MICHAEL REACTIONS OF β-KETO PHOSPHONATES WITH ARYLMETHYLENEMALONONITRILES: THE FIRST SYNTHESIS OF DENSELY FUNCTIONALIZED 5-DIETHYLPHOSPHINYL-2-AMINO-4*H*-PYRANS

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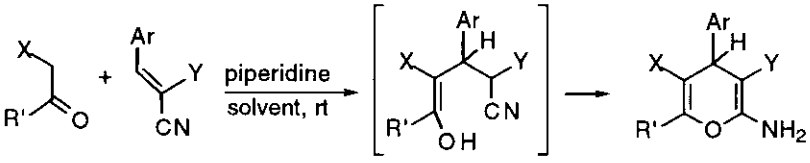
Abstract - A convenient synthesis of densely functionalized derivatives of 5-diethylphosphinyl-2-amino-4*H*-pyrans (**1a-d**) is described for the first time.

The Michael reaction is one of the most useful processes in organic synthesis.[1] The 1,4-conjugate additions of stabilized carbanions to unsaturated acceptors is one of the fundamental and efficient methods for the formation of carbon-carbon bonds.[2] In our laboratory, in the last years we have addressed for the first time the chiral Michael reaction of stabilized carbanions derived from 1,3-dicarbonyl compounds with suitable Michael acceptors.[3] As a result, we have reported the first synthesis of enantiomerically pure, polyfunctionalized 2-amino-4*H*-pyrans.[4,5] The success of this process relies on the ability of the functional group in the Michael donor to stabilize the intermediate in the enol form to promote the final *O*-ring closure affording final 2-amino-4*H*-pyrans (Scheme 1). Usual functional groups that have proved to be useful are electrowithdrawing substituents such as cyano,[4] ester,[4] azido,[6] sulfoxide and sulfone.[7] In this context, we have hypothesized that the phosphonate group could also work in these reactions. In addition, and very recently, the replacement of the carboxylic ester by a phosphonate group has been tried in the 1,4-dihydropyridine-3,5-dicarboxylate type of compounds in a new molecular design.[8] Pyran derivatives display also several interesting biological activities.[5] As an extension of our work on this topic, the need for new pyran substituted derivatives for biological screening and the unprecedented Michael addition of β-keto phosphonates to arylmethylenemalononitriles, moved us to undertake this project. In this paper we describe the successful 1,4-conjugate additions of β-keto phosphonates with arylmethylenemalononitriles, that has resulted in a convenient synthesis of new 5-diethylphosphinyl-2-amino-4*H*-pyrans.

Starting form commercially available diethyl (2-oxo-2-phenylethyl)phosphonate (**2**) and and the arylmethylenemalononitriles (**3a-d**),[9] following the **General procedure** (see **EXPERIMENTAL**), products (**1**) have obtained as solids after filtration and recrystallization form hexane/ethyl acetate mixtures, in good to moderate yields [(**1a**): 68%, (**1b**): 87%, (**1c**): 84%, (**1d**): 66%]. The analytical and spectroscopic data of these samples are in good agreement with these new pyran derivatives. Particular significant was the strong band at 2150 cm^{-1} for the unsaturated cyano group in the IR spectrum; in the ^1H

spectra H4 appears as a doublet (J= 9 Hz) at ≈ 4.4 ppm and the NH_2 group as broad singlet (4.60-4.50 ppm). In the ^{13}C NMR spectra, and as expected,[4] C-3 is very shielded, at ≈ 62 ppm, and very close to the methylenes of the ethyl rests (61 ppm), and C-4 appears at ≈ 39 ppm.

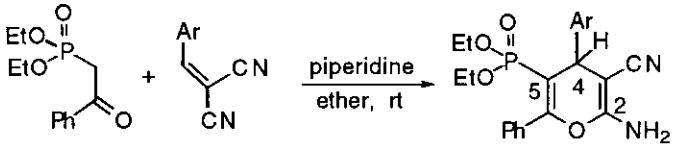


X= CN, COOR, COR (ref. 3, 4,5a); X= sulfoxide, sulfone (ref. 8)

X= phosphonates (this work)

(Y= CN, COOR, COAr; R, R'= aryl, alkyl)

Scheme 1



2 **3** **1**

Ar= (**a**) Ph, (**b**)*p*-$MeOC_6H_4$, (**c**) *p*-MeC_6H_4, (**d**) *p*-ClC_6H_4

Scheme 2

In summary, we have obtained the desired target molecules in good yield, in a simple synthetic scheme. Work is now in progress to extend these protocols to other triple substituted Michael acceptors and β-keto phosphonates.[10]

EXPERIMENTAL

Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous $MgSO_4$ was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as eluent unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as internal standard.

