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Studies on the 4-benzoylpyridine-3-carboxamide entity as a fragment model of the Isoniazid–NAD adduct

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An *ortho*-metallation–electrophilic substitution sequence was employed as a key step to build the 4-benzoylpyridine framework. It was found that 4-benzoylpyridine-3-carboxamide and an *N*-pyridyl alkylated derivative both exist in a unique cyclized hemiamidal structure, not in the usually expected keto-amide open form. These structures represent fragment models of the Isoniazid–NAD adducts involved in the mechanism of action of the antituberculous drug Isoniazid.

Introduction

Isoniazid (INH) (**1**; Fig. 1) is one of the most common and efficient drugs used in treatment of tuberculosis.[1] After activation by the catalase-peroxydase KatG,[2] it inhibits long-chain enoyl acyl carrier protein reductase (InhA), an enzyme involved in the biosynthesis of mycolic acids which are an integral part of the mycobacterial cell wall.[3] Data from X-ray crystallography[4] and mass spectrometry[5] reveal that the mechanism of the inhibition involves a covalent attachment of the activated form of the drug (isonicotinoyl radical) with the nicotinamide ring of NAD(H) (nicotinamide adenine dinucleotide), thereby modifying the nature of the coenzyme and its interaction with the target enzyme InhA. Recent studies have suggested that the 1,4-dihydropyridine INH–NAD adduct(s) and oxidized analogue(s) (of a pyridinium type) exhibit the keto-carboxamide structures **2** and **5**, respectively (Fig. 1).[4–6a,b] On the other hand, our group has reported that the biomimetic activation of INH with manganese(III) pyrophosphate in the presence of the coenzyme NAD^+ results mainly in the formation of cyclized hemiamidal dihydropyridines **3** (with creation of two new chiral carbons C-4 and C-7 leading to four diastereoisomers) along with the open keto-amide structures **2** as minor compounds (two epimers, 4*S* and 4*R*).[7,8] It is interesting to note that these adducts have been shown, when tested as a purified pool, to be effective inhibitors of InhA. Recently, Rawat *et al.* have reported that the analogue of the INH–NAD adduct derived from benzoic hydrazide (BH–NAD **4**; Fig. 1) is also a tight-binding inhibitor of InhA.[6b] Concerning the oxidized adduct **5**, preliminary NMR results support its existence as two diastereoisomeric cyclic adducts (form **6**).[8]

In connection with our research program on the synthesis of simplified models of INH–NAD adducts, we were interested in the preparation of the 4-benzoylpyridine-3-carboxamide core **14** (Scheme 1). This compound, which represents a fragment model and a synthetic precursor of simplified analogues of the INH–NAD adduct, would be useful to understand more about the different structures of the INH–NAD inhibitors and also for further design and access to potential antituberculous compounds.

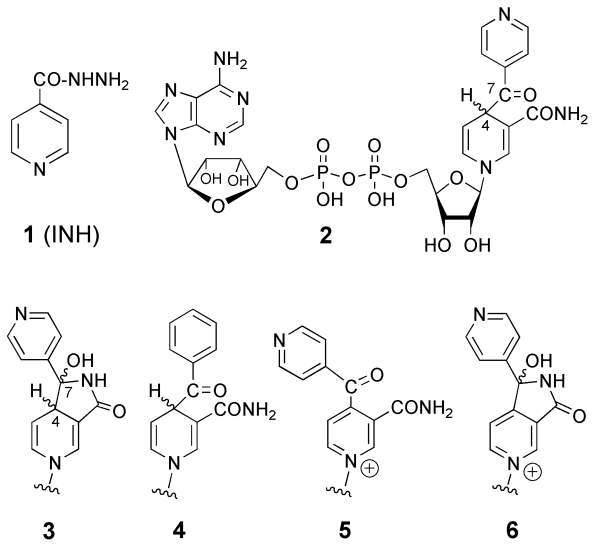

Fig. 1 Isoniazid (INH) and proposed structures for Isoniazid–NAD and benzoic hydrazide–NAD adducts.

