Pergamon

Tetrahedron Letters, Vol. 36, No. 19, pp. 3307-3310, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00615-X

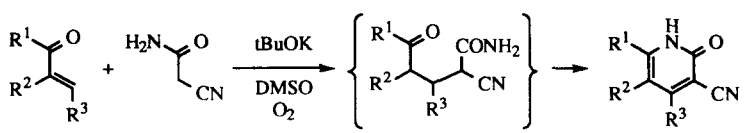
A One-Step Preparation of Functionalized 3-Cyano-2-Pyridones

Rajul Jain, Frank Roschangar, and Marco A. Ciufolini,*[1]

Department of Chemistry, Rice University, P.O. Box 1892, Houston, Texas 77251, U.S.A.

ABSTRACT: *Reaction of various enones and enals with cyanoacetamide in DMSO-tBuOK under an oxygen atmosphere furnishes 3-cyanopyridones directly and in good yield.*

In response to a need to prepare substituted 3-cyano-2-pyridones, we considered the possibility of achieving a one-step synthesis through combination of an enone with cyanoacetamide (cf. Eq. 1). The format of Eq. 1 is generally advantageous, because enones **1** are readily available with diverse permutations of R groups, and intermediates **3** may be obtained regiospecifically through a Michael process.[2] Surprisingly, the great volume of literature dealing with the preparation of pyridones[3] contains no examples of similar "direct" syntheses. Aromatization of adducts **3** is instead accomplished as a separate operation (SeO_2, halogens),[4] often after cyclization of **3** to dihydropyridones with dehydrating agents (3 steps total). We now report that *in situ* oxidation of adducts of α,β-unsaturated carbonyls with cyanoacetamide may be induced by the use of O_2 as an environmentally benign oxidant. Yields of pyridones are good to excellent, and reaction times are short.



Eq. 1

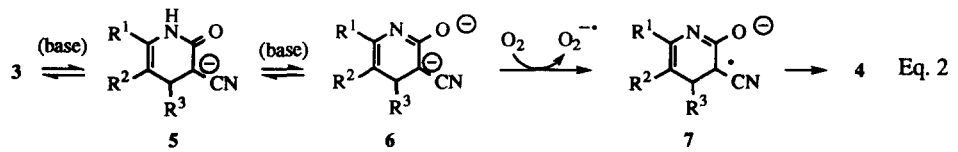
1 **2** **3** **4**

Addition of 4 mol equivalents of tBuOK, in one portion, to a 0.5 M DMSO solution of an α,β-unsaturated carbonyl compound **1** (1 equiv.) and cyanoacetamide (1.1. equiv.), at room temperature, *and under an oxygen atmosphere* (O_2 balloon), induced an exothermic reaction (*procedure A*). After stirring for 30 min without external cooling, the reaction mixture was diluted with 4 volumes of water followed by 5 volumes of 4N aqueous HCl, added slowly and with good stirring. Filtration of the precipitated, powdery pyridone, washing with water, and air drying, gave a crude product, often of > 90 % purity (NMR), in 65-90 % yield. Procedure A may not be satisfactory if the starting carbonyl compound can form an extended enolate (cf. entries **g-h**, Table 1). In such cases, the following *procedure B* is advantageous. Addition of the carbonyl substrate to an equimolar DMSO solution of tBuOK and cyanoacetamide (0.5 M, room temperature, argon atmosphere) resulted in rapid Michael addition. Upon completion of this process (10-15 min, TLC), further tBuOK (3 equiv.) was added, and the argon was displaced by O_2 (balloon, bubbling). Aromatization of the Michael adduct required 30-60 min. (TLC), and the reaction was subsequently worked up as described above. Analytical samples were obtained by either recrystallization or chromatography. Representative examples of the new procedure appear in Table 1.[5]

