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A Second-Generation Cycloaddition Approach to 3-Acyl-4-hydroxypyridin-2-ones

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Abstract: The 1,3-dipolar cycloaddition of the β-aminonitrile oxide, formed from β-alanine, to the enamine of a β-ketoester affords a 3-(2-aminoalkyl)isoxazole-4-carboxylic ester that is converted *via* isoxazolo[4,5-*c*]pyridin-4-ones into 3-acetyl-4-hydroxypyridin-2-ones.

The 3-acyl-4-hydroxypyridin-2-one nucleus **1** is the common motif of a group of metabolites with a range of biological activities, and exemplified by the elfamycin antibotics,[1] and the pigments tenellin **2a** and bassianin **2b** isolated from insect pathogenic fungi.[2] Examples of 5,6-dihydropyridones are also known. As part of our synthetic studies on (enolised) tricarbonyl metabolites,[3] we have reported a nitrile oxide 1,3-dipolar cycloaddition approach that generates a 4-carboxyisoxazole as a masked non-polar synthon for the polar tricarbonyl moiety, Scheme 1 (path A), and proceeds *via* a dihydroisoxazolo[4,5-*c*]pyridin-4-one **3**.[4] To use bicyclic isoxazole **3** as a building block for elaboration of the pyridone 3-acyl substituent, requires elaboration at C-3 of **3**. However, the preference for isoxazoles to undergo metallation[5] and radical (H-abstraction) reactions[6] at their C-5 substituent (C-7 in the bicycle **3**) suggested that C-3 elaboration would necessitate repeating the sequence with a more functionalized nitrile oxide. As an alternative, and since the N–O cleavage–hydrolysis of an isoxazole renders the N–O regiochemistry irrelevant,[7] we determined to explore a revised strategy, path B, wherein the 4-carboxyisoxazole substitution is reversed. The bicyclic isoxazole is now **4**, a dihydroisoxazolo[4,3-*c*]pyridin-4-one, and the 'isoxazole C-5' substituent is now at C-3 of the bicycle **4**. We report here the demonstration of viability of this alternative approach.

Path B reverses the origins of dipole and dipolarophile relative to path A, i.e. uses the regiospecific cycloaddition of a β-aminonitrile oxide to the enamine of a β-ketoester.[8] Thus, N-benzyloxycarbonyl-β-

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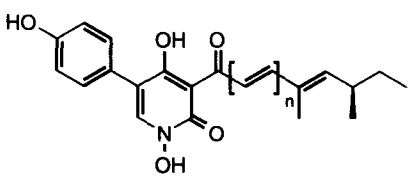
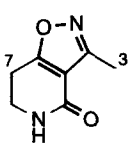


2a; n = 1
2b; n = 2



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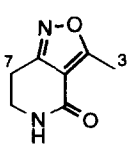

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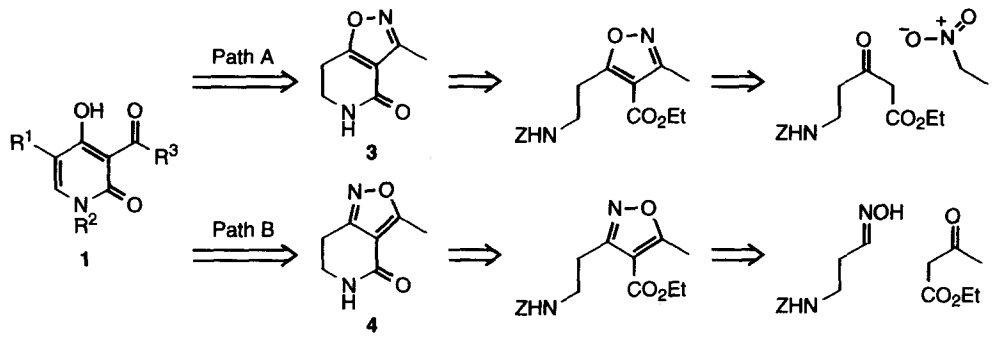
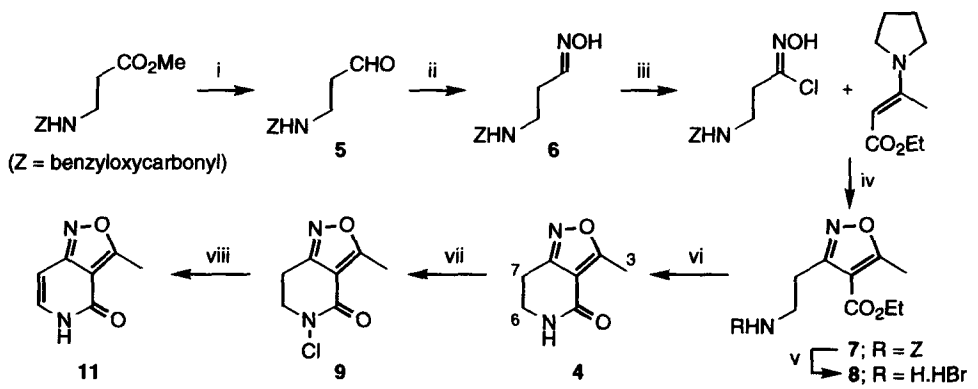