Results and discussion

The preparation of functionalized 3,4-disubstituted pyridines in which both substituents are carbon atoms by an *ortho*-metallation–electrophilic substitution sequence is a well-established strategy in organic synthesis.[9] However, to our knowledge, this route has not yet been explored for the synthesis of 4-benzoylpyridine-3-carboxamide **14**. Therefore, we decided to adapt two previous procedures[10,11] to realize the first synthesis of this molecule.

Because tertiary amides are extremely powerful *ortho*-directing groups,[12] the starting nicotinic acid **7** was converted to *N*,*N*-diisopropylnicotinamide **8** *via* the intermediate acid chloride (Scheme 1).[13] When **8** was treated with LDA in THF at −78 °C followed by addition of *N*,*N*-dimethylbenzamide, a useful benzoylation agent, the condensation product **9** was obtained regioselectively in a very good yield.[14] Although tertiary carboxamide can be seen as a masked carboxylic acid, all attempts to realize its hydrolysis to obtain directly **12** failed. So, in order to overcome this obstacle, the keto-amide **9** was first reduced by action of $NaBH_4$ to give the alcohol-carboxamide **10**. By treatment with formic acid, **10** was then cyclized to the lactone **11** with loss of diisopropyl amine. In our hands, the use of other acid catalysts such as *p*-toluenesulfonic acid decreased the yield of this transformation. Subsequently, the unstable

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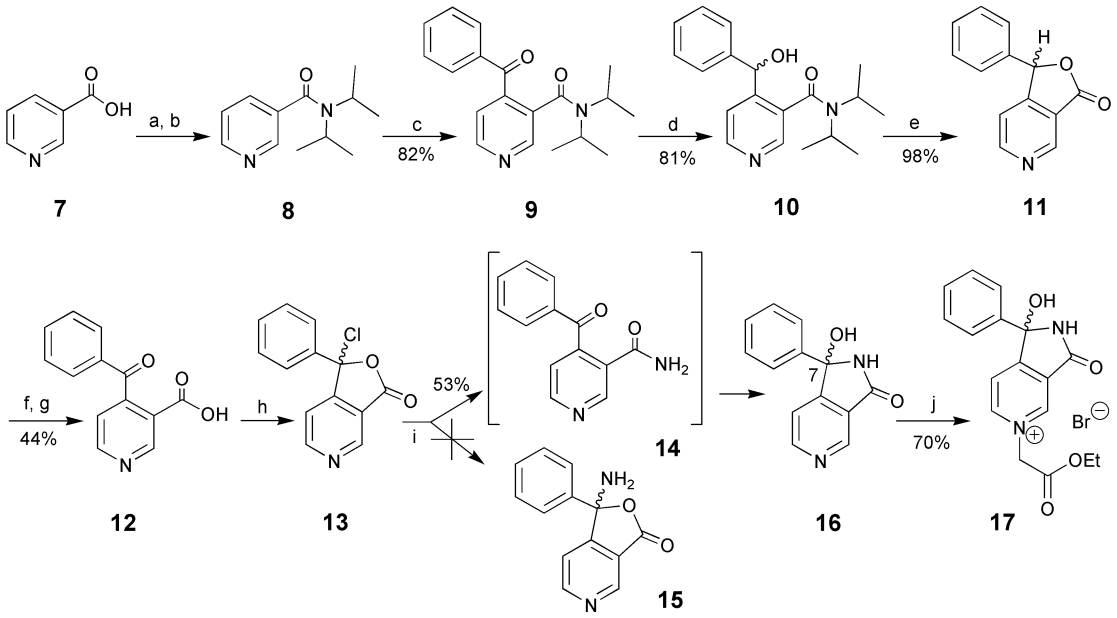

Scheme 1 *Reagents and conditions*: a) $SOCl_2$, b) $(iPr)_2NH$, c) LDA, THF, $C_6H_5CON(CH_3)_2$, d) $NaBH_4$, ethanol, e) HCOOH, reflux, f) Na_2CO_3, $MeOH–H_2O$, then conc. HCl, g) MnO_2, acetone, h) $SOCl_2$, i) aq. NH_4OH, j) $BrCH_2COOEt$, THF.

