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Rapid communication

Chlorotrimethylsilane-promoted one-pot synthesis of steroidal[17,16-d]pyrimidines

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ABSTRACT

A novel and practical procedure was developed for the preparation of steroidal[17,16-d]pyrimidines by chlorotrimethylsilane (TMSCl)-promoted one-pot multicomponent Biginelli-like condensations of steroid-17-ones, urea and aromatic aldehydes. First, treatment of the steroid-17-ones with urea and aromatic aldehydes in dimethylformamide (DMF)/acetonitrile (ACN) gives the corresponding Biginelli products, following the aromatising reaction of the Biginelli products at the same time under air to yield the desired steroidal[17,16-d]pyrimidines (78–88%). Since steroidal[17,16-d]pyrimidines with hydroxyl group can be subsequently converted into steroidal[17,16-d]pyrimidine derivatives, this general method provides a highly efficient route to these biologically important compounds.

1. Introduction

Pentacyclic steroids and their derivatives are a very important class of steroids. There are many examples of pentacyclic steroidal derivatives of pharmacological and biological importance [1–5]. For many years, the preparation of pentacyclic steroids has attracted considerable attention from medicinal and synthetic organic chemists. Further, it is proved that a number of biologically important properties of modified steroids are dependent upon structural features of the steroid D-ring [6]. Chemical modification of the steroid D-ring provides a way to alter the functional groups, sizes and stereochemistry of the D-ring, and numerous structure–activity relationships have been established by such synthetic alterations.

It is known that substituted pyrimidines are an important class of heterocyclic compounds. A number of synthetic pharmacophores based upon the pyrimidyl structure exhibit biological activities, which were used widely as anti-inflammatory agents, antimalarial, anti-hypertensive, antibacterial, antiasthmatic, antiprotozoan, anti-rubella virus, antituberculosis, tyrosine kinase-inhibiting agents, anti-HIV and anticancer activity [7–9]. On the other hand, steroids' fused heterocyclic rings are pharmaceutically important compounds due to their inherent biological properties [10–13]. For example, the *in vitro* antibacterial evaluation of the pyrimidinoandrostane derivatives showed that they have high significant antibacterial activity against the used strains of Gram-positive and Gram-negative bacteria [12c]. Pyrimidines of the estratriene series are agents for the treatment of hypercholesterolaemia [10l]. Considerable attention is being paid to the annelate steroidal moiety with isoxazole, pyrazole, pyridine and pyrrole rings using various synthetic methods. Nevertheless, the effort made towards the development of newer preparation for annelated steroidal pyrimidines is still limited [10l,11–13].

Realising that the structure–activity relationship of the pentacyclic steroids indicates that the fusion of the carbocyclic or heterocyclic ring plays an important role of biological activity, we synthesised steroidal D-ring fused pyrimidines as new pentacyclic steroid skeletons for promising potential drug candidates.

In view of the remarkable importance from the pharmacological and synthetic viewpoints, the development of new pentacyclic steroids promising biological activity by new synthetic approaches using mild reaction conditions remains an active research area. Many previous studies proved that chlorotrimethylsilane (TMSCl) has been used as a mild and efficient promoter for various organic transformations [14,15]. It has also been reported as a mild useful and inexpensive Lewis acid catalyst or promoter for biguanide formation with benzylamine and dicyandiamide, [16] 'direct' cross aldol additions and the related Claisen condensation using $TiCl_4/Bu_3N$ [17]. In our previous work [18], TMSCl was employed to carry out several unusual cyclo-condensations including one-pot synthesis of substituted quinolines and pyrroles. The search for novel steroid libraries with potential biological activities is a major focus for chemical biology and medicinal chemistry. Therefore, efficient methodologies to access new steroid skele-

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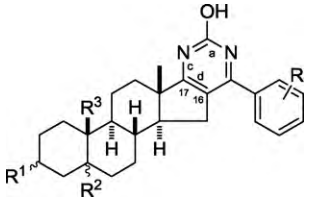


Fig. 1. Structure and numbering of the steroidal[17,16-d]pyrimidine ring systems.

tons of privileged structures are of special interest. Some studies observed that pentacyclic steroids obtained by fusion of a carbocyclic ring, such as benzene or cyclohexane or cyclopentane, to the steroid nucleus or pentacyclic steroids derived from the fusion of a carbocyclic ring to a heterosteroid skeleton was a convenient procedure [4].

