SYNTHESIS OF 5-PHOSPHONYL-2(1*H*)-PYRIDONES FROM PRIMARY β-ENAMINOPHOSPHONATE AND ACETYLENIC ESTERS

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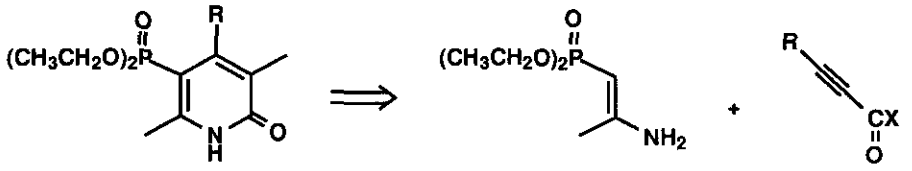
Abstract- Primary β-enaminophosphonates (2) are obtained from metallated diethyl methylphosphonate and nitriles. Reaction of enamines (2) with ethyl propiolate and dimethyl acetylenedicarboxylate yields 1:1 adducts (7) and (8), respectively. Treatment of monoadducts (7) with sodium hydride leads to 5-phosphonyl-2(1H)-pyridones (1). Functionalized enamines (8) undergo thermal cyclocondensation to give pyridones (9).

The group of compounds containing the 2(1*H*)-pyridone moiety are a prominent structural feature in a variety of natural products, as well as in other compounds of medicinal interest[1] and have attracted attention for their biological activities.[2] They constitute the skeleton of elfamycin antibiotics[3] and the antifungal compound ilicocilin[4] and even simple 2(1*H*)-pyridones find many applications in pharmacology due to their antimicrobial activity against *Candida albicans*[5] and for their ability to induce leukemia cell differentiation *"in vitro"*.[6] On the other hand, β-aminoalkyl phosphonates, phosphonic isostere analogues of β-amino acids are gaining in interest in medicinal chemistry[7] since they are simple mimetics of amino acids, can provide useful substrates for biochemical, pharmacological and immunochemical studies and are used as potential enzyme inhibitors,[8] anti-inflamamatory and anti-arthritic agents,[9] as inhibitors of calcium release[10] and as fungicides and bactericidal agrochemicals.[11]

Classical approaches[12] to 2(1*H*)-pyridones involving condensation reactions[12,13] or cycloaddition reactions[12,14] to effect the ring closure of appropriate precursors, have been reported. However, to the best of our knowledge, the entry to phosphorus substituted 2-pyridones is restricted to the synthesis of 3-triphenylphosphoranopyrid-2-ones[15] obtained by [4+2] cycloaddition processes, λ^5-phosphazenylpyridones obtained by cyclocondensation reactions[15] and 3-phosphonyl substituted 2-pyridones[17] obtained from simple pyridones. These latter heterocyclic phosphonate derivatives have *"in vitro"* activity as cyclic adenosine monophosphonate-dependent protein kinase agonists.[17]

Recently, we interested in the preparation of new families of heterocycles derived from aminophosphonates[18] and in the use of β-enaminophosphorus derivatives as intermediates in the synthesis of acyclic allylamines,[19] 1-azadienes[20] and α,β-unsaturated hydrazones.[21] In this context, it is noteworthy

