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A facile three-component solid phase synthesis of steroidal A-ring fused pyrimidines under microwave irradiation

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ABSTRACT

The preparation of ring-A fused pyrimidines at the steroidal 2,3-position is herein described. The novel steroidal pyrimidines were prepared from the solid phase three-component reaction of 2-hydroxymethylene-3-keto steroids, arylaldehydes and ammonium acetate under microwave irradiation.

1. Introduction

The pyrimidine heterocyclic core is an important subunit because of its widespread abundance in the basic structure of numerous natural products [1]. A number of synthetic pharmacophores based upon the pyrimidyl structure exhibit antibacterial, antimicrobial, anticancer, anti-HIV-1 and antirubella virus activities [2–4]. On the other hand, A-ring heterosteroids are pharmaceutically important compounds due to their inherent biological properties [5,6]. A great deal of attention is being paid to annelate steroidal moiety with pyrazole, pyridine, isoxazole, pyrrole rings using various synthetic strategies [7–13]. Nevertheless, the effort made towards development of newer synthetic approaches for A-ring annelated steroidal pyrimidines is still limited. For example, Clinton and his co-workers have described the preparation of biologically active steroidal[3,2-b]pyrimidines from condensation of 2-hydroxymethylene-3-ketosteroids with acetamidine-hydrochloride [14]. Laitonjam et al. utilized 2-bis(methylthio) methylene-3-ketosteroid and guanidine nitrate for the synthesis of A-ring fused steroidal pyrimidine [15]. Recently we forwarded a microwave promoted facile synthesis of A- and D-ring annelated pyrimidines from steroidal β-formyl enamides and urea catalysed by Lewis acids [16].

The multi-component reactions (MCR) attract enormous importance from the point of combinatorial chemistry and inherit importance over two-component reactions in several aspects such as the simplicity of a one-pot procedure, possible structural variations, complicated synthesis and a large number of accessible compounds [17–19]. In view of the therapeutic importance of pyrimidines, we were interested to prepare pyrimidine fused steroids from readily available 2-hydroxymethylene-3-ketosteroids utilizing multi-component reaction [20]. Herein, we wish to report a microwave promoted convenient preparation of steroidal[3,2-b]pyrimidines from the three-component reaction of 2-hydroxymethylene-3-ketosteroids, arylaldehydes and ammonium acetate.

2. Experimental

2.1. General remarks

All reactions were performed as per standard procedure using silica gel (60–120 mesh, Merck chemicals) and monitored on Merck aluminium thin layer chromatography (TLC, $UV_{254\,nm}$) plates. Column chromatography was carried out on silica gel (60–120 mesh, Merck chemicals). Melting points were determined in open capillary tubes on Buchi B-540 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer using KBr pellets or on a thin film using chloroform. All the ^{1}H and ^{13}C NMR spectra were recorded on Brucker Avance DPX 300 MHz spectrometer using tetramethylsilane (TMS) as internal standard. Chemical shift values were given as δ (ppm) values. ESI mass spectra were recorded on a Brucker Daltonic Data Analysis 2.0 spectrometer. Elemental analysis was performed on Perkin Elmer

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Series II CSNS/O Model 2400 machine calibrated against standard acetanilide.

2.2. Organic synthesis

General procedure for the preparation of 2′-Aryl-steroidal[3,2-d]pyrimidine: 2-Hydroxymethylene-3-ketosteroid (**1a**, 1 mmol), aromatic aldehyde (**2a**, 2 mmol) and ammonium acetate (2 mmol) were intimately mixed with silica gel (60–120 mesh, 2.0 g) in a mortar and the mixture was irradiated in an open reaction vessel of a Synthwave 402 Prolabo focused microwave reactor for 6 min after setting reaction temperature at 120 °C and power at 60% (maximum output 300 W). On completion of reaction (vide TLC), the reaction mixture was treated with water (50 ml), extracted with dichloromethane (3 × 30 ml). The organic portion was washed with water, dried over anhydrous sodium sulfate and the solvent removed to obtain a crude product. Silica gel column chromatography separation using EtOAc/hexane (1:9) as eluant over silica gel afforded the purified product **3a**.

