A new 3-ethoxycarbonylisoxazolopyridone as a precursor to acylpyridones

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Dedicated to Professor Al Padwa on his 65th birthday
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Abstract

A new 3-ethoxycarbonylisoxazolo[4,5-*c*]pyridone has been prepared as a potential precursor to 3-acyl-4-hydroxypyridones, by a route involving dipolar cycloaddition of carboethoxyformonitrile with an enamino-ester derived from β-alanine.

Keywords: Nitrile oxide, dipolar cycloaddition, isoazolopyridine, acylpyridone

During a programme of synthesis towards metabolites containing the enolised heterocyclic tricarbonyl motif **1** (Figure 1), we have reported dipolar cycloaddition strategies to access dihydroisoxazolo-[4,5-*c*]pyridin-4-one **2** (Scheme 1; enamine from a β-ketoester plus nitrile oxide from a nitro compound) and the [4,3-*c*] isomer **3** as masked non-polar synthons for the 3-acyl-4-hydroxypyridin-2-one nucleus **4**. This unit is found in a group of metabolites with a range of biological activities, exemplified by pigments tenellin **5a** and bassianin **5b** isolated from insect pathogenic fungi, and by the elfamycin antibiotics. In order to exploit the strategy of Scheme 1, it was essential to elaborate the bicycle **2** at C-3. We have reported on simple 4-alkoxycarbonylisoxazoles with electrophilic carbon substituents at C-3, and now wish to communicate our studies towards a 3-ethoxycarbonyl analogue of **2**.

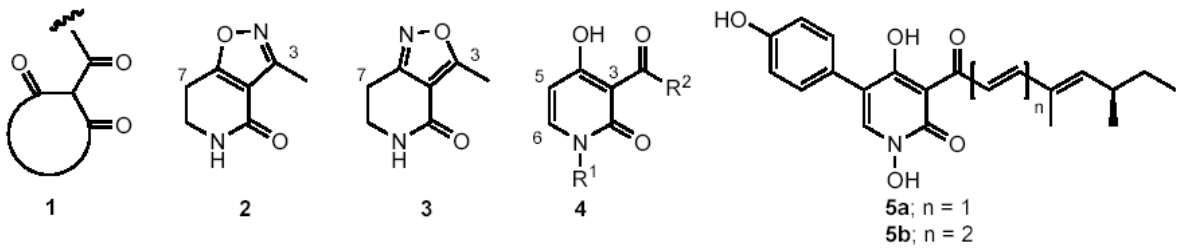
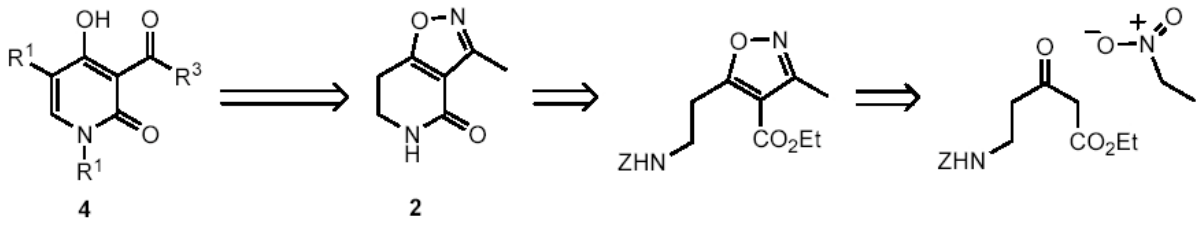
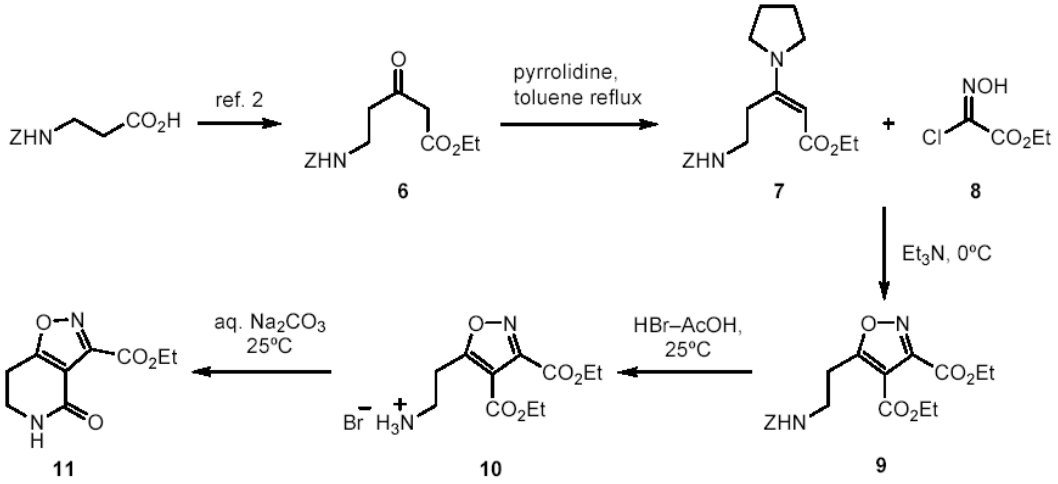


