Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 2053–2056

A facile three-step synthesis of (±)-crispine A via an acyliminium ion cyclisation

Frank D. King*,†

Neurology and GI CEDD, GlaxoSmithKline, New Frontiers Science Park (North), Third Avenue, Harlow, Essex CM19 5AW, UK

Received 6 October 2006; revised 29 November 2006; accepted 14 December 2006
Available online 17 December 2006

Abstract—A high yielding cyclisation of the readily available *N*-(4,4-diethoxybutyl)-2-(3,4-dimethoxyphenyl)acetamide to 8,9-bis(methyloxy)-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one is described. The latter can be reduced with either AlH_3 or BH_3 to (±)-crispine A in an overall yield of 55%.

1. Introduction

Over the past 30 years, cyclic acyliminium ions have provided a fertile area for the synthesis of alkaloids and other substituted azacycles.[1] The most common method of synthesising the cyclic acyliminium ions is by acid treatment of α-alkoxyamides, in turn prepared either by the reduction of imides or by the anodic oxidation of amides. Some time ago we published the in situ generation of cyclic iminium ions by the intramolecular condensation of an aminoaldehyde diethylacetal to give a facile, one-pot synthesis of indolizidines and quinolizidines.[2,3] However, in the intervening time, this simple generation of iminium ions from readily available starting materials has been little explored. In this paper, we apply this methodology to the generation of a cyclic acyliminium ion to give a simple, high yielding, three-step synthesis of the alkaloid (±)-crispine A, **1**, from the commercially available 4-aminobutyraldehyde diethylacetal (Scheme 1).[4] Crispine A was selected as a test of the methodology, as it had been reported that the anodic oxidation of phenacylpyrrolidines with a *p*-methoxy substituent oxidised on the benzylic position, rather than the amide α-position.[5] In addition, there has recently been an upsurge of interest in the synthesis of crispine A due to the potential use of the close analogue, crispine B, in oncology.[6]

2. Results and discussion

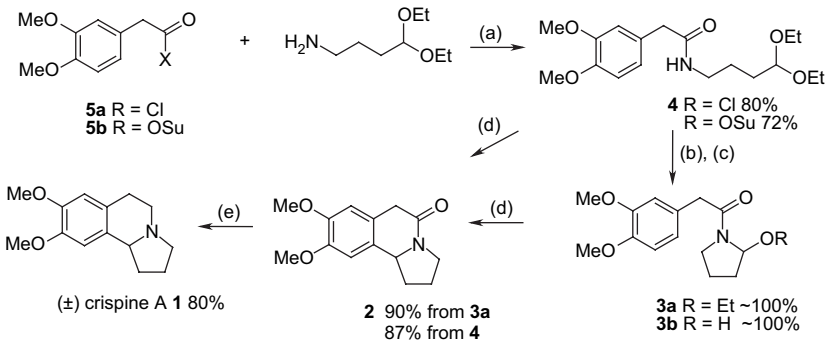
The retrosynthetic strategy was to aim for the lactam **2**, which should be obtainable from the acid-catalysed cyclisation of α-ethoxyamide **3a**. $TiCl_4$-mediated[5] cyclisations of α-methoxyamides have been previously reported, but no optimisation of this cyclisation had been undertaken.[7] It was anticipated that **3a** should be obtainable from the amido-aldehyde diethylacetal **4**.

Compound **4** was readily prepared from either 3,4-dimethoxyphenacylchloride **5a**, or the hydroxysuccinimide (HOSu) ester **5b**. The acetal **4** was found to be extremely acid sensitive. Attempts to wash out any excess base from reaction mixtures in either ethyl acetate or dichloromethane with either 2 M HCl or 1 M H_2SO_4 resulted in partial cleavage of the acetal group. The crude **4** solidified on drying under high vacuum and a portion of this solid was used to seed the recrystallisation from Et_2O/hexane. A slightly less pure product was obtained from **5a**, although in higher yield (80% vs 72%), as the coloured impurities in the commercially available material carried through into the product, even after recrystallisation.