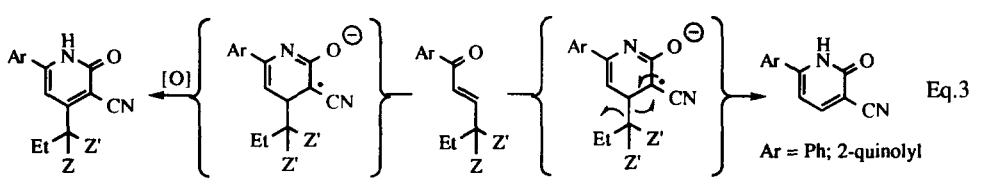
We find that base-resistant functionality is well tolerated on the carbonyl compound. DMSO is the solvent of choice. Oxygen is clearly required to promote pyridone formation, as reactions run under inert atmosphere gave only Michael adducts. Pyridones are obtained in generally good yields from enones and even from aromatic

enals, but exceedingly base sensitive carbonyls (methyl vinyl ketone, crotonaldehyde), or certain dienones (dibenzylideneacetone), were not good substrates for the reaction.

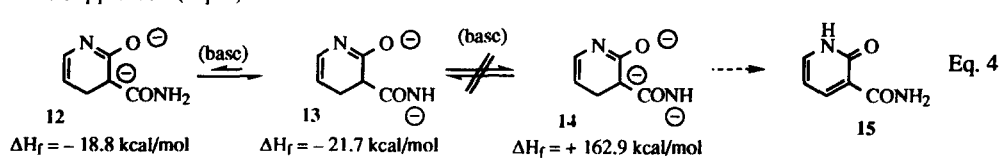
A mechanistic picture for the pyridone-forming process emerged as shown in Eq. 2. Seemingly, the initial Michael adduct **3** must first undergo base-promoted cyclization to a dihydropyridone. Subsequently, a dianion of the type **6** must form *from the cyclic intermediate*. SET from **6** to O_2 yields radical anion **7**, aromatization of which may involve either H atom transfer to O_2, or further SET chemistry, or even combination with an oxygen



species, followed by elimination. This general mechanistic outline finds support in the following observations. Substrates possessing strongly electron-releasing substituents in conjugation with the carbonyl group, e.g., 2,6-difurylidenecyclohexanone, gave only Michael adducts under our conditions, but no products of cyclization or oxidation thereof. Evidently, conjugation with the furan reduces the electrophilicity of the carbonyl group, and retards base-catalyzed cyclization to a structure of the type **5**. This prevents aromatization, as polyanionic forms of acyclic Michael adducts do not seem to advance to pyridones. The intervention of species **7** is suggested by the fact that substrates **8**, wherein Z and Z' are groups that can stabilize neighboring radical sites, furnished varying quantities of "abnormal" pyridones **11**, besides the expected **10**, depending on the radical-stabilizing ability of Z (Eq. 3). Small amounts (≈ 5 %) of **11** were observed when Z = Z' = OEt; Z = OMOM, Z' = 2-(1,3-dioxolanyl); Z-Z' = 2,2-dimethyl-1,3-dioxolane; but the abnormal pyridone was the exclusive product when Z = OH, Z' = vinyl. Fragmentation is most likely to occur at the stage of **9**, a radical of the type **7**.

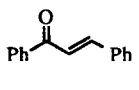
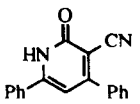
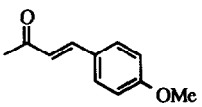
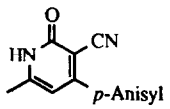
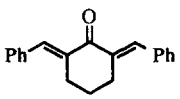
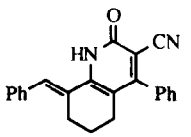
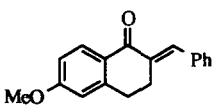
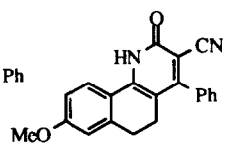
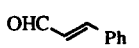
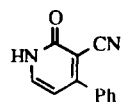
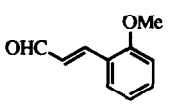
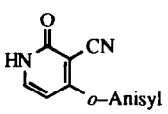
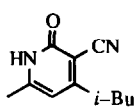
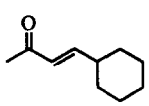
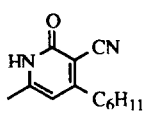


The mechanism of Eq. 2 implies that a cyclic structure that cannot readily equilibrate with a dianion such as **6** is not likely to advance to a pyridone. Indeed, malonamide produced only Michael adducts upon base-promoted reaction with chalcones, but no pyridones. MNDO calculations[6] on **12-14**, computationally better tractable congeners of dianionic intermediates arising from Michael adducts of malonamide, revealed that dianion **13** is thermodynamically more stable than **12**, and therefore it must be the prevailing dianionic species at equilibrium. Further deprotonation of **13** at the ring position, as required for aromatization, would produce an exceedingly energetic trianion **14**, formation of which must be severely disfavored. Aromatization to pyridone **15** is therefore suppressed (Eq. 4).



