.9, H-6), 7.30 (1H, s, C**H**Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$): 159.6, 142.6, 138.0 (C-3, d, J = 190), 133.7, 129.3, 129.1, 126.0, 124.9, 123.3, 70.3; *m*/*z* (EI): 260 (M + 4, 5%), 259 (M + 3, 4), 258 (M + 2, 32), 257 (M + 1, 6), 256 (M, 49), 228 (16), 226 (23), 223 (32), 222 (30), 221 (100), 174 (27), 140 (92), 129 (41), 113 (25).

4-(Methoxycarbomethyl)-3-nitropyridine (6a). 3-Nitropyridine (373 mg, 3.0 mmol) and methyl chloroacetate (543 mg, 5.0 mmol) in dry THF (12.0 ml) was added dropwise to a slurry of potassium *tert*-butoxide (1.35 g, 12.0 mmol) in dry THF (12.0 ml) at room temperature. After the addition was complete the mixture was stirred for 20 minutes and quenched with excess NH_4Cl (10% aq.). The layers were separated and the aqueous phase extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and concentrated to give a red oil (543 mg). The oil was purified by flash chromatography (EtOAc, yield 312 mg, 53%) or sublimation. mp: 37–38 °C; IR (neat) ν_{max}/cm^{-1}: 3480 (m), 3343 (m), 3978 (s), 1740 (s), 1670 (s), 1608 (s), 1556 (s), 1529 (s), 1437 (s), 1353 (s), 1230 (s); Found: C, 49.1; H, 4.0; N, 14.3. $C_8H_8N_2O_4$ requires: C, 49.0; H, 4.1; N, 14.3%; ^{1}H NMR (400 MHz, $CDCl_3$): 9.31 (1H, s, H-2), 8.79 (1H, d, J = 4.9, H-6), 7.34 (1H, d, J = 4.9, H-5), 4.08 (2H, s, ArC**H$_2$**), 3.73 (3H, s, OC**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): 169.1 (s), 154.0 (d), 146.7 (d), 145.3 (s), 138.7 (s), 127.4 (d), 52.8 (q), 39.0 (t); *m*/*z* (EI) 197 (M + 1, 0.3%), 165 (13), 150 (100), 135 (8), 92 (19).

4-(1-Ethoxycarboethyl)-3-nitropyridine (6b) and 2-(1-ethoxycarboethyl)-5-nitropyridine (5b). 3-Nitropyridine (373 mg, 3.0 mmol) and ethyl 2-chloropropionate (683 mg, 5.0 mmol) in dry DMF (3.0 ml) were added dropwise to a solution of potassium *tert*-butoxide (1.35 g, 12.0 mmol) in dry DMF (12.0 ml) at room temperature during 5 minutes. Stirring was continued for 20 minutes before the reaction was quenched with an excess of saturated aqueous ammonium chloride. An additional 100 ml of water was added before the aqueous phase was extracted with CH_2Cl_2 (4 × 50 ml). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil (470 mg) which was a mixture of **6b** and **5b**. These were separated by flash chromatography (CH_2Cl_2/acetone) to give **6b** as a brown-red oil (161 mg, 24%). Found: C, 53.6; H, 5.4; N, 12.0. $C_{10}H_{12}N_2O_4$ requires: C, 53.6; H, 5.4; N, 12.5%. IR (neat) ν_{max}/cm^{-1}: 3451 (br), 2985 (s), 2941 (s), 1735 (s), 1603 (s), 1529 (s), 1464 (s), 1407 (s), 1354 (s), 1301 (s); ^{1}H NMR (400 MHz, $CDCl_3$): 9.17 (1H, s, H-2), 8.79 (1H, d, J = 5.3, H-6), 7.46 (1H, d, J = 5.3, H-5), 4.40 (1H, q, J = 7.2, ArC**H**), 4.16 (2H, m, OC**H$_2$**), 1.63 (3H, d, J = 7.2, CHC**H$_3$**), 1.21 (3H, t, J = 7.1, CH_2C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): 171.6 (s), 153.6 (d), 146.0 (d), 145.2 (s), 144.0 (s), 123.8 (d), 61.6 (t), 41.0 (d), 17.0 (q), 13.9 (q); *m*/*z* (EI) 225 (M + 1, 0.1%), 178 (24), 150 (26), 135 (26), 104 (24), 93 (41), 85 (65), 83 (100). Also obtained from the flash chromatography was **5b** as a red oil (196 mg, 29%): Found: C, 53.3; H, 5.6; N, 12.2. $C_{10}H_{12}N_2O_4$ requires: C, 53.6; H, 5.4; N, 12.5%. IR (neat) ν_{max}/cm^{-1}: 3453 (br), 3083 (w), 2984 (s), 2939 (s), 2468 (w), 1724 (s), 1599 (s), 1518 (s), 1470 (s), 1348 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 9.38 (1H, dd, J = 2.6; 0.6, H-6), 8.46 (1H, dd, J = 8.6; 2.7, H-4), 7.52 (1H, dd, J = 8.6; 0.6, H-3), 4.18 (2H, m, OC**H$_2$**), 4.07 (1H, q, J = 7.2, ArC**H**), 1.61 (3H, d, J = 7.3, CHC**H$_3$**), 1.23 (1H, t, J = 7.1, CH_2C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): 171.9 (s), 166.0 (s), 144.3 (d), 143.2 (s), 132.4 (d), 123.4 (d), 60.6 (t), 46.8 (d), 16.8 (q), 13.9 (q). *m*/*z* (EI): 224 (M$^+$, 3%), 152 (42), 151 (100), 135 (28), 121 (39), 105 (95), 104 (24), 78 (19), 77 (15).

