HETEROCYCLES, Vol. 68, No. 10, 2006, pp. 2165 - 2170. © The Japan Institute of Heterocyclic Chemistry
Received, 27th June, 2006, Accepted, 17th August, 2006, Published online, 22nd August, 2006. COM-06-10828

STEREOSELECTIVE SYNTHESIS AND ISOMERIZATION OF THE INDOLE ALKALOID MURRAYACARINE

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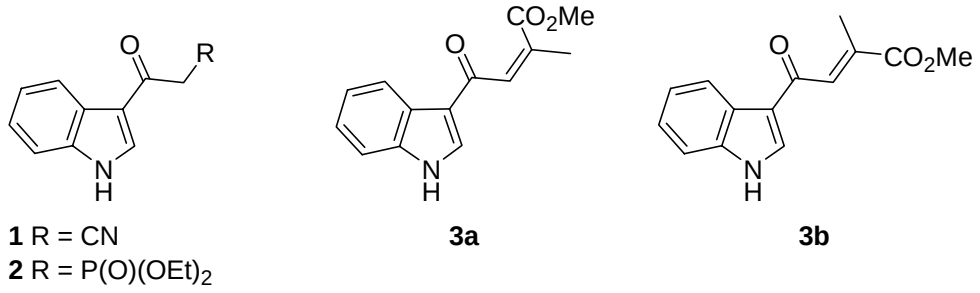
Abstract – A short and efficient stereoselective synthesis of the indole alkaloid murrayacarine is described, including studies on its acid-induced isomerization.

INTRODUCTION

Recent studies in our laboratory regarding the cyanoacetylation of indole and related compounds have resulted in several readily accessible and useful synthetic building blocks for the construction of various indole-containing systems.[1,2] The practical method for the preparation of 3-(cyanoacetyl)indole (**1**) has also been modified to give diethyl 2-(1*H*-indol-3-yl)-2-oxoethylphosphonate (**2**) in a simple one-pot reaction from indole.[2] Similar compounds are known in the literature, but have been prepared *via* a lengthy procedure from 3-(chloroacetyl)indoles and triethyl phosphite in an Arbuzov reaction.[3]

RESULTS AND DISCUSSION

The β-keto phosphonate (**2**), apart from being a possible starting material for β-aminophosphonates,[4] is also expected to undergo Horner-Wadsworth-Emmons (HWE) reactions resulting in α,β-unsaturated carbonyl compounds. Herein, we would like to demonstrate the successful use of **2** in a synthesis of murrayacarine (**3**) (Figure 1), an indole alkaloid isolated from the root bark of *Murraya paniculata* var. *omphalocarpa* Hayata (Rutaceae).[5] Although the geometry of the alkene moiety in murrayacarine was initially not determined, it was later deduced having (*Z*)-configuration [i.e. compound (**3a**)] by comparison with synthetic material. The first synthesis giving a mixture of both isomers of murrayacarine in 61% overall yield was achieved by condensation of indole-3-acetaldehyde (a quite unstable molecule) and methyl 2-(diethylphosphono)propionate, followed by dehydrogenation with DDQ.[6]