2.2.1. 2′-Phenyl-5α-cholest[3,2-d]pyrimidine (*3a*)

White crystals, yield (398 mg 80%); mp: 169–170 °C; IR cm^{-1}: 2930, 1587, 1575, 1547, 1467, 1454, 1424, 770; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1H, aromatic proton of pyrimidine), 8.37 (d, 1H, J = 6.20 Hz), 7.52–7.14 (m, 4H, aromatic protons), 2.88–0.86 (m, 38H, alkane protons), 0.86 (s, 3H, 19-CH_3), 0.75 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.0, 161.7, 157.4, 137.7, 129.8, 128.2 (2C), 127.6 (2C), 126.9, 56.0, 55.9, 53.2, 42.1, 41.1, 39.4, 39.2, 36.0, 35.5, 35.2, 34.7, 32.3, 28.3, 27.9, 27.7 (2C), 23.9, 23.6, 22.6, 22.3 (2C), 21.0, 18.4, 11.7, 11.4. ESI mass m/z = 498 [M^+]. Anal calcd for $C_{35}H_{50}N_2$: C, 84.28; H, 10.10; N, 5.62. Found: C, 84.48; H, 10.34; N, 5.43.

2.2.2. 2′-(p-Tolyl)-5α-cholest[3,2-d]pyrimidine (*3b*)

White crystals, yield (435 mg 85%); mp: 174–175 °C; IR cm^{-1}: 2931, 1582, 1561, 1541, 1466, 1424, 760; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40 (s, 1H, aromatic proton of pyrimidine), 8.26 (d, 1H, J = 7.94 Hz), 7.48 (d, 1H, J = 7.95 Hz), 7.26 (d, 1H, J = 7.94 Hz), 7.02 (d, 1H, J = 7.95 Hz), 2.40 (s, 3H, tolyl methyl), 2.86–0.88 (m, 38H, alkane protons), 0.86 (s, 3H, 19-CH_3), 0.76 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.9, 161.8, 157.3, 139.9, 135.0, 129.0, 128.5, 127.5, 126.6, 125.6, 56.0, 53.2, 42.1, 41.1, 39.2, 35.9, 35.5, 35.2, 34.7, 31.2, 29.0, 27.9, 27.7 (2C), 23.9, 23.6, 22.6 (2C), 22.3 (2C), 21.2, 21.0, 18.4 (2C), 11.7, 11.4. ESI mass m/z = 512 [M^+]. Anal calcd for $C_{36}H_{52}N_2$: C, 84.32; H, 10.22; N, 5.46. Found: C, 84.53; H, 10.45; N, 5.64.

2.2.3. 2′-(p-Chlorophenyl)-5α-cholest[3,2-d]pyrimidine (*3c*)

White crystals, yield (416 mg 78%); mp: 155–56 °C; IR cm^{-1}: 2928, 1582, 1560, 1543, 1466, 1426, 786; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1H, aromatic proton of pyrimidine), 8.33 (d, 1H, J = 7.68), 7.38–7.25 (m, 3H), 2.87–0.88 (m, 38H, alkane protons), 0.86 (s, 3H, 19-CH_3), 0.77 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.1, 161.7, 157.4, 135.8, 128.9 (2C), 128.4 (2C), 127.3, 125.6, 55.9 (2C), 53.2, 41.9, 41.1, 39.5, 39.3, 35.9, 35.5, 35.2, 34.8, 31.2, 27.9, 27.7, 23.9, 23.6, 22.5 (2C), 22.3 (2C), 21.0, 21.0, 18.4, 11.7, 11.4. ESI mass m/z = 532 [M^+]. Anal calcd for $C_{35}H_{49}N_2Cl$: C, 78.84; H, 9.26; N, 5.25. Found: C, 78.59; H, 9.41; N, 5.15.