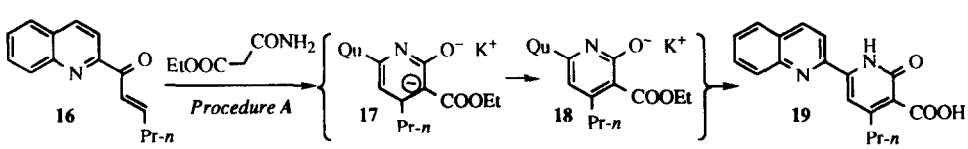
By contrast, malonamic ester[7] reacted normally with enone **16** to give carboxylic acid **19**, m.p. 217-218° C,

Table 1: Pyridones obtained by the new procedure.

Carbonyl	Pyridone	Entry	Procedure	Yield[a]	m.p. (°C, solvent)
		a	A	88	> 300 (AcOH[b])
		b	A	83	276-278 (DMF/MeOH[b])
		c	A	89	> 300 (DMF/MeOH[b])
		d	A	81	> 300 (DMF/MeOH[b])
		e	A	65	237-238 (MeOH[b])
		f	A	61	219-221 (MeOH[b])
		g	B	64	231-233 (1:1 EtOAc/Hex[c])
		h	B	63	261-263 (EtOAc[c])

[a]Yields of recrystallized or chromatographed products; [b]Recrystallization solvent; [c]Chromatographic eluant

after *in situ* hydrolysis of **18** during aqueous workup (Eq. 5). Clearly, in this case pyridone formation occurs because dianion **17** is accessible.



Eq. 5

A one-step protocol that achieves the transformation of Eq. 1 is now available. This procedure will surely facilitate preparation of various heterocyclic substances, both natural and artificial, that contain a 2-pyridone subunit. Applications to the total synthesis of natural products of current interest will be described in due course.

Acknowledgement. We are grateful to the National Institutes of Health (CA-55268), the National Science Foundation (CHE 91-16820), the Robert A. Welch Foundation (C-1007) and the Alfred P. Sloan Foundation for support of this work.

