

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

Raymond C F Jones,^{*a} Claire E Dawson,^a Mary J O'Mahony^b and Pravin Patel^a

^aChemistry Department, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK

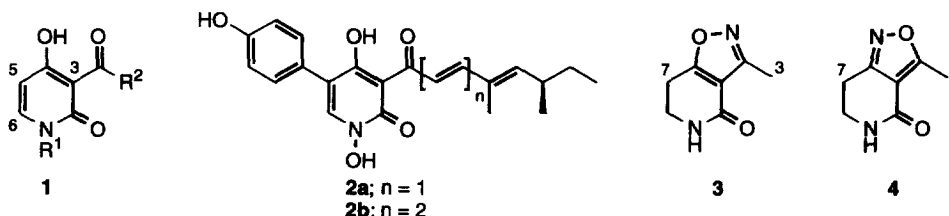
^bAgrEvo UK Ltd, Chesterford Park, Saffron Walden, Essex CB10 1XL, UK

Received 1 March 1999; accepted 29 March 1999

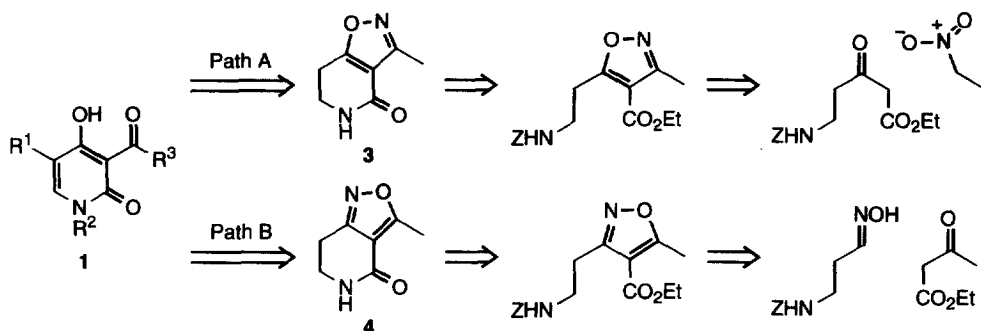
Abstract: The 1,3-dipolar cycloaddition of the β -aminonitrile oxide, formed from β -alanine, to the enamine of a β -ketoester affords a 3-(2-aminoalkyl)isoxazole-4-carboxylic ester that is converted *via* isoxazolo[4,5-*c*]pyridin-4-ones into 3-acetyl-4-hydroxypyridin-2-ones. © 1999 Elsevier Science Ltd. All rights reserved.

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 antibiotics,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 metallation⁵ and radical (H-abstraction) reactions⁶ 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 regioselective cycloaddition of a β -aminonitrile oxide to the enamine of a β -ketoester.⁸ Thus, N-benzyloxycarbonyl- β -

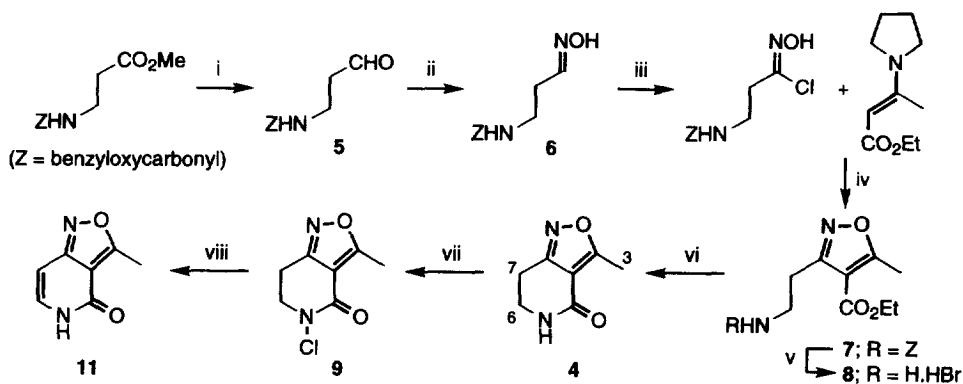


* E-mail: R.C.F.Jones@open.ac.uk



Scheme 1

alanine methyl ester was reduced (DIBAL-H, toluene, -78°) to the corresponding β -aminoaldehyde **5** that was converted immediately ($\text{NH}_2\text{OH}\cdot\text{HCl}$, 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 ($\text{HBr}\text{-AcOH}$, 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, $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaOAc , EtOH aq., 70°C ; iii, *N*-chlorosuccinimide, CHCl_3 , reflux; iv, Et_3N ; v, $\text{HBr}\text{-AcOH}$, 20°C ; vi, Na_2CO_3 aq.; vii, *tert*-BuOCl, MeOH , 0°C ; viii, hv (medium-pressure Hg lamp, quartz vessel), MeOH .

