Indoles as Nucleophiles in a Self-Catalytic Michael Reaction

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Abstract: C-3 Substituted indoles 7a–c were regioselectively synthesized in high yields by reacting indole 2 and electron-rich indoles 3,4 with acrylate 1. Additions of electron-deficient indoles 5,6 to the acrylate 1 gave N-substituted indoles 9a,b.

Key words: indoles, Michael reaction, regioselectivity, phosphonic acids

Alkylation of indoles by means of the Michael addition has been the subject of a number investigations for more than sixty years.1,2 It is well established that regioselectivity in the additions of indoles to electron-deficient alkenes is strongly controlled by the reaction medium. Indoles are N-alkylated by conjugate addition under alkaline conditions. On the other hand, the formation of C-3 substituted indoles is usually achieved in the acid catalyzed additions. Recently, particularly useful catalysts promoting C-3 addition of indoles to α,β-unsaturated compounds have been introduced. Montomorillonite clay3 and boron trifluoride etherate4 have been shown to facilitate C-3 alkylation of indoles with methyl vinyl ketone. Moreover, ytterbium triflate catalysis has been demonstrated to extend considerably the useful scope of C-3 indole addition to a variety of Michael acceptors at both high and ambient pressures.5,6

Previously, we demonstrated that the Michael additions of various C- and N-nucleophiles to dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate (1) proceed effectively without any external catalyst.7,8 These self-catalytic reactions have also been shown to be a valuable tool for C-alkylation of electron rich hydroxyarenes.9 In an extension of this work, we have now investigated the reaction of selected 3-unsubstituted indoles 2–6 with the acrylate 1 expecting that it would provide 2-(diethoxyphosphoryl)-3-(1H-indol-3-yl)propionates 7 (Scheme 1). These adducts might prove useful as synthons for the constructions of biologically active and medicinally attractive amino phosphonic acids. It is worth noting that 2-(diethoxyphosphoryl)-3-(1H-indol-3-yl)propionic acid 8a has been used as a key intermediate in phosphonotryptophan synthesis.10,11

The addition of indole (2) (1.05 equiv) to acrylate 1 in methylene chloride at room temperature was first investigated (Scheme 1). Monitoring the reaction progress by 31P NMR spectroscopy revealed the formation of a sole regioisomeric adduct (δ = 28.2 ppm). The reaction was completed after six weeks (31P NMR) giving C-3 substituted indole 7a in 73% yield. Ion exchange-chromatography of the salt 7a afforded quantitatively the acid 8a. Using the conditions stated above, we explored the generality of the addition by varying the indole substitution pattern. We

Scheme 1

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found that electron rich indoles, 5-methoxyindole (3) and 2-methylindole (4) were converted into C-3 adducts 7b and 7c, respectively within one week. The isolated yields were high (75–80%) and no detectable formation of the corresponding N-1 substituted indoles was observed by 1H and 31P NMR analysis of the crude reaction mixtures. We next sought to extend the scope of our reaction to electron-deficient indoles 5 and 6. Treatment of 5-nitroindole (5) and 5-cyanoindole (6) with the acrylate 1 under conditions described previously afforded N-substituted indoles 9a and 9b, respectively in high yields (78–83%) and no signs of the corresponding C-3 adducts were observed (Scheme 2).

The formation of N-substituted indoles 9a and 9b implies that the regioselectivity of the addition is strongly controlled by electronic effects. It is likely that the electron-withdrawing group at C-5 of homoaromatic indole ring overtures entirely the relative hardness and softness of its C-3 and N-nucleophilic centers. Attempts to prove reversibility of the N-addition of indoles 5 and 6 to the acrylate 1 failed. The adducts 9a,9b remain unchanged under heating in boiling benzene for a prolonged time.

The salts 7b,7c and 9a,9b were converted to carboxylic acids 8b,8c and 10a,10b, respectively by ion exchange chromatography.

In summary, the described Michael reaction is remarkable in its efficiency and regioselectivity. Regioselective additions may offer a convenient entry toward the construction of new phosphonic acids and might be competitive to already published syntheses of phosphoronytryophan.10–13 Moreover, this reaction has many obvious advantages including mild conditions, simplicity of the methodology and the ease of product isolation.

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for 1H and 62.97 MHz for 13C NMR, respectively using tetramethylsilane as internal and 85% H3PO4 as external standard. The multiplicity of carbons were determined by DEPT experiments. IR spectra were measured on a Specord M80 (Zeiss) instrument. Elemental analyses were performed on a Perkin-Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. Dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate (I) was prepared according to the literature procedure.7 Analytical data of the acid 8a has not been previously reported.10,11

Dicyclohexylammonium 2-(Diethoxyphosphoryl)-3-(1H-indol-3-yl)propionate (7a); General Procedure

To a soln of acrylate I (3.89 g, 10 mmol) in CH2Cl2 (20 mL) was added indole (1.23 g, 10.5 mmol) and the reaction mixture was stirred for 6 weeks at r.t. The solvent was evaporated off. The solid residue was suspended in Et2O and the crystals were collected by filtration to afford the crude product. Recrystallization of the solid from CHCl3–acetone afforded the propionate 7a; yield 3.7 g (73%).