2-(1-Ethoxycarboethyl)-5-nitro-4-phenylpyridine (7a). 3-Nitro-4-phenylpyridine (3.0 mmol) and ethyl 2-chloropropionate (5.0 mmol) in dry DMF (12.0 ml) were added dropwise to a solution of potassium *tert*-butoxide (12.0 mmol) in dry DMF (12.0 ml) at 0 °C. After the addition was complete (3 min), the mixture was stirred overnight and quenched with an excess of saturated aqueous ammonium chloride and extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and concentrated to give an red oil (918 mg). The oil was purified by flash chromatography (EtOAc/pet.ether; 3/17) to give a light yellow oil, 632 mg (78%). Found: C, 63.7; H, 5.5; N, 9.0. $C_{16}H_{16}N_2O_4$ requires: C, 64.0; H, 5.4; N, 9.3%. IR (neat) ν_{max}/cm^{-1}: 2983 (s), 2938 (s), 1753 (s), 1547 (s), 1469 (s), 1446 (s), 1355 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 9.21 (1H, s, H-6), 7.53–7.42 (3H, m, Ph), 7.38 (1H, s, H-3), 7.37–7.31 (m, 2H, Ph), 4.27–4.12 (m, 2H, OC**H$_2$**), 4.05 (1H, q, J = 7.2, ArCH), 1.62 (3H, d, J = 7.1, CHC**H$_3$**), 1.25 (3H, t, J = 7.1, CH_2C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): 172.5 (s), 164.0 (s), 145.0 (d), 144.7 (s), 144.3 (s), 134.7 (s), 129.6 (d), 129.0 (d), 127.7 (d), 124.3 (d), 61.4 (t), 47.9 (d), 17.2 (q), 14.1 (q). *m*/*z* (EI) 300.11076 (M$^+$, $C_{16}H_{16}N_2O_4$ requires 300.11101), 300 (33%), 272 (16), 227 (100), 181 (50), 155 (26).