lactone **11** was opened in a basic medium (Na_2CO_3) to give, after acidification, the corresponding hydroxy-acid derivative, which upon air oxidation slowly afforded 4-benzoylnicotinic acid **12**. To accelerate this last transformation, a manganese dioxide oxidation reaction was performed. It is interesting to note that the keto-acid intermediate **12** exists exclusively in the uncyclized form (^{13}C NMR: ketone CO at 195.4 ppm and carboxylic acid CO at 166.4 ppm). Finally, to convert the acid **12** into the amide **14**, the classical reaction of ammonia with the corresponding acid chloride was employed. In fact, when **12** was treated with $SOCl_2$, the cyclized structure **13** was obtained[15] (IR: $\nu_{C=O}$ 1803 cm^{-1}). This intermediate possesses two different electrophilic centres able to react with ammonia:[16] the carbonyl carbon atom (acylation of the amine with opening of the ring), which gives the desired product **14**, or the halogenated carbon atom (alkylation of the amine) to give the lactone **15**. The reaction of ammonia with **13** gave exclusively **16**. This result suggests that this compound arises from the attack of ammonia upon the carbonyl group of **13** to give the open intermediate **14** which instantaneously isomerizes to afford the cyclized hemiamidal **16**. No trace of the open isomer **14** could be isolated or detected. The structure of **16** was unambiguously confirmed by ^{13}C NMR (tetrahedral carbon C-7 at 88.5 ppm) and X-ray structural analysis (Fig. 2). These experiences confirm that the formation of the open structure **14** is *less favourable* than the corresponding cyclized hemiamidal compound **16**, in which a 5-membered ring is constructed. The overall yield of **16** from **8** was 15%.

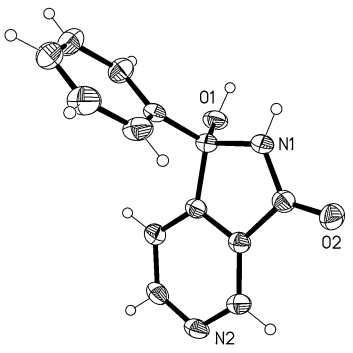

Fig. 2 X-Ray structure of compound **16**.

In order to verify whether this tendency to ring closure can also be found in the pyridinium analogue, the hemiamidal **16** was alkylated with ethyl bromoacetate. The resulting product showed spectroscopic data (^{13}C NMR, IR) in favour of the cyclized structure **17**. No equilibrium between the ring-chain isomers could be observed.

Conclusion

In conclusion, the elaboration of the 4-benzoylpyridine framework using nicotinic acid as a starting material is possible using an *ortho*-metallation–electrophilic substitution sequence. However, the target compound **14** was shown to exist exclusively in a hemiamidal structure that results from cyclization involving the 3-carboxamide group and the ketone function. Furthermore, quaternization of the pyridine nitrogen did not affect this cyclized structure and provided the pyridinium derivative **17** in a cyclized form. In light of these observations, the question of the exact structures of the parent reduced and oxidized INH–NAD adducts (opened or cyclized structures), which are the inhibitors resulting of Isoniazid activation, should be reconsidered. In addition, compounds **16** and **17** may be useful as synthetic precursors of simplified analogues of the INH–NAD adducts with potential interest as antituberculous drugs.

Experimental

Materials and methods

Melting points were determined on an Electrothermal 9300 capillary melting point apparatus and are not corrected. ^1H NMR spectra were recorded on an AC Bruker spectrometer at 250 and 300 MHz using $CDCl_3$ or d_6-DMSO as the solvent. For ^1H NMR the residual proton signal of the deuteriated solvent was used as an internal reference: $CDCl_3$ $\delta = 7.29$ ppm and d_6-DMSO $\delta = 2.50$ ppm. ^{13}C NMR spectra were recorded on an AC Bruker spectrometer at 63 and 75 MHz. Infra-red spectra were recorded on a Perkin–Elmer spectrometer GX FT-IR. Mass spectra (EI and CI) were obtained on a MS-Nermag R10–10 spectrometer. For MS-ESI, in the positive mode, a Perkin–Elmer SCIEX API 365 spectrometer was used. Elemental analysis were performed in the "Laboratoire de Chimie de Coordination du CNRS". Column chromatography was performed on silica gel

(Acros 0.035–0.070 mm). All reagents were obtained from commercial suppliers and were used without purification. Anhydrous solvents were freshly distilled before use. THF was dried over sodium in the presence of benzophenone.

