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Synthesis of 11,12-dimethoxy-9-p-toluene sulphonyl-6,7,8,9-tetrahydro-5H-benzo[2,3]azepino[5,4-c]quinolin-5-one using MCM-41(H)

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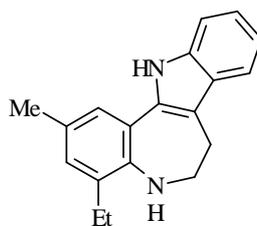
ABSTRACT

The development in the benzazepine field for medicinal interests, attention has been paid almost exclusively to substituent changes, with the adjustment of open chain and cyclic groups attached to both the aromatic and the azepine ring. In some instances the benzene ring has been replaced with other aromatic ring systems, e.g. Indoles^{1,2} which is particularly true in the benzodiazepine field. Herein, we report the New Synthesis of 11,12-dimethoxy-9-(4-phenylsulphonyl)-6,7,8,9-tetrahydro-5H-benzo[2,3]azepino[5,4-c]quinolin-5-one.

Keywords: 11,12-dimethoxy-9-p-toluene sulphonyl-6,7,8,9-tetrahydro-5H- benzo [2,3]azepino[5,4-c]quinolin-5-one, methyl-4,5-dimethoxy anthranilate, MCM-41(H), azepine ring, high yields conditions.

INTRODUCTION

Due to the upsurge in the development in the benzazepine field for medicinal interests, attention has been paid almost exclusively to substituent changes, with the adjustment of open chain and cyclic groups attached to both the aromatic and the azepine ring. In some instances the benzene ring has been replaced with other aromatic ring systems, e.g. Indoles^{1,2} which is particularly true in the benzodiazepine field. However, little attention appears to have been fused heterocyclic derivatives of benzazepines and only a limited number of such compounds have been recorded in the literature. Macphillamy³ when working on the synthesis of some dehydrogenated products from the alkaloids of Tabernanthe Iboga, prepared the indolo [3,2-d]-1-benzazepine (1). This was achieved, not by Fischer indolisation of the appropriate ketone, but by a lengthy stepwise-procedure, ending with cyclization to form the azepine ring as the final stage.



(1)
Figure 1

MATERIALS AND METHODS

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), ¹H and ¹³C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-*d*₆ and CDCl₃ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up.

Preparation of 4,5-Dimethoxy-2-nitro benzoic acid (2)

Veratraldehyde (7 g) was nitrated as described in the literature⁵¹ except that concentrated nitric acid (30 mL) was used and after the first reaction was conducted at 20°C, the reaction vessel (foil covered) was kept at 35-40°C for 6 hr and cooled. The acidic material (6.1 g) was the desired material. m.p. 187-190°C (lit⁵², 189-191°C). The yellow neutral material (4 g) was 3,4-dinitro veratrole, m.p. 129°C.

Preparation of methyl 2-nitro-4,5-dimethoxy benzoate (3)

The above acid (10.1 g) and phosphorous pentachloride (11 g) were stirred and heated together at 90°C for 1.5 h. After removal of phosphoryl chloride in vacuo, the reaction mixture was cooled (ice) while dry methanol (excess) was added with stirring. The usual work-up gave the product (8 g). m.p. 141-145°C (lit⁵³ 144-145°C).

Preparation of methyl 2-amino-4,5-dimethoxy benzoate (4)

The nitro-ester (8 g) from above was hydrogenated in methanol (90 ml) using platinum oxide (0.28 g). After the uptake of hydrogen (2.5 L) ceased, the usual work-up gave product (6 g) sufficiently pure for most purposes. Recrystallisation from methanol gave material, m.p. 130°C. (lit.,⁵⁴ m.p. 133°C). The N-tosyl derivative had m.p. 128°C.

Preparation of ethyl-N-p-tolylsulphonyl-4-(4,5-dimethoxy-2-methoxy carbonyl anilino) butyrate (8)

Methyl 2-(*N*-*p*-tolylsulphonylamino-4,5-dimethoxy benzoate (4) and anhydrous potassium carbonate (2.3 g) were vigorously stirred at 140°C while ethyl γ -bromobutyrate (3.28 g) was added over 0.5 h. After a further 20 h at 130°C the reaction was worked⁵⁵ up to give the product (6 g) pure enough for cyclisation. Chromatography on silica gel and recrystallisation from methanol gave colourless needles. m.p. 78-79°C.