2-(1-Ethoxycarboethyl)-4-methyl-5-nitropyridine (7b). 4-Methyl-3-nitropyridine (414 mg, 3.0 mmol) and ethyl 2-chloropropionate (683 mg, 5.0 mmol) dissolved in dry DMF (3.0 ml) were added dropwise to a solution of potassium *tert*-butoxide in dry DMF (12.0 ml) at 0 °C and stirred for 20 minutes before the reaction was quenched with an excess of saturated aqueous ammonium chloride. Extraction with chloroform, washing of the chloroform phase with brine, drying (Na_2SO_4) and evaporation under reduced pressure gave a dark red oil (655 mg) which was purified by flash chromatograpy (EtOAc/pet.ether; 3/8) to give an yellow oil (394 mg, 54%). Found: C, 55.7; H, 6.0; N, 11.2. $C_{11}H_{14}N_2O_4$ requires: C, 55.5; H, 5.9; N, 11.8%; IR (neat) ν_{max}/cm^{-1}: 2983 (w), 2938 (w), 1735 (s), 1607 (s), 1559 (s), 1522 (s), 1448 (s), 1350 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 9.12 (1H, s, H-6), 7.28 (1H, s, H-3), 4.18 (2H, m, OC**H$_2$**), 3.98 (1H, q, J = 7.2, ArC**H**), 2.66 (3H, s, ArC**H$_3$**), 1.57 (3H, d, J = 7.1, CHC**H$_3$**), 1.23 (3H, t, J = 7.1, CH_2C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): 172.5 (s), 164.3 (s), 145.8 (d), 144.5 (s), 143.7 (s), 139.3 (s), 125.5 (d), 61.3 (t), 47.7 (d), 20.3 (q), 17.1 (q), 14.1 (q). *m*/*z* (EI) 238 (7%), 209 (7), 193(12), 166 (43), 165 (100), 119 (84), 84 (62).

4-Acetyl-2-(1-ethoxycarboethyl)-5-nitropyridine (7c). 4-Acetyl-3-nitropyidine (500 mg, 3.0 mmol) and ethyl 2-chloropropionate (683 mg, 5.0 mmol) in dry DMF (3.0 ml) were added dropwise to a stirred solution of potassium *tert*-butoxide (1.35 g, 12.0 mmol) in dry DMF (12.0 ml) at 0 °C and stirred for 20 minutes before the reaction was quenched with an excess of saturated aqueous ammonium chloride. The mixture was extracted with chloroform, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a dark red oil (474 mg) which was purified by column chromatography (EtOAc/pet.ether = 3/8) to give a yellow oil (89 mg, 11%). IR (neat) ν_{max}/cm^{-1}: 2983, 2931, 1718, 1606, 1555, 1526, 1458, 1351; ^{1}H NMR (400 MHz, $CDCl_3$): 9.29 (1H, s, H-6), 7.30 (1H, s, H-3), 4.18 (2H, m, OC**H$_2$**), 4.06 (1H, q, J = 7.2, ArC**H**), 2.59 (3H, s, C(O)C**H$_3$**), 1.59 (3H, d, J = 7.3, CHC**H$_3$**), 1.24 (3H, t, J = 7.1, CH_2C**H$_3$**); ^{13}C NMR (100 MHz, $CDCl_3$): 198.0 (s), 172.0 (s), 166.8 (s), 145.6 (d), 144.5 (s), 119.3 (d), 61.6 (q), 48.0 (q), 30.0 (q), 17.2 (d), 14.1 (t); *m*/*z* (EI) 266.09029 (M$^+$, $C_{12}H_{14}N_2O_5$ requires 266.09027), 221 (17%), 194 (59), 193 (100), 177 (37), 119 (53), 105 (28).

2-(Methoxycarbomethyl)-3-nitro-6-*tert*-butoxypyridine (13) and 2-(1-*tert*-butyloxycarbomethyl)-3-nitro-6-*tert*-butoxypyridine (14). 2-Methoxy-5-nitropyridine (**9**, 0.50 mmol) and methyl chloroacetate (68 mg, 0.66 mmol) in dry THF (1.0 ml) was added dropwise to potassium *tert*-butoxide (672 mg, 6.0 mmol) in dry THF (9.0 ml) at 0 °C. After the addition was complete the mixture was stirred for 20 minutes and quenched with excess NH_4Cl (10% aq.). The layers were separated and the aqueous phase extracted with CH_2Cl_2, this was washed with brine, dried ($MgSO_4$) and concentrated to give a red oil (67 mg) with compounds **13** and **14** as the main products (3 : 1 respectively). These were separated by flash chromatography (1 : 20; EtOAc : cyclohexane) to give **13** as a yellow oil (42 mg, 38%): IR (neat) ν_{max}/cm^{-1}: 3019 (s), 2980 (m), 1741 (s), 1590(s), 1513 (s), 1449 (s), 1389 (m), 1367 (m), 1328 (s); ^{1}H NMR (300 MHz, $CDCl_3$): 8.30 (1H, d, J = 9.1, H-4), 6.65 (1H,