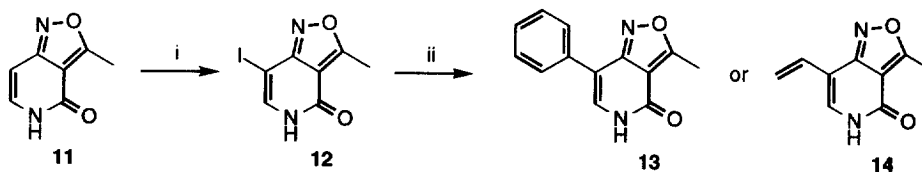
The double bond needed between C-6 and C-7 of **4** could not be inserted *via* C-7 deprotonation, followed by the phenylselenation–oxidative elimination sequence we had employed in path A,⁴ since the metallation reactivity is now transferred to C-3 of the bicycle **4**. After a number of largely unsuccessful 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



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

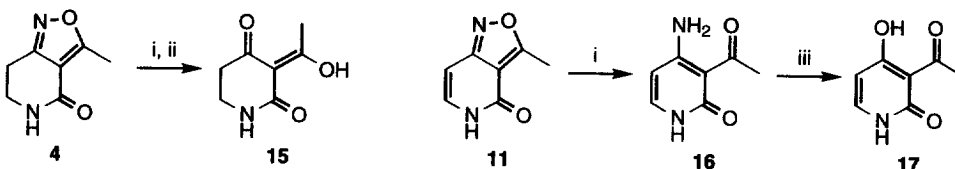
To demonstrate the potential for attachment of substituents at C-7 of the isoxazolopyridone **11** (C-5 of the target pyridones), the 7-iodo derivative **12** was prepared (ICl, CH₂Cl₂-MeOH, 20°C; 70%), Scheme 3. Using Pd₂(dibenzylideneacetone)₃ (5 mol%) as catalyst in the presence of Ph₃As (4:1 As:Pd),¹⁷ 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



Scheme 3

Reagents: i, ICl, CH₂Cl₂-MeOH, 20°C; ii, Pd₂(dibenzylideneacetone)₃, Ph₃As, & either PhSnBu₃, 1,4-dioxan, reflux (for **13**) or CH₂=CHSnBu₃, 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. H₂, Pd-C, MeOH, 20°C) afforded a solid enamionone 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 4.¹⁹ 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 (NaNO₂, HCl aq., 0→50°C).



Scheme 4

Reagents: i, H₂, Pd-C, MeOH, 20°C; ii, 1M NaOH aq., reflux; iii, NaNO₂, 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.

We thank EPSRC and AgrEvo UK for a CASE studentship (C.E.D.), Dr D A Whiting (University of Nottingham) for helpful discussion, and the EPSRC National Mass Spectrometry Service Centre and the EPSRC X-Ray Crystallography Service for measurements.

REFERENCES AND NOTES:

- For leading references, see: Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.
- Wat, C.-K.; McInnes, A. G.; Smith, D. G.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4090, and refs. therein.
- For leading refs., see: Jones, R. C. F.; Duller, K. A. M. *J. Chem. Soc., Perkin Trans 1* **1998**, 411; Jones, R. C. F.; Tankard, M. *ibid.* **1991**, 240.
- Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Vulto, S. I. E. *Synlett* **1995**, 149; Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Dunn, S. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 765.
- Natale, N. R.; McKenna, J. I.; Niou, C.-S.; Borth M. *J. Org. Chem.* **1985**, *50*, 5660.
- Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Vulto, S. I. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2513
- For a discussion of isoxazoles as masked 1,3-dicarbonyl compounds, see: Torrsell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988, pp 9, 129; Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857.
- Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5461.
- Cf.* Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081; Chung, Y. J.; Ryu, E. J.; Keum, G.; Kim, B. H. *Bioorg. Chem.* **1996**, *4*, 209.
- Larsen, K. E.; Torrsell, K. B. G. *Tetrahedron* **1984**, *40*, 2985.
- McMurry, J. E. *Org. Synth.* **1973**, *53*, 59.
- Key data for **4**: colourless needles, m.p. 190°C (Found: C, 55.18; H, 5.26; N, 18.23%; M⁺, 152.0586. C₇H₈N₂O₂ requires C, 55.26; H, 5.30; N, 18.40%; M, 152.0586); λ_{max}(EtOH)/nm 224 (ε/dm³ mol⁻¹ cm⁻¹ 9 000); ν_{max}(CHCl₃)/cm⁻¹ 3421, 3010, 1677, 1641, 1517, 1476, 1443, 1385, 1332, 1235, 1152, 1057; δ_H(400 MHz; CDCl₃) 2.69 (3H, s, CH₃), 3.01 (2H, t, J 6.4, CH₂CH₂N), 3.60 (2H, dt, J 2.4, 6.4, CH₂N), 6.13 (1H, br s, NH); δ_C(100 MHz; CDCl₃) 12.2 (CH₃), 21.3 (CH₂CH₂N), 40.6 (CH₂N), 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.
- 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.
- Phan, X. T.; Shannon, P. J. *J. Org. Chem.* **1983**, *48*, 5164.
- No α-methoxylactam is observed (from capture of methanol).
- 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. C₇H₆N₂O₂ requires C, 56.00; H, 4.03; N, 18.65%; M, 150.0429); λ_{max}(EtOH)/nm 233 (ε/dm³ mol⁻¹ cm⁻¹ 7 100), 294 (3 500); ν_{max}(CDCl₃)/cm⁻¹ 3416, 3197, 3079, 1684, 1650, 1595, 1510, 1456, 1367, 1334, 1271; δ_H(400 MHz; CDCl₃) 2.88 (3H, s, CH₃), 6.40 (1H, d, J 7.8, CHCHN), 6.98 (1H, m, CHN), 9.20 (1H, br s, NH); δ_C(100 MHz; CDCl₃) 13.4 (CH₃), 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*: C₇H₆N₂O₂, M = 150.14, orthorhombic, a = 7.4800(7), b = 12.9880(9), c = 13.529(2) Å, U = 1314.3(2) Å³, 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 F². The final cycle (for 124 parameters) converged with wR2 = 0.0993 (for all data) and R1 = 0.0416 [I > 2σ(I)].
- Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
- To date, Suzuki coupling to arylboronic acids has been less successful, with incomplete reactions.
- The illustrated tautomer is based on the major tautomer found for the 5-ring analogues, see ref. 6.