However, none of the synthetic procedures provides a general route for one-pot synthesis of the steroids' D-ring of fused pyrimidines promoted by TMSCl described here. Thus, as part of our ongoing research on the development of new synthetic methods, we report a TMSCl-promoted one-pot synthesis of steroidal[17,16-d]pyrimidines (Fig. 1) from steroid-17-ones, urea and aromatic aldehydes (Scheme 1 and Table 1).

2. Experimental section

2.1. General remarks

All melting points (mps) were determined on a Yanaco melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet FT-IR 5DX spectrometer as KBr pellets. The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Bruker ACF-300 spectrometer with TMS as internal reference. The *J* values are given in hertz. The elemental analyses were performed on a Perkin–Elmer 240C instrument.

2.2. Organic synthesis

General procedures for the synthesis of steroidal[17,16-d]pyrimidines: To a mixture of steroid-17-one (1 mmol), urea (120 mg, 2 mmol) and aromatic aldehyde (1.5 mmol) in dimethylformamide (DMF)/CH_3CN (6/12 ml) were added TMSCl (0.26 ml, 2 mmol) at room temperature. The resultant mixture was heated at 90 °C for 12 h. After the mixture was cooled to room temperature, water (20 ml) was added to the reaction mixture and the resulting mixture was extracted with CH_2Cl_2 (2× 15 ml), the organic phase was washed with water and brine, and dried over Na_2SO_4. After removal of solvent, the residue was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2/MeOH, 1:1:0.05) to give the desired product (**3aa**–**cc**; Table 1).

2.3. (2aS,4S,6aS,6bS,8aS,13aS,13bR)-10-Hydroxy-6a,8a-dimethyl-12-phenyl-2,2a,3,4,5,6,6a,6b,7,8,8a,13,13a,13b-tetradecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (*3aa*)

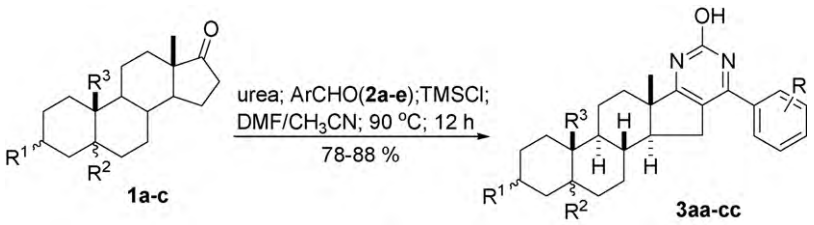
Following the general procedure, the title compound **3aa** (85%) was obtained as a white solid. Mp 320 °C (dec); IR (KBr) υ 3413, 2939, 1733, 1648, 1578, 1464, 1378, 1245, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.77–7.73 (m, 2H, aromatic H), 7.28–7.51 (m, 3H, aromatic H), 4.69–4.67 (m, 1H, C3-H), 2.63–2.48 (m, 2H, C15-H), 2.19 (s, 1H, C14-H), 2.02 (s, 3H, CH_3CO_2), 1.08 (s, 3H, C18-H), 0.89 (s, 3H, C19-H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 171.8 (C17), 170.4 (CH_3CO_2), 160.5 (pyimidinyl *C*2-OH), 150.5 (pyimidinyl *C*6-Ar), 131.6 (Ar), 130.7 (Ar), 128.9 (2C, Ar), 128.3 (2C, Ar), 114.6 (C16), 73.4 (C3), 54.8 (C14), 54.3 (C9), 46.7 (C13), 44.6 (C10), 36.4 (C5), 35.6 (C8), 34.3 (C12), 33.8 (C4), 32.5 (C1), 31.3 (C2), 28.7 (C15), 28.2 (C7), 27.3 (C6), 21.3 (C11), 20.6 (*CH*$_3$CO$_2$), 16.6 (C18), 12.1 (C19). Anal. Calcd for $C_{29}H_{36}N_2O_3$: C, 75.62; H, 7.88; N, 6.08. Found: C, 75.48; H, 7.64; N, 6.23.