2.2.4. 2′-(p-Anisyl)-5α-cholest[3,2-d]pyrimidine (*3d*)

White crystals, yield (465 mg 88%); mp: 162–64 °C; IR cm^{-1}: 2933, 1607, 1584, 1564, 1531, 1509, 1465, 1436, 1417, 1249, 801, 760; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1H, aromatic proton of pyrimidine), 7.63 (d, 1H, J = 8.85), 7.16 (d, 1H, J = 8.60), 6.79 (d, 1H, J = 8.66), 6.74 (d, 1H, J = 8.92), 3.79 (s, 3H, –OMe), 2.90–0.88 (m, 38H, alkane protons), 0.86 (s, 3H, 19-CH_3), 0.70 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.1, 160.9, 158.1, 136.4, 131.7, 129.6 (2C), 129.1, 125.6, 113.3, 56.0, 55.1, 54.9, 42.2, 41.1, 39.2, 36.1, 35. 8, 35.5, 34.8, 31.6, 27.7 (2C), 23.9, 23.4, 22.6 (2C), 22.3 (2C), 20.9 (2C), 18.4, 13.3 (2C), 12.5, 11.4. ESI mass m/z = 528 [M^+]. Anal calcd for $C_{36}H_{52}N_2O$: C, 81.77; H, 9.91; N, 5.29. Found: C, 81.59; H, 9.82; N, 5.14.

2.2.5. 2′-Phenyl-(24R)-24-ethyl-5α-cholest[3,2-d]pyrimidine (*3e*)

Pyrimidine (**3e**) was prepared from **1b**: White crystals, yield (426 mg 81%); mp: 170–71 °C; IR cm^{-1}: 2957, 1586, 1574, 1546, 1465, 1454, 1424, 759; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (s, 1H, aromatic proton of pyrimidine), 8.38 (d, 1H, J = 7.20 Hz), 7.57-7.35 (m, 4H, aromatic protons), 2.88-0.88 (m, 42H, alkane protons), 0.85 (s, 3H, 19-CH_3), 0.74 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.0, 161.7, 157.4, 137.7, 129.8, 128.2, 127.6 (2C), 126.9, 125.6, 56.0, 55.9, 53.2, 45.5, 42.1 (2C), 41.1, 39.4 (2C), 36.0, 35.9, 34.7, 33.6, 31.5, 28.8, 28.0 (2C), 25.7, 23.90 23.9, 22.7 (2C), 19.6, 18.8, 18.5, 11.7, 11.4. ESI mass m/z = 526 [M^+]. Anal calcd for $C_{37}H_{54}N_2$: C, 84.35; H, 10.33; N, 5.32. Found: C, 84.52; H, 10.20; N, 5.18.

2.2.6. 2′-Phenyl-cholest[3,2-d]pyrimidin-4-ene (*3f*)

Pyrimidine (**3f**) was prepared from **1c**: White crystals, yield (392 mg 79%); mp: 122–124 °C; IR cm^{-1}: 2934, 1586, 1572, 1548, 1492, 1454, 1425, 761; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1H, aromatic proton of pyrimidine), 8.17 (d, 1H, J = 6.80), 7.35–7.29 (m, 4H, aromatic protons), 5.99 (bs, 1H, C_4-H), 2.91–0.93 (m, 35H, alkane protons), 0.85 (s, 3H, 19-CH_3), 0.74 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 157.2, 153.9, 138.0, 128.1, 128.1, 127.97, 127.7, 127.6, 127.5, 126.7, 122.8, 58.0, 56.0, 66.7, 54.3, 42.1 (2C), 39.2 (2C), 38.3, 35.8, 35.5, 34.2, 29.4, 27.7 (2C), 23.6, 22.6 (2C), 22.3 (2C), 18.4, 18.1, 11.7. ESI mass m/z = 496 [M^+]. Anal calcd for $C_{35}H_{48}N_2$: C, 84.62; H, 9.74; N, 5.64. Found: C, 84.48; H, 9.90; N, 5.48.