Figure 1. The heterocyclic tricarbonyl motif and examples.



Scheme 1. The cycloaddition strategy.

The β-ketoester **6** was prepared from *N*-benzyloxycarbonyl-β-alanine as we have reported,[2] and converted into the pyrrolidine enamine **7** (pyrrolidine, toluene, Dean–Stark trap for water removal). Attempted reaction with nitrile oxides derived from 2-(2-nitroethyoxy)tetrahydro-2*H*-pyran or 2,2-diethoxynitroethane ($POCl_3$, Et_3N, 0°C)[6] did not lead to any isoxazole cycloadduct even with a ten-fold excess of nitro-compound, in various solvents and using other protocols for dipole generation. We thus resorted to generating a 3-substituent at the carboxylate oxidation level. The required dipole, carboethoxyformonitrile oxide (CEFNO), was generated *in situ* by base treatment of ethyl chlorohydroxyiminoacetate **8** (Et_3N, Et_2O, 25°C), itself available from ethyl glycinate hydrochloride ($NaNO_2$, aq. HCl). Reaction of CEFNO with the enamine **7** (Scheme 2) afforded the 3,4-bis(ethoxycarbonyl)isoxazole **9** (56%). CEFNO is recognised as a reactive dipole, so success with this reagent was not unexpected.



Scheme 2

Removal of the benzyloxycarbonyl protection was efficiently accomplished to afford the amine hydrobromide salt **10** (HBr–AcOH, 25°C, 4 h; 85%), and subsequent basification (aq. Na_2CO_3, 25°C, 16 h) resulted in cyclisation to give 3-ethoxycarbonyl-4,5,6,7-tetrahydro-isoxazolo[4,5-*c*]pyridin-4-one **11** (70%). The NMR spectral data for **11** are interesting, in that two sets of signals are observed in the ^1H and ^{13}C spectra. We have reported a related

phenomenon in the isoxazolopyridine **12** (Figure 2) and suggested it may be attributed to a pyridone–hydroxypyridine tautomer mixture.[2] It is possible this may be the case also for **11**, with the hydroxy-tautomer stabilized by hydrogen bonding to the ester carbonyl group. The proportion of the two sets varies with concentration, but we have no further evidence at this stage.