Preparation of 4-ethoxy carbonyl-7,8-dimethoxy-1,2,3,4-tetrahydro-1-*p*-toluene sulphonyl-1-benzazepin-5-one (9)

The foregoing ester (5 g) was cyclised using potassium-*t*-butoxide in toluene as previously described. The usual work-up gave product (3.5 g) which could be conveniently used. Purification by chromatography on silica gel and crystallisation from methanol gave material, m.p. 139-140°C (Lit⁵⁶, m.p. 140°C). ¹H NMR (CDCl₃): δ 1.40 (t, 3H, -CH₃), 1.61-1.82 (m, 2H, -CH₂-), 2.25 (t, 1H, -CH-), 2.41 (s, 3H, Ar-CH₃), 3.95 (q, 2H, -OCH₂), 3.98 (s, 3H, -OCH₃), 3.99 (s, 3H, -OCH₃), 4.15 (t, 2H, -NCH₂-), 6.90 (s, 1H, Ar-H₆), 7.25 (s, 1H, Ar-H₉), 7.19 (d, 2H, Ar-H_a, 9.3 Hz) and 7.39 (d, 2H, Ar-H_b, 9.3 Hz). Anal. Cald. for C₂₂H₂₅NO₇S: C, 59.05; H, 5.65; N, 3.15%. Found: C, 59.3; H, 5.85; N, 3.35%.

Preparation of 7,8-dimethoxy-5-oxo-1-*p*-toluene sulphonyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-4-carboxylic acid (10)

Ethoxy carbonyl compound was hydrolysed, m.p. >298 °C (dec.). IR (KBr): ν 3304 (-OH), 2927, 2857, 1678 (C=O), 1596, 1151, 1461, 1341, 1277, 1157, 1018, 973, 882, 599, 545 cm⁻¹.

Preparation of 2,3,4,5-tetrahydro-7,8-dimethoxy-1-*p*-toluene sulphonyl-1-benzazepin-4-benzamide (11)

A solution of **10** (0.01 mole) and thionylchloride (0.02 mole) was refluxed on a water-bath for 3 h, excess thionylchloride was removed by distillation and the resultant acid chloride taken in dry benzene. This was added dropwise to a cooled (0 °C) and stirred solution of aniline (0.01 mole) and pyridine (0.02 mole) in dry benzene. After 1 h, the reaction mixture was poured over crushed ice. The solid separated was filtered, washed successively with ice-cold dil. HCl (5%), water and sodium bicarbonate (10%) solution. It was purified by column chromatography over silica gel using pet-ether-chloroform (7:3) as eluent afforded benzamide **11** in 50% yield, m.p. 298°C (dec.). IR (KBr): ν 3310 (-OH), 1665 (-NH-CO-) cm⁻¹. ¹H NMR (CDCl₃ + DMSO-*d*₆): δ 2.21 (s, 3H, Ar-CH₃), 3.22 (m, 2H, -CH₂-), 3.85 (s, 6H, 2 x -OCH₃), 4.88 (m, 1H, -COCH-), 4.38 (t, 2H, -NCH₂-), 6.88-7.26 (m,

1H, Ar-H), 8.85 (brs, 1H, -NH). MS : m/z = 494 + H (M⁺), 480, 388, 217 (100%), 189, 158, 129, 103. Anal. Cald. for C₂₆H₂₆N₂O₆S : C, 63.14; H, 5.29; N, 5.66%. Found: C, 63.18; H, 5.30; N, 5.68%.

Preparation of 11,12-dimethoxy-9-p-toluene sulphonyl-6,7,8,9-tetrahydro-5H-benzo[2,3]azepino[5,4-c]quinolin-5-one (12)

A mixture of **11** (3 mmol) and freshly prepared polyphosphoric acid (6.0 g) was heated in an oil-bath for 5 h at 100 °C, cooled and poured on to crushed ice. The solid separated was filtered, washed with water and sodium bicarbonate solution (10%). It was purified by column chromatography over silica gel using pet. ether-chloroform (4:6) as eluent to give azepino quinoline **12**. Yield 43%, m.p. 198-201. IR (KBr): ν 3250 (-OH), 1685 (-NH-CO-) cm⁻¹. ¹H NMR (CDCl₃): δ 2.40 (s, 3H, Ar-CH₃), 2.85 (t, 2H, -CH₂-), 3.58 (s, 3H, -OCH₃), 3.70 (s, 3H, -OCH₃), 4.20 (t, 2H, -NCH₂-), 7.08-7.62 (m, 10H, Ar-H), 8.65 (brs, 1H, -NH). MS : m/z = 476 + H (M⁺), 459, 304, 299, 203, 177 (100%), 147, 108. Anal. Cald. for C₂₆H₂₄N₂O₅S : C, 65.53; H, 5.07; N, 5.87%. Found: C, 65.55; H, 5.00; N, 5.88%.