All attempts to convert **4** directly into **3a** via acid catalysis were unsuccessful. However, **4** could be converted to **3b** in effectively quantitative yield by rapidly stirring an Et_2O solution of **4** with 2 M HCl. Surprisingly, much of **3b** was extracted into the 2 M HCl solution and advantage was taken of this for purification. The Et_2O layer as diluted with an equal volume of hexane, and **3b** was extracted into H_2O. The combined aqueous extracts were then basified with solid K_2CO_3 and **3b** back-extracted into CH_2Cl_2. Consistent with the literature on related *N*-acyl 2-hydroxypyrrolidines, the NMR spectrum of **3b** indicates that it exists in equilibrium with about 10% of the ring-opened amido-aldehyde, which probably prevents crystallisation. It was noted that **3b** is also acid-labile, with the $CDCl_3$ NMR solution decomposing over a period of few weeks, presumably due to the presence of a small amount of acid. Compound **3b** has also been reported

Keywords: (±)-Crispine A; Acyliminium; Cyclisation.
* Tel.: +44 (0)207 6794583; e-mail: fd.king@btinternet.com
† Present address: Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.12.041



Scheme 1. (a) Either X=Cl, 1.1 equiv Et_3N/CH_2Cl_2 or X=OSu, EtOAc; (b) 2 M HCl, Et_2O for 30 min, add hexane, extract product into H_2O, then K_2CO_3, CH_2Cl_2 (see text); (c) 0.1 equiv TFA, 3 Å molecular sieves, Et_2O; (d) 1.5 equiv $AlCl_3$, CH_2Cl_2 2 h at rt and (e) LAH, 0.5 equiv concd H_2SO_4, THF.

as a non-isolated intermediate, prepared by ozonolysis of an olefin and treatment with dimethyl sulfide. Subsequent cyclisation with formic acid gave **2** in 60% yield.[8] Treatment of our isolated **3b** with formic acid did, indeed, give a cyclic product. LC/MS of the crude product indicated ~25% of a dimer, which probably prevented efficient crystallisation. However, column chromatography (SiO_2; CH_2Cl_2/2% MeOH) resulted in the isolation of **2** as a crystalline solid with the quoted literature yield.

The α-ethoxyamide **3a** was obtained from **3b** in effectively quantitative yield by treatment with a catalytic quantity of acid in the presence of EtOH and 3 Å molecular sieves to capture the water. The ^{1}H NMR spectrum of **3a** showed two equal triplets for the ethyl CH_3, each integrating for 1.5 protons, and two doublets for the C*H*OEt proton, each integrating for 0.5 protons, consistent with a restricted rotation of the amide bond with a 1:1 ratio of rotamers. The ^{13}C spectrum similarly showed a doubling of most of the signals. Various acid-catalysed cyclisation conditions of **3a** were investigated. Most Brőnsted acids attempted (TFA, TFMSA, acetic acid, H_2SO_4 and HCl) did not give the expected cyclisation, but a product resulting from dimerisation of the acyliminium ion was obtained. However, the Lewis acids $AlCl_3$ and $TiCl_4$ were both successful. More than 1 equiv of Lewis acid was required for successful cyclisation. Optimisation with $AlCl_3$ showed that more than 2 equiv resulted in the formation of an oily precipitate and, finally, a cyclic product contaminated with demethylated phenol product (which could be removed with a 2 M NaOH wash); 1.5–2 equiv consistently gave a relatively clean reaction, with the product being obtained in >95% purity from a simple Et_2O trituration of the worked-up crude product in ~90% yield. $TiCl_4$ gave similar results and it was noted that the dropwise addition of a CH_2Cl_2 solution of $TiCl_4$ could be made at 0 °C, rather than the reported −78 °C.[5] Also 1.5 equiv was found to be as effective as the reported 2.8 equiv.

Having confirmed the cyclisation of **3a**, the Lewis-acid mediated cyclisation was attempted directly on **4**.[9] Surprisingly the cyclisation of **4** was as effective as that of **3a**. Optimisation of the cyclisation of **4** using $AlCl_3$ gave similar results to **3a**. Using more than 2 equiv again resulted in demethylation. More than 1 equiv was required, but amounts close to 1 equiv again gave a much slower, less clean reaction. Approximately 1.5 equiv was highly effective, with no purification of the product required other than Et_2O trituration. In addition, formic acid cyclisation of **4** afforded **2** in exactly the same manner as with **3a**.