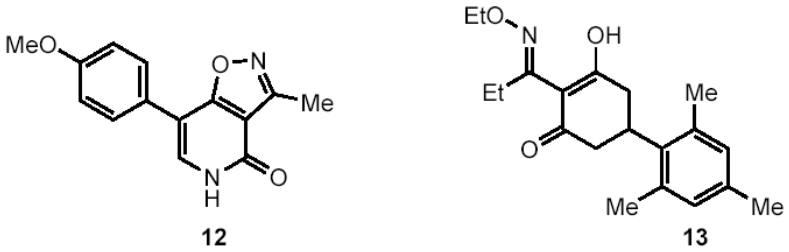
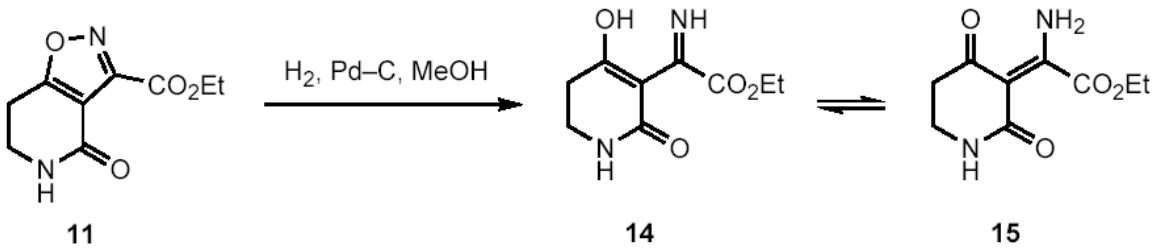


Figure 2

A variety of hydride reagents ($LiBH_4$, $NaBH_4$, $NaBH(OMe)_3$, DIBAL) was employed without success in an attempt to reduce the 3-ethoxycarbonyl function (to, for example, an aldehyde for C–C bond forming processes). We have since learnt of reductions to isoxazolidines and ring cleavages of 4-acylisoxazoles under related conditions, which are consistent with our observations.

Finally we unmasked the tricarbonyl functionality by hydrogenolysis (H_2, Pd–C, MeOH) to afford a product of N–O bond cleavage (Scheme 3). NMR data indicated the product to be a 1:1 tautomer mixture in CD_3OD solution, which we draw as the enolised dicarbonylimine **14** and a dicarbonylenamine such as **15**, although we have no definitive evidence. This functional array is closely related to that observed in the herbicide GRASP **13** (Figure 2).

We thus report a 3-ethoxycarbonylisoxazolopyridone with potential as a precursor to 4-hydroxy-3-acylpyridones of biological significance.



Scheme 3

Experimental Section

General Procedures. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1720X FT spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded using the following instruments: ^{1}H spectra at 250 MHz on a Bruker WM250 PFT or at 400 MHz on a Bruker AM400 PFT; ^{13}C spectra on a Jeol JNM-EX270 at 68 MHz or a Bruker AM400 PFT at 100 MHz and multiplicities were determined using DEPT sequences. NMR Spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as an internal standard unless otherwise stated. Chemical shifts are reported in parts per million (ppm) with the following abbreviations: s - singlet, d - doublet, t - triplet, q - quartet and br - broad; coupling constants (*J*) are quoted in Hz. Mass spectra were recorded on AEI MS902, VG 7070E or VG Autospec spectrometers using electron impact as the ionisation technique. Microanalytical data were obtained using a Perkin-Elmer 240B elemental analyser. Solvents were distilled prior to use; methanol was dried over magnesium turnings and diethyl ether over sodium. Column chromatography was carried out at medium pressure using Merck Kieselgel 60 silica (ART. 7729), and thin layer chromatography (tlc) was carried out using silica G plates F254 (Merck 5554). Solvent extracts were dried ($MgSO_4$) for 10–30 min. before filtration and the solvent removed using a Büchi rotary evaporator.