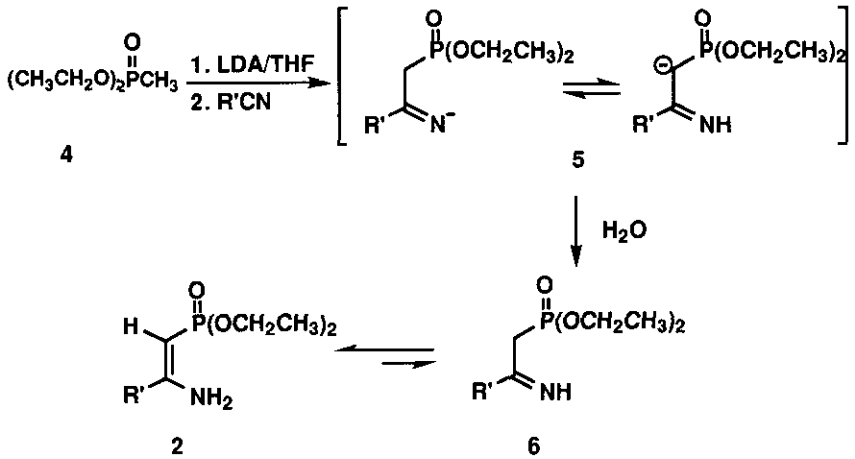
that, retrosynthetically, pyridones substituted by a phosphonate group in 5-position could be envisaged by reaction of primary enamines (**2**) with electrophilic acetylenes (**3**) (Scheme 1). In previous papers we have reported a preparation of primary β-enamines derived from phosphazenes[22] and we have used them in the synthesis of cyclic[23] and acyclic[24] compounds. Continuing with our interest in the synthesis of new phosphorus substituted heterocycles and with the reactivity of functionalized enamines, we report here a synthesis of 5-phosphonylpyridones (**1**) from primary β-enaminophosphonates (**2**) and acetylenic esters (**3**).



1 **2** **3**

Scheme 1

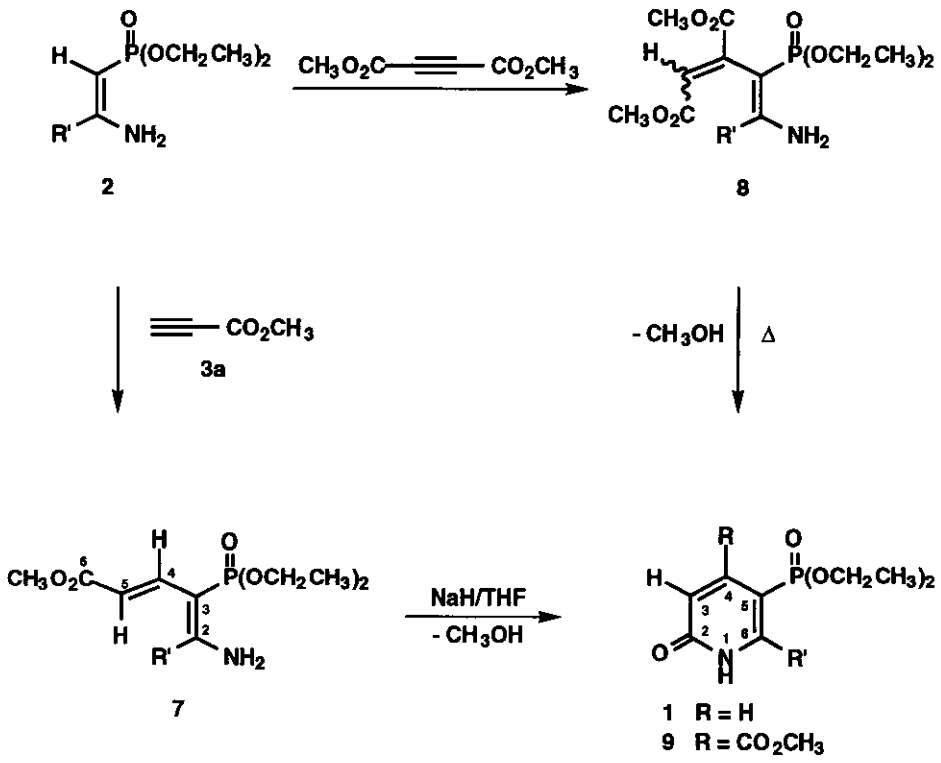
Required enamines derived from phosphonates (**2**) are obtained through α-lithiation of methyl phosphonate (**4**) followed by reaction with nitriles in a similar way to that previously reported for other phosphorus derivatives such as phosphazenes and phosphine oxides.[22] Thus, when diethyl methylphosphonate (**4**) was treated with LDA followed by addition of nitriles and aqueous work-up,[25] primary β-enamino-phosphonates (**2**) were isolated (Scheme 2). Spectroscopy data are consistent with the proposed structure. Formation of primary enamines (**2**) can be assumed to proceed *via* hydrolysis of ketimino intermediates (**5**) followed by *prototropic tautomerization of β-iminophosphonates* (**6**).(Scheme 2). Recently, the reaction of diethyl lithiomethylphosphonate with nitriles followed by reduction[26] or by addition of carbonyl compounds[27] has been used in the preparation of allylamines[26] and α,β-unsaturated ketones.[27] However, neither β-imino (**6**) nor β-enamine (**2**) has been isolated and reported.