Finally, the reduction of **2** to **1** was investigated. Using LAH, the addition of **2** gave a rapid evolution of gas, presumably hydrogen, and subsequent reduction was slow, with multiple products being formed. Presumably under the basic conditions, the enolate was rapidly formed and deactivated the system to reduction. Diborane had previously been used on closely related lactams.[10] Following this reported procedure, a 77% yield of **1** was obtained, but refluxing acid cleavage of the borane adduct of the product was required. We had previously used alane, formed from adding ½ molar equivalents of concd H_2SO_4 to LAH in THF,[11] for the reduction of oxime to avoid anion formation. Reduction of **2** with alane gave a high yield (80%) of **1**, but with a much simpler aqueous base treatment of the reaction mixture.

In conclusion, a facile, three step, high yielding (55% overall) synthesis of (±)-crispine A via an acyliminium ion is described. The scope of this acyliminium ion formation is being further investigated.

3. Experimental

3.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer using Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on a Bruker AMX300 spectrometer. All solvents and reagents were of commercial grade and used without purification. All solvent evaporations were carried out under reduced pressure. All compounds and crude reaction mixtures were analysed by LC/MS using an HP1050 LC system operating under reverse phase using a 3.3 cm×4.6 mm ID, 3 μm ABZ+PLUS column with a 5 min run, starting with 0.1% formic acid+10 mM ammonium acetate 95% and finishing with acetonitrile+0.05% formic acid, with a UV detection range of 215–330 nm. MS detection used a Waters ZQ mass spectrometer and all products were >98% pure. HRMS measurements were performed with a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer, equipped with a Z-spray interface and the elemental composition was calculated using MassLynx v4.0.

3.1.1. Synthesis of *N*-(4,4-diethoxybutyl)-2-(3,4-dimethoxyphenyl)acetamide (4). *Method (A)*. DCC (7.3 g, 0.035 mol) was added in one portion to a stirred solution of (3,4-dimethoxyphenyl)acetic acid (6.9 g, 0.035 mol) and HOSu (4.2 g, 0.036 mol) in EtOAc (250 mL), at ambient temperatures under argon. After stirring for 3 h, a solution of 4-aminobutyraldehyde diethylacetal (ex. Aldrich, 90% pure) (6 mL, 0.035 mol) in EtOAc (25 mL) was added in one portion. The reaction mixture was stirred over night. Et_2O (200 mL) was then added and the precipitated DCU collected by filtration, and washed with Et_2O (100 mL). The combined filtrates were washed with 2 M NaOH (50 mL), H_2O (50 mL) and brine (50 mL), and then dried ($MgSO_4$), filtered and concentrated by rotary evaporation. On further drying on a high vacuum line, the oil solidified. The solid was triturated, initially with Et_2O (50 mL), and subsequently hexane (150 mL) was added in portion. The white solid was collected, washed with hexane (100 mL) and dried to give **4** as a white crystalline solid (8.5 g, 72%); mp 56–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, J=7.2 Hz, 6H), 1.49–1.60 (m, 4H), 3.23 (m, 2H), 3.40–3.48 (m, 2H), 3.51 (s, 2H), 3.55–3.63 (m, 2H), 3.88 (s, 6H), 4.43 (t, J=5.2 Hz, 1H), 5.53 (br s, 1H), 6.77 (s, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H). ^{13}C NMR+DEPT (75 MHz, $CDCl_3$) δ=12.27 (CH_3), 24.51 (CH_2), 30.79 (CH_2), 39.25 (CH_2), 43.37 (CH_2), 55.86 (CH_2), 61.09 (CH_3), 61.26 (CH_3), 102.49 (CH), 111.50 (CH), 112.42 (CH), 121.56 (C), 127.46 (C), 148.26 (C), 149.23 (C), 171.31 (C). HRMS: calcd for $C_{18}H_{29}NO_5Na$ $[M+Na]^+$ 362.1943, found 362.1949. The mother liquors from the crystallisation contained **4** (~2 g), which could be used for the subsequent hydrolysis reaction.

