

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

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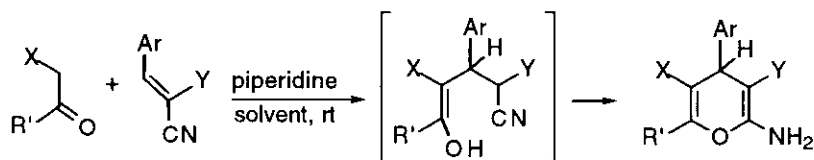
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Abstract - A convenient synthesis of densely functionalized derivatives of 5-diethylphosphinyl-2-amino-4H-pyrans (**1a-d**) is described for the first time.

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-4H-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-4H-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-4H-pyrans.

Starting from commercially available diethyl (2-oxo-2-phenylethyl)phosphonate (**2**) and the arylmethylenemalononitriles (**3a-d**),⁹ following the **General procedure** (see **EXPERIMENTAL**), products (**1**) have obtained as solids after filtration and recrystallization from 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.

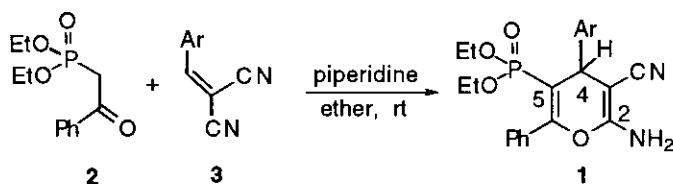


X = CN, COOR, COR (ref. 3, 4,5a); X = sulfoxide, sulfone (ref. 8)

X = phosphonates (this work)

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

Scheme 1



Ar = (a) Ph, (b) $p\text{-MeOC}_6\text{H}_4$, (c) $p\text{-MeC}_6\text{H}_4$, (d) $p\text{-ClC}_6\text{H}_4$

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 (CDCl₃) δ 7.60-7.22 (m, 10H, aromatic), 4.63 (br s, 2H, NH₂), 4.49 (d, *J* = 9.2 Hz, 1H, H₄), 3.73-3.58 (m, 2H) and 3.57-3.39 (m, 2H, [OP(OCH₂CH₃)₂]), 0.95 (t, *J* = 7.0 Hz, 3H) and 0.82 (t, *J* = 7.0 Hz, 3H, [OP(OCH₂CH₃)₂]); ¹³C NMR (CDCl₃) 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(OCH₂CH₃)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(OCH₂CH₃)₂]). Anal. Calcd for C₂₂H₂₃N₂O₄P: 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 (CDCl₃) 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, NH₂), 4.47 (d, *J* = 9.2 Hz, 1H, H₄), 3.80 (s, 3H, OCH₃), 3.73-3.58 (m, 2H) and 3.57-3.39 (m, 2H, [OP(OCH₂CH₃)₂]), 0.97 (t, *J* = 7.2 Hz, 3H) and 0.86 (t, *J* = 7.2 Hz, 3H, [OP(OCH₂CH₃)₂]); ¹³C NMR (CDCl₃) 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(OCH₂CH₃)₂]), 55.3 (OCH₃), 39.4 (d, *J* = 9.2 Hz, C4), 16.0 (d, *J* = 6.9 Hz) and 15.6 (d, *J* = 6.9 Hz, [OP(OCH₂CH₃)₂]). Anal. Calcd for C₂₃H₂₅N₂O₅P: 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 (CDCl₃) δ 7.61 (m, 2H), 7.45 (m, 3H), 7.27-7.17 (m, 4H), 4.51 (br s, 2H, NH₂), 4.49 (d, *J* = 9.2 Hz, 1H, H₄), 3.74-3.64 (m, 2H) and 3.59-3.48 (m, 2H, [OP(OCH₂CH₃)₂]), 2.35 (s, 3H, ArCH₃), 0.98 (t, *J* = 7.2 Hz, 3H) and 0.87 (t, *J* = 7.1 Hz, 3H, [OP(OCH₂CH₃)₂]); ¹³C NMR (CDCl₃) 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(OCH₂CH₃)₂]), 39.8 (d, *J* = 8.6

Hz, C4), 21.1 (ArCH₃), 16.0 (d, J = 6.6 Hz) and 15.6 (d, J = 7.0 Hz, [OP(OCH₂CH₃)₂]). Anal. Calcd for C₂₃H₂₅N₂O₄P: 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 (CDCl₃) δ 7.61-7.17 (m, 9H, aromatic), 4.54 (br s, 2H, NH₂), 4.50 (d, J = 9.2 Hz, 1H, H4), 3.74-3.64 (m, 2H) and 3.59-3.48 (m, 2H, [OP(OCH₂CH₃)₂]), 0.98 (t, J = 7.2 Hz, 3H) and 0.87 (t, J = 7.1 Hz, 3H, [OP(OCH₂CH₃)₂]); ¹³C NMR (CDCl₃) 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(OCH₂CH₃)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(OCH₂CH₃)₂]). Anal. Calcd for C₂₂H₂₂N₂O₄ClP: C, 59.40; H, 4.98; N, 6.30. Found: C, 59.58; H, 4.87; N, 6.57.

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10. Using chiral β -keto phosphonates (see, for instance: S.-K. Chung, and D.-H. Kang, *Tetrahedron: Asymmetry*, 1997, **8**, 3027), we could prepare enantiomerically pure 2-amino-4-aryl-5-phosphinyl-4*H*-pyrans.