Regiospecific Electrocyclization of β-Arylvinyl Ketenimines. Formal Syntheses of the Alkaloid from Marine Origin Aaptamine

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Preparation of 6,7-dimethoxy-1-methyl-8-nitroisoquinoline and 6,7-dimethoxy-1-methylisoquinoline, used as precursors in the synthesis of the alkaloid aaptamine, is reported. The method is based on the regiospecific electrocyclization of the appropriate β-arylvinyketenimine available byaza-Wittig reaction of the corresponding vinyl iminophosphorane with (trimethylene)ethene.

The aqueous ethanol extracts of the Okinawan sea sponge Aaptos aaptos afforded a bright yellow substance christened aaptamine and assigned structure 1.1 Also demethylaaptamine and demethylated and oxidised variant 2 have been isolated from the same natural source.2 Aaptamine 1 exhibits α-adrenoceptor blocking activity, while demethylaaptamine 2 possesses antitumor and antimicrobial activity.3 This novel group of bases represents the only known derivatives of 1H-benzo[de][1,6]naphthyridine ring system in a naturally occurring substance. This unusual nature of compound 1 has focused considerable attention on its synthesis. From a synthetic viewpoint the 1H-benzo[de][1,6]naphthyridine ring system can be viewed either as a quinoline or as an isoquinoline, but with an additional fused six-membered nitrogen-containing ring (Figure 1).

![Figure 1](image)

Of the seven syntheses4−10 of aaptamine 1 previously reported, four took an approach in which the third ring was fused to an existing isoquinoline.7−10 In this sense, compounds 3 (Joule, Cava and Yamanaka syntheses) and 4 (Tollari synthesis) have been used as suitable building blocks in the synthesis of aaptamine 1 (Figure 2).

![Figure 2](image)

In connection with the synthesis of a number of isoquinoline and β-carboline-containing alkaloids,11 we sought to find methods that could provide convenient entries to highly functionalized isoquinoline derivatives. It occurred to us that an iminophosphorane-based approach could be suitably applied to the synthesis of the key intermediates 3 and 4, successfully used in the above mentioned syntheses of the alkaloid aaptamine 1.

Condensation of 3,4-dimethoxy-5-nitrobenzaldehyde5 with ethyl azidoacetate in the presence of NaOEt at −10°C provided the vinyl azide 5 in 47% yield, which was converted into the iminophosphorane 6 in 93% yield by Staudinger reaction12 with triphenylphosphine in dichloromethane/diethyl ether at room temperature. Iminophosphorane 6 was converted into the 1-substituted isoquinoline 9 in 24% overall yield by an one-flask process involving sequential treatment with carbon disulfide, (carbethoxyethylidene)triphenylphosphorane and further heating at 160°C. The conversion 6 → 9 probably involves an initialaza-Wittig-type reaction13 between the iminophosphorane 6 and carbon disulfide to give the vinyl thiocyanate 7, which reacts with (carbethoxyethylidene)triphenylphosphorane to afford the ketenimine14 8 (as evidenced by IR). Eventually thermally induced electrocyclic ring closure of the vinyl ketenimine 8, involving the aryl ring as a 2π-component, yields the isoquinoline derivative 9. This compound may be converted into the 3-methylaaptamine in a straightforward manner4 (Scheme 1).

Likewise, vinyl azide 5 was converted into 3-ethoxycarbonyl-6,7-dimethoxy-1-methyl-8-nitroisoquinoline (13) in 62% overall yield by a one-flask process involving sequential treatment with trimethylphosphane, (trimethylsilyl)ethene,15 heating at 160°C and chromatographic separation using a silica gel column. The conversion 5 → 13 can be understood by an initial Staudinger reaction between the vinyl azide 5 and trimethylphosphane to give the iminophosphorane 10, which was used without purification for the next step. The azaza-Wittig-type reaction of 10 with (trimethylsilyl)ethene provides the ketenimine16 11 (evidenced by a strong band at 2004 cm−1 in the IR), which undergoes electrocyclic ring closure to give 12 and, finally, carbon–silicon bond cleavage in compound 12 by the action of silica gel affords 13 (Scheme 1). The later assumption is supported by the fact that compound 12 was isolated and fully characterized. In addition, when a solution of 12 was stirred in the presence of silica gel at room temperature, compound 13 was obtained in almost quantitative yield. Compound 13 was converted into the desired 6,7-dimethoxy-1-methyl-8-ni-
troisoquinoline (3a) by hydrolysis with LiOH in THF/H₂O (86%) followed by thermal decarboxylation (68%).