Preparation of 2,3,4,5-tetrahydro-7,8-dimethoxy-1-p-toluene sulphonyl-1-benzazepin-5-one (14)

The previously described β -oxo-ester (**9**, 6.2 g), acetic acid (38 mL), ethanol (12.5 mL) water (6 mL) and concentrated hydrochloric acid (6 mL) were refluxed together for 48 h work-up as usual followed by chromatography on alumina (benzene elution) and recrystallisation from ethanol yielded prisms, m.p. 143-144°C (Lit⁵⁷, m.p.142-144°C). IR (KBr): ν 2940, 2865, 1678, 1596, 1511, 1460, 1341, 1276, 1156, 972, 880, 597, 543 cm⁻¹. ¹H NMR (CDCl₃): δ 1.82-2.00 (m, 2H, -CH₂-), 2.12-2.23 (t, 2H, -COCH₂), 2.45 (s, 3H, Ar-CH₃), 3.80-3.89 (t, 2H, -NCH₂-), 3.90 (s, 6H, 2 x -OCH₃), 6.98 (s, 1H, Ar-H₆), 7.19 (s, 1H, Ar-H₉), 7.25 (d, 2H, J=9.3 Hz, Ar-H_a), 7.55 (d, 2H, J=9.3 Hz, Ar-H_b). ¹³C NMR (CDCl₃): δ 20.1 (C₇¹), 23.0 (C₃), 29.0 (C₄), 38.0 (C₂), 49.0 (OC) 55.1 (OC), 110.1 (C₉), 112.0 (C₆), 126.1 (C₂¹+C₆¹), 128 (C₁¹), 129.9 (C₃¹+C₅¹), 132.1 (C₄¹), 138.9 (C₁₀), 143.0 (C₁₁), 148.0 (C₇), 152.0 (C₈), 199.5 (C₅). MS : m/z = 375 (M⁺), 230, 220, 192 (100%), 166, 141, 104, 91, 65. Anal. Cald. for C₁₉H₂₁NO₅S : C, 60.85; H, 5.65; N, 3.75. Found: C, 61.1; H, 5.8; N, 3.8%.

Preparation of 5-chloro-7,8-dimethoxy-1-p-toluene sulphonyl-2,3, -dihydro-1H-benzo[b]azepin-4-carbaldehyde (15)