4 **5** **2** **6**

Scheme 2

When primary β-enaminophosphonates (**2**) was allowed to react with an equimolecular amount of methyl propiolate (**3a**) in toluene at 90°C, dienamino esters (**7**) were obtained with excellent yields (77-82%) in a regioselective fashion (Scheme 3). The structure of the 1:1 adducts (**7**) is supported by the spectroscopic data. Functionalized primary β-enaminophosphonates (**7**) were thermally stable and did not cyclize in refluxing toluene for 72 hours. Enamines (**7**) underwent cyclocondensation to 2(1*H*)-pyridones by expulsion of a molecule of methanol when adducts (**7**) were treated with sodium hydride in tetrahydrofuran.[28] Compounds (**1**) were characterized on the basis of their spectroscopic data, and can alternatively be prepared in "one pot" synthesis from β-enamines (**2**), when crude 1:1 adducts (**7**), obtained after evaporation of the solvent, are directly treated, without their isolation, with sodium hydride in THF.



Scheme 3

Table 1. Enamines (**2**, **7**, **8**) and 2(1*H*)-pyridones (**1**, **9**).

Compound	R'	Yield(%)		mp (°C)
2a	p-CH_3-C_6H_4	90[a]		oil[b]
2b		82[a]		oil[b]
2c		81[a]		oil[b]
7a	p-CH_3-C_6H_4	82[c]		117-118
7b		78[c]		93-94
7c		77[c]		105-106
8a	p-CH_3-C_6H_4	80[c]		oil[d]
8c		83[c]		oil[d]
1a	p-CH_3-C_6H_4	81[e]	73[c]	112-113
1b		76[e]	70[c]	131-132
1c		74[e]	68[c]	154-155
9a	p-CH_3-C_6H_4	92[f]		193-194
9c		91[f]		oil[d]

[a]Yield of isolated products (**2**) based on **4** . [b]Oils isolated after "trap to trap" high vacuum distillation (10^{-5} torr). [c]Yield of isolated products based on (**2**). [d]Purified by flash chromatography. [e]Yield of isolated products based on (**7**). [f]Yield of isolated products based on (**8**).

In order to enhance the scope and the synthetic use of this reaction, the synthesis of pyridone derivatives substituted with phosphonic and carboxylic ester groups (**9**) was explored, and the regiospecific addition of methyl propiolate to primary β-enamines (**2**) was extended to dimethyl acetylendicarboxylate. Thus, the reaction of enamines (**2**) with acetylene diester (**3b**) in tetrahydrofuran at room temperature (24 hours) yielded dienamino esters (**8**).[29] Spectral data are in agreement with structure (**8**) and are consistent with previously reported data.[24] Heating of functionalized enamines (**8**) for 12 hours at 50 °C afforded substituted 2(1*H*)-pyridones (**9**) containing phosphonic and carboxylic ester groups in the heterocyclic ring. In conclusion, the synthesis described in this paper provides an efficient and easy access to 2(1*H*)-pyridones substituted with a phosphonate group in 5-position, making use of readily available starting materials.