Scheme 1

alanine methyl ester was reduced (DIBAL-H, toluene, –78°) to the corresponding β-aminoaldehyde **5** that was converted immediately ($NH_2OH.HCl$, NaOAc, EtOH aq, 70°C, 10 min) into the stable, solid oxime **6** as a single isomer (60% from the ester), Scheme 2.[9] C-Chlorination of **6** was accomplished with N-chlorosuccinimide ($CHCl_3$, reflux).[10] Treatment of the chloro-oxime with ethyl 3-pyrrolidinobut-2-enoate (itself formed from pyrrolidine and ethyl acetoacetate;[11] toluene, reflux) followed by triethylamine (reflux, 2 h) resulted in cycloaddition of the nitrile oxide formed *in situ*, then spontaneous elimination of pyrrolidine, to give the 3-(2-benzyloxycarbonylaminoethyl)isoxazole-4-carboxylate **7** (69%). Removal of the N-protecting group (HBr–AcOH, 33% w/v, 25°C, 16h) gave the amine HBr salt **8** (82%), which on basification (Na_2CO_3 aq.) underwent spontaneous cyclisation to the isoxazolo[4,3-*c*]pyridone **4** (58% after recrystallisation).[12]

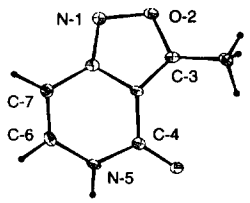


Scheme 2

Reagents: i, DIBAL-H, toluene, –78°C; ii, $NH_2OH.HCl$, NaOAc, EtOH aq., 70°C; iii, N-chlorosuccinimide, $CHCl_3$, reflux; iv, Et_3N; v, HBr–AcOH, 20°C; vi, Na_2CO_3 aq.; vii, *tert*-BuOCl, MeOH, 0°C; viii, hv (medium-pressure Hg lamp, quartz vessel), MeOH.

The double bond needed between C-6 and C-7 of **4** could not be inserted *via* C-7 deprotonation, followed by the phenylselenation–oxidative elimination sequence we had employed in path A,[4] since the metallation reactivity is now transferred to C-3 of the bicycle **4**. After a number of largely unsuccessful dehydrogenation protocols, we selected an N-halogenation–dehydrohalogenation approach. Thus lactam **4** was treated with *tert*-butyl hypochlorite (MeOH, 0°C) in the absence of direct light to give N-chlorolactam **9** (94%). Treatment with base (e.g. DBU, 25°C) did not lead to the desired elimination of HCl, but afforded a mixture of parent lactam **4** and the 3-trichloromethyl derivative **10**. This suggests deprotonation at the C-3

substituent does indeed occur readily (as we speculated when devising path B), followed by a haloform-type reaction with N-chlorolactam **9** as the 'positive halogen' source.[13] To avoid basic conditions, the dehydrochlorination was completed by photolysis (medium-pressure Hg lamp, water-cooled quartz vessel, MeOH, 10 min) which afforded, along with the parent lactam **4** (32%), the isoxazolopyridine **11** (55%; 82% based on recovered starting material).[14] Presumably this proceeds *via* an acylimine that tautomerises to the desired enamide.[15] The constitution of **11** was confirmed by an X-ray crystal structure, Fig. 1.[16]