2.2.7. 2′-Phenyl-(24R)-24-ethyl-cholest[3,2-d]pyrimidin-4,22-diene (*3g*)

Pyrimidine (**3g**) was prepared from **1d**: White crystals, yield (417 mg 80%); mp: 202–204 °C; IR cm^{-1}: 2957, 1586, 1572, 1547, 1492, 1455, 1424, 759; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H, aromatic proton of pyrimidine), 8.25 (d, 1H, J = 6.50 Hz), 7.50–7.37 (m, 4H, aromatic protons), 6.07 (bs, 1H, C_4-H), 5.18–4.96 (m, 2H, olefinic protons), 2.99–0.89 (m, 35H, alkane protons), 0.84 (s, 3H, 19-CH_3), 0.76 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 157.2, 153.9, 143.1, 142.7, 138.0, 137.9, 128.1, 128.0, 128.0, 127.7, 127.5, 126.8, 122.8, 58.0, 55.7 (2C), 51.0, 45.4, 42.0 (2C), 41.5, 40.2, 38.3 (2C), 35.5, 34.1, 31.6 (2C), 25.2, 20.9 (2C), 18.7 (2C), 18.1, 12.0, 11.9. ESI mass m/z = 522 [M^+]. Anal calcd for $C_{37}H_{50}N_2$: C, 85.00; H, 9.64; N, 5.36. Found: C, 84.88; H, 9.48; N, 5.43.

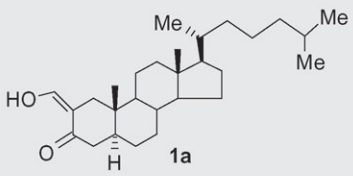
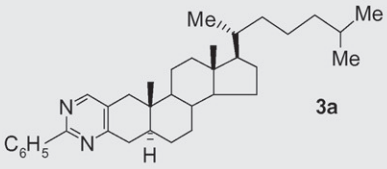
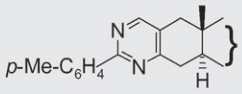
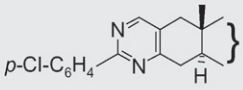
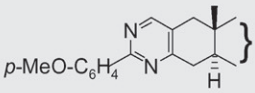
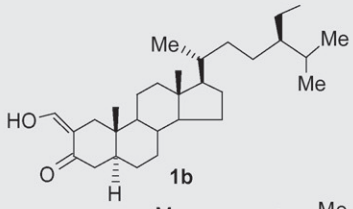
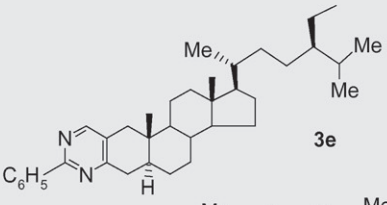
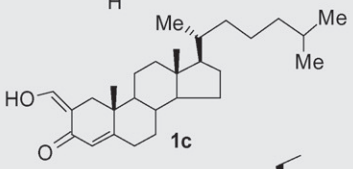
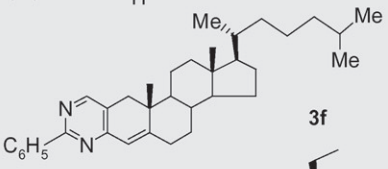
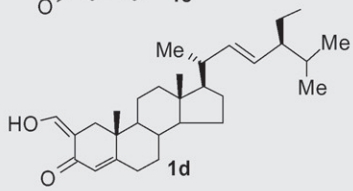
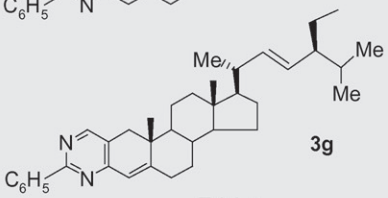
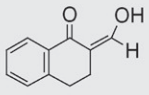
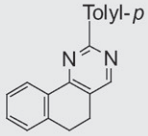
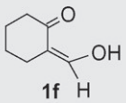
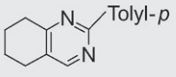
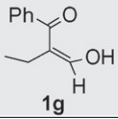
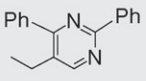
2.2.8. 2-(p-Tolyl)-5,6-dihydro-benzo[h]quinazoline (*3h*)