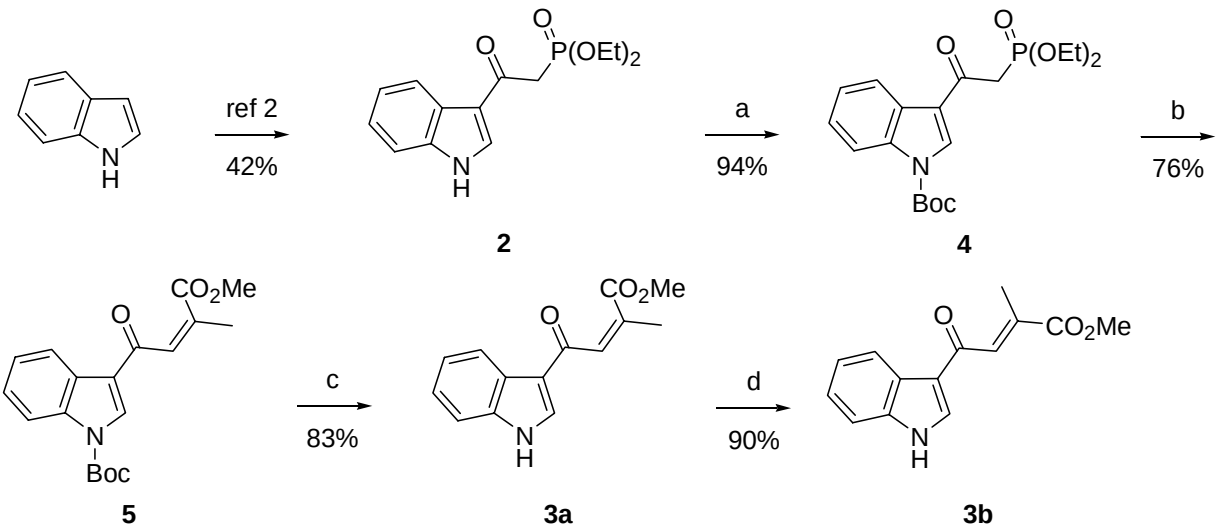


1 R = CN
2 R = P(O)(OEt)$_2$

3a **3b**

Figure 1

It was envisaged that the phosphonate ester (**2**) might serve as a starting point for the synthesis of murrayacarine. Thus, protection of **2** under standard conditions gave the *tert*-butoxycarbonyl protected compound (**4**), which was employed in an HWE-reaction with methyl pyruvate and sodium hydride in refluxing toluene, to afford **5** as a single isomer in a good yield (Scheme 1). Deprotection of **5** with TFA gave murrayacarine (**3a**) as a beige solid, mp 149–150 °C (lit.,[5] mp 146–148 °C, lit.,[6] 146 °C).



2 **4**

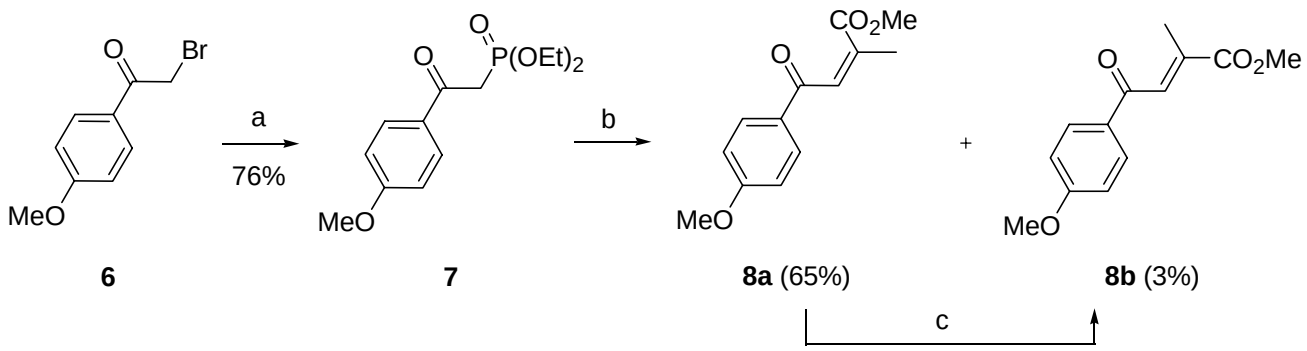
5 **3a** **3b**

Scheme 1. (a) Boc_2O, DMAP, THF, rt 51 h. (b) NaH, methyl pyruvate, toluene, reflux 2 h. (c) TFA, CH_2Cl_2, rt 20 h. (d) HCl (g), Et_2O, $CHCl_3$, rt 1 h.

However, it was noted that murrayacarine (**3a**) quickly isomerized in $CDCl_3$ (an immediate colour change to bright yellow was seen upon dissolution in $CDCl_3$), and two sets of signals could be discerned in the ^1H NMR spectrum. After several hours, bright yellow crystals could be collected from the $CDCl_3$ solution. This behaviour of **3a** was not noted in other deuterated solvents, e.g. DMSO-d_6. Hence, we speculated that the small amount of HCl in the $CDCl_3$ was responsible for the isomerization, which was supported by the fact that **3a** did not isomerize in normal (EtOH stabilized) $CHCl_3$ (not even at room temperature for several days), until HCl was added to the mixture, which quickly led to the formation of yellow crystals of **3b**. Compound (**3b**) is slightly less polar than **3a**, as indicated previously.[6] All data of **3a** and **3b** were

in agreement with those already published.[5,6] In addition, the (*Z*)-configuration of murrayacarine (**3a**) was supported by a NOE between the olefinic proton and the methyl group on the adjacent carbon atom. It is also noteworthy that formation of **3b** was not observed during deprotection of **5** with TFA.