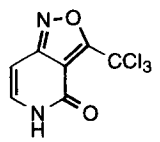


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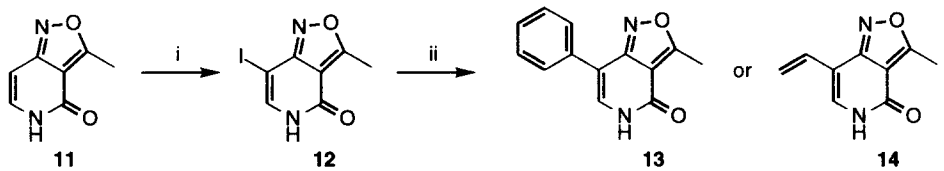
Fig. 1: X-Ray crystal structure of pyridone **11**

To demonstrate the potential for attachment of substituents at C-7 of the isoxazolopyridone **11** (C-5 of the target pyridones), the 7-iodo derivative **12** was prepared (ICl, CH_2Cl_2–MeOH, 20°C; 70%), Scheme 3. Using Pd_2(dibenzylideneacetone)$_3$ (5 mol%) as catalyst in the presence of Ph_3As (4:1 As:Pd),[17] Stille couplings of **12** to phenyltrimethyltin (1,4-dioxan, reflux; 58%) and vinyltributyltin (THF, 20→50°C; 67%) were performed to give the 7-substituted compounds **13** and **14**, respectively.[18]

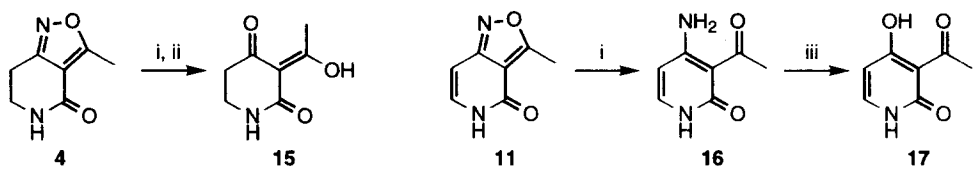


11 **12** **13** **14**

Scheme 3

Reagents: i, ICl, CH_2Cl_2–MeOH, 20°C; ii, Pd_2(dibenzylideneacetone)$_3$, Ph_3As, & either $PhSnBu_3$, 1,4-dioxan, reflux (for **13**) or CH_2=$CHSnBu_3$, THF, 20°C→50°C (for **14**).

Unmasking of the bicyclic pyridones to reveal the 3-acyl-4-hydroxypyridin-2-one moiety was readily accomplished. Hydrogenolysis of dihydroisoxazolopyridone **4** (1 atm. H_2, Pd–C, MeOH, 20°C) afforded a solid enaminone intermediate that underwent hydrolysis (1M NaOH aq., reflux, 2 h) to give 3-acetyl-4-hydroxy-5,6-dihydropyridin-2(1*H*)-one **15** (78%), Scheme 4.[4,19] Hydrogenolysis of the isoxazolopyridin-4-one **11** likewise gave aminopyridone **16** (92%) that was stable to base hydrolysis, presumably because the pseudoaromatic nature of the pyridone hinders nucleophilic substitution, but was successfully converted into 3-acetyl-4-hydroxypyridin-2(1*H*)-one **17** (90%) by diazotisation ($NaNO_2$, HCl aq.,0→50°C) .



4 **15** **11** **16** **17**

Scheme 4

Reagents: i, H_2, Pd–C, MeOH, 20°C; ii, 1M NaOH aq., reflux; iii, $NaNO_2$, HCl aq., 0→50°C.