Table 2. Selected spectral data for the compounds.

Compound	^{31}P-nmr($CDCl_3$)[a] δ (ppm)	^{1}H-nmr ($CDCl_3$)[b] δ (ppm)	^{13}C-nmr ($CDCl_3$)[b] δ (ppm)	ir[c] υ (cm^{-1})	ms[d] (m/z)
2a	27.1	1.26 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.30 (s, 3H, CH_3), 4.00 (m, 4H, $^{3}J_{HH}$=7.0 Hz, OCH_2), 4.04 (d, 1H, $^{2}J_{PH}$=12.1 Hz, CH), 5.83 (s, 2H, NH_2)[e], 7.12-7.37 (m, 4H, arom)	16.3 (CH_3), 21.2 (CH_3), 61.0 (OCH_2), 73.0 (d, $^{1}J_{PC}$=192.8 Hz, CH), 125.4-139.4 (C-arom), 135.1 (d, $^{3}J_{PC}$=20.7 Hz, C-ipso arom), 162.0 (d, $^{2}J_{PC}$=7.0 Hz, C-N)	3410 and 3326 (NH_2) 1203 (P=O)	269 (M^+, 20%)
2b	26.1	1.26 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 3.98 (q, 4H, $^{3}J_{HH}$=7.1 Hz, OCH_2), 4.29 (d, 1H, $^{2}J_{PH}$=11.0 Hz, CH), 5.85 (s, 2H, NH_2)[e], 6.39-7.39 (m, 3H, arom)	16.0 (CH_3), 60.7 (OCH_2), 70.0 (d, $^{1}J_{PC}$=197.9 Hz, CH), 108.7-143.1 (C-arom), 149.6 (d, $^{3}J_{PC}$=26.0 Hz, C-ipso arom), 150.3 (d, $^{2}J_{PC}$=8.1 Hz, C-N)	3416 and 3332 (NH_2) 1213 (P=O)	245 (M^+, 59%)
2c	23.8	1.25 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 4.00 (q, 4H, $^{3}J_{HH}$=7.0 Hz, OCH_2), 4.20 (d, 1H, $^{2}J_{PH}$=11.0 Hz, CH), 6.17 (s, 2H, NH_2)[e], 6.96-7.36 (m, 3H, arom)	15.7 (CH_3), 60.3 (OCH_2), 72.2 (d, $^{1}J_{PC}$=194.0 Hz, CH), 125.0-127.0 (C-arom), 140.0 (d, $^{3}J_{PC}$=24.0 Hz, C-ipso arom), 154.4 (d, $^{2}J_{PC}$=7.7 Hz, C-N)	3410 and 3340 (NH_2) 1207 (P=O)	261 (M^+, 12%)
7a	23.9	1.28 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.33 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 4.00 (m, 4H, OCH_2), 4.85 (s, 1H, NH_2), 5.74 (d, 1H, $^{3}J_{HH}$=15.7 Hz, HC=), 7.29 (dd, 1H, $^{3}J_{HH}$=15.7 Hz, $^{3}J_{PH}$=31.9 Hz, =CH), 7.19-7.38 (m, 4H, arom), 8.93 (s, 1H, NH_2)[e]	16.3 (CH_3), 21.3 (CH_3), 50.9 (OCH_3), 61.4 (OCH_2), 86.5 (d, $^{1}J_{PC}$=179.8 Hz, C-3), 109.2 (C-5), 128.2-140.5 (C-arom), 134.0 (d, $^{3}J_{PC}$=15.7 Hz, C-ipso arom), 144.3 (d, $^{2}J_{PC}$=8.2 Hz, C-4), 168.4 (d, $^{2}J_{PC}$=12.2 Hz, C-2), 168.9 (C=O)	3347 (NH_2) 1681 (C=O) 1220 (P=O)	353 (M^+, 26%)