2.4. (2aS,4S,6aS,6bS,8aS,13aS,13bR)-12-(4-Fluorophenyl)-10-hydroxy-6a,8a-dimethyl-2,2a,3,4,5,6,6a,6b,7,8,8a,13,13a,13b-tetradecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (*3ab*)

Following the general procedure, the title compound **3ab** (88%) was obtained as a white solid. Mp 310–312 °C (methanol); IR (KBr) υ 3415, 2939, 1734, 1647, 1605, 1583, 1510, 1453, 1376, 1244, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): 7.84 (m, 2H, aromatic H), 7.27 (m, 2H, aromatic H), 4.73 (m, 1H, C3-H), 2.63–2.53 (m, 2H, C15-H), 2.28 (s, 1H, C14-H), 2.07 (s, 3H, CH_3CO), 1.14 (s, 3H, C18-H), 0.95 (s, 3H, C19-H); ^{13}C NMR ($CDCl_3$, ppm): 170.3 (CH_3CO_2), 165.7 (C17), 162.3 (d, $^1J_{CF}$ = 246 Hz, *Ar*-F), 160.5 (pyimidinyl C2-OH), 150.5 (pyimidinyl *C*6-Ar), 130.6 (Ar), 130.5 (Ar), 128.0 (Ar), 115.9 (d, $^2J_{CF}$ = 21.6 Hz, (2C)Ar), 114.5 (C16), 73.2 (C3), 54.7 (C14), 54.2 (C9), 46.6 (C13), 44.5 (C10), 36.3 (C5), 35.5 (C8), 34.2 (C12), 33.7 (C4), 32.3 (C1), 31.2 (C2), 28.7 (C15), 28.0 (C7), 27.2 (C6), 21.2 (C11), 20.4 (*CH*$_3$CO$_2$), 16.5 (C18), 12.0 (C19). Anal. Calcd for $C_{29}H_{35}FN_2O_3$: C, 72.78; H, 7.37; N, 5.85. Found: C, 72.74; H, 7.32; N, 5.76.

2.5. (2aS,4S,6aS,6bS,8aS,13aS,13bR)-10-Hydroxy-12-(4-methoxyphenyl)-6a,8a-dimethyl-2,2a,3,4,5,6,6a,6b,7,8,8a,13,13a,13b-tetradecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (*3ac*)

Following the general procedure, the title compound **3ac** (88%) was obtained as a white solid. Mp 265–267 °C (methanol); IR (KBr) υ 3415, 2939, 1732, 1640, 1606, 1563, 1512, 1443, 1378, 1251, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm): 7.73 (d, *J* = 6.9 Hz, 2H, aromatic H), 7.04 (d, *J* = 6.9 Hz, 2H, aromatic H), 4.67 (m, 1H, C3-H), 3.87 (s, 3H, OCH_3), 2.61–2.51 (m, 2H, C15-H), 2.18 (s, 1H, C14-H), 2.02



Scheme 1. Novel preparation of some steroidal[17,16-d]pyrimidines promoted by TMSCl.

(s, 3H, CH_3CO), 1.07 (s, 3H, C18-H), 0.89 (s, 3H, C19-H); ^{13}C NMR ($CDCl_3$, ppm): 171.8 (C17), 170.5 (CH_3CO_2), 161.7 ((Ar)$COCH_3$), 160.6 (pyimidinyl C2-OH), 150.6 (pyimidinyl *C*6-Ar), 130.0 (2C, Ar), 123.8 (Ar), 114.4 (2C, Ar), 113.9 (C16), 73.4 (C3), 55.3 ((Ar)COCH_3), 54.9 (C14), 54.4 (C9), 46.6 (C13), 44.6 (C10), 36.5 (C5), 35.7 (C8), 34.3 (C12), 33.9 (C4), 32.5 (C1), 31.4 (C2), 29.0 (C15), 28.2 (C7), 27.3 (C6), 21.3 (C11), 20.6 (CH_3CO_2), 16.6 (C18), 12.1 (C19). Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. found: C, 73.28; H, 7.72; N, 5.76.

*2.6. (2aS,4S,6aS,6bS,8aS,13aS,13bR)-10-Hydroxy-6a,8a-dimethyl-12-(2-nitrophenyl)-2,2a,3,4,5,6,6a,6b,7,8,8a,13,13a,13b-tetradecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (**3ad**)*