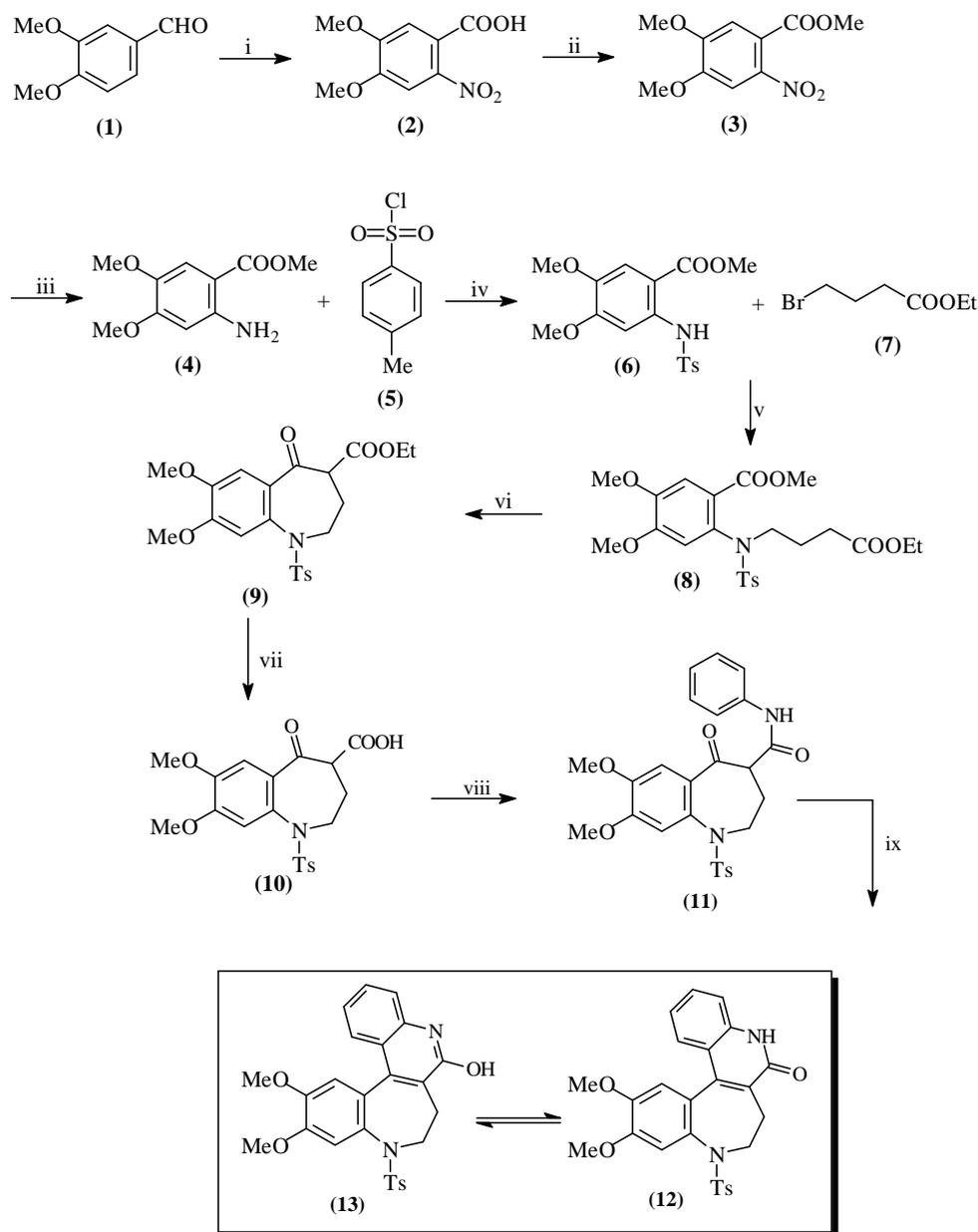
Phosphoryl chloride (0.75 g, 5 mmol) was added dropwise with stirring and cooling to dry dimethyl formamide (10 mL) at such a rate that the temperature did not exceed 5 °C. 2,3,4,5-tetrahydro-7,8-dimethoxy-1-p-toluene sulphonyl-1-benzazepin-5-one (**14**, 0.85 g, 5 mmol) was added dropwise to the resulting solution at 0-5 °C and the mixture was stirred for 30 min. at 0 °C and for 1.5 h, at 80 °C, then poured into cold aqueous sodium acetate (20%, w/v, 25 mL). Extraction with ether, drying over Na₂SO₄, and removal of the solvent under vacuum afforded benzoazepin carbaldehyde **15** as pale yellow solid. Yield 85%, m.p. 161-162 °C. IR (KBr): ν 1668 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 2.38 (s, 3H, Ar-CH₃), 2.80-2.91 (t, 2H, -CH₂-), 3.80 (s, 3H, -OCH₃), 3.98 (s, 3H, -OCH₃), 4.10-4.18 (t, 2H, -NCH₂-), 6.81 (s, 1H, Ar-H), 7.09 (s, 1H, Ar-H), 7.18 (d, 2H, J=8.65 Hz, Ar-H), 7.37 (d, 2H, J=8.66 Hz, Ar-H), 9.58 (s, 1H, -CHO).

Preparation of 7,8-dimethoxy-5-oxo-1-p-toluene sulphonyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-4-carbaldehyde (16)

To a stirred solution of 5-chloro-7,8-dimethoxy-1-p-toluene sulphonyl-2,3, -dihydro-1H-benzo[b]azepin-4-carbaldehyde (**15**, 10 mmol), in 4M HCl (20 mL) was refluxed for 1 h, upon usual workup gave 7,8-dimethoxy-5-oxo-1-p-toluene sulphonyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-4-carboxylic acid (**16**) in 85% yield, this was converted into corresponding carboxylic acid without any purification.

Preparation of 7,8-dimethoxy-5-oxo-1-p-toluene sulphonyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-4-carboxylic acid (10) from 16.

To a stirred solution of 7,8-dimethoxy-5-oxo-1-p-toluene sulphonyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-4-carbaldehyde (**16**, 10 mmol), in water (40 mL) and alkaline KMnO₄ (0.15 mole), 105 NaOH was added slowly. The flask was surrounded by hot water and stirring continued for 30 min. Thereafter, the reaction mixture was filtered. The filtrate on neutralization with aq. HCl (v/v) gave the corresponding carboxylic acid in 68% yield.



Reagents : (i) Conc. HNO_3 ; (ii) $MeOH, PCl_5, 90^\circ C, 1.5 h$; (iii) $Platinum\ oxide / H_2, MeOH$; (iv) $Dry\ pyridine, 24\ hr$; (v) NaH, DMF ; (vi) $NaH, EtOH$; (vii) $AcOH, H_2O, HCl, 48\ h, reflux$; (viii) $SOCl_2, aniline/pyridine, 0^\circ C$; (ix) $MCM-41(H), 3\ h, 100^\circ C$.