This constitutes a formal total synthesis of aaptamine since 3a is the isoquinoline derivative of the Joule synthesis of aaptamine, and may be easily converted into the target molecule.

On the other hand, condensation of 3,4-dimethoxybenzaldehyde with ethyl azidoacetate under standard conditions afforded the vinyl azide 15 in 72% yield. This compound was transformed into the 3-ethoxycarbonyl-6,7-dimethoxy-1-methylisoquinoline (18) in 86% overall yield as previously described for the conversion 5 → 13.

When, in this reaction sequence, acetaldehyde was used instead of (trimethylsilyl)ethenone isoquinoline derivative 18 was also obtained, although the completion of the reaction required a longer period of time (48 h) and the yield was dramatically lower (25%). Conversion of the isoquinoline derivative 18 into the key intermediate 20 was achieved by hydrolysis with LiOH in THF/H₂O.

Scheme 1

Scheme 2
(91 %) followed by decarboxylation in diphenyl ether at 180 °C (64 %) (Scheme 2).

This constitutes a second formal total synthesis of aaptamine 1. Compound 20 may be easily transformed into 1 either by the sequence oxidation, condensation with nitromethane and further nitrene insertion, or by nitration, oxidation, condensation with nitromethane and finally reduction.

A final word about the thermal behaviour of ketenimines 8, 11 and 17 is relevant. These compounds underwent electrolysis to give the isoquinoline derivatives 9, 13 and 18 respectively in a regiospecific fashion. NOE difference experiments confirmed the proposed structures of 9 and 13. Thus, in compound 13 irradiation of the H-4 proton signal induced a 14 % enhancement of the H-5 signal, whereas irradiation of the H-5 proton induced in addition a 5 % enhancement of the methoxy group signal at position 6.

In conclusion, we have demonstrated that the tandemaza-Wittig/electrolytic ring closure of vinyl ketenimines affords a convenient entry to the preparation of polysubstituted isoquinolines, used as building blocks in the synthesis of the alkaloid aaptamine.

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC-200 (200 MHz) or a Varian Unity 300 (300 MHz). Mass spectra were recorded on a Hewlett-Packard 5993 C spectrometer. Microanalyses were performed on a Perkin-Elmer 240C instrument.

Ethyl-2-(3-Ethoxy carbonyl)-6,7-dimethoxy-8-nitro-1-isouquinoline-propanoate (9):
To a solution of 6 (0.28 g, 0.5 mmol) in anhyd benzene (25 mL), C6H5O2 (5 mL) was added. The mixture was stirred at reflux temperature for 48 h. After cooling, the solvent was removed under reduced pressure. The residue was dissolved in anhyd toluene (25 mL) and (carbethoxythiylidene)triphenylphosphoramine (0.18 g, 0.5 mmol) was added at once. The mixture was heated at reflux temperature for 1 h and then 8 h at 160 °C in a sealed tube. The solvent was evaporated and the crude mixture was chromatographed on a silica gel column using EtOAc/hexane (1 : 1) as eluent to give 9 (0.049 g, 0.12 mmol); yield 24 %.

SSYTHESIS 1201

MS (EI, 70 eV): m/z (%): 406 (M+7, 7), 360 (100).

IR (Nujol): ν = 1737, 1537, 1360, 1268 cm⁻¹.