Following the general procedure, the title compound **3ad** (78%) was obtained as a white solid. Mp 216–218 °C (methanol); IR (KBr) υ 3425, 2939, 1732, 1646, 1564, 1529, 1452, 1348, 1247, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 8.13 (d, J = 7.8 Hz, 1H, aromatic H), 7.76 (t, J = 7.2 Hz, 1H, aromatic H), 7.67–7.53 (m, 2H, aromatic H), 4.67 (m, 1H, C3-H), 2.40–2.08 (m, 3H, C15-H and C14-H), 2.02 (s, 3H, CH_3CO), 1.05 (s, 3H, C18-H), 0.85 (s, 3H, C19-H); ^{13}C NMR ($CDCl_3$, ppm): 171.8 (C17), 170.5 (CH_3CO_2), 160.1 (pyimidinyl C2-OH), 150.2 (pyimidinyl *C*6-Ar), 147.3 ((Ar)CNO_2), 133.9 (Ar), 131.1 (Ar), 131.0 (Ar), 130.8 (Ar), 124.9 (Ar), 116.5 (C16), 73.1 (C3), 54.6 (C14), 54.3 (C9), 46.9 (C13), 44.6 (C10), 36.4 (C5), 35.6 (C8), 34.0 (C12), 33.8 (C4), 32.2 (C1), 31.2 (C2), 28.0 (C15), 27.3 (C7), 26.9 (C6), 21.3 (C11), 20.4 (CH_3CO_2), 16.6 (C18), 12.0 (C19). Anal. Calcd for $C_{29}H_{35}N_3O_5$: C, 68.89; H, 6.98; N, 8.31. found: C, 68.82; H, 7.06; N, 8.22.

*2.7. (2aS,4S,6aS,6bS,8aS,13aS,13bR)-10-Hydroxy-6a,8a-dimethyl-12-(3-nitrophenyl)-2,2a,3,4,5,6,6a,6b,7,8,8a,13,13a,13b-tetradecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (**3ae**)*

Following the general procedure, the title compound **3ae** (81%) was obtained as a white solid. Mp 210–212 °C (methanol); IR (KBr) υ 3425, 3330, 2939, 1732, 1640, 1576, 1531, 1452, 1349, 1247, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 8.58 (s, 1H, aromatic C2-H), 8.37 (d, J = 8.1 Hz, 1H, aromatic C4-H), 8.23 (d, J = 7.8 Hz, 1H, aromatic C6-H), 7.77 (t, J = 8.1 Hz, 1H, aromatic C5-H), 4.68 (m, 1H, C3-H), 2.65 (d, J = 6.3 Hz, 2H, C15-H), 2.34 (s, 1H, C14-H), 2.03 (s, 3H, CH_3CO), 1.15 (s, 3H, C18-H), 0.91 (s, 3H, C19-H); ^{13}C NMR ($CDCl_3$, ppm): 170.9 (C17), 170.2 (CH_3CO_2), 160.1 (pyimidinyl C2-OH), 150.3 (pyimidinyl *C*6-Ar), 148.0 ((Ar)CNO_2), 134.1 (Ar), 131.5 (Ar), 130.0 (Ar), 125.0 (Ar), 123.3 (Ar), 115.4 (C16), 73.1 (C3), 54.9 (C14), 54.1 (C9), 46.5 (C13), 44.4 (C10), 36.2 (C5), 35.4 (C8), 34.0 (C12), 33.6 (C4), 32.1 (C1), 31.1 (C2), 28.6 (C15), 27.9 (C7), 27.1 (C6), 21.1 (C11), 20.3 (CH_3CO_2), 16.6 (C18), 11.9 (C19). Anal. Calcd for $C_{29}H_{35}N_3O_5$: C, 68.89; H, 6.98; N, 8.31. Found: C, 68.78; H, 7.00; N, 8.34.

*2.8. (4S,6aR,6bS,8aS,13aS,13bR)-10-Hydroxy-6a,8a-dimethyl-12-phenyl-3,4,5,6,6a,6b,7,8,8a,13,13a,13b-dodecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (**3ba**)*

Following the general procedure, the title compound **3ba** (83%) was obtained as a white solid. Mp 292–294 °C (methanol); IR (KBr) υ 3445, 2943, 1734, 1646, 1558, 1499, 1439, 1377, 1246, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 7.53 (m, 3H, aromatic H), 7.42 (d, J = 6.9 Hz, 2H, aromatic H), 5.30 (s, 1H, C=*CH*), 4.60 (m, 1H, C3-H), 2.61–2.51 (m, 2H, C15-H), 2.35 (m, 3H, =C-*CH*), 2.04 (s, 3H, CH_3CO), 1.17 (s, 3H, C18-H), 1.09 (s, 3H, C19-H); ^{13}C NMR ($CDCl_3$, ppm): 171.7 (C17), 170.2 (CH_3CO_2), 160.5 (pyimidinyl *C*2-OH), 150.5 (pyimidinyl *C*6-Ar), 140.0 (*C*=CH), 131.6 (Ar), 130.5 (Ar), 129.0 (2C, Ar), 128.3 (2C, Ar), 121.6 (C=*CH*), 114.5 (C16), 73.5 (C3), 55.0 (C14), 50.1 (C9), 46.4 (C13), 38.0 (C4), 36.7 (2C, C10 and C12), 32.4 (C8), 31.1 (C1), 30.7 (C2), 28.8 (C7), 27.6 (C15), 21.2 (C11), 20.2 (CH_3CO_2), 19.2 (C19), 16.3 (C18). Anal. Calcd for $C_{29}H_{34}N_2O_3$: C, 75.95; H, 7.47; N, 6.11. Found: C, 75.80; H, 7.38; N, 6.32.