4-Benzoyl-*N*,*N*-diisopropylnicotinamide (9). To a solution of *N*,*N*-diisopropylnicotinamide **8** (1.24 g, 6.00 mmol) in THF (100 cm^3) at −80 °C, lithium diisopropylamide (6 cm^3, 10.8 mmol in heptane–THF–ethylbenzene 4 : 8 : 3) was added dropwise. After 15 min stirring, a solution of *N*,*N*-dimethylbenzamide (894 mg, 6 mmol) in THF (10 cm^3) was added dropwise at −80 °C and the mixture was allowed to warm to room temperature (3 h). Water was added (50 cm^3) and the product was extracted with diethyl ether (3 × 100 cm^3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, elution with CH_2Cl_2–MeOH 95 : 5) to give **9** (1.52 g, 82%). IR ν_{max}(KBr)/cm^{-1} 1627 and 1670 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, 1H, J = 5.1 Hz, *H*6-Py), 8.65 (d, 1H, J = 0.9 Hz, *H*2-Py), 7.82 (m, 2H, *H*-phenyl), 7.61 (m, 1H, *H*-phenyl), 7.48 (m, 2H, *H*-phenyl), 7.36 (dd, 1H, J = 5.0 Hz and J = 0.8 Hz, *H*5–Py), 3.84 (m, 1H, C*H*(CH_3)$_2$), 3.48 (m, 1H, C*H*(CH_3)$_2$), 1.39 (d, 6H, J = 6.6 Hz, C*H*$_3$), 1.24 (d, 6H, J = 6.6 Hz, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4 (C), 167.0 (C), 149.6 (CH), 147.3 (CH) 144.9 (C), 136.2 (C), 134.3 (CH), 134.2 (C), 130.7 (2 × CH), 129.0 (2 × CH), 123.0 (CH), 52.1 (CH), 46.5 (CH), 21.0 (CH_3), 20.5 (CH_3). MS (EI) m/z 310 (M^+), 210, 100, 77. Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C 73.52; H 7.14; N 9.02. Found : C 73.33; H 7.50; N 8.98.

4-[Hydroxy(phenyl)methyl]-*N*,*N*-diisopropylnicotinamide (10). To a solution of amide **9** (2.50 g, 8.1 mmol) in ethanol was added $NaBH_4$ (1.47 g, 39.7 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere for 1.5 h and then acetone (20 cm^3) and water (50 cm^3) were added. The final mixture was extracted with dichloromethane, the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, elution with CH_2Cl_2–MeOH 98 : 2, 95 : 5) to give the alcohol-amide **10** as a mixture of two diastereoisomers[17] (2.04 g, 81%). IR ν_{max}(KBr)/cm^{-1}: 3277 (O–H), 2969, 2934, 1621 (C=O), 1591, 1443, 1028. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.62 (d, 1H, J = 5,0 Hz, *H*6-Py), 8.53 (d, 1H, J = 5.1 Hz, *H*6-Py), 8.41 (s, 1H, *H*2-Py), 8.37 (s, 1H, *H*2-Py), 7.42 (d, 1H, J = 5.0 Hz, *H*5-Py), 7.21–7.37 (m, 11H, 2 × (5 × *H*-phenyl) + *H*5-Py), 6.04 (d, 1H, J = 3.3 Hz, C*H*OH), 5.75 (d, 1H, J = 10.0 Hz, C*H*OH), 5.69 (d, 1H, J = 9.9 Hz, O*H*), 3.85 (d, 1H, J = 3.4 Hz, O*H*), 3.23–3.63 (m, 4H, C*H*(CH_3)$_2$), 1.52 (d, 3H, J = 6.7 Hz, CH(C*H*$_3$)$_2$), 1.50 (d, 3H, J = 6.7 Hz, CH(C*H*$_3$)$_2$), 1.42 (d, 3H, J = 6.8 Hz, CH(C*H*$_3$)$_2$), 1.28 (d, 3H, J = 6.8 Hz, CH(C*H*$_3$)$_2$), 1.15 (d, 3H, J = 6.8 Hz, CH(C*H*$_3$)$_2$), 1.11 (d, 3H, J = 6.6 Hz, CH(C*H*$_3$)$_2$), 0.67 (d, 3H, J = 6.6 Hz, CH(C*H*$_3$)$_2$), 0.45 (d, 3H, J = 6.6 Hz, CH(C*H*$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 168.6 (C), 151.4 (2 × C), 150.9 (CH), 150.5 (CH), 147.6 (CH), 146.0 (CH), 142.9 (C), 141.6 (C), 132.6 (C), 132.3 (C), 129.1 (2 × CH), 128.8 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 127.6 (CH), 126.5 (2 × CH), 125.2 (CH), 122.3 (CH), 75.7 (CH), 71.9 (CH), 51.8 (CH), 51.7 (CH), 46.8 (CH), 46.7 (CH), 21.1 (CH_3), 21.0 (CH_3), 20.8 (2 × CH_3), 20.7 (CH_3), 20.5 (2 × CH_3), 20.3 (CH_3). MS (EI) m/z 312 (M^+), 269, 210, 106, 84, 49.