7b	24.3	1.26 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 3.65 (s, 3H, OCH_3), 3.95 (m, 4H, OCH_2), 5.87 (d, 1H, $^{3}J_{HH}$=15.7 Hz, HC=), 6.51 (s, 2H, NH_2)[e], 6.76-7.50 (m, 3H, arom), 7.80 (dd, 1H, $^{3}J_{HH}$=15.7 Hz, $^{3}J_{PH}$=30.8 Hz, =CH)	16.3 (CH_3), 51.1 (OCH_3), 61.6 (OCH_2), 86.0 (d, $^{1}J_{PC}$=182.3 Hz, C-3), 111.0-144.2 (C-arom), 117.3 (C-5), 142.5 (d, $^{2}J_{PC}$=6.5 Hz, C-4), 147.0 (d, $^{3}J_{PC}$=22.7 Hz, C-ipso arom), 154.0 (d, $^{2}J_{PC}$=15.1 Hz, C-2), 169.0 (C=O)	3382 (NH_2) 1705 (C=O) 1219 (P=O)	329 (M^+, 54%)
7c	23.8	1.28 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 3.60 (s, 3H, OCH_3), 4.02 (m, 6H, OCH_2 and NH_2)[e], 5.84 (d, 1H, $^{3}J_{HH}$=15.9 Hz, HC=), 7.06-7.40 (m, 3H, arom), 7.60 (dd, 1H, $^{3}J_{HH}$=15.9 Hz, $^{3}J_{PH}$=30.9 Hz, =CH)	16.2 (CH_3), 51.0 (OCH_3), 61.6 (OCH_2), 88.5 (d, $^{1}J_{PC}$=168.5 Hz, C-3), 110.6 (C-5), 127.6-130.8 (C-arom), 137.1 (d, $^{3}J_{PC}$=19.1 Hz, C-ipso arom), 143.5 (d, $^{2}J_{PC}$=7.5 Hz, C-4), 159.7 (d, $^{2}J_{PC}$=14.0 Hz, C-2), 168.9 (C=O)	3368 (NH_2) 1696 (C=O) 1216 (P=O)	345 (M^+, 26%)
8a	24.3	1.24 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.15 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 4.00 (m, 6H, OCH_2 and NH_2)[e], 5.93 (d, 1H, $^{4}J_{PH}$=2.4 Hz, HC=), 7.05-7.22 (m, 4H, arom)	16.2 (CH_3), 21.2 (CH_3), 51.4 (OCH_3), 51.7 (OCH_3), 61.7 (OCH_2), 103.7 (d, $^{1}J_{PC}$=130.2 Hz, C-3), 120.5 (d, $^{3}J_{PC}$=5.8 Hz, C-5), 128.6-140.4 (C-arom), 134.4 (d, $^{3}J_{PC}$=16.0 Hz, C-ipso arom), 145.1 (d, $^{2}J_{PC}$=7.2 Hz, C-4), 165.9, 166.4 and 166.6 (C-2, C-6 and C=O)	3410 (NH_2) 1735 (C=O) 1729 (C=O) 1209 (P=O)	411 (M^+, 6%)