5-(2-Benzyloxycarbonylaminoethyl)-3,4-bis(ethoxycarbonyl)isoxazole (9). Ethyl 5-benzyloxy -carbonylamino-3-oxopentanoate **6** (2.93 g, 0.01 mol) in toluene (40 cm^3) was treated with pyrrolidine (0.71 g, 0.011 mol) at reflux under a Dean–Stark trap. After 2 h, water had separated (0.18 cm^3), the mixture was cooled and the excess solvent evaporated under reduced pressure. To the residue of enamine **7** in anhydrous diethyl ether (40 cm^3) was added ethyl chloro-hydroxyiminoacetate **8** (1.52 g, 0.01 mol). To this solution was added triethylamine (1.01 g, 0.01 mol) in anhydrous diethyl ether (20 cm^3) over 2 h and the mixture stirred at RT for a further 16 h. The resultant dark mixture was washed with water (40 cm^3) and the organic phase dried and evaporated under reduced pressure to yield an orange oil which was purified by chromatography on silica gel, eluted with petroleum ether (b.p. 40–60°C) : ethyl acetate (1:1 v/v) to yield the *title compound* **9** as a clear oil (1.73 g, 45%) (Found M+, 390.1439; C, 58.5; H, 5.7; N, 6.9%. $C_{19}H_{22}N_2O_7$ requires M^+, 390.1427; C, 58.44; H, 5.68; N, 7.18%); ν_{max} (film) /cm^{-1} 3390, 2984, 1725, 1603, 1529, 1454, 1311, 1218 and 1101; δ_H (250 MHz) 1.31 and 1.39 (each t, 3H, *J* 7Hz, OCH_2CH_3), 3.32 (t, 2H, *J* 6Hz, NCH_2CH_2), 3.58 (t, 2H, *J* 6Hz, NCH_2CH_2), 4.29 and 4.44 (each q, 2H, *J* 7Hz, OCH_2CH_3), 5.08 (s, 2H, $PhCH_2$), 5.30 (br. s, 1H, NH) and 7.33 (s, 5H, Ar-H); δ_C (68 MHz) 13.8 (2 x CH_3), 27.4 and 38.5 (CH_2), 61.3 and 62.6 (3 x OCH_2), 109.2 (C), 127.85, 127.9 and 128.3 (CH), 136.2, 155.5 and 156.1 (C), 159.9, 160.1 and 175.7 (CO); *m/z* 390 (M^+), 283, 227, 108 and 91 ($C_7H_7^+$, 100%).

5-(2-Aminoethyl)-3,4-bis(ethoxycarbonyl)isoxazole hydrobromide (10). 5-(2-Benzyloxycarbonyl -aminoethyl)-3,4-bis(ethoxycarbonyl)isoxazole **9** (1.00 g, 2.56 mmol) was treated with hydrogen

bromide in glacial acetic acid (32% w/v, 0.83 cm^3, 3.07 mmol) and the solution stirred at RT for 4 h. To this was added dry ether (30 cm^3) and the resultant precipitate filtered under suction, washed with dry ether (3 x 40 cm^3) and dried to yield the *title compound* **10** as a white solid (0.73 g, 85%), m.p. 195–196°C [Found $(MH^{81}Br–CH_2NH_3{}^{81}Br)^+$, 227.0791; C, 39.0; H, 5.2; N, 8.7%. $C_{11}H_{17}N_2O_5Br$ requires $MH^{81}Br–CH_2NH_3{}^{81}Br$, 227.0794; C, 39.17; H, 5.08; N, 8.41%]; ν_{max} (film)/cm^{-1} 2921, 2852, 1747, 1608, 1463, 1375, 1216 and 1130; λ_{max}(EtOH)/nm 211(ε/dm^3 mol^{-1} cm^{-1} 7169); δ_H (250 MHz) 1.29 and 1.33 (each t, 3H, *J* 7Hz, OCH_2CH_3), 3.26 (m, 2H, NCH_2CH_2), 3.43 (m, 2H, NCH_2CH_2), 4.28 and 4.40 (each q, 2H, *J* 7Hz, OCH_2CH_3) and 7.96 (br. s, 3H, NH); δ_C (68 MHz) 14.4 and 14.5 (CH_3), 25.45 and 36.55 (CH_2), 62.0 and 63.5 (OCH_2), 109.5, 156.1 and 160.2 (C), 160.4 and 175.0 (CO); *m/z* 227 [$(MH^{81}Br–CH_2NH_3{}^{81}Br)^+$, 100%], 152, 81 and 79.

