2-Pyridones from Cyanoacetamides and Enecarbonyl Compounds: Application to the Synthesis of Nothapodytine B

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The condensation of an enone or enal with cyanoacetamide derivatives and *t*-BuOK furnishes either 3-cyano-2-pyridones or 3-unsubstituted-2-pyridones, depending on whether the reaction is carried out in the presence or in the absence of O_2. In the first case, in situ oxidation of Michael-type intermediates takes place; in the second case, the products result from "decyanidative aromatization" of such intermediates. A one-step synthesis of 3-alkyl-2-pyridones has been devised on the basis of decyanative union of an enone/enal and a 2-alkylcyanoacetamide. The new reaction forms the centerpiece of an unusually concise synthesis of nothapodytine B (mappicine ketone).

Introduction

2-Pyridones are of significant interest in current medicinal chemistry.[1] Many syntheses of these heterocycles[2] proceed through the regioselective cyclocondensation of an acetonitrile derivative (cyanoacetate ester,[3] cyanoacetamide,[4] or malononitrile[5]) with an appropriate carbonyl substrate in a [3 + 3] mode, resulting in overall formation of 3-cyano-2-pyridones. The efficiency of these reactions is somewhat variable: good results are obtained in some cases, but moderate to mediocre yields are not uncommon. In 1995, we described a technique to effect the union of various enones and enals **1** with cyanoacetamide **2** (R^4 = H), leading to 3-cyano-2-pyridones **3** in good to excellent yield, by operating in DMSO and in the presence of excess *t*-BuOK under an oxygen atmosphere.[6,7] We have recently observed that the conduct of this transformation on significant scales may result in formation of variable quantities of descyano pyridones **4**, which become the major, or even the exclusive, products with particular substrates (Scheme 1).

Compounds **4** emerge through the fusion of an enecarbonyl compound and an active methylene agent, in a [3 + 3] mode, via "de-cyanidative aromatization" of an intermediate Michael adduct. 2-Pyridones unsubstituted at C-3 are customarily obtained through cyclization of

[†] Mass spectral facility of the LSMO.

(1) E.g.: Nadin, A.; Harrison, T. *Tetrahedron Lett.* **1999**, *40*, 4073 and references cited therein.

(2) Reviews on the synthesis of pyridones: (a) McKillop, A.; Boulton, A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 2, Part 2A, p 67 ff. (b) Jones, G. In *Comprehensive Heterocylic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 2, Part 2A, p 395.

(3) Representative examples of the principal classes of reactions leading to pyridones through condensation of cyanoacetic esters and ammonium salts (source of ammonia) with: (i) preformed enones or Knoevenagel adducts, or ketone/aldehyde pairs (in situ formation of enones or Knoevenagel adducts): (a) Abadi, A.; Al-Deeb, O.; Al-Afify, A.; El-Kashef, H. *Farmaco* **1999**, *54*, 195. (b) El-Emary, T. I.; Bakhite, E. A. *Pharmazie* **1999**, *54*, 106. (c) Grant, N.; Mishriky, N.; Asaad, F. M.; Fawzy, N. G. *Pharmazie* **1998**, *53*, 543. (d) Abadi, A. H.; Al-Khamees, H. A. *Arch. Pharm.* **1998**, *331*, 319. (e) Kamel, M. M.; Omar, M. T.; Refai, M.; Fahmy, H. H.; Nofal, Z.; Ismail, N. S. *Egypt. J. Chem.* **1996**, *39*, 591. (f) Hataba, A. A. *Pol. J. Chem.* **1996**, *70*, 41. (g) Latif, N.; Mishriky, N.; Haggag, B.; Basyouni, W. *Indian J. Chem. Sect. B* **1995**, *24*, 1230. (h) Ibrahim, E. S.; Elgemeie, G. E. H.; Abbasi, M. M.; Abbas, Y. A.; Elbadawi, M. A.; Attia, A. M. E. *Nucleosides Nucleotides* **1995**, *14*, 1415. (i) Manna, F.; Chimenti, F.; Bolasco, A.; Filippelli, A.; Palla, A.; et al.; *Eur. J. Med. Chem. Chim. Ther.* **1992**, *27*, 627. (j) Moustafa, A. H.; Kaddah, A. M.; El-Abbady, S. A.; Gado, S. H. *J. Prakt. Chem.* **1982**, *324*, 1045. (k) Chorvat, R. J.; Desai, B. N. *J. Heterocycl. Chem.* **1980**, *17*, 1313. (ii) *β*-Enaminones and related substances: (l) Badr, M. Z. A.; Geies, A. A.; Abbady, M. S.; Dahy, A. A. *Can. J. Chem.* **1998**, *76*, 469. (m) Al-Omran, F.; Khalik, M. M. A.; Al-Awadhi, H.; Elnagdi, M. H. *Tetrahedron* **1996**, *52*, 11915. See also ref 2.