H NMR (300 MHz, CDCl3/ TMS): δ = 1.11 (t, 3 H, J = 7.1 Hz), 1.33 (t, 3 H, J = 7.1 Hz), 1.52 (d, 3 H, J = 6.8 Hz), 3.95 (s, 3 H), 3.99 (s, 3 H), 4.04-4.19 (m, 3 H), 4.28-4.41 (m, 2 H), 7.25 (s, 1 H), 8.23 (s, 1 H).


3-Ethoxy carbonyl-6,7-dimethoxy-1-methyl-8-nitroisoquinoline (13):
To a solution of 5 (0.64 g, 2 mmol) in anhyd toluene (20 mL), PMe3 (2 mL of a 1 M solution) was added dropwise at r.t. and the mixture was stirred for 15 min. Then, (trimethylsilyl)ethene (0.23 g, 2 mmol) was added and the new mixture was heated in a sealed tube at 130 °C for 2 h. After cooling, the solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column using EtOAc as eluent to give 13 (0.39 g, 1.23 mmol); yield 62 %; mp 140 °C (EtOAc/hexane).

MS (EI, 70 eV): m/z (%): 320 (M+11, 7), 248 (100).

IR (Nujol): ν = 1712, 1535, 1359 cm⁻¹.

H NMR (300 MHz, CDCl3/TMS): δ = 1.47 (t, 3 H, J = 7.2 Hz), 2.86 (s, 3 H), 4.04 (s, 3 H), 4.08 (s, 3 H), 4.51 (q, 2 H, J = 7.2 Hz), 7.33 (s, 1 H), 8.35 (s, 1 H).


This reaction can be isolated and identified 3-ethoxy carbonyl-6,7-dimethoxy-8-nitro-1-(trimethylsilyl)methylisoquinoline (12); mp 128–130 °C (Et2O).

MS (EI, 70 eV): m/z (%): 392 (M+7, 7), 248 (100).

IR (Nujol): ν = 1711, 1536, 1359 cm⁻¹.

H NMR (200 MHz, CDCl3/TMS): δ = 0.01 (s, 9 H), 1.42 (t, 3 H, J = 7.1 Hz), 2.52 (s, 2 H), 3.99 (s, 3 H), 4.03 (s, 3 H), 4.43 (q, 2 H, J = 7.1 Hz), 7.27 (s, 1 H), 8.19 (s, 1 H).


C13H17N2O4Si calc. C 55.08, H 6.16, N 7.14 (392.5) found 55.29, 6.02, 7.25.
6,7-Dimethoxy-1-methyl-8-nitroisoquinoline-3-carboxylic Acid (14):
To a stirred solution of 13 (0.32 g, 1 mmol) in THF (20 mL) was added in one portion LiOH·H₂O (0.13 g, 3 mmol) in H₂O (6 mL). The mixture was stirred at r.t. for 12 h. After removing the THF under reduced pressure, H₂O (10 mL) was added to the remaining aqueous solution. Then HCl (2 M) was added until pH = 5. The precipitate which formed was filtered off, washed with H₂O, dried and recrystallized from toluene to give 14 (0.25 g, 0.86 mmol); yield 86%; mp 204–205°C.

MS (EI, 70 eV): m/z (%) = 292 (M⁺, 22), 115 (100).

IR (Nujol): ν = 1718, 1535, 1359 cm⁻¹.

¹H NMR (300 MHz, DMSO-d₆/TMS): δ = 2.66 (s, 3 H), 3.98 (s, 3 H), 4.08 (s, 3 H), 7.98 (s, 1 H), 8.48 (s, 1 H), 10.39 (br s, 1 H).

¹C NMR (75 MHz, DMSO-d₆/TMS): δ = 21.98, 57.00, 62.61, 111.18, 114.42 (s), 121.26, 134.17 (s), 140.57 (s), 141.20 (s), 143.54 (s), 152.36 (s), 154.38 (s), 163.95 (s).