We speculated that the fast isomerization of murrayacarine in $CDCl_3$ solution was induced by the electron releasing properties of the indole nitrogen. The known model compound (**8**) was therefore chosen for similar isomerization studies (Scheme 2). The phosphonate (**7**)[7] was obtained from the commercially available 2-bromo-4′-methoxyacetophenone (**6**) and triethyl phosphite. Treatment of **7** with methyl pyruvate and sodium hydride gave compound (**8**)[8] as a mixture of isomers, in contrast to the corresponding reaction in the murrayacarine synthesis. Even though **8a** did isomerize to **8b** in $CDCl_3$ in the same fashion as murrayacarine, complete isomerization was not observed until after ~1.5 days. It should also be noted that the intermediate (**5**) displayed similar isomerization behaviour, although at a significantly slower rate, as complete isomerization occurred upon standing for 4 days in $CDCl_3$ at room temperature.



Scheme 2. (a) $(EtO)_3P$, Bu_4NI, CH_3CN, reflux 8 h. (b) NaH, methyl pyruvate, toluene, reflux 2 h. (c) $CDCl_3$, rt, ~1.5 days, quantitative yield.

Isomerization of α,β-unsaturated carbonyl compounds is particularly readily promoted by protonation, which presumably enables involvement of an enolic resonance hybrid wherein the original double bond is weakened.[9] It appears that the electron rich nature of the unprotected indole nucleus is an important factor in the isomerization of murrayacarine, possibly due to the influence of additional resonance hybrids.

EXPERIMENTAL

NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C, respectively, using the residual solvent signal as reference. Coupling constants are given in Hz. The IR spectra were acquired using a FT-IR instrument. HRMS data were recorded by Dr. E. Nilsson, University of Lund, Sweden. Melting points were determined on a capillary melting point or a hot stage apparatus. All reagents were

commercially available and used as received. All solvents were purified by distillation or were of analytical grade. Chromatographic separations were performed on silica gel 60 (230–400 mesh).

3-[2-(Diethoxyphosphoryl)acetyl]indole-1-carboxylic acid *tert*-butyl ester (4)

To compound (**2**)[2] (4.00 g, 13.6 mmol) in dry THF (54 mL), di-*tert*-butyl dicarbonate (3.54 g, 16.2 mmol) and 4-(dimethylamino)pyridine (38 mg 0.14 mmoL) were added. The resulting mixture was stirred at rt for 51 h and was thereafter diluted with EtOAc (100 mL), washed with H_2O (2 × 50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. The oily residue was subjected to column chromatography using EtOAc/heptane (80/20) to give the title compound (5.02 g, 94%) as a colourless glass. IR (neat) 2979, 1748, 1662, 1545, 1454, 1383, 1360, 1242, 1151, 1093, 1028, 948, 829, 742 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.36–8.34 (m, 2H), 8.12–8.09 (m, 1H), 7.38–7.29 (m, 2H), 4.16–4.11 (m, 4H), 3.54 (d, J_{H-P} = 22.5, 2H), 1.68 (s, 9H), 1.31 (t, J = 7.2, 6H); ^{13}C NMR ($CDCl_3$) δ 186.9 (J_{C-P} = 6.5), 149.0, 135.6, 134.2, 127.4, 125.8, 124.6, 122.8, 120.3 (J_{C-P} = 2.1), 115.1, 85.7, 62.7 (J_{C-P} = 6.5), 40.3 (J_{C-P} = 129.5), 28.2, 16.4 (J_{C-P} = 6.3); HRMS (FAB+) *m/z* calcd for $C_{19}H_{27}NO_6P$ $[M + H]^+$ 396.1576, found 396.1583.

3-[(*Z*)-3-Methoxycarbonylbut-2-enoyl]indole-1-carboxylic acid *tert*-butyl ester (5)

A solution of compound (**4**) (1.54 g, 3.90 mmol) in dry toluene (7 mL) was added in small portions to a suspension of NaH (172 mg, 4.29 mmol, 60% dispersion in mineral oil) in dry toluene (3 mL). After the evolution of H_2 (g) had subsided, methyl pyruvate (0.35 mL, 3.90 mmol) was added and the resulting mixture was heated at reflux for 2 h. The reaction mixture was allowed to cool, diluted with EtOAc (20 mL) and transferred to a separatory funnel. The organic phase was washed with H_2O (20 mL), brine (20 mL) and dried over $MgSO_4$. The solvents were evaporated and the residue was purified by column chromatography using EtOAc/hexane (40/60) to give **5** (1.01 g, 76%) as a colourless glass. IR (neat) 2976, 1731, 1662, 1620, 1448, 1361, 1243, 1141, 1105, 748 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.64 (s, 1H), 8.28–8.24 (m, 1H), 8.10–8.07 (m, 1H), 7.42–7.35 (m, 2H), 7.20 (q, J = 1.6, 1H), 3.71 (s, 3H), 2.10 (d, J = 1.6, 3H), 1.67 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 184.4 (s), 169.8 (s), 148.5 (s), 142.8 (s), 135.0 (s), 133.8 (d), 127.0 (s), 126.7 (d), 125.6 (d), 124.3 (d), 122.0 (d), 119.4 (s), 114.9 (d), 85.5 (s), 51.9 (q), 27.5 (q), 20.0 (q); HRMS (FAB+) *m/z* calcd for $C_{19}H_{22}NO_5$ $[M + H]^+$ 344.1498, found 344.1501.