Pyrimidine (**3h**) was prepared from **1e**: Light yellow crystals, yield (0.22 g, 80%); mp: 101–103 °C; R_f = 0.4 (EtOAc:hexane = 5:95); IR ($CHCl_3$): ν 2932, 1585, 1565, 1538, 1432, 1419, 1390, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H, aromatic proton of pyrimidine), 8.57–8.43 (m, 2H, aromatic protons), 7.45–7.39 (m, 2H, aromatic protons), 7.33–7.25 (m, 4H), 3.04–2.92 (m, 4H, alkane protons), 2.43 (s, 3H, –CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 158.8, 155.5, 140.1, 139.0, 135.1, 132.5, 130.7, 129.0 (2C), 127.8 (2C), 127.7, 127.0, 125.6, 125.4, 27.3, 24.1, 21.2. MS (ESI): m/z = 273 [M^+ + 1]. Anal. calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.96; H, 5.88; N, 10.30.

2.2.9. 2-(p-Tolyl)-5,6,7,8-tetrahydro-quinazoline (*3i*)

Pyrimidine (**3i**) was prepared from **1f**: Light yellow crystals, yield (0.17 g, 76%); mp: 67–69 °C; R_f = 0.5 (EtOAc:hexane = 5:95); IR ($CHCl_3$): ν 2923, 1582, 1561, 1531, 1417, 772 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H, aromatic proton of pyrimidine), 8.40 (d, 1H, J = 7.95 Hz), 7.37–7.16 (m, 3H, aromatic protons), 2.72

Table 1
Synthesis of steroidal and non-steroidal pyrimidines (**3a–j**) from 2-hydroxymethylene-ketones (**1a–g**) under microwave irradiation[a].

Substrates[b]	Arylaldehyde		Products	Yield[c] (%)
 **1a**	C_6H_5CHO	**2a**	 **3a**	80
1a	*p*-Me-C_6H_4CHO	**2b**	 **3b**	85
1a	*p*-Cl-C_6H_4CHO	**2c**	 **3c**	78
1a	*p*-MeO-C_6H_4CHO	**2d**	 **3d**	88
 **1b**		**2a**	 **3e**	81
 **1c**		**2a**	 **3f**	79
 **1d**		**2a**	 **3g**	80
 **1e**		**2b**	 **3h**	78
 **1f**		**2b**	 **3i**	76
 **1g**		**2a**	 **3j**	75

[a]The reactions were conducted under microwave for 6–9 min.
[b]All 2-hydroxymethyleneketones **1a–g** were prepared from corresponding 3-oxosteroids and non-steroidal ketones in 88–96% yields.
[c]Isolated yields based on starting 2-hydroxymethyleneketones **1a–g**.

(m, 2H, alkane), 2.60 (m, 2H, alkane), 2.39 (s, 3H, $-CH_3$), 1.79 (m, 4H, alkane). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 159.2, 157.4, 139.9, 137.2, 130.0, 129.7, 129.0, 127.7, 126.3, 27.4, 26.1, 21.9, 21.3, 21.1. MS (ESI): m/z = 224 [M^+]. Anal. calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.09; H, 7.12; N, 12.56.