The viability of an alternative isoxazole strategy for the synthesis of the heterocyclic core of the acylpyridone metabolites has therefore been demonstrated. The reactivity at C-3 is currently being explored.

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12 Key data for **4**: colourless needles, m.p. 190°C (Found: C, 55.18; H, 5.26; N, 18.23%; M^+, 152.0586. $C_7H_8N_2O_2$ requires C, 55.26; H, 5.30; N, 18.40%; M, 152.0586); λ_{max}(EtOH)/nm 224 (ε/dm^3 mol^{-1} cm^{-1} 9 000); ν_{max}($CHCl_3$)/cm^{-1} 3421, 3010, 1677, 1641, 1517, 1476, 1443, 1385, 1332, 1235, 1152, 1057; δ_H(400 MHz; $CDCl_3$) 2.69 (3H, s, CH_3), 3.01 (2H, t, *J* 6.4, CH_2CH_2N), 3.60 (2H, dt, *J* 2.4, 6.4, CH_2N) , 6.13 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 12.2 (CH_3), 21.3 (CH_2CH_2N), 40.6 (CH_2N), 107.8 (C-3a), 160.6 (C-7a), 163.4 (C-3), 171.9 (CONH); *m/z* (EI) 152 (M^+, 100%), 123, 109, 81, 54.
13 Compound **11** was also found from treatment of lactam **4** with potassium hexamethyldisilazide and N-chlorosuccinimide, *cf.* Back, T. G.; Lai, E. K. Y.; Morzycki, J. W. *Heterocycles* **1991**, *32*, 481.
14 Phan, X. T.; Shannon, P. J. *J. Org. Chem.* **1983**, *48*, 5164.
15 No α-methoxylactam is observed (from capture of methanol).
16 Key data for **11**: yellow crystals (from ethyl acetate:methanol), m.p. 206°C (Found: C, 56.01; H, 4.02; N, 18.65%; M^+, 150.0429. $C_7H_6N_2O_2$ requires C, 56.00; H, 4.03; N, 18.65%; M, 150.0429); λ_{max} (EtOH)/nm 233 (ε/dm^3 mol^{-1} cm^{-1} 7 100), 294 (3 500); ν_{max}($CDCl_3$)/cm^{-1} 3416, 3197, 3079, 1684, 1650, 1595, 1510, 1456, 1367, 1334, 1271; δ_H(400 MHz; $CDCl_3$) 2.88 (3H, s, CH_3), 6.40 (1H, d, *J* 7.8, CHCHN), 6.98 (1H, m, CHN), 9.20 (1H, br s, NH); δ_C(100 MHz; $CDCl_3$) 13.4 (CH_3), 95.3 (CHCHN), 108.9 (C-3a), 133.2 (CHN), 158.6 (C-7a), 161.3 (C-3) and 174.4 (CONH); *m/z*(EI) 150 (M^+, 80%), 108, 95, 80, 53 and 43 (100). *Crystal data*: $C_7H_6N_2O_2$, *M* = 150.14, orthorhombic, *a* = 7.4800(7), *b* = 12.9880(9), *c* = 13.529(2) Å, *U* = 1314.3(2) Å^3, *T* = 150(2) K, space group *Pbca*, Mo-Kα radiation, λ = 0.71069 Å, *Z* = 8, D_c = 1.517 Mg m^{-3}, *F*(000) = 624, crystal dimensions 0.18 x 0.14 x 0.12 mm, μ(Mo-Kα) = 0.115 mm^{-1}, 3.01 < 2θ < 25.08°, 4823 reflections measured, 1042 unique reflections. Solved by direct methods and refined by full-matrix least-squares on F^2. The final cycle (for 124 parameters) converged with *wR*2 = 0.0993 (for all data) and *R*1 = 0.0416 [$I > 2\sigma(I)$].
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18 To date, Suzuki coupling to arylboronic acids has been less successful, with incomplete reactions.
19 The illustrated tautomer is based on the major tautomer found for the 5-ring analogues, see ref. 6.