General procedure for the synthesis of 5-diethylphosphinyl-2-amino-4-*H*-pyrans (1a-d):

Starting from commercially available diethyl (2-oxo-2-phenylethyl)phosphonate (**2**) (1 equiv) and the arylmethylenemalononitriles (**3a-d**)[9] (1 equiv), using ether as solvent, at rt (from 3 to 7 h), in the presence of catalytic amounts of piperidine (3 drops), products (**1a-d**) have been obtained after filtration, washing with cold ether and recrystallization.

2-Amino-3-cyano-5-diethylphosphinyl-4,6-diphenyl-4-*H*-pyran (1a).
Following the **General procedure**, from diethyl (2-oxo-2-phenylethyl)phosphonate (**2**) (100 mg, 0.39 mmol) and phenylmethylenemalononitrile (60.0 mg, 0.39 mmol), compound (**1a**) (108 mg, 68%) was obtained: mp 210-212 °C (hexane, ethyl acetate); IR (KBr): 3500-3200, 3120, 2150, 1650, 1210, and 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60-7.22 (m, 10H, aromatic), 4.63 (br s, 2H, NH_2), 4.49 (d, *J*= 9.2 Hz, 1H, H4), 3.73-3.58 (m, 2H) and 3.57-3.39 (m, 2H, [OP(OC*H*$_2$CH$_3$)$_2$]), 0.95 (t, *J*= 7.0 Hz, 3H) and 0.82 (t, *J*= 7.0 Hz, 3H, [OP(OCH$_2$C*H*$_3$)$_2$]); ^{13}C NMR ($CDCl_3$) δ 158.1 (C2), 156.6 (d, *J*= 25.7 Hz, C6), 143.4 and 132.9 (d, *J*= 3.5 Hz)-127.4 (aromatic), 118.8 (CN), 105.1 (d, *J*= 195.9 Hz, C5), 62.0 (C3), 61.8 (d, *J*= 14.1 Hz) and 61.7 (d, *J*= 14.1 Hz, [OP(OCH$_2$CH$_3$)$_2$]), 40.1 (d, *J*= 8.6 Hz, C4), 15.9 (d, *J*= 6.6 Hz) and 15.6 (d, *J*= 7.6 Hz, [OP(OCH$_2$CH$_3$)$_2$]). Anal. Calcd for $C_{22}H_{23}N_2O_4P$: C, 64.38; H, 5.65; N, 6.83. Found: C, 64.57; H, 5.43; N, 6.68.

2-Amino-3-cyano-5-diethylphosphinyl-4-(4-methoxyphenyl)-6-phenyl-4-*H*-pyran (1b).
Following the **General procedure**, from diethyl (2-oxo-2-phenylethyl)phosphonate (**2**) (100 mg, 0.39 mmol) and (4-methoxyphenyl)methylenemalononitrile (71.9 mg, 0.39 mmol), compound (**1b**) (82 mg, 87%) was obtained: mp 190-192 °C (hexane, ethyl acetate); IR (KBr): 3500-3200, 3120, 2150, 1645, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (m, 2H), 7.44 (m, 3H), 7.27 (dd, *J*= 2.2, 6.6 Hz, 2H), 6.89 (dd, *J*= 2.0, 6.7 Hz, 2H), 4.50 (br s, 2H, NH_2), 4.47 (d, *J*= 9.2 Hz, 1H, H4), 3.80 (s, 3H, OCH_3), 3.73-3.58 (m, 2H) and 3.57-3.39 (m, 2H, [OP(OC*H*$_2$CH$_3$)$_2$]), 0.97 (t, *J*= 7.2 Hz, 3H) and 0.86 (t, *J*= 7.2 Hz, 3H, [OP(OCH$_2$C*H*$_3$)$_2$]); ^{13}C NMR ($CDCl_3$) δ 157.9 (C2), 156.3 (d, *J*= 25.3 Hz, C6), 159.0, 135.7, 133.1-127.9 and 114.1 (aromatic), 118.8 (CN), 108.7 (d, *J*= 195.9 Hz, C5), 62.5 (d, *J*= 18.3 Hz, C3), 61.8 (d, *J*= 13.8 Hz) and 61.7 (d, *J*= 13.8 Hz, [OP(O*C*H$_2$CH$_3$)$_2$]), 55.3 (OCH_3), 39.4 (d, *J*= 9.2 Hz, C4), 16.0 (d, *J*= 6.9 Hz) and 15.6 (d, *J*= 6.9 Hz, [OP(OCH$_2$C*H*$_3$)$_2$]). Anal. Calcd for $C_{23}H_{25}N_2O_5P$: C, 62.72; H, 5.72; N, 6.36. Found: C, 62.58; H, 5.63; N, 6.64.