Table 2. (continuation)

Compound	^{31}P-nmr($CDCl_3$)[a] δ (ppm)	^{1}H-nmr ($CDCl_3$)[b] δ (ppm)	^{13}C-nmr ($CDCl_3$)[b] δ (ppm)	ir[c] υ (cm^{-1})	ms[d] (m/z)
8c	22.0	1.25 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 3.32 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 4.03 (m, 6H, OCH_2 and NH_2)[e], 6.00 (d, 1H, $^{4}J_{PH}$=2.7 Hz, HC=), 6.92-7.32 (m, 3H, arom)	15.9 (CH_3), 51.4 (OCH_3), 51.8 (OCH_3), 61.5 (OCH_2), 86.0 (d, $^{1}J_{PC}$=186.1 Hz, C-3), 121.5 (d, $^{3}J_{PC}$=5.5 Hz, C-5), 125.2-127.0 (C-arom), 137.3 (d, $^{3}J_{PC}$=20.7 Hz, C-ipso arom), 143.8 (d, $^{2}J_{PC}$=7.6 Hz, C-4), 158.0, 167 0 and 167.8 (C-2, C-6 and C=O)	3414 (NH_2) 1736 (C=O) 1723 (C=O) 1219 (P=O)	403 (M^+, 4%)
1a	17.0	1.08 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.37 (s, 3H, CH_3), 3.87 (m, 4H, OCH_2), 6.42 (dd, 1H, $^{3}J_{HH}$=9.8 Hz, $^{4}J_{PH}$=2.9 Hz, HC=), 7.22-7.41 (m, 4H, arom), 7.79 (dd, 1H, $^{3}J_{HH}$=9.8 Hz, $^{3}J_{PH}$=10.7 Hz, =CH), 10.10 (s, 1H, NH)[e]	16.0 (CH_3), 21.5 (CH_3), 62.0 (OCH_2), 105.0 (d, $^{1}J_{PC}$=209.0 Hz, C-5), 118.0 (d, $^{3}J_{PC}$=13.1 Hz, C-3), 128.6-144.2 (C-arom and C-4), 154.0 (d, $^{2}J_{PC}$=19.1 Hz, C-6), 163.9 (C-2)	3065 (NH) 1670 (C=O) 1229 (P=O)	321 (M^+, 100%)
1b	16.4	1.22 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 4.00 (m, 4H, OCH_2), 6.40 (dd, 1H, $^{3}J_{HH}$=9.6 Hz, $^{4}J_{PH}$=2.5 Hz, HC=), 6.56-7.60 (m, 3H, arom), 7.83 (dd, 1H, $^{3}J_{HH}$=9.6 Hz, $^{3}J_{PH}$=10.9 Hz, =CH), 10.15 (s, 1H NH)[e]	16.1 (CH_3), 62.4 (OCH_2), 102.0 (d, $^{1}J_{PC}$=205.5 Hz, C-5), 112.8-144 1 (C-arom, C-3 and C-4), 144.9 (C-6), 162.9 (C-2)	3137 (NH) 1670 (C=O) 1242(P=O)	297 (M^+, 100%)
1c	15.7	1.11 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 3.92 (m, 4H, OCH_2), 6.42 (dd, 1H, $^{3}J_{HH}$=9.8 Hz, $^{4}J_{PH}$=1.8 Hz, HC=), 7.08-7.52 (m, 3H, arom), 7.80 (dd, 1H, $^{3}J_{HH}$=9.8 Hz, $^{3}J_{PH}$=11.0 Hz, =CH), 10.22 (s, 1H, NH)[e]	16.0 (CH_3), 62.1 (OCH_2), 106.0 (d, $^{1}J_{PC}$=208.0 Hz, C-5), 118.5 (d, $^{3}J_{PC}$=13.1 Hz, C-3), 127.2-144.2 (C-arom and C-4), 146.9 (C-6), 163.9 (C-2)	3074 (NH) 1684 (C=O) 1228 (P=O)	313 (M^+, 100%)
9a	12.5	1.15 (t, 6H, $^{3}J_{HH}$=7.0 Hz, CH_3), 2.33 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.96 (m, 4H, OCH_2), 7.04 (s, 1H, HC=), 7.17-7 54 (m, 4H, arom), 9.09 (s, 1H, NH)[e]	16.1 (CH_3), 21.6 (CH_3), 52.3 (OCH_3), 61 9 (OCH_2), 119.1 (d, $^{1}J_{PC}$=198 8 Hz, C-5), 126.8-142 0 (C-arom, C-3 and C-4), 136.0 (d, $^{3}J_{PC}$=12.2 Hz, C-ipso arom), 156.0 (d, $^{2}J_{PC}$=13.7 Hz, C-6), 167.0 (C-2), 167.6 (d, $^{3}J_{PC}$=2.3 Hz, C=O)	3091 (NH) 1742 (C=O) 1728 (C=O) 1222 (P=O)	379 (M^+, 59%)
9c	12.3	1.19 (t, 6H, $^{3}J_{HH}$=7.1 Hz, CH_3), 3.76 (s, 3H, OCH_3), 3.98 (m, 4H, OCH_2), 7.60-7.80 (m, 4H, arom and HC=), 9.31 (s, 1H, NH)[e]	16.0 (CH_3), 52 2 (OCH_3), 62.0 (OCH_2), 111-150 (C-arom, C-3, C-4 and C-5), 167.1 (C-2), 167.5 (d, $^{3}J_{PC}$=2.3 Hz, C=O)	3111 (NH) 1749 (C=O) 1730 (C=O) 1235 (P=O)	371 (M^+, 6%)