*2.2.10. 5-Ethyl-2,4-diphenyl-pyrimidine (**3j**)*

Pyrimidine (**3j**) was prepared from **1g**: Yellow gum, yield (0.2 g, 75%); R_f = 0.6 (EtOAc:hexane = 5:95); IR ($CHCl_3$): ν 2927, 1585, 1563, 1532, 1493, 1423, 1025, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H, aromatic proton of pyrimidine), 8.50–8.46 (m, 2H, aro-

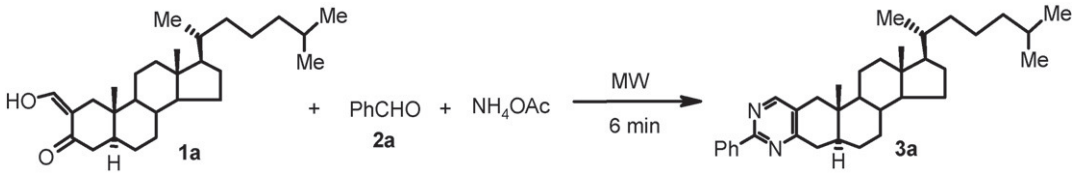


Fig. 1. Synthesis of steroidal pyrimidines **3a** from 2-hydroxymethylene-3-ketocholestan **1a**.

matic protons), 7.66–7.63 (m, 2H, aromatic protons), 7.52–7.45 (m, 6H, aromatic protons), 2.77 (q, 2H, J = 7.53 Hz, $-CH_2$), 1.20 (t, 3H, J = 7.53 Hz, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 162.2, 158.2, 138.5, 137.8, 131.6, 130.4, 129.2, 128.9 (2C), 128.5 (2C), 128.4 (2C), 128.1 (2C), 23.1, 15.0. MS (ESI): m/z = 260 [M$^+$].

3. Results and discussion

The 2-hydroxymethylene-3-ketosteroids (**1a–d**) were readily prepared from 5α-cholestan-3-one, (24*R*)-24-ethyl-5α-cholestan-3-one, cholest-4-en-3-one and (*24R*)-24-ethyl-cholest-4,22-dien-3-one in excellent yields by following a procedure of Weisenborn et al. [21]. The bicyclic, monocyclic and acyclic 2-hydroxymethylene derivatives (**1e–g**) were similarly prepared from 1-tetralone, cyclohexanone and butyrophenone respectively (Table 1).

We carried out the three-component reaction of 2-hydroxymethylene-3-ketosteroids, using silica gel (60–120 mesh) as solid phase reaction medium under microwave irradiation and isolating the product over silica gel by column chromatography. Under these conditions, 2-hydroxymethylene-cholestan-3-one (**1a**) reacted with benzaldehyde (**2a**) and ammonium acetate to afford 2′-Phenyl-5α-cholest[3,2-d]pyrimidine (**3a**) in 80% yield (Fig. 1). The product was characterized by spectral and analytical analysis. The ^{1}H NMR showed a singlet signal at δ 8.42 due to aromatic proton of pyrimidine ring and absence of the 2-hydroxymethylene olefinic proton at δ 8.75. The ^{13}C NMR spectrum of **3a** exhibited characteristic aromatic carbon signals at δ 165.0, 161.7, 157.4, 137.7, 129.8, 128.2, 127.6 and 126.9. The ESI mass spectrum showed molecular ion peak at m/z 498 (M$^+$).

We examined the feasibility of this synthetic route by carrying three-component reaction of **1a** with other aromatic aldehydes such as *p*-tolualdehyde (**2b**), *p*-chlorobenzaldehyde (**2c**) and *p*-anisaldehyde (**2d**) in presence of ammonium acetate under identical conditions and obtained 2′-(*p*-tolyl)-5α-cholest[3,2-d] pyrimidine (**3b**), 2′-(*p*-chlorophenyl)-5α-cholest[3,2-d]pyrimidine (**3c**) and 2′-(*p*-anisyl)-5α-cholest[3,2-d]pyrimidine (**3d**) respectively in 78–88% yields. Similarly, 2′-Phenyl-(24*R*)-24-ethyl-5α-cholest[3,2-d]pyrimidine (**3e**), 2′-Phenyl-cholest[3,2-d]pyrimidin-4-ene (**3f**) and 2′-Phenyl-(*24R*)-24-ethyl-cholest[3,2-d]pyrimidin-4,22-diene (**3g**) were prepared from 2-hydroxymethylene-(24*R*)-24-ethyl-cholestan-3-one (**1b**), 2-hydroxymethylene-cholest-4-en-3-one (**1c**) and 2-hydroxymethylene-(24*R*)-24-ethyl-cholestan-4,22-dien-3-one (**1d**) respectively in 79–81% yields.