1-Phenyl-1,3-dihydrofuro[3,4-*c*]pyridin-3-one (11). A solution of **10** (0.413 g, 1.32 mmol) in formic acid (50 cm^3) was heated under reflux for 23 h. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (25 cm^3). The organic phase was washed with 5% aqueous Na_2CO_3, and the aqueous phase was extracted with dichloromethane. The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 0.275 g (98%) of the unstable lactone **11**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.23 (d, 1H, J = 1.0 Hz, *H*2-Py), 8.83 (d, 1H, J = 5.1 Hz, *H*6-Py), 7.32 (dd, 1H, J = 1.0 Hz and J = 5.1 Hz, *H*5-Py), 7.30–7.38 (m, 5H, *H*-phenyl), 6.42 (s, 1H, C*H*O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C), 158.1 (C), 154.1 (CH), 148.4 (CH), 135.1 (C), 130.2 (CH), 129.6 (2 × CH), 137.2 (2 × CH), 122.2 (C), 118.8 (CH), 82.7 (CH).

4-Benzoylnicotinic acid[10] (12). To a solution of **11** (0.252 g, 1.20 mmol) in MeOH–H_2O (60 : 40) (25 cm^3), was added Na_2CO_3 (0.120 g). The reaction mixture was stirred at room temperature for 2 h, acidified with concentrated hydrochloric acid to pH 1, and then concentrated *in vacuo*. The residue was dissolved in acetone (40 cm^3) and MnO_2 (0.520 g, 6.00 mmol) was added. The mixture was stirred at room temperature for 24 h and then filtered through Celite (eluant: ethyl acetate) to remove MnO_2. The filtrate was concentrated *in vacuo*, diluted with ethyl acetate and washed with water. The aqueous phase (pH adjusted to 7) was extracted 4 times with ethyl acetate, the combined organic extracts were dried over $MgSO_4$ and concentrated by rotary evaporation. The solid obtained was purified by washing with dichloromethane to afford after drying 0.120 g (44%) of keto-acid **12**. Mp 228 °C (dec.). IR ν_{max}(KBr)/cm^{-1} 3063, 2446, 1713 and 1673 (C=O), 1596, 1293, 1268. ^{1}H NMR (250 MHz, CD_3OD) δ 9.23 (s, 1H, *H*2-Py), 8.85 (d, 1H, J = 5.1Hz, *H*6-Py), 7.49–7.74 (m, 6H, 5 × *H*-phenyl + *H*5-Py). NMR ^{13}C (75 MHz, d_6-DMSO) δ 195.4 (C), 166.4 (C), 154.2 (CH), 151.7 (CH), 149.5 (C), 136.5 (C), 134.6 (CH), 129.9 (2 × CH), 129.7 (2 × CH), 125.2 (C), 122.4 (CH). MS (EI) m/z 227 (M^+), 183 (M^+ − COO), 105 (M^+ − pyCOOH), 77, 51.