[a] Obtained on a Varian VXR 300 Spectrometer [b] Recorded in a Brucker AC-250 Spectrometer [c] Recorded in a Nicolet FTIR Magna 550. [d] Obtained on a Hewlett Packard 5890 Spectrometer.[e] Deuterium oxide exchangeable proton.

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25. Typical procedure for the preparation of compound (**2a**). A dry flask, 100 ml, 2 necked, fitted with a dropping funnel, gas inlet, and magnetic stirred, was charged 5 mmol of LDA and 25 ml of THF at -78°C under N_2 atmosphere, and a solution of methyl phosphonate (0.76 g, 5 mmol) in 25 ml of THF was then added. After stirring for 1 h at -78°C, a solution of *p*-tolunitrile (0.6 g, 5 mmol) in 10 ml of THF was added. The mixture was stirred until tlc indicated the disappearance of the nitrile compound (18 h). The mixture was then diluted with 50 ml of water and extracted with CH_2Cl_2. The CH_2Cl_2 layers were washed with water. The organic layers were dried over $MgSO_4$, filtered. Removal of the solvent under reduced pressure gave the crude product, which was purified by high vacuum distillation (10^{-5} Torr).
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27. K. Lee and D. Y. Oh, *Synthesis*, 1991, 213.
28. Typical procedure for the synthesis of 2(1*H*)-pyridone (**1a**). To a solution of enamine (**2a**) (1.35 g, 5 mmol) in toluene was added methyl propiolate (0.42 g, 5 mmol), and the reaction mixture was stirred for 72 h at 90°C. Evaporation of the solvent afforded a solid, which was recrystallized from hexane: CH_2Cl_2 to give compound (**7a**). Adduct (**7a**) (0.88 g, 2.5 mmol) was slowly added at 0°C to a stirred suspension of NaH (0.07 g, 2.5 mmol) in 15 ml of dry THF and stirring is continued at room temperature until completion (tlc control). The reaction mixture was washed with water. After extraction with CH_2Cl_2, the separated organic layer was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was recrystallized from hexane:CH_2Cl_2.
29. Typical procedure for the preparation of the adduct (**8a**). Dimethyl acetylendicarboxylate (0.71 g, 5 mmol) was added to a solution of enamine (**2a**) (1.35 g, 5 mmol) in 25 ml of dried THF. The mixture was stirred at room temperature until tlc indicated the completion of the reaction, aproximately 24 h. Solvent evaporation of the reaction mixture followed by flash column cromatography (neutral aluminum oxide, 18 g; eluent, 5:1, *n*-hexane:ether), afforded 1.64 g of compound (**8a**). (R_f = 0.64 for **8a**). Adduct (**8a**) (1.03 g, 2.5 mmol) was heated in 15 ml of dried THF for 12 h at 50°C. Removal of the solvent at reduced pressure gave very crude pyridone (**9a**).

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