SYNTHESIS OF DIACETOXY BENZOCYCLOHEPTA THIENO PYRIMIDINONE

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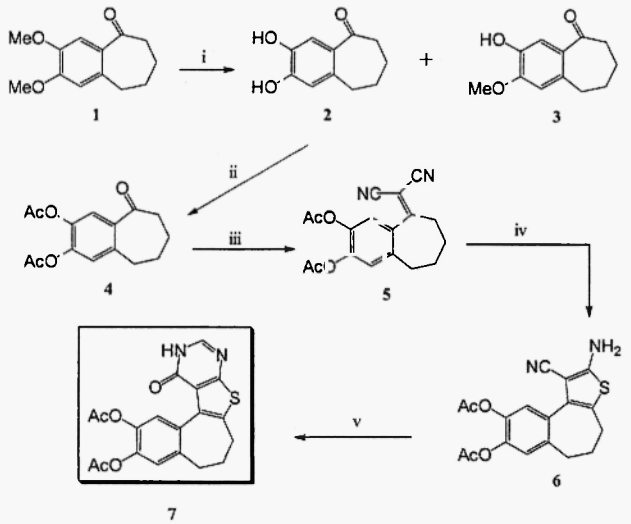
Abstract: New heterocyclic system namely 2,3-diacetoxy-6,7,11,12-tetrahydro-5*H*-benzo[3',4'] cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-12-one (**7**) have been synthesized via the reaction of 2-amino-8,9-diacetoxy-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[*b*]thiophene-1-carbonitrile (**6**) intermediate with formic acid in presence of MCM-41(H), in good yield.

Introduction

A number of biologically interesting polynuclear compounds incorporating a fused thiophene ring viz. Thiasteroids,[1] analogues of indole alkaloids,[2,3] carcinogenic compounds[4] etc., consists of six-membered ring annelated to thiophene. But examples of polycondensed systems incorporating a thiophene, imidazole or thiazole ring fused to a seven membered ring (viz benosuberones and benzazepines) are sparse. Accoding to previous studies[5-7] in the synthesis of biologically active fused heterocycles we have synthesized the hitherto unreported 2,3-diacetoxy-6,7,11,12-tetrahydro-5*H*-benzo[3',4']cyclohepta[4,5] thieno[2,3-*d*]pyrimidin-12-one (**7**) starting from the 2,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-one **1**[8].

Chemistry

2,3-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (**1**) on demethylation with aluminium bromide obtained 2,3-Dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (**2**) and partially demethylated 2-methoxy-3-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (**3**). Compound 2 was treated with acetic anhydride in presence of dry pyridine afforded 2,3-Diacetoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (**4**) in quantitative yield. Thiophene **6** was obtained from **4** when it was condenced with malononitrile under standard Knoevenagel conditions to afford the ylidinemalononitrile **5** in 75% yield, which reacted with sulphur and morpholine in the usual way to furnish the thiophene derivative **6** in good yield, finally cyclization was done by formic acid in presence of MCM-41(H)[9-11] on 2-amino-8,9-diacetoxy-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[*b*]thiophene-1-carbonitrile (**6**), which afforded good yield of 2,3-diacetoxy-6,7,11,12-tetrahydro-5*H*-benzo[3',4']cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-12-one (**7**) (**Scheme-1**).The advantage of this cyclization method is simpler experimental conditions, easy isolation procedure, shorter reaction time and MCM-41(H) can be recovered and reused for two cycles without substantial loss in the yield of product. Their structures were established by ^{1}H NMR, IR and Mass.



Reagents and Conditions : (i) $AlBr_3$, dry benzene; (ii) Ac_2O, dry pyridine; (iii) Malanonitrile, Et_3N, EtOH, reflux; (iv) sulfur, morpholine, EtOH, reflux; (v) HCOOH, MCM-41(H).

Scheme-1

Experimental Section

Melting points were determined in open glass capillaries on a polmon melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Gemini (200 MHz) spectrometers (chemical shifts are recorded in δ, ppm); internal standard was TMS and IR spectra were recorded in KBr on a Perkin-Elmer bio-spectrometer.

2,3-Dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (2)

2,3-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (**1,** 2.6g, 0.0118 mole), anhydrous aluminium bromide (10.5g, 0.0795 mole) and dry benzene (30mL) were refluxed together for 32h and poured on to an excess of ice and hydrochloric acid. This suspention was freed from benzene and extracted with (a) chloroform and (b) *n*-butanol-benzene. The extracts were dried and evaporated leaving the diol needles (1.35g, 70%), m.p.160.3°C (lit.,[12] m.p.161°C); IR (KBr) : υ 3300-3250, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.70-2.00 (m, 4H, 6&8-H), 2.61-3.21 (m, 4H, 6 & 9-H), 7.58 (s, 1H, 4-H), 6.65 (s, 1H, 1-H) and 5.58 (brs, 2H, 2-OH).