1-Hydroxy-1-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*c*]pyridin-3-one (16). A solution of **12** (0.230 g, 1.02 mmol) in $SOCl_2$ (7.5 cm^3) was stirred at 60 °C for 2.5 h. The reaction mixture was concentrated, the crude residue was dissolved in dichloromethane and the solvent removed *in vacuo*. This last operation was done twice. The oil obtained (IR ν_{max} 1803 cm^{-1}) was diluted in acetone (1.5 cm^3) and a solution of 28% NH_4OH (5 cm^3) was added dropwise. The mixture was stirred at room temperature for 1.5 h, diluted with water (15 cm^3) and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The precipitate, obtained after addition of dichloromethane, was filtered and washed with this same solvent to give, after drying, 120 mg (53%) of **16**. Mp 223 °C. IR ν_{max}(KBr)/cm^{-1} 3157, 1699, 1679, 1612, 1448, 1323, 1066. ^{1}H NMR (250 MHz, d_6-DMSO) δ 9.50 (s, 1H, N*H*), 8.87 (s, 1H, *H*2-Py), 8.71 (d, 1H, J = 5.1 Hz, *H*6-Py), 7.33–7.52 (m, 6H, 5 × *H*-phenyl and *H*5-Py), 7,18 (s, 1H, O*H*). ^{13}C NMR (75 MHz, d_6-DMSO) δ 167.9 (C), 158.4 (C), 153.8 (CH), 145.4 (CH), 141.4 (C), 129.3 (2 × CH), 129.1 (CH), 127.0 (C), 126.4 (2 × CH), 118.7 (CH), 88.1 (C). MS (DCI) m/z 227 (M + H^+), 244 (M + NH_4^+). Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found : C, 69.28; H, 4.16; N, 12.31.

Crystal data for compound 16. $C_{13}H_{10}N_2O_2$, M 226.23, monoclinic, $P2_1/c$, a = 10.245(2) Å, b = 7.160(1) Å, c = 15.020(3) Å, β = 107.943(4)°, V = 1048.2(3) Å^3, Z = 4, T = 193(2) K. 5860 reflections (2147 independent, R_{int} = 0.0343) were collected at low temperature using an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer with MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97)[18] and all non-hydrogen atoms were refined anisotropically using the least-squares method on F^2.[19] Largest electron density residue: 0.271 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0411 and wR_2 = 0.0962 (all data) with R_1 = ($\sum$ $||F_0| - |F_c||$)/$\sum$ $|F_0|$ and wR_2 = $\{\sum w(F_0^2 - F_c^2)^2 / \sum w(F_0^2)^2\}^{0.5}$. CCDC reference number 252382. See http://www.rsc.org/suppdata/ob/b4/b415439h/ for crystallographic data in .cif format.

5-[(Ethoxycarbonyl)methyl]-1-hydroxy-3-oxo-1-phenyl-1,2-dihydro-3*H*-pyrrolo[3,4-*c*]pyridinium bromide (17). To a refluxing solution of hemiamidal **16** (100 mg, 0.35 mmol) in THF (10 cm^3), ethyl bromoacetate (88 mg, 5.3 mmol) was added. After 15 h of reaction, the white precipitate was filtered,

washed three times with THF and ether, and dried under vacuum to give 100 mg (70%) of **17**. IR ν_{max}(KBr)/cm^{-1} 3089, 1755, 1717 (C=O), 1653 (C=O), 1228, 1215, 1051, 702. ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.29 (s, 1H, N*H*), 9.57 (s, 1H, *H*2-Py), 9.18 (d, 1H, J = 6 Hz, *H*6-Py), 8.31 (d, 1H, J = 6 Hz, *H*5-Py), 7.80 (s, 1H, O*H*), 7.58 (m, 2H, *H*-phenyl), 7.44 (m, 3H, *H*-phenyl), 5.73 (s, 2H, NCH_2CO), 4.24 (q, 2H, J = 7 Hz, OCH_2CH$_3$), 1.26 (t, 3H, J = 7 Hz, OCH$_2$CH_3). ^{13}C NMR (75 MHz, d_6-DMSO δ 167.1 (C), 166.5 (C), 163.9 (C), 151.3 (CH), 143.8 (CH), 138.9 (C), 130.6 (C), 130.1 (CH), 129.7 (2 × CH), 126.7 (2 × CH), 122.7 (CH), 88.5 (C), 63.3 (CH$_2$), 61.3 (CH$_2$), 14.8 (CH$_3$). MS (EI) m/z 313 (M$^+$). HRMS (FAB$^+$) found 313.1185, calc. 313.1188.

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