d, J = 9.1, H-5), 4.22 (2H, s, ArC**H$_2$**), 3.75 (3H, s, C(O)O**Me**), 1.61 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): 169.9 (s), 165.1 (s), 149.7 (s), 138.5 (s), 135.8 (d), 112.5 (d), 82.8 (s), 52.2 (q), 43.4 (t), 28.3 (q); *m*/*z* (EI) 268.10506 (M+, $C_{12}H_{16}N_2O_5$ requires 268.10592), 213 (40), 212 (57), 181 (37), 59 (19), 57 (100), 56 (48), 41 (42), and **14** as a yellow oil: (25 mg, 12%): IR (neat) ν_{max}/cm^{-1}: 1728 (s), 1591(s), 1512 (s), 1449 (s), 1328 (s), 1216 (s); ^{1}H NMR (300 MHz, $CDCl_3$): 8.29 (1H, d, J = 9.1, H-4), 6.63 (1H, d, J = 9.1, H-5), 4.12 (2H, s, ArC**H$_2$**), 1.63 (9H, s, *t*-Bu), 1.48 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): 168.5 (s), 165.0 (s), 150.1 (s), 139.0 (s), 135.7 (d), 112.2 (d), 82.6 (s), 81.7 (s), 44.9 (t), 28.4 (q), 28.0 (q); *m*/*z* (EI) 310 (0.6%), 254 (11), 199 (69), 198 (65), 181 (40), 57 (100), 56 (19), 41 (25).

Potassium 4-methoxycarbomethyl-5-nitropyridine-2-sulfonate (10). Potassium 5-nitropyridine-2-sulfonate (**9**, 5.4 mmol) was to added DMF (200 ml) and stirred for 2 hours. The mixture was then filtered, the filtrate was concentrated under reduced pressure to a volume of 100 ml and methyl chloroacetate (2.0 ml, 24 mmol) added. This solution was then added dropwise over a period of 10 minutes to a solution of potassium *tert*-butoxide (6.0 g, 54 mmol) in DMF (100 ml). The reaction was run at 0 °C under N_2. After 0.5 hours, a new portion of methyl chloroacetate (2.0 ml, 24 mmol) dissolved in DMF (50 ml) was added dropwise, and the mixture was reacted for another 0.5 hour. The reaction was then quenched by addition of aq. NH_4Cl (10%, 500 ml) and extracted with CH_2Cl_2 (4 × 150 ml). The combined aqueous layers were concentrated under reduced pressure and added DMF (150 ml). After 1.5 hours of stirring, the salts insoluble in DMF were filtered off, and the filtrate was concentrated under reduced pressure. This crude product was then purified by flash column chromatography (eluent: 20% MeOH in CH_2Cl_2). Solid material precipitated in some of the eluent fractions. Filtration and drying under reduced pressure gave a white powder (0.33 g, 1st batch). The filtrate and the other fractions containing product were concentrated to dryness under reduced pressure and added to 20% MeOH in CH_2Cl_2 (25 ml). The solids not soluble were filtered off, and drying of these under reduced pressure gave more of the white powder (0.16 g, 2nd batch). ^{1}H NMR copy with internal standard showed the two batches to contain compound **10** with purities of 98 wt% and 62 wt%, respectively. This gave an overall yield of 43%. Both batches had no defined melting point up to 330 °C. IR (KBr) ν_{max}/cm^{-1}: 3446 (s, br.), 3099 (w), 2990 (w), 2958 (w), 1744 (s), 1531 (s), 1384 (s), 1355 (s), 1245 (s), 1229 (s), 1202 (s); ^{1}H NMR (400 MHz; D_2O): δ 9.33 (1H, s, H-6), 8.10 (1H, s, H-3), 4.30 (2H, s, C**H$_2$**), 3.75 (3H, s, OC**H$_3$**); ^{13}C NMR (100 MHz; D_2O): δ 174.7, 165.1, 149.3, 148.6, 144.7, 128.2, 56.0, 41.7; *m*/*z* (EI): 231 (5%), 227 (44), 219 (6), 181 (28), 150 (66), 69 (37), 59 (32), 57 (36), 45 (100), 44 (42), 43 (27), 28 (75); No satisfactory elemental analysis of **10** was obtained. The low purities were due to inorganic salts not detectable by ^{1}H NMR. Compound **10** with both 98 and 62 wt% purity were used as substrates in substitution reactions giving the same results. Dissolving **10** in DMSO gave a deep purple solution. The ^{1}H NMR spectrum showed an extra set of signals, which originated from the enol form of **10** (**10a**), when DMSO-d_6 was used as solvent instead of D_2O. ^{1}H NMR (400 MHz; DMSO-d_6): Signals due to **10**: δ 9.18 (1H, s, H-6), 7.99 (1H, s, H-3), 4.23 (2H, s, C**H$_2$**), 3.65 (3H, s, OC**H$_3$**); Signals due to **10a** (40% of the signals from **10**): δ 8.74 (1H, s, H-pyr), 8.67 (1H, s, H-pyr), 6.15 (1H, s, C**H**), 3.47 (3H, s, OC**H$_3$**).