(4) Representative examples of the principal classes of reactions leading to pyridones through condensation of cyanoacetamide with the following. (i) Enones or *β*-dicarbonyl compounds: (a) Salman, A. S. S. *Pharmazie* **1999**, *54*, 178. (b) Attia, A.; Abdel-Salam, O. I.; Abo-Ghalia, M. H.; Amr, A. E. *Egypt. J. Chem.* **1995**, *38*, 543. (c) Attia, A. M. E.; Elgemeie, G. E. H. *Nucleosides Nucleotides* **1995**, *14*, 1211. (d) Mijin, D. Z.; Misic-Vukovic, M. M. *Indian J. Chem. Sect. B* **1995**, *34*, 348. (e) Attia, A.; Abo-Ghalia, M. H.; El-Salam, O. I. A. *Pharmazie* **1995**, *50*, 455. (f) O'Callaghan, C. N.; McMurry, T. B. H.; Cardin, C. J.; Wilcock, D. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2479. (g) Elgemeie, G. E. H.; El-Zanate, A. M.; Mansour, A.-K. E. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 555. (h) Elgemeie, G. E. H.; Ali, H. A.; Eid, M. M. *J. Chem. Res. Miniprint* **1993**, *7*, 1517. (i) Kaiho, T.; San-nohe, K.; Kajiya, S.; Suzuki, T.; Otsuka, K.; et al. *J. Med. Chem.* **1989**, *32*, 351. (j) Paronikyan, E. G.; Sirakanyan, S. N.; Lindeman, S. V.; Aleksanyan, M. S.; Karapetyan, A. A.; et al. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1989**, *25*, 953. (k) Hishmat, O. H.; Miky, J. A. A.; Saleh, N. M. *Pharmazie* **1989**, *44*, 823. (l) Singh, L. W.; Ila, H.; Junjappa, H. *Indian J. Chem. Sect. B* **1987**, *26*, 607. (m) Shestopalov, A. M.; Sharanin, Yu. A. *J. Org. Chem. USSR (Engl. Transl.)* **1986**, *22*, 1163. (n) Al-Hajjar, F. H.; Jarrar, A. A. *J. Heterocycl. Chem.* **1980**, *17*, 1521. (ii) Ynones: see ref 4n. See also ref 2.

(5) Representative examples of the principal classes of reactions leading to pyridones through condensation of various acceptors with malononitrile derivatives: (a) Kandeel, K. A.; Vernon, J. M.; Dransfield, T. A.; Fouli, F. A.; Youssef, A. S. A. *J. Chem. Res. Miniprint* **1990**, *9*, 2101. (b) Alberola, A.; Andres, C.; Ortega, A. G.; Pedrosa, R.; Vicente, M. *J. Heterocycl. Chem.* **1987**, *24*, 709. (c) Rodinovskaya, L. A.; Sharanin, Y. A.; Litvinov, V. P.; Shestopalov, A. M.; Promonenkov, V. K.; et al. *J. Org. Chem. USSR (Engl. Transl.)* **1985**, *21*, 2230. (d) Nasakin, O. E.; Nikolaev, E. G.; Terent'ev, P. B.; Bulai, A. K.; Zakharov, V. Y. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1985**, *21*, 1019. See also ref 2.

(6) (a) Jain, R.; Roschangar, F.; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 3307. This work was based on an observation reported by: (b) Al-Hajjar, F. H.; Jarrar, A. A. *J. Heterocycl. Chem.* **1980**, *17*, 1521.