Method (B). A solution of (3,4-dimethoxyphenyl)acetyl chloride (ex. Aldrich) (10 g, 0.047 mol) in anhydrous CH_2Cl_2 (20 mL) was added, dropwise, over 20 min to stirred solution of 4-aminobutyraldehyde diethylacetal (7.8 mL, 0.045 mol) and Et_3N (6.5 mL, 0.047 mol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C. The reaction mixture was stirred and allowed to warm to ambient temperatures over 2 h. The CH_2Cl_2 was removed by rotary evaporation and replaced with Et_2O (300 mL). After washing with H_2O (2×50 mL) and brine (50 mL), the separated organic layer was dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The resultant oil was re-dissolved in Et_2O (200 mL) and hexane added until the mixture was slightly cloudy. A seed crystal from Method (A) was added to initiate crystallisation. Additional hexane was added to approximately 1:1 Et_2O/hexane and the solid collected, washed with hexane (2×100 mL) and dried to give **4** (12.2 g, 80%) as a beige-coloured solid.

3.1.2. 1-{[3,4-Bis(methyloxy)phenyl]acetyl}-2-(ethyloxy)-pyrrolidine (3a). A solution of **4** (8.4 g, 0.025 mol), dissolved in EtOAc (20 mL) and Et_2O (100 mL) was stirred vigorously at ambient temperatures with aqueous 2 M HCl (50 mL) for 1 h. Hexane (100 mL) was then added and the aqueous layer separated. The organics were washed with H_2O (2×50 mL) and the combined aqueous extracts basified with solid K_2CO_3. The product (**3b**) was extracted into CH_2Cl_2 (3×100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **3b** as an oil in equilibrium with ~10% of the amidoaldehyde (6.7 g, ~100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.7–2.2 (m, 4H), 3.59 (s, 2H), 3.87 (br s, 6H), 4.12 (br s, 1H), 5.66 (br s, 1H), 6.77–6.90 (m, 3H), 9.74 (br s, 0.1H). ^{13}C NMR+DEPT (75 MHz, $CDCl_3$) δ=23.23 (CH_2), 32.04 (CH_2), 41.63 (CH_2), 46.67 (CH_2), 55.87 (CH_3), 55.90 (CH_3), 81.90 (CH), 111.24 (CH), 112.16 (CH), 121.14 (CH), 126.55 (C), 148.04 (C), 149.07 (C), 171.70 (C). The crude **3b** (6.7 g) was dissolved in CH_2Cl_2 (150 mL) and stirred at ambient temperatures with EtOH (4 mL), 3 Å molecular sieves (25 g) and TFA (0.5 mL) for 3.5 h. Et_3N (1 mL) was added and the reaction mixture filtered through a pad of Kieselghur, washing the collected solids with CH_2Cl_2 (2×100 mL). The combined organics were washed with H_2O (50 mL) and brine (50 mL), and dried ($MgSO_4$). Concentration of the filtered organics under reduced pressure gave **3a** as a colourless oil (6.9 g, ~100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J=7.2 Hz, 1.5H), 1.27 (t, J=7.2 Hz, 1.5H), 1.64–2.21 (m, 4H), 3.31–3.72 (m, 6H), 3.86 (s, 6H), 5.10 (d, J=4.8 Hz, 0.5H), 5.55 (d, J=4.8 Hz, 0.5H), 6.77–6.88 (m, 3H). ^{13}C NMR+DEPT (75 MHz, $CDCl_3$) δ=15.37 (CH_3), 15.44 (CH_3), 21.06 (CH_2), 23.08 (CH_2), 31.55 (CH_2), 31.88 (CH_2), 40.70 (CH_2), 41.76 (CH_2), 45.86 (CH_2), 46.31 (CH_2), 55.85 (CH_3), 55.91 (CH_3), 62.08 (CH_2), 64.46 (CH_2), 85.94 (CH), 87.51 (CH), 111.18 (CH), 111.23 (CH), 112.19 (CH), 112.33 (CH), 121.15 (CH), 121.30 (CH), 127.04 (C), 127.66 (C), 147.92 (C), 148.97 (C), 149.03 (C), 171.02 (C), 171.32 (C). HRMS: calcd for $C_{16}H_{23}NO_4Na$ $[M+Na]^+$ 316.1525, found 316.1530.