2-Methoxy-3-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (3)

Partially methylated product, yield 30%, m.p.117°C; IR (KBr) : υ 3250, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.79-1.88 (m, 4H, 6&8-H), 2.70 (t, 2H, 6-H), 2.85 (t.2H, 9-H), 3.85 (s, 3H, OMe), 7.48 (s, 1H, 4-H), 6.69 (s, 1H, 1-H) and 5.79 (brs, 1H, -OH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$) : δ 20.5, 24.5, 32.0, 40.1, 56.0, 110.1, 114.1, 130.1, 136.0, 144.0, 150.0, 204.0. MS; m/z 206 (M^+ 100%), 177 (52%), 165 (36%), 137 (75%), 107 (28%).

2,3-Diacetoxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (4)

2,3-Dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (**2,** 4.0g, 0.052 mole), and dry pyridine (6.6mL) and acetic anhydride (6.4g, 0.062 mol)were kept at room temperature for 24h and then poured over ice, extracted with benzene. The benzene layers washed with water and dried over Na_2SO_4. Evaporation of solvent gave solid, which crystallized from ethanol as colourless crystals (5.33g, 93.5%), m.p.132°C (lit.,[12] m.p.129-130°C); IR (Nujol) : υ 1770 (O-C=O) and 1680 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.70-1.95 (m, 4H, 7&8-H), 2.65 (t, 2H, 6-H), 2.80 (t, 2H, 9 -H), 2.25 (s, 6H, 2 x OAc),7.45 (s, 1H, 4-H), 6.65 (s, 1H, 1-H). MS : m/z 276 (M^+ 20%), 250 (15%), 240 (22%), 207 (59%), 193 (100%), 178 (37%), 164 (71%), 152 (49%), 136 (!00%), 123 (75%), 107 (20%), 77 (45%).

2-(5-Dicyanomethylene-2,3-Diacetoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-ylidene) malononitrile (5)

2,3-Dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptenone (**2,** 4.0g, 0.052 mole), and dry pyridine (6.6mL) and acetic anhydride (6.4g, 0.062 mol)were kept at room temperature for 24h and then poured over ice, extracted with benzene. The benzene layers washed with water and dried over Na_2SO_4. Evaporation of solvent gave solid, which crystallized from ethanol as colourless crystals (75%), m.p.300°C (dec.); IR (KBr) : υ 2225 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.65-1.85 (m, 4H, 7&8-H), 2.60 (t, 2H, 6-H), 2.80 (t, 2H, 9 -H), 2.28 (s, 6H, 2 x OAc),7.50 (s, 1H, 4-H), 6.60 (s, 1H, 1-H).

2-Amino-8,9-diacetoxy-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[*b*]thiophene-1-carbonitrile (6)

Dicyanomethylene compound **5** (0.4g), sulphur (0.1g) and morpholine (3 drops) were refluxed together for 1 h in dry ethanol (5mL). Addition of cold water afforded a solid (0.3g), and extraction of aqueous portion with chloroform gave further material (0.1g). The product was purified by chromatography over alumina (5% EtOAc-benzene) and crystallized from EtOAc-benzene giving amino carbonitrile **6** as prisms 72.8%, m.p.260°C (dec.); IR (KBr) : υ 2220 (CN), 3350 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.60-1.80 (m, 2H, 8-H), 2.05 (t, 2H, 7-H), 3.00 (t, 2H, 9 -H), 2.23 (s, 6H, 2 x OAc),7.20 (s, 1H, 4-H), 6.88 (s, 1H, 1-H).

2,3-Diacetoxy-6,7,11,12-tetrahydro-5*H*-benzo[3',4']cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-12-one (7)

A mixture of 2-amino-8,9-diacetoxy-5,6-dihydro-4*H*-benzo[3,4]cyclohepta[*b*]thiophene-1-carbonitrile (**6,** 0.25g), was added in portion wise over1h to a mildly refluxing mixture of 88% formic acid and MCM-41(H) (0.1g). After 15 min. the mixture was allowed to cool to 60°C [filtered, MCM-41(H) was washed thoroughly with ethanol (2 x 20mL) and activated for recycle], poured onto crushed ice (100g) and allowed to stand for 30min. The resulting precipitate was collected and washed well with water, upon drying afforded an off white seme-solid (65%). ^1H NMR ($CDCl_3$) : δ 1.60-1.78 (m, 2H, 6-H), 1.85 (t, 2H, 7-H), 2.45 (t, 2H, 5 -H), 2.25 (s, 6H, 2 x OAc), 7.12 (s, 1H, 4-H), 7.26 (s, 1H, 1-H), 8.42 (s, 1H, 10-H), 11.40 (brs, 1H, CONH).

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