Preparation of 11,12-dimethoxy-9-p-toluene sulphonyl-6,7,8,9-tetrahydro-5H-benzo[2,3]azepino[5,4-c]quinolin-5-one (12) using MCM-41(H).

A mixture of **11** (3 mmol) in ethanol (20 mL) and MCM-41(H) (10 mg) was heated in an oil-bath for 6 h at $100^\circ C$, cooled, diluted with ethanol, separated MCM-41(H). Ethanol layer was removed by under reduced pressure and gummy material was poured on to crushed ice. The solid separated was filtered, washed with water and sodium bicarbonate solution (10%). It was purified by column chromatography over silica gel using pet. ether-chloroform (4:6) as eluent to give azepino quinoline **12**. Yield 50%,

RESULTS AND DISCUSSION

As a part of the ongoing research program Herein, we report the New Synthesis of 11,12-dimethoxy-9-(4-phenylsulphonyl)-6,7,8,9-tetrahydro-5H-benzo[2,3]azepino[5,4-c]quinolin-5-one.

The key intermediate (**9**) was prepared by the following route (**Scheme-1**). Part of the synthesis was achieved by application of published procedure⁵¹ to methyl-4,5-dimethoxy anthranilate (**4**). For moderate-scale preparations of latter, modifications were required for methods in the literature.

Thus veratraldehyde (**1**) was nitrated in the dark, to give 4,5-dimethoxy-2-nitro benzaldehyde which, without isolation, was oxidized in the same vessel using nitric acid at a higher temperature to yield 4,5-dimethoxy-2-nitrobenzoic acid (**2**) in moderate yield. The acid chloride was conveniently converted into the ester (**3**) by the reaction with methanol; catalytic hydrogenation then yielded the desired aminoester (**4**). This was refluxed with tosylchloride (**5**) in dry pyridine for 24 h to give *N*-tosylanthranilate (**6**). Then the reaction of methyl *N*-tosylanthranilate (**6**) with ethyl γ -bromo valerate (**7**) at 100°C resulted diester (**8**) and its treatment with sodium hydride afforded ethyl-oxo-benzazepine (**9**), which was further hydrolyzed to give the 7,8-dimethoxy-5-oxo-1-*p*-toluene sulphonyl-2,3,4,5-tetrahydro-1H-benzo[*b*]azepin-4-carboxylic acid (**10**). The IR spectrum of this compound showed at 3403 (-OH) and 1678 (C=O) cm^{-1} .

The compound **10** on refluxing with thionyl chloride followed by condensation with aniline gave an yellow precipitate, which on purification afforded a compound with m.p. >298 °C in 50% yield. Its IR spectrum showed absorptions at 1665 (-NH-CO-) and 3300 (-NH) cm^{-1} . The mass spectrum of the compound gave the molecular ion peak at $m/z = 494+H$. based on the data the compound was identified as 2,3,4,5-tetrahydro-7,8-dimethoxy-1-*p*-toluene sulphonyl-1-benzazepin-4-carbaldehyde (**11**).

Compound **11** when heated with MCM-41(H) at 100 °C for 3 h, gave a product which was purified by column chromatography furnishing a pure compound with m.p. 198-201°C in 43% yield. Its IR spectrum showed absorptions at 1685(-NH-CO) and 3250 cm^{-1} (br, -NH). The IR spectrum also showed a weak absorption at 3350 cm^{-1} a due to -OH group formed as a result of amidoimine of tautomerism. The ¹H NMR spectrum of the compound showed a singlet at δ 8.65 due to NH proton. The absence of one of the multiplet from seven membered ring protons clearly indicating that it has undergone cyclization giving the product with the elimination of a molecule of water. The mass spectrum of the product exhibited the molecular ion peak at $m/z = 476+H$, also supporting the elimination of a water molecule from it. The compound was thus identified as 11,12-dimethoxy-9-(*p*-toluene sulphonyl)-6,7,8,9,-tetrahydro-5H-benzo[2,3]azepino[5,4-c]quinolin-5-one (**12**) (**Scheme 1**).

CONCLUSION

In conclusion, we developed an efficient process for synthesis of 11,12-dimethoxy-9-*p*-toluene sulphonyl-6,7,8,9-tetrahydro-5H- benzo [2,3]azepino[5,4-c]quinolin-5-one using MCM-41(H)

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