C₁₃H₁₄N₂O₆ calc. C 53.43 H 4.14 N 9.58
found 53.59 4.21 9.37

6,7-Dimethoxy-1-methyl-8-nitroisoquinoline (3a):
A solution of 14 (0.146 g, 0.5 mmol) in Ph₂O (4 mL) was heated at 180°C for 12 h. After cooling, the mixture was chromatographed directly on a silica gel column using EtOAc/hexane (7:3) as eluent to give 3a (0.084 g, 0.34 mmol); yield 68%.

Ethyl α-Azido-3,4-dimethoxycinnaminate (15):
A mixture of ethyl azidacetate (10.32 g, 80 mmol) and 3,4-dimethoxycinnaldehyde (3.32 g, 20 mmol) in anhyd EtOH (25 mL) was added dropwise under N₂ at -10°C to a well-stirred solution containing Na (1.84 g, 80 mmol) in anhyd EtOH (100 mL). The mixture was stirred for 6 h, poured into aq NaHCl (200 mL), and then extracted with Et₂O (3×100 mL). The combined organic layers were washed with H₂O, brine and dried (MgSO₄). The MgSO₄ was removed by filtration, the solvent concentrated to dryness and the resulting solid was recrystallized from EtOH to give 15 (3.99 g, 14.40 mmol); yield 72%; mp 93°C.

MS (EI, 70 eV): m/z (%) = 277 (M⁺, 4), 176 (100).

IR (Nujol): ν = 2105, 1696 cm⁻¹.

¹H NMR (200 MHz, CDCl₃/TMS): δ = 1.39 (t, 3 H, J = 7.2 Hz), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.35 (q, 2 H, J = 7.2 Hz), 6.86 (s, 1 H), 6.87 (d, 1 H, J = 8.4 Hz), 7.35 (dd, 1 H, J = 1.9, 8.4 Hz), 7.51 (d, 1 H, J = 1.9 Hz).

¹C NMR (50 MHz, CDCl₃/TMS): δ = 14.23, 55.86, 55.98, 62.08, 110.74, 113.04, 123.42 (s), 124.82, 125.54, 126.27 (s), 148.57 (s), 150.19 (s), 163.69 (s).

C₁₃H₁₄N₂O₄ calc. C 56.51 H 5.45 N 15.15
found 56.09 5.53 15.09

3-Ethoxycarbonyl-6,7-dimethoxy-1-methylisoquinoline (17):
To a solution of 15 (0.55 g, 2 mmol) in anhyd toluene (20 mL), PMe₃ (2 mL of a 1 M solution) was added dropwise at r.t. and the mixture was stirred for 15 min. Then, (trimethylsilyl)thiophene (0.23 g, 2 mmol) was added and the new mixture was heated in a sealed tube at 160°C for 2 h. After cooling, the solution was removed under reduced pressure and the residual material was chromatographed on a silica gel column using EtOAc as eluent to give 17 (0.47 g, 1.70 mmol); yield 86%; mp 171–173°C (EtOAc/hexane).

MS (EI, 70 eV): m/z (%) = 275 (M⁺, 5), 203 (100).

IR (Nujol): ν = 1722, 1509, 1255 cm⁻¹.

¹H NMR (300 MHz, CDCl₃/TMS): δ = 1.47 (t, 3 H, J = 7.2 Hz), 2.97 (s, 3 H), 4.04 (s, 3 H), 4.07 (s, 3 H), 4.50 (q, 2 H, J = 7.2 Hz), 7.18 (s, 1 H), 7.32 (s, 1 H), 8.32 (s, 1 H).

¹C NMR (75 MHz, CDCl₃/TMS): δ = 14.40, 22.77, 56.07, 56.13, 61.54, 103.96, 106.49, 121.63, 125.00 (s), 132.09 (s), 139.75 (s), 151.59 (s), 152.87 (s), 156.44 (s), 166.18 (s).

C₁₃H₁₄N₂O₄ calc. C 56.25 H 5.03 N 8.74
found 56.44 5.10 8.89

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