White crystals, mp 189–190 °C.

IR (KBr): 1632, 1584, 1216, 1032 cm –1.

1H NMR (CDCl3): δ = 0.95–1.35 (m, 10 H, 5 × CH2), 1.32 (t, 6 H, J = 7.0 Hz, 2 × CH3), 1.55 (m, 2 H, CH2), 1.67 (m, 4 H, 2 × CH2), 1.86 (m, 4 H, 2 × CH2), 2.74 (m, 2 H, 2 × CHN), 3.15–3.50 (m, 3 H, CH2, CH3), 4.17 (m, 4 H, 2 × CH2O), 7.02–7.16 (m, 3 H, 3 × CH), 7.31 (m, 1 H, CH) 7.61 (m, 1 H, CH), 7.68 (br s, 1 H, NH).

IR (KBr): 1632, 1568, 1360, 1224, 1032 cm –1.

White crystals, mp 189–190 °C.

IR (KBr): 1628, 1564, 1360, 1240, 1024 cm –1.

(75%); white crystals; mp 194–195 °C.

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for 1H and 62.97 MHz for 13C NMR, respectively using tetramethylsilane as internal and 85% H3PO4 as external standard. The multiplicity of carbons were determined by DEPT experiments. IR spectra were measured on a Specord M80 (Zeiss) instrument. Elemental analyses were performed on a Perkin-Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. Dicyclohexylammonium 2-(diethoxyphosphoryl)acrylate (I) was prepared according to the literature procedure.7 Analytical data of the acid 8a has not been previously reported.10,11
1.93 (m, 4 H, 2 CH₂), 2.17 (s, 3 H, CH₃), 2.77 (m, 2 H, 2 CHN), 3.16–3.44 (m, 3 H, C H₂ CH), 4.17 (m, 4 H, 2 CH₂ O), 7.02 (m, 2 H, 2 CH), 7.19 (m, 1 H, CH), 7.55 (m, 1 H, CH₆), 7.68 (br s, 1 H, NH).

13C NMR (CD₃ OD): δ = 11.63 (CH₃), 16.58 (2 CH₂), 23.95 (CH₃), 25.35 (4 CH₂), 25.99 (2 CH₂), 30.27 (4 CH₂), 50.36 (d, 1JCP = 123.7 Hz, CH), 54.09 (2 CH₂), 63.22 (d, 1JCP = 6.8 Hz, CH₂O), 63.48 (d, 1JCP = 6.8 Hz, CH₂O), 109.70 (d, 1JCP = 16.3 Hz, C), 111.06 (CH), 115.52 (CH), 120.97 (CH), 129.62 (C), 133.40 (C), 137.12 (C), 174.53 (COO).

31P NMR (CDCl₃): δ = 28.19.

Anal. Calc. for C₅H₅N₂O₅P: C, 64.59; H, 8.71; N, 5.38. Found C, 64.47; H, 8.62; N, 5.24.

Dicyclohexylammonium 3-(5-Nitro-indol-3-yl)-2-(Diethoxy-phosphoryl)propionate (9a)

Following the general procedure using 5-nitroindole (1.70 g, 10 mmol) and performing the reaction for one week at r.t.; yield 4.3 g (78%); white crystals; mp 147–148 °C.

IR (KBr): 1716, 1208, 1020 cm⁻¹.

1H NMR (acetone-d₆): δ = 1.22 (t, 3 H, J = 7.0 Hz, 2 CH₂), 2.24 (m, 4 H, 2 CH₂), 2.76 (m, 4 H, 2 CH₂), 4.17 (m, 4 H, 2 CH₂), 7.06 (d, 1 H, J = 7.0 Hz, CH), 7.13 (s, 1 H, CH), 7.26 (br d, 1 H, J = 8.7 Hz, CH). 7.43 (m, 1 H, CH), 7.78 (br s, 1 H, NH).

13C NMR (CD₃ OD): δ = 16.55 (d, 1JCP = 3.5 Hz, CH₂, 16.67 (d, 1JCP = 3.5 Hz, CH₂), 25.38 (4 CH₂), 26.00 (2 CH₂), 30.24 (4 CH₂), 46.17 (CH₂N), 50.59 (d, 1JCP = 125.8 Hz, CH₄P), 54.09 (2 CH₂), 63.85 (d, 1JCP = 7.0 Hz, CH₂O), 64.06 (d, 1JCP = 7.0 Hz, CH₂O), 104.63 (CH), 117.50 (CH), 118.38 (CH), 129.10 (C), 133.21 (CH), 139.94 (C), 142.49 (C), 171.43 (d, 1JCP = 4.4 Hz, COO).

31P NMR (CDCl₃): δ = 23.85.

Anal. Calc. for C₁₅H₂₆NO₇P: C, 58.79; H, 7.67; N, 7.61. Found C, 58.62; H, 7.54; N, 7.45.