(7) This general type of reaction was featured in a total synthesis of (+)-camptothecin: (a) Ciufolini, M. A.; Roschangar, F. *Angew. Chem.* **1996**, *108*, 1789. (b) Ciufolini, M. A.; Roschangar, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1692. (c) Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *53*, 11049.

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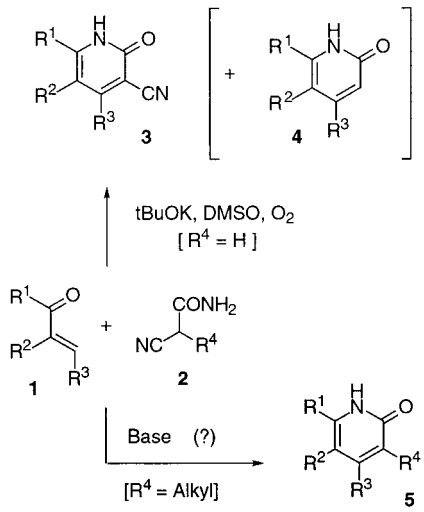
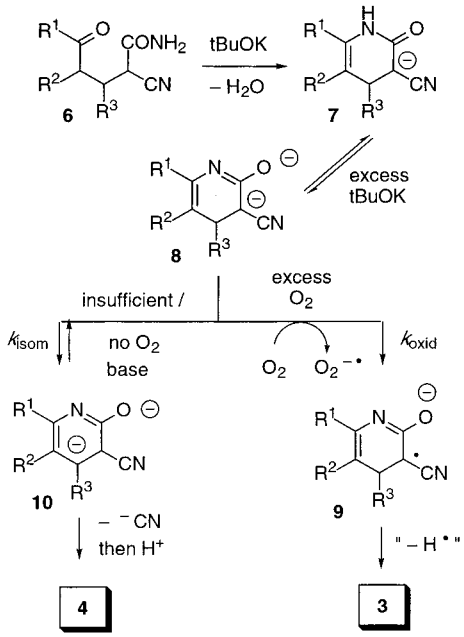
Scheme 1



Scheme 2



appropriate acyclic educts,[2] whereas their assembly in a [3 + 3] format is extremely unusual. Limited precedent for a [3 + 3] de-cyanative aromatization avenue to these heterocycles from particular substrates may be found in the work of Eweiss,[8] but the literature records only two methods of sufficient scope that accomplish a similar construction. In 1957, Thesing and Müller described a route involving condensation of α,β-unsaturated ketones with *N*-(2-carbamoylmethyl)pyridinium ylide.[9] More recently, Katritzky demonstrated a variant of this approach in which the nucleophilic component is the anion of 1-cyanomethyl- or 1-carbamoylmethylbenzotriazole.[10] A conceptually different method that relies on the condensation of maleimide with β-alkylthio-β-enaminones appears to be more limited in scope.[11] It thus seemed that a useful "dichotomous" synthesis of 2-pyridones would result if the interaction of cyanoacetamide (**2**, R^4 = H) with enecarbonyl compounds could be controlled so as to produce either **3** or **4**. Furthermore, the use of a generic 2-cyano*carboxamide* (**2**, R^4 = alkyl) in this chemistry vis à vis an enecarbonyl substrate could produce a 3-alkyl-2-pyridone **5** in a [3 + 3] mode (Scheme 1). The only documented example of [3 + 3] assembly of a 3-alkyl-2-pyridone appears to be Katritzky's base-promoted condensation of 2-(1-benzotriazolyl)propionamide with chalcone, leading to 3-methyl-4,6-diphenyl-2-pyridone.[10]

Experiment revealed that the genesis of **4** is largely attributable to an insufficient rate of diffusion of molecular oxygen into the reaction solution. We refer to this phenomenon as "oxygen starvation". The problem may become especially significant when larger volumes of solvent are involved, i.e., when the reaction is scaled up. In this paper, we describe a solution to the problem of decyanative aromatization under conditions of oxygen starvation and we disclose that formation of either 3-cyano-2-pyridones or 3-unsubstituted-2-pyridones may be controlled simply by admitting or excluding O_2 during the reaction. We also disclose a new method for the [3 + 3] preparation of 3-alkyl-2-pyridones from enecarbonyl educts and 2-alkylcyanoacetamides, and we demonstrate this reaction as the centerpiece of a concise total synthesis of nothapodytine B, an antiviral alkaloid structurally related to camptothecin.