2-Methoxy-4-methoxycarbomethyl-5-nitropyridine (12a). To a mixture of **10** (0.19 mmol) in methanol (10 ml) was added NaH (32 mg, 1.3 mmol). The mixture was stirred under N_2 at room temperature for 23 hours. Conc. HCl was added until pH = 3 and the solvent concentrated under reduced pressure. To the residue was added CH_2Cl_2 (15 ml) and it was stirred for 1.5 hours. The mixture was filtered, and the filtrate concentrated under reduced pressure. The yellow oil obtained was purified by flash column chromatography (eluent: 0.5% MeOH in CH_2Cl_2). Compound **12a** was obtained as a white solid (27 mg, 63% yield) with mp 73.5–74.5 °C. IR (KBr) ν_{max}/cm^{-1}: 3045 (w), 3004 (w), 2955 (m), 1734 (s), 1616 (s), 1555 (s), 1511 (s), 1336 (s), 1315 (s); ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.04 (1H, s, H-6), 6.66 (1H, s, H-3), 4.04 (3H, s, pyrOC**H$_3$**),4.01 (2H, s, C**H$_2$**), 3.73 (3H, s, C(O)OC**H$_3$**); ^{13}C NMR (150 MHz; $CDCl_3$): δ 169.9, 167.2, 147.2, 142.0, 140.3, 114.8, 55.3, 53.1, 40.2; *m*/*z* (EI) 226.05841 (M$^+$, $C_9H_{10}N_2O_5$ requires 226.05897), 225 (8%), 195 (13), 181 (10), 180 (100).

2-Amino-4-carboxamidomethyl-5-nitropyridine (12b). A 25 vol.% solution of ammonia in water (10 ml) was added to **10** (0.17 mmol) and stirred at room temperature for 24 hours. During this time the product precipitated. Filtration and drying under reduced pressure gave **12b** as yellow crystals (22 mg, 65% yield) which decomposed between 261.5–263.5 °C. The filtrate was stripped of solvent under reduced pressure and water (5 ml) was added. The yellow, insoluble solids were filtered off and dried under reduced pressure, giving an additional amount of compound **12b** (1 mg, 3% yield). The total isolated yield in the reaction was then 68%. IR (KBr) ν_{max}/cm^{-1}: 3454 (s), 3435 (s), 3313 (s), 3192 (m), 3115 (s, br.), 1660 (s), 1609 (s), 1546 (m), 1341 (s), 1310 (s), 1289 (s); ^{1}H NMR (400 MHz; DMSO-d_6): δ 8.81 (1H, s, H-6), 7.54 (1H, s, br., C(O)N**H$_2$**), 7.42 (2H, s, br., pyr-N**H$_2$**), 7.03 (1H, s, br., C(O)N**H$_2$**), 6.38 (1H, s, H-3), 3.79 (2H, s, C**H$_2$**); ^{13}C NMR (100 MHz; MeOH-d_4): δ 176.4, 165.4, 151.1, 145.0, 138.8, 114.2, 43.3; *m*/*z* (EI) 196.05957 (M$^+$, $C_7H_8N_4O_3$ requires 196.059), 150 (100%), 149 (11), 136 (7), 105 (6), 81 (7), 78 (7), 57 (6), 44 (7), 41 (6); UV-Vis(EtOH): λ_{max} (ε) 224 (8500), 346 (11000).