3-Ethoxycarbonyl-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one (11). To 5-(2-aminoethyl)-3,4-bis(ethoxycarbonyl)isoxazole hydrobromide **10** (2.93 g, 7.10 mmol) was added sodium carbonate (1.13g, 10.65 mmol) in water (30 cm_3) and the solution stirred at room temperature for 16 h. The light brown solution was extracted with ethyl acetate (3 x 50 cm_3) and the combined organic extracts were dried and evaporated under reduced pressure to yield the *title compound* **11** as a cream solid (1.05 g, 70%), m.p. 134-136°C (Found $M^+–CH_3$, 195.0602; C, 51.7; H, 4.9; N, 13.1%. $C_9H_{11}N_2O_4$ requires $M^+–CH_3$, 195.0405; C, 51.43; H, 4.80; N, 13.33%); ν_{max} (film)/cm^{-1} 2954, 1745, 1687, 1458 and 1103; δ_H (250 MHz) 1.35 and 1.40 (2 x t, 3H, *J* 7Hz, OCH_2CH_3), 3.20 and 3.45 (2 x t, 2H, NCH_2CH_2), 3.78 and 3.92 (2 x dt, 2H, $NHCH_2CH_2$), 4.28 and 4.42 (2 x q, 2H, *J* 7Hz, OCH_2CH_3) and 6.62 (br. s, 1H, NH); $\ddot{a}_C$ (100 MHz) 14.0 (CH_3), 22.6, 27.05, 37.1 and 39.9 (CH_2), 61.6 and 62.8 (OCH_2), 107.6, 109.5, 154.9, 155.8, 157.65 and 160.1 (C), 160.2, 163.9, 175.5 and 177.05 (CO); *m/z* 195 ($M^+–CH_3$), 168, 104 and 91 (100%).

3-(1-Iminoethoxycarbonylmethyl)-4-hydroxy-1,2,5,6-tetrahydropyridin-2-one (14). 3-Ethoxycarbonyl -4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-4-one **11** (0.12 g, 0.57 mmol) in methanol (20 cm^3) was treated with palladium on charcoal (10% Pd–C, 10 mol %, 0.012 g) and stirred under an atmosphere of hydrogen (1 atm, uptake 0.049 mmol) over 16 h. After this period the solution was filtered through kieselguhr and the filtrate evaporated under reduced pressure to yield a white solid which was purified by flash column chromatography on silica, eluted with dichloromethane : methanol (92:8 v/v) to yield the *title compound* **14** as a white solid (0.118 g, 100 %), m.p. 208°C (Found M^+, 212.0744; C, 50.7; H, 5.8; N, 13.2%. $C_9H_{12}N_2O_4$ requires M^+, 212.0796; C, 50.92; H, 5.70; N, 13.21%); ν_{max} (film)/cm^{-1} 3450, 2960, 1760, 1599; δ_H (400 MHz; CD_3OD) indicated a 1:1 mixture of tautomers with δ 1.33 and 1.37 (each t, 1.5H, *J* 7Hz, OCH_2CH_3), 2.56 (m, 1H, NCH_2CH_2), 3.14 (m, 1H, $NHCH_2CH_2$), 3.40 (m, 1H, NCH_2CH_2), 3.60 (m, 1H, $NHCH_2CH_2$), 4.21 and 4.34 (each q, 1H, *J* 7Hz, OCH_2CH_3); δ_C (100 MHz) 14.5 and 14.7 (CH_3), 22.6, 27.05, 37.1 and 39.9 (CH_2), 61.6 and 62.8 (OCH_2), 107.6, 109.5, 154.9, 155.8, 157.65, 160.1, 160.2, 163.9, 175.5 and 177.05 (C); *m/z* 212, 16, 139 (100%), 68, 55 and 45.

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