Discussion

A mechanistic hypothesis for the appearance of **4** was formulated on the basis of our proposal for the formation of **3**.[6] The initial interaction of cyanoacetamide and enecarbonyl substrate in the presence of *t*-BuOK leads to an isolable Michael product **6**. We had previously assumed that **6** undergoes base-promoted dehydrative cyclization to a dihydropyridone, which is rapidly and irreversibly deprotonated to furnish anion **7** (Scheme 2). Subsequently, this species would be reversibly converted to dianion **8**, which in the presence of O_2 undergoes oxidative aromatization to **3** via single electron transfer (SET) and formal loss of a hydrogen atom from the intervening radical anion **9**. It seemed plausible that the strongly basic medium could induce equilibration of **8** with an isomeric dianion **10**, especially if both R^1 and R^3 were anion-stabilizing substituents such as aryl groups. The hypothetical intermediate **10** would aromatize through expulsion of cyanide ion, leading to formation of the anion of pyridone **4**. Compound **4** itself would emerge following the usual aqueous workup.

The foregoing considerations suggest that the extent of formation of **4** reflects the proportion of dianion **8** that partitions between the oxidation (cf. k_{oxid}, Scheme 2) and equilibration (k_{isom}) pathways. If the oxygen concentration in solution were too low to promote rapid oxidation of **8**, then more of **4** would be observed. Likewise, substrates leading to anions **8** that are more likely to isomerize to **10** would produce more **4**, the ease of isomerization being largely determined by the nature of substituents R^1 and

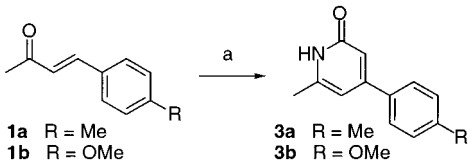
(8) Eweiss, N. F. *J. Heterocycl. Chem.* **1982**, *19*, 273. This paper reports that 2-benzylidene-1-indanones combine with cyanoacetamide under basic conditions to furnish a mixture of C-3 unsubtituted 2-pyridones and 3,4-dihydro-3-cyano-2-pyridones, while 2-benzylidene-1,3-indandiones react to provide only 3-descyanopyridones.

(9) (a) Thesing, J.; Müller, A. *Chem. Ber.* **1957**, *90*, 711. Recent examples: (b) Besidsky, Y.; Luthman, K.; Claesson, A.; Fowler, C. J.; Csoeregh, I.; Hacksell, U. *J. Chem. Soc., Perkin Trans. 1* **1995**, 465. Variants of the original Thesing-Mmuller procedure: (c) Grosche, P.; Hoeltzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis* **1999**, 1961. (d) Katoh, A.; Kitamura, Y.; Fujii, H.; Horie, Y.; Satoh, T.; Ohkanda, J.; Yokomori, Y. *Heterocycles* **1998**, *49*, 281.

(10) Katritzsky, A. R.; Belayakov, S. A.; Sorochinski, A. E.; Henderson, S. A.; Chen, J. *J. Org. Chem.* **1997**, *62*, 6210.

(11) Gupta, A. K.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 284.

Scheme 3[a]



[a] Cyanoacetamide (**2**, R^4 = H), *t*-BuOK, DMSO, O_2, 55% **3a**, 58% **3b**.

R^3. In any event, a more efficient diffusion of O_2 in the medium should diminish/suppress the side reaction producing **4**.