Dicyclohexylammonium 3-(5-Cyano-indol-3-yl)-2-(Diethoxy-phosphoryl)propionate (9b)

Following the general procedure using 5-cyanoindole (1.49 g, 10.5 mmol) and performing the reaction for one week at r.t.; yield 4.4 g (83%); white crystals; mp 150–151 °C.

IR (KBr): 2224, 1630, 1224, 1032 cm⁻¹.

1H NMR (CDCl₃): δ = 0.9–1.35 (m, 10 H, 5 CH₃), 1.32 (t, 6 H, J = 7.0 Hz, 2 CH₃), 1.66 (m, 6 H, 3 CH₂), 1.86 (m, 4 H, 2 CH₂), 2.83 (m, 2 H, 2 CHN), 3.22 (dtd, 1 H, JHH = 10.2 Hz, JHP = 6.8 Hz, 2 CH₂), 4.17 (m, 4 H, 2 CH₂), 4.55 (dd, 1 H, JP = 3.5 Hz, JCP = 16.3 Hz, C), 50.59 (d, 1JCP = 125.8 Hz, CH₄P), 54.09 (2 CH₂), 63.85 (d, 1JCP = 7.0 Hz, CH₂O), 64.06 (d, 1JCP = 7.0 Hz, CH₂O), 104.63 (CH), 117.50 (CH), 118.38 (CH), 129.10 (C), 133.21 (CH), 139.94 (C), 142.49 (C), 171.43 (d, 1JCP = 4.4 Hz, COO).

31P NMR (CDCl₃): δ = 23.85.

Anal. Calc. for C₁₅H₂₆NO₇P: C, 58.79; H, 7.67; N, 7.61. Found C, 58.62; H, 7.54; N, 7.45.
3-(5-Nitro-indol-3-yl)-2-(diethoxyphosphoryl)propionic Acid (10a)

Yellow crystals; mp 169–170 °C.

IR (KBr): 1724, 1512, 1216, 1012 cm⁻¹.

¹H NMR (Acetone-d₆): δ = 1.31 (t, 3 H, J = 7.0 Hz, CH₃), 1.32 (t, 3 H, J = 7.0 Hz, CH₃), 3.70 (ddd, 1 H, J HH = 4.2 Hz, J HH = 10.0 Hz, J HP = 23.7 Hz, CHP), 4.19 (m, 4 H, 2 × CH₂O), 4.72 (ddd, 1 H, J HH = 4.2 Hz, J HP = 7.2 Hz, J HP = 14.7 Hz, CH₂N), 4.90 (ddd, 1 H, J HH = 8.0 Hz, J HP = 8.2 Hz, J HP = 14.7 Hz, CH₂N), 6.76 (d, 1 H, J = 3.7 Hz, CH), 7.56 (d, 1 H, J = 3.7 Hz, CH), 7.65 (d, 1 H, J = 9.0 Hz, CH), 8.10 (dd, 1 H, J = 2.2, 9.0 Hz, CH), 8.55 (d, 1 H, J = 2.2 Hz, CH).

¹³C NMR (CD₃OD): δ = 16.43 (d, J CP = 6.0 Hz, 2 × CH₃), 44.87 (CH₂N), 47.55 (d, J CP = 126 Hz, CHP), 64.76 (d, 2 × CH₂O), 105.22 (CH), 110.69 (CH), 117.83 (CH), 118.52 (CH), 129.21 (C), 132.86 (CH), 139.95 (C), 142.81 (C), 169.72 (d, 2 × CP = 5.0 Hz, C).


Anal. Calcd for C₁₅H₁₉N₂O₇P: C, 48.65; H, 5.17; N, 7.56. Found C, 48.52; H, 5.08; N, 7.44.

3-(5-Cyano-indol-3-yl)-2-(diethoxyphosphoryl)propionic Acid (10b)

Pink crystals; mp 105–106 °C.

IR (KBr): 2224, 1724, 1224, 1020 cm⁻¹.

¹H NMR (acetone-d₆): δ = 1.32 (t, 3 H, J = 7.0 Hz, CH₃), 1.33 (t, 3 H, J = 7.0 Hz, CH₃), 3.64 (ddd, 3 H, J HH = 4.0 Hz, J HH = 9.7 Hz, J HP = 23.7 Hz, CHP), 4.16 (m, 4 H, 2 × CH₂O), 4.70 (dd, 1 H, J HH = 7.5 Hz, J HP = 14.5 Hz, CH₂N), 4.91 (dd, 1 H, J HP = 8.2 Hz, J HH = 14.5 Hz, CH₂N), 6.63 (d, 1 H, J = 3.2 Hz, CH), 7.50 (dd, 1 H, J = 1.5, 8.7 Hz, CH), 7.55 (d, 1 H, J = 3.2 Hz, CH), 7.68 (d, 1 H, J = 8.7 Hz, CH), 8.03 (d, 1 H, J = 1.5 Hz, CH).

¹³C NMR (acetone-d₆): δ = 16.15 (d, 2 × CP = 5.0 Hz, COO).

³¹P NMR (acetone-d₆): δ = 20.23.


References