2-Amino-3-cyano-5-diethylphosphinyl-4-(4-methylphenyl)-6-phenyl-4-*H*-pyran (1c).
Following the **General procedure**, from diethyl (2-oxo-2-phenylethyl)phosphonate (**2**) (100 mg, 0.39 mmol) and (4-methylphenyl)methylenemalononitrile (65.6 mg, 0.39 mmol), compound (**1c**) (117 mg, 84%) was obtained: mp 222-224 °C (hexane, ethyl acetate); IR (KBr): 3500-3200, 3120, 2150, 1645, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (m, 2H), 7.45 (m, 3H), 7.27-7.17 (m, 4H), 4.51 (br s, 2H, NH_2), 4.49 (d, *J*= 9.2 Hz, 1H, H4), 3.74-3.64 (m, 2H) and 3.59-3.48 (m, 2H, [OP(OC*H*$_2$CH$_3$)$_2$]), 2.35 (s, 3H, $ArCH_3$), 0.98 (t, *J*= 7.2 Hz, 3H) and 0.87 (t, *J*= 7.1 Hz, 3H, [OP(OCH$_2$C*H*$_3$)$_2$]); ^{13}C NMR ($CDCl_3$) δ 158.0 (C2), 156.5 (d, *J*= 25.0 Hz, C6), 140.0, 137.1 and 133.1-127.8 (aromatic), 118.7 (CN), 105.5 (d, *J*= 195.9 Hz, C5), 62.6 (C3), 61.8 (d, *J*= 6.6 Hz) and 61.7 (d, *J*= 6.6 Hz, [OP(O*C*H$_2$CH$_3$)$_2$]), 39.8 (d, *J*= 8.6

Hz, C4), 21.1 ($ArCH_3$), 16.0 (d, J= 6.6 Hz) and 15.6 (d, J= 7.0 Hz, [$OP(OCH_2CH_3)_2$]). Anal. Calcd for $C_{23}H_{25}N_2O_4P$: C, 65.09; H, 5.94; N, 6.60. Found: C, 65.18; H, 5.88; N, 6.47.

2-Amino-4-(4-chlorophenyl)-3-cyano-5-diethylphosphinyl-6-phenyl-4-*H*-pyran (1d).

Following the **General procedure**, from diethyl (2-oxo-2-phenylethyl)phosphonate (**2**) (100 mg, 0.39 mmol) and (4-chlorophenyl)methylenemalononitrile (73.6 mg, 0.39 mmol), compound (**1d**) (115 mg, 66%) was obtained: mp 208-210 °C (hexane, ethyl acetate); IR (KBr): 3500-3200, 3120, 2150, 1645, and 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61-7.17 (m, 9H, aromatic), 4.54 (br s, 2H, NH_2), 4.50 (d, J= 9.2 Hz, 1H, H4), 3.74-3.64 (m, 2H) and 3.59-3.48 (m, 2H, [$OP(OCH_2CH_3)_2$]), 0.98 (t, J= 7.2 Hz, 3H) and 0.87 (t, J= 7.1 Hz, 3H, [$OP(OCH_2CH_3)_2$]); ^{13}C NMR ($CDCl_3$) δ 158.0 (C2), 156.5 (d, J= 25.0 Hz, C6), 141.9-127.9 (aromatic), 118.4 (CN), 105.0 (d, J= 195.9 Hz, C5), 62.1 (C3), 61.9 (d, J= 6.6 Hz) and 61.7 (d, J= 6.6 Hz, [$OP(OCH_2CH_3)_2$]), 39.6 (d, J= 8.6 Hz, C4), 15.9 (d, J= 6.6 Hz) and 15.6 (d, J= 7.0 Hz, [$OP(OCH_2CH_3)_2$]). Anal. Calcd for $C_{22}H_{22}N_2O_4ClP$: C, 59.40; H, 4.98; N, 6.30. Found: C, 59.58; H, 4.87; N, 6.57.

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