Enones **1** wherein both R^1 and R^3 are aryl groups, e.g., chalcone, displayed a marked propensity to yield descyanopyridones **4** under our original conditions,[6] whereas enones in which R^1 is alkyl and R^3 is aryl were significantly less susceptible to produce **4**. Evidently, the isomerization of **8** to **10** is more likely to occur when both R^1 and R^3 can mesomerically stabilize a negative charge at C-4 of the pyridone. To illustrate, several benzylideneacetone derivatives were readily converted to pyridones **3** under our usual conditions, and without significant formation of **4** (= below detection by ^{1}H NMR; Scheme 3). On the other hand, chalcone and other substrates particularly prone to form the descyano products were best advanced to **3** by ensuring a high O_2 flow through the solution during pyridone synthesis and by controlling the exothermicity of the reaction by cooling. This is accomplished by the use of the simple reactor shown in Figure 1. For instance, reaction of **1d** with cyanoacetamide in accord with our original procedure (*t*-BuOK, DMSO, O_2 balloon, no cooling) on scales greater than 300 mg afforded the corresponding cyanopyridone **3** ($R^1 = R^3$ = Ph, R^2 = H) contaminated with 20−80% of **4d** depending on precise conditions (concentration, rate of base addition and therefore of heat evolution, etc.). The same reaction run on a 15 g scale in the apparatus of Figure 1 produced 3-cyano-4,6-diphenyl-2-pyridone containing less than 5% (^{1}H NMR) of **4d**. The impurity is easily removed by recrystallization.

The logic of Scheme 2 suggested that rigorous exclusion of oxygen should result in selective formation of **4**. Indeed, treatment of various enones/enals with cyanoacetamide or 2-alkyl variants thereof and excess *t*-BuOK in degassed DMSO under Ar atmosphere furnished 3-unsubstituted pyridones or 3-alkylpyridones, respectively. Representative examples of the new reaction appear in Tables 1 and 2. Notice that all substrates display an aromatic substituent at the conjugate position. Such a group appears to favor formation of dianion **10** and consequent expulsion of cyanide ion. Indeed, enones **1** in which R^3 = alkyl produced no pyridones of the type **4** under anoxic conditions, but, surprisingly, they were converted to 3-cyanopyridones **3** (45−50%, unoptimized) signaling that a pathway for the aromatization of a presumed intermediate of the type **8** subsists even in the absence of O_2 (Scheme 4). The oxidant in these reactions may be DMSO itself. Indeed, the literature records instances of DMSO-promoted dehydrogenation of various substrates, especially under basic conditions.[12] An example that is particularly relevant to the present discussion was reported by Massiot,[13] who observed aromatization of **11** to **12** upon treatment with *t*-BuOK in DMSO, in the absence of O_2.

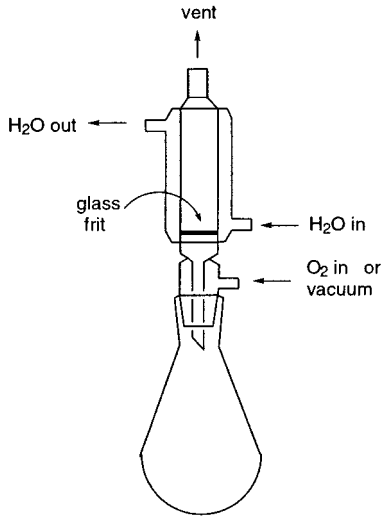


Figure 1. Jacketed reactor for 3-cyano-2-pyridone synthesis. The barrel-shaped device is secured to a flask of appropriate size and charged with a DMSO solution of cyanoacetamide and α,*β*-unsaturated carbonyl compound (enone or enal). The viscosity of DMSO prevents the solution from flowing through the frit into the flask. *t*-BuOK is added, oxygen flow is started, and the device is loosely stoppered to permit venting of the gas. An exothermic reaction occurs, and significant foaming is observed. With substrates particularly prone to form the descyanopyridones, cooling may be applied to moderate the exothermicity. When the reaction is finished, O_2 flow is halted and vacuum is applied. The reaction mixture is filtered through the frit (removal of suspended matter) into the receiver flask and then it is cautiously poured into aqueous 4 N HCl solution, resulting in precipitation of the solid pyridone, which is recovered by simple filtration.

Attempts to replace the cyano function in the amide component with other substituents that may simultaneously activate the molecule toward enolate formation, and act as leaving groups to permit aromatization, were unfruitful. Thus, the propionyl analogue **13** of the Thesing−Müller reagent [14] as well as 2-phenylsulfonyl amides **14** and **15** (Scheme 5) failed to give the desired heterocycles in our hands.