To extend the scope of the reaction, we employed the three-component reaction strategy to bicyclic, monocyclic and acyclic 2-hydroxymethylene ketones (**1e–g**) with **2a–b** to afford 2-(*p*-tolyl)-5,6-dihydro-benzo[h]quinazoline (**3h**), 2-(*p*-tolyl)-5,6,7,8-tetrahydro-quinazoline (**3i**), 5-ethyl-2,4-diphenyl-pyrimidine (**3j**) in 75–78% yields.

A mechanism is proposed for the formation of pyrimidine derivatives **3a** from three-component reaction of **1a**, benzaldehyde (**2a**) and ammonium acetate as shown in Fig. 2. Under the influence microwave, the 2-hydroxymethylene-3-ketosteroid (**1a**) reacted with ammonia, released from decomposition of ammonium acetate, to facilitate amination to afford β-aminoketoimine intermediate **A** [14]. Condensation of intermediate **A** with **2a** led to diimine intermediate **B** which participated in cyclisation reaction by nucleophilic attack of the ketoimine to aldeimine affording dihydropyrimidine intermediate **C** with subsequent auto oxidation to afford **3a**.

In conclusion, we have developed an efficient microwave promoted three-component reaction of 2-hydroxymethylene-3-ketosteroids, aryldehydes and ammonium acetate for the facile synthesis of A-ring fused steroidal pyrimidines. The reaction strategy has been successfully extended to non-steroidal 2-hydroxymethyleneketone derivatives. The methodology reported herein represents a new preparation of A-ring fused steroidal

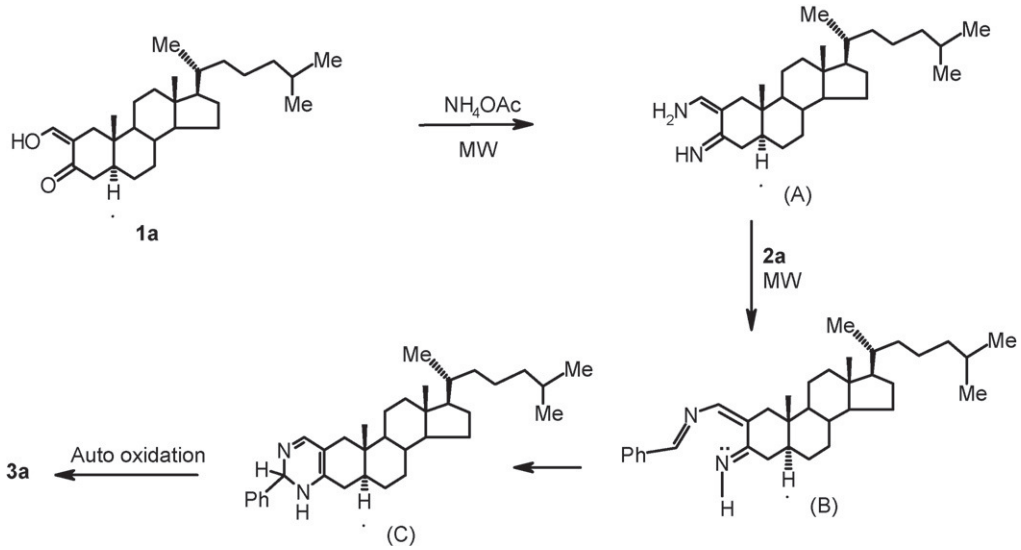


Fig. 2. Proposed mechanism for the formation of pyrimidine derivative **3a**.

as well as non-steroidal pyrimidines using easily available 2-hydroxymethyleneketones as starting materials. The methodology also provides a facile strategy for A-ring steroidal pyrimidines with an aryl substitution at 2′-position.

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