2-Butylamino-4-butylcarboxamidomethyl-5-nitropyridine (12c). A 25 vol.% solution of butylamine in water (5 ml) was added to **10** (0.17 mmol) and stirred at room temperature for 24 hours. During this time one product precipitated. Filtration and drying under reduced pressure gave **12c** as pale, yellow crystals (14 mg, 29% yield) with mp 144.5–145.5 °C. IR (KBr) ν_{max}/cm^{-1}: 3380 (s), 3241 (s), 3097 (s, br.), 2954 (m), 1676 (s), 1616 (s), 1578 (s), 1541 (s), 1344 (s), 1319 (s), 1297 (s), 1282 (s), 1249 (m); ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.97 (1H, s, H-6), 6.33 (1H, s, H-3), 6.01 (1H, s, br., N**H**), 5.32 (1H, s, br., N**H**), 3.79 (2H, s, pyr-C**H$_2$**), 3.37 (2H, m, br., NHC**H$_2$**), 3.25 (2H, m, NHC**H$_2$**), 1.25–1.65 (8H, m, 2 × NHCH$_2$C**H$_2$**C**H$_2$**), 0.94 (6H, m, 2 × C**H$_3$**); ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.85 (1H, s, H-6), 8.00 (2H, t, br., 2 × N**H**), 6.41 (1H, s, H-3), 3.77 (2H, s, pyr-C**H$_2$**), 3.38 (2H, m, br., NHC**H$_2$**), 3.08 (2H, m, NHC**H$_2$**), 1.57 (2H, m, NHCH$_2$C**H$_2$**CH$_2$), 1.31–1.42 (6H, m, NH CH$_2$C**H$_2$**CH$_2$ + NHCH$_2$C**H$_2$**C**H$_2$**), 0.93 (6H, m, 2 × C**H$_3$**); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.8, 160.9, 149.6, 135.6, 42,1 (br.), 41.9, 39.9, 31.7, 31.5, 20.3, 20.2, 14.0, 13.9; *m*/*z* (EI) 308.18458 (M$^+$, $C_{15}H_{24}N_4O_3$ requires 308.18484), 265 (9%), 263 (18), 262 (100), 206 (13), 192 (6), 166 (18), 148 (8), 120 (8); UV-Vis (EtOH): λ_{max} (ε) 222 (8500), 335 (12500).

2-Butylamino-4-carboxymethyl-5-nitropyridine (12d). The filtrate from which 2-butylamino-4-butylcarboxamidomethyl-5-nitropyridine (**12c**) was isolated was concentrated to dryness under reduced pressure. Compound **12d** (19 mg, 45% yield) with mp 138.5–140.0 °C was isolated by flash column chromatography (eluent: 10% MeOH in CH_2Cl_2). IR (KBr) ν_{max}/cm^{-1}: 3353 (s), 2963 (s), 2935 (s), 2470 (m), 2362 (m), 1792 (m), 1709 (s), 1625 (s), 1568 (s), 1506 (s), 1344 (s), 1304 (s), 1225 (s), 1201 (s); ^{1}H NMR (300 MHz; DMSO-d_6): δ 12.5 (1H, s, br., COO**H**), 8.89 (1H, s, H-6), 8.05 (1H, s, br., N**H**), 6.42 (1H, s, H-3), 3.87 (2H, s, pyr-C**H$_2$**), 3.37 (2H, m, br., NHC**H$_2$**), 1.53 (2H, m, NHCH$_2$C**H$_2$**), 1.36 (2H, m, NHCH$_2$CH$_2$C**H$_2$**), 0.92 (3H, t, J = 7.3, C**H$_3$**); ^{13}C NMR (100 MHz; DMSO-d_6) δ 162.4, 150.1, 144.7 (br.), 136.9, 125.9, 111.5 (br.), 32.5, 22.7, 21.3, 15.4; *m*/*z* (EI) 253 (M+, 4%), 210 (23), 209 (25), 180 (32), 167 (30), 166 (100), 153 (29), 120 (58).

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