As an application of the new method for 3-alkylpyridone assembly, we now describe a total synthesis of nothapodytine B, **16** (Scheme 6), an alkaloid that displays interesting antiviral properties.[15] This substance was isolated in 1996 from *Nothapodytes foetida*, a plant native to the Indian subcontinent.[16] The compound is structurally related to mappicine, **17**,[17] and to camptothecin, **18**, also metabolites of *N. foetida*.[18] Indeed, nothapodytine B may be obtained by thermolysis of **18**.[19] Interestingly, **16** was first prepared as a synthetic intermediate toward

(12) Cf., e.g., the oxidation of compound **10** to **11** in: Grieco, P. A.; Ferriño, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586.

(13) Massiot, G.; Sousa Oliveira, F.; Levy, J. *Tetrahedron Lett.* **1982**, *23*, 177.

(14) Unpublished results from this laborartory.

(15) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623. (b) Pendrak, I.; Wittrock, R.; Kinsbury, W. D. *J. Org. Chem.* **1995**, *60*, 2912.

(16) Wu, T. S.; Chan, Y. Y.; Leu, Y. L.; Chern, C. Y.; Chen, C. F. *Phytochemistry* **1996**, *42*, 907.

(17) Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215.

(18) The primary source of **18** is *Camptotheca acuminata*, a tree native to the Chinese mainland. *N. foetida*, earlier known as *Mappia foetida*, is native to the Indian subcontinent and represents a secondary source of **18**.

Table 1. Pyridones 4 Obtained from Enecarbonyls and Cyanoacetamide in the Absence of O_2

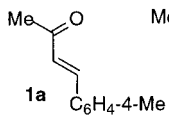
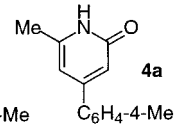
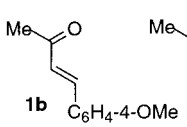
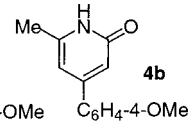
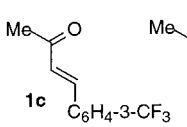
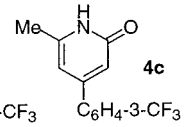
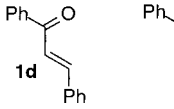
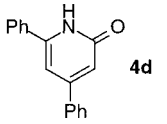
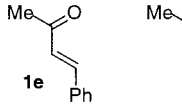
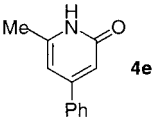
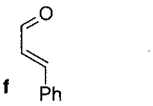
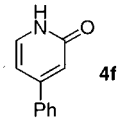
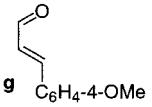
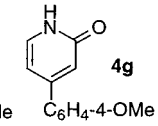
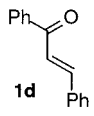
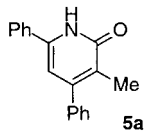
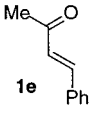
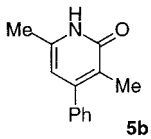
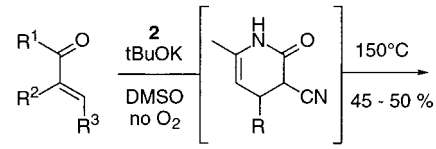
Substrate	Pyridone	Yield %	m.p. (°C)
	 **4a**	60	210-211
	 **4b**	55	213-214
	 **4c**	84	212-213
	 **4d**	99	205-206
	 **4e**	89	197-198
	 **4f**	69	226-227
	 **4g**	80	213-214

Table 2. Representative Pyridones 5 Obtained from Enones and 2-Cyanoproionamide in the Absence of O_2

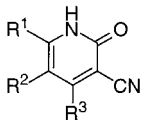
Substrate	Pyridone	Yield %	m.p. (°C)
	 **5a**	88	> 250
	 **5b**	70	> 250

17,[20] and being an oxidized form thereof, it became known as "mappicine ketone". The rarity of *Nothapodytes* metabolites and the cost of **18** have stimulated substantial synthetic activity toward mappicine ketone.[21] The Comins synthesis of **16** is especially concise, proceeding in just six steps from 2-fluoro-3-iodopyridine and 2-bromo-3-(bromomethyl)quinoline.[22] Our pyridone synthesis permits access to **16** in four steps from quinoline **19**[23] and boronic acid **20**.[24] Suzuki coupling[25] of these two educts provided **21**, which underwent oxidative cleavage of the