Murrayacarine (3a)

To a solution of compound (**5**) (470 mg, 1.37 mmol) in CH_2Cl_2 (20 mL) was added TFA (3.17 mL, 41.1 mmol) and the resulting solution was kept at rt for 20 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and transferred to a separatory funnel, washed with H_2O (20 mL), sat. aq. $NaHCO_3$ (20 mL) and

brine (20 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness. The residue was subjected to column chromatography, using EtOAc/hexane (70/30) to give murrayacarine (**3a**) (277 mg, 83%) as a slightly beige solid. Mp 149–150°C (lit.,[5] mp 146–148 °C, lit.,[6] mp 146 °C); IR (neat) 3335, 1719, 1649, 1578, 1519, 1416, 1251, 1227, 1152, 1119, 749, 717 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.08, (s, 1H), 8.42 (d, J = 3.2, 1H), 8.21–8.18 (m, 1H), 7.50–7.47 (m, 1H), 7.27–7.17 (m, 2H), 7.05 (q, J = 1.6, 1H), 3.69 (s, 3H), 2.07 (d, J = 1.6, 3H); ^{13}C NMR (DMSO-d_6) δ 183.1 (s), 170.3 (s), 140.9 (s), 136.8 (s), 134.7 (d), 127.2 (d), 125.5 (s), 123.2 (d), 121.9 (d), 121.5 (d), 116.6 (s), 112.2 (d), 51.7 (q), 20.1 (q); MS (ESI) *m/z* 244 $[M + H]^+$.

(*E*)-4-(1*H*-Indol-3-yl)-2-methyl-4-oxobut-2-enoic acid methyl ester (3b)

Murracyacarine (**3a**) (122 mg, 0.50 mmol) was dissolved in $CHCl_3$ (5 mL). Two drops of a saturated solution of HCl (g) in Et_2O was added to the solution, which immediately changed colour from colourless to bright red. After approximately 1 h at rt, the solution gradually turned yellow and crystals began to appear. The solvent was evaporated and the residue was filtered through a short column of silica gel, using EtOAc/hexane (70/30) to give the isomerized material (**3b**) (110 mg, 90%) as a yellow solid. Mp 180–181 °C; IR (neat) 3241, 1707, 1638, 1576, 1519, 1431, 1262, 1240, 1160, 1121, 754, 711 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.14 (s, 1H), 8.37 (s, 1H), 8.27–8.24 (m, 1H), 7.64 (q, J = 1.5, 1H), 7.51–7.48 (m, 1H), 7.28–7.19 (m, 2H), 3.79 (s, 3H), 2.18 (d, J = 1.5, 3H); ^{13}C NMR (DMSO-d_6) δ 185.9 (s), 167.9 (s), 137.0 (s), 136.8 (s), 135.0 (d), 133.1 (d), 125.3 (s), 123.3 (d), 122.1 (d), 121.4 (d), 117.7 (s), 112.3 (d), 52.3 (q), 14.3 (q); MS (ESI) *m/z* 244 $[M + H]^+$.

[2-(4-Methoxyphenyl)-2-oxoethyl]phosphonic acid diethyl ester (7)

A mixture of **6** (2.29 g, 10.0 mmol), triethyl phosphite (1.90 mL, 11.1 mmol) and Bu_4NI (10 mg) in MeCN (50 mL) was heated at reflux for 8 h. After cooling, the solvent was evaporated, and the residue was subjected to column chromatography initially using EtOAc/hexane (70/30) with increasing amounts of EtOAc, to give **7** (2.63 g, 92%) as a colourless glass; IR (neat) 2981, 1668, 1598, 1575, 1512, 1250, 1173, 1020, 957, 804, 566 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, J = 8.7, 2H), 7.27 (d, J = 0.6, 1H), 6.96 (d, J = 8.7, 2H), 4.18–4.09 (m, 4H), 3.87 (s, 3H), 3.62 (d, J = 22.7, 2H), 1.31 (t, J = 7.1, 6H); ^{13}C NMR ($CDCl_3$) δ 190.5 ($J_{C–P}$ = 6.3), 164.2, 131.7, 129.9 ($J_{C–P}$ = 1.8), 114.0, 62.8 ($J_{C–P}$ = 6.5), 55.7, 38.5 ($J_{C–P}$ = 128.8), 16.5 ($J_{C–P}$ = 8.6).