REFERENCES AND FOOTNOTES

1. Alfred P. Sloan Foundation Fellow, 1994-1996
2. Many syntheses similar to the one proposed here involve condensation of a 1,3 dicarbonyl compounds with an active methylene amide. Mixture of regioisomers are obtained from such reactions, unless the electrophilic reactivities of the carbonyl groups differ significantly (ref. 3).
3. Reviews: (a) Meislich, H. in: *Pyridine and its Derivatives*; Klingsberg, E., Ed.; Interscience: New York, N.Y. 1962; vol. 3, pp. 509-890; (b) Jones, G. in: *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, U.K., 1984; vol 2A, pp. 395-510.
4. Cf. (a) Ruby, P. R. in: *Pyridine and its Derivatives*; Klingsberg, E., Ed.; Interscience: New York, N.Y. 1960; vol. 1, pp. 99-589, esp. pp. 286 ff. and references cited therein; (b) Wojcik, M. *Dissertation*; Harvard University, 1970.
5. Spectral data for representative pyridones [^{1}H (300 MHz) & ^{13}C (75 MHz) NMR; EI-MS]: **b** (DMSO-D6) 12.47 (br s, NH), 7.59 (app. d, 2 H, app. J = 8.7 Hz, BB' part of AA'BB'), 7.08 (app. d, 2 H, app. J = 8.7 Hz, AA' part of AB), 6.31 (s, 1H, pyridone H), 3.82 (s. 3H), 2.28 (s, 3H); 161.6, 161.0, 160.9, 159.5, 151.6, 129.7, 128.0, 116.9, 114.2, 106.3, 96.4, 55.4, 19.0; 241 (M^++1), 240 (M^+, 100 %), 239, 225, 197, 169. **c** (DMSO-D6) 12.18 (br. s, NH), 7.61-7.31 (c. m., 11 H), 2.72-2.67 (c. m., 2H), 2.21-2.16 (c. m., 2H), 1.63, 1.56 (c. m., 2H); 160.8, 160.2, 146.5, 136.0, 135.5, 131.1, 129.9, 129.7, 129.3, 129.1, 128.7, 128.4, 128.0, 127.6, 116.0, 26.5, 25.9, 22.0; 339 (M^++1), 338 (M^+), 337 (100 %). **d** (DMSO-D6) 12.53 (br. s, NH), 8.01 (app. br. d, 1H, J = 8.52), 7.51 (br. m, 3H), 7.38 (br. m., 2H), 6.90 (br. m, 2H), 3.80 (s, 3H), 2.70 (br. m, 2H), 2.30(br. m, 2H); 329 (M^++1), 328 (M^+, 100%), 327, 326, 264, 186, 91. e (DMSO-D6) 12.8 (br. s, NH), 7.99 (d, pyridone α-H, J = 6.3 Hz), 7.60 (br. m, 2H), 7.53 (br. m, 3H) 6.42 (d, pyridone β-H, J = 6.3 Hz); 160.8, 160.6, 140.4, 135.9, 130.5, 128.9, 128.0, 116.3, 106.7, 100.9; 197 (M^++1), 196 (M^+, 100 %), 195, 158, 130, 99. **f** (DMSO-D6) 12.5 (br. s, NH), 7.75 (d, pyridone α-H, J = 6.3 Hz), 7.47 (app. t, 1H, J = 7.5 Hz), 7.30 (app. br. d, 1H, J = 6.9 Hz), 7.17 (app. br. d, 1H, J = 8.3 Hz), 7.06 (app. t., 1H, J = 7.5 Hz), 6.31 (d, pyridone β-H, J = 6.3 Hz), 3.79 (s, 3H); 160.5, 158.8, 155.7, 139.8, 131.6, 129.4, 124.9, 120.6, 116.0, 112.0, 107.9, 103.3, 55.6; 227 (M^++1), 226 (M^+), 225, 198, 147, 121, 91 (100 %). **h** ($CDCl_3$) 13.4 (br. s, NH), 6.14 (s, 1H, pyridone H), 2.91-2.84 (c. m., 1H), 2.43 (s, 3H), 1.87-1.76 (c. m, 4 H), 1.50-1.20 (c. m, 6 H); 169.5, 164.0, 151.2, 115.1, 109.9, 105.3, 98.9, 43.5, 32.0, 26.0, 25.8, 19.8; 217 (M^++1), 216 (M^+), 201, 188, 175, 161, 154 (100 %). **19** ($CDCl_3$) 15.26 (br. s, 1H), 11.40 (br. s, 1H), 8.37 (d, 1H, J = 8.3 Hz), 8.11 (d, 1H, J = 8.7 Hz), 7.99 (d, 1H, J = 8.6 Hz), 7.90 (d, 1H, J = 8.3 Hz), 7.82 (br. app. t, 1H, J = 7.0 Hz), 7.66 (br. app. t, 1H, J = 7.2 Hz), 7.10 (s, 1H), 3.27 (m, 2H), 1.74 (br. sextet, 2H, J = 7.3 Hz), 1.08 (t, 3H, J = 7.3 Hz). 167.0, 165.3, 165.2, 147.0, 145.2, 142.2, 138.3, 131.2, 129.6, 128.8, 128.6, 127.7, 116.7, 115.7, 110.6, 37.8, 23.6, 14.3. 308 (M^+), 290, 275, 266, 249, 236, 223 (100 %).
6. Restricted Hartree-Fock. Calculations were carried out with the HYPERCHEM® package, available from Hypercube, Inc., Waterloo, Ontario, and running on a Windows® based 486 PC system.
7. Snyder, H. R.; Elston, C. T. *J. Am. Chem. Soc.* **1954**, *76*, 3039.

(*Received in USA* 22 *February* 1995; *revised* 3 *March* 1995; *accepted* 17 *March* 1995)