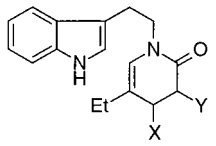
Scheme 4



1i R^1 = Me; R^2 = H, R^3 = C_5H_{11}-n
1j R^1 = R^2 = R^3 = Me

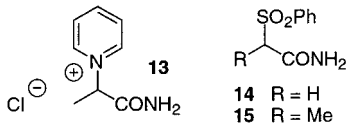


3d R^1 = Me; R^2 = H, R^3 = C_5H_{11}-r
3e R^1 = R^2 = R^3 = Me



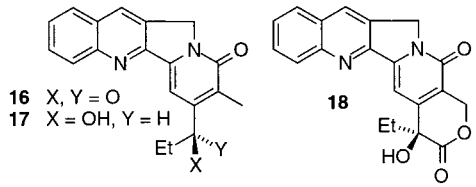
11 X= Y = H
12 X, Y = π bond

Scheme 5



13
14 R = H
15 R = Me

Scheme 6



16 X, Y = O
17 X = OH, Y = H
18

furan[26] to furnish **22** (Scheme 7). The carbonyl group connected to the quinoline is particularly electrophilic, due to the electron-withdrawing character of the quinoline unit; therefore, we expected that it would effectively direct 1,4-addition to the π system. This was indeed the case; however, we also observed that 1,2-diacylethylene substrates such as **22** are generally intolerant of excess

(19) (a) Kingsbury, W. D. *Tetrahedrom Lett.* **1988**, *29*, 6847. (b) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Wood, J. L. *Tetrahedron Lett.* **1994**, *35*, 5763. (c) Das, B.; Madhusudhan, P.; Kashinatham, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1403. (d) Das, B.; Madhusudhan, P.; Kashinatham, A. *Tetrahedron Lett.* **1998**, *39*, 431. See also: (e) Das, B.; Madhusudhan, P.; Venkataiah, B. *J. Ind. Chem. Soc.* **1998**, *75*, 662. This transformation presumably involves thermal extrusion of CO_2 by formal [4 + 2] cycloreversion, followed by tautomerization of the resulting enol intermediate.

(20) Kametani, T.; Takeda, H.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1825, and references cited therein.

(21) (a) Josien, H.; Curran, D. P. *Tetrahedron* **1997**, *53*, 8881. (b) Boger, D. L.; Hong, J. Y. *J. Am. Chem. Soc.* **1998**, *120*, 1218. (c) Boger, D. L. *J. Hetercycl. Chem.* **1998**, *35*, 1003. (d) Yadav, J. S.; Sarkar, S.; Chandrasekhar S. A. *Tetrahedron* **1999**, *55*, 5449. Das, B.; Madhusudhan P. *Tetrahedron* **1999**, *55*, 7875. See also: (e) Takayama, H.; Kitajima, M.; Aimi, N. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 181. (f) Mekouar, K.; Genisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212. (g) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110. (h) Das, B.; Madhusudhan, P. *J. Chem. Res., Synopses* **2000**, 476. (i) Ishibashi, H.; Kato, I.; Takeda, Y.; Tamura, O. *Tetrahedron Lett.* **2001**, *42*, 931. (j) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765.

(22) Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623.

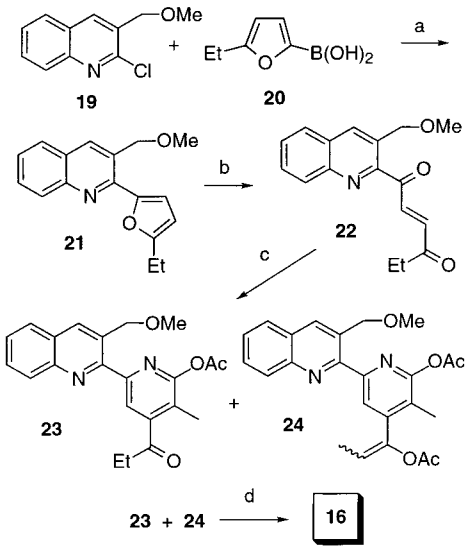
(23) Readily available in two steps from commercial materials: Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *53*, 11049.

(24) Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237.