(*Z*)-4-(4-Methoxyphenyl)-2-methyl-4-oxobut-2-enoic acid methyl ester (8a)

Compound (**7**) (860 mg, 3.0 mmol) dissolved in dry toluene (7 mL) was added in small portions to a suspension of NaH (132 mg, 3.3 mmol, 60% dispersion in mineral oil) in dry toluene (3 mL). After the

evolution of H_2 (g) had subsided, methyl pyruvate (0.27 mL, 3.0 mmol) was added and the resulting mixture was heated at reflux for 2.5 h. The reaction mixture was allowed to cool, diluted with EtOAc (15 mL) and transferred to a separatory funnel. The organic phase was washed with H_2O (20 mL), brine (20 mL) and dried over $MgSO_4$. The solvents were evaporated and the residue was purified by column chromatography using hexane/EtOAc (60/40) to give **8b** (33 mg, 5%) followed by **8a** (459 mg, 65%), both as pale yellow oils. IR (neat) 2951, 1724, 1662, 1595, 1510, 1443, 1255, 1212, 1166, 1127, 1025, 831, 603 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.93–7.90 (m, 2H), 7.12 (q, J = 1.6, 1H), 7.07–7.04 (m, 2H), 3.85 (s, 3H), 3.59 (s, 3H), 2.08 (d, J = 1.6, 3H); ^{13}C NMR (DMSO-d_6) δ 188.8 (s), 168.7 (s), 163.4 (s), 140.5 (s), 130.7 (d), 129.5 (d), 129.3 (s), 114.1 (d), 55.6 (q), 51.8 (q), 19.7 (q); MS (ESI) *m/z* 235 $[M + H]^+$.

(*E*)-4-(4-Methoxyphenyl)-2-methyl-4-oxobut-2-enoic acid methyl ester (8b)

Compound (**8a**) was kept at rt in $CDCl_3$ until complete isomerization (~ 1.5 days) whereby the solution gradually became more yellow. The solvent was evaporated to give the product in quantitative yield as an yellow oil which solidified upon standing. IR (neat) 2952, 1725, 1655, 1597, 1571, 1425, 1261, 1238, 1173, 1111, 1020, 928, 838, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97–7.91 (m, 2H), 7.68 (q, J = 1.5, 1H), 6.97–6.91 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.15 (d, J = 1.5, 3H); ^{13}C NMR ($CDCl_3$) δ 191.3 (s), 168.2 (s), 164.2 (s), 139.4 (s), 132.8 (d), 131.3 (d), 130.7 (s), 114.2 (d), 55.7 (q), 52.7 (q), 14.9 (q).

ACKNOWLEDGEMENT

Mr. John Ogden, Varian Inc., is gratefully acknowledged for acquisition of the low resolution MS data.

REFERENCES

1. J. Slätt, I. Romero, and J. Bergman, *Synthesis*, 2004, 2760.
2. J. Slätt, T. Janosik, N. Wahlström, and J. Bergman, *J. Heterocycl. Chem.*, 2005, **42**, 141.
3. P. Craniadès, *J. Recherches Centre Natl. Recherche Sci.*, 1956, **35**, 119 [*Chem. Abstr.*, 1957, **51**, 27226].
4. A. Ryglowski and P. Kafarski, *Tetrahedron*, 1996, **52**, 10685.
5. S.-T. Wu, M.-J. Liou, T.-T. Jong, Y.-J. Chen, and J.-S. Lai, *Phytochemistry*, 1989, **28**, 2873.
6. A. Boumendjel, J. M. Nuzillard, and G. Massiot, *Bull. Soc. Chim. Fr.*, 1990, **127**, 645.
7. C. Yuan and R. Xie, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1994, **90**, 47.
8. K. Bowden and M. P. Henry, *J. Chem. Soc. (B)*, 1971, 156.
9. E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, John Wiley & Sons; New York, 1994, p. 580.