3.1.3. 8,9-Bis(methyloxy)-2,3,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5(1*H*)-one (2). *Method (A)*. $AlCl_3$ (3.5 g, 0.026 mol) was added to a stirred solution of **3a** (5.0 g, 0.017 mol) in dry CH_2Cl_2 (100 mL) at ambient temperatures under argon. After 2 h, ice (50 g) was added and the reaction stirred for a further 15 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo. Trituration with Et_2O (50 mL) gave **2** (3.8 g, 90%); mp 164–165 °C (lit.[8] 163–165 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83–1.93 (m, 1H), 1.96–2.09 (m 1H), 2.12–2.19 (m, 1H), 2.58–2.64 (m, 1H), 3.46–3.71 (m, 4H), 3.88 (s, 3H), 3.89 (s, 3H), 4.57–4.62 (m, 1H), 6.67 (s, 1H), 6.68 (s, 1H). ^{13}C NMR+DEPT (75 MHz, $CDCl_3$) δ=23.09 (CH_2), 31.81 (CH_2), 38.14 (CH_2), 44.72 (CH_2), 56.06 (CH_3), 56.19 (CH_3), 59.56 (CH), 107.69 (CH), 111.27 (CH), 124.93 (C), 127.99 (C), 147.88 (C), 148.56 (C), 167.60 (C). HRMS: calcd for $C_{14}H_{17}NO_3$ $[MH]^+$ 248.1287, found 248.1291.

Method (B). The method was identical to Method (A) except that **4** (1.0 g, 0.003 mol) was used to give **2** (0.65 g, 87%), identical to that obtained from Method (A).

3.1.4. 8,9-Bis(methyloxy)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline [(±)-crispine A] (1). Concd H_2SO_4 (0.13 mL, 0.0025 mol) was added, dropwise over 5 min, to a stirred solution of LAH (5 mL of a 1 M solution, 0.005 mol) at 0 °C under argon. After stirring at 0 °C for 15 min, **2** (0.33 g, 0.0013 mol) was added in one portion and the reaction stirred at room temperature for 14 h. The reaction mixture was then cooled to 0 °C and 2 N NaOH (0.6 mL) was then carefully added and the reaction mixture stirred for 15 min. The solid was collected and washed with

Et_2O (2×30 mL). The combined organics were then evaporated in vacuo and the residue purified by column chromatography (Al_2O_3, CH_2Cl_2/2% MeOH). Crystallisation from hexane afforded the pure **1** (0.25 g, 80%); mp 88–89 °C (lit.[12] 88–89 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63–1.98 (m, 3H), 2.28–2.36 (m, 1H), 2.50–2.76 (m, 3H), 2.99–3.11 (m, 2H), 3.16–3.21 (m, 1H), 3.41 (br t, J=8 Hz), 3.83 (s, 3H), 3.84 (s, 3H), 6.57 (s, 1H), 6.61 (s, 1H).

Acknowledgements

I am grateful to the GSK Neurology and GI CEDD for funding this research, to Prof. S. Caddick for the recent use of his laboratory and to many of my colleagues for sharing my enthusiasm.

References and notes

1. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856 and references therein.
2. King, F. D. *Tetrahedron Lett.* **1983**, *24*, 3281–3282.
3. King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 447–453.
4. For recent syntheses, see: Knőlker, H.-J.; Agarwal, S. *Tetrahedron Lett.* **2005**, *46*, 1173–1175 and Meyer, N.; Opatz, T. *Eur. J. Org. Chem.* **2006**, 3997–4002.
5. Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058–1067.
6. Szawkało, J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Drabowicz, J.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 3619–3621 and references therein; Kapat, A.; Sen, S. K.; Baskaran, S. Annual IIT Madras Chemistry Symposium; July 12–13, 2006; 40 p; Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795–6798.
7. Moeller, K. D., personal communication.
8. Kano, S.; Yuasa, Y.; Shibuya, S. *Synth. Commun.* **1985**, *15*, 883–889.
9. For a similar reaction on solid phase, see: Veerman, J. J. N.; Klein, J.; Aben, R. W. M.; Scheeren, H. W.; Kruse, C. G.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J Org. Chem.* **2002**, 3133–3139.
10. Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433–1454.
11. King, F. D.; Martin, R. T. *Tetrahedron Lett.* **1991**, *32*, 2281–2284.
12. Bremner, J. B. *Aust. J. Chem.* **1984**, *37*, 1203–1215.