(25) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

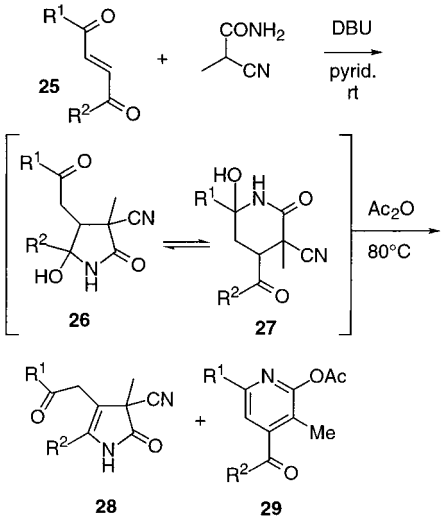
(26) cf. Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505.

Scheme 7[a]



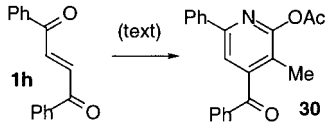
[a] Reagents and conditions: (a) cat. $Pd(PPh_3)_4$, $Ba(OH)_2$, DME, 86%; (b) NBS, $NaHCO_3$, pyridine, aqueous acetone, 87%; (c) **2** (R^4 = Me), pyridine, DBU, 80 °C, 12 h then Ac_2O, 80 °C, 50% of **24**/**25**; (d) HBr, CF_3CH_2OH, 91%.

Scheme 8



t-BuOK, so that their conversion to pyridone required a modification of the procedure detailed earlier. It was ultimately determined that pyridone formation proceeds best through in situ dehydration/decyanidation with Ac_2O/pyridine at 80 °C of a preformed Michael adduct of a generic 1,2-diacylethylene **25** (Scheme 8) and a substituted cyanoacetamide. The product thus emerging is actually the *O*-acetyl derivative of the expected pyridone (cf. **29**), from which the parent heterocycle may be easily retrieved by hydrolysis under appropriate conditions.

Scheme 9



Furthermore, it was observed that prolonged heating of the crude Michael product (80 °C, 12 h), which exists as a mixture of hemiamidals **26** and **27**, *prior* to addition of acetic anhydride improved the yield of pyridone and diminished the extent of formation of a byproduct tentatively assigned as structure **28**. Thermal treatment appears to favor accumulation of the six-membered cyclic species **27** at the expense of the five-membered tautomer **26** and, therefore, formation of the pyridone. Reaction of **22** with 2-cyanopropionamide under these modified conditions provided a mixture of **23** and **24** (variable ratio) in 50% yield. In a like manner, 1,2-dibenzoylethylene, **1h**, afforded **30**, mp 117−118 °C, in 48% yield (Scheme 9).

Compounds **23** and **24** are separable by silica gel chromatography. However, we found it expedient to perform only a rough purification of the crude mixture of **23** and **24**, both of which converged to fully synthetic nothapodytine B upon treatment HBr gas in trifluoroethanol as described by Boger.[21b,27] The overall yield of **16** for the 4-step sequence is 34%. The enantioselective reduction of **16** to **17** has been demonstrated.[21b] Consequently, a synthesis of mappicine ketone represents also a formal synthesis of mappicine.

In summary, the union of cyanoacetamide and an enone/enal may lead to either 3-cyano-2-pyridones or 3-unsubstituted-2-pyridones, in a [3 + 3] mode, depending on whether O_2 is admitted or excluded during the reaction, whereas the use of a 2-alkyl cyanoacetamide results in formation of 3-alkyl-2-pyridones. The new process has been demonstrated in a concise synthesis of nothapodytine B.

Acknowledgment. We thank Aventis Crop Science (doctoral fellowship to L.C.), the MENRT, the CNRS (postdoctoral fellowship to K.N.), and the Région Rhône-Alpes for support of our research program. M.A.C. is the recipient of a Merck & Co. Academic Development Award (2000 and 2001).

Supporting Information Available: Experimental section and hardcopy spectra of various nothapodytine B intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) This procedure represents a variant of a technique the we devised in connection with the synthesis of camptothecin (ref 7), and that in its original form would have involved treatment of **23**/**24** with hot ethanolic H_2SO_4. This seemed likely to promote undesirable side reactions (condensation, etc.) of the free ethyl ketone in **23** and **14**; hence the interest of the Boger method.