*2.9. (4S,6aR,6bS,8aS,13aS,13bR)-12-(4-Fluorophenyl)-10-hydroxy-6a,8a-dimethyl-3,4,5,6,6a,6b,7,8,8a,13,13a,13b-dodecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (**3bb**)*

Following the general procedure, the title compound **3bb** (83%) was obtained as a white solid. Mp 230–232 °C (methanol); IR (KBr) υ 3445, 2943, 1734, 1646, 1558, 1499, 1439, 1377, 1246, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 7.79 (d, J = 8.1 Hz, 2H, aromatic H), 7.23 (d, J = 8.1 Hz, 2H, aromatic H), 5.39 (s, 1H, C=*CH*), 4.60 (m, 1H, C3-H), 2.63–2.57 (m, 2H, C15-H), 2.34 (m, 3H, =C-*CH*), 2.04 (s, 3H, CH_3CO), 1.13 (s, 3H, C18-H), 1.10 (s, 3H, C19-H); ^{13}C NMR ($CDCl_3$, ppm): 171.3 (C17), 170.2 (CH_3CO_2), 162.4 (d, $^1J_{CF}$ = 246 Hz, *Ar*-F), 160.5 (pyimidinyl *C*2-OH), 150.5 (pyimidinyl *C*6-Ar), 140.0 (*C*=CH), 131.6 (Ar), 130.7 (Ar), 129.0 (Ar), 121.5 (C=*CH*), 116.0 (d, $^2J_{CF}$ = 21.6 Hz, (2C)Ar), 114.5 (C16), 73.5 (C3), 55.0 (C14), 50.1 (C9), 46.4 (C13), 37.9 (C4), 36.7 (2C, C10 and C12), 32.3 (C8), 31.0 (C1), 30.6 (C2), 28.8 (C7), 27.5 (C15), 21.2 (C11), 20.2 (CH_3CO_2), 19.1 (C19), 16.3 (C18). Anal. Calcd for $C_{29}H_{33}FN_2O_3$: C, 73.09; H, 6.98; N, 5.88. Found: C, 73.02; H, 6.88; N, 5.72.

*2.10. (4S,6aR,6bS,8aS,13aS,13bR)-10-Hydroxy-12-(4-methoxyphenyl)-6a,8a-dimethyl-3,4,5,6,6a,6b,7,8,8a,13,13a,13b-dodecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-4-yl acetate (**3bc**)*

Following the general procedure, the title compound **3bc** (87%) was obtained as a white solid. Mp 242–244 °C (ethanol); ^1H NMR ($CDCl_3$, ppm): 7.75 (d, J = 6.6 Hz, 2H, aromatic H), 7.05 (d, J = 8.1 Hz, 2H, aromatic H), 5.39 (s, 1H, C=*CH*), 4.60 (m, 1H, C3-H), 3.87 (s, 3H, CH_3OAr), 2.62–2.56 (m, 2H, C15-H), 2.35–2.12 (m, 3H, =C-*CH*), 2.03 (s, 3H, CH_3CO), 1.23 (s, 2 × 3H, C18-H and C19-H); ^{13}C NMR ($CDCl_3$, ppm): 171.0 (C17), 170.2 (CH_3CO_2), 161.6 ((Ar)$COCH_3$), 160.6 (pyimidinyl *C*2-OH), 150.0 (pyimidinyl *C*6-Ar), 140.0 (*C*=CH), 130.0 (2C, Ar), 123.7 (Ar), 121.6 (C=*CH*), 114.4 (2C, Ar), 113.7 (C16), 73.5 (C3), 55.2 ((Ar)COCH_3), 54.9 (C14), 50.1 (C9), 46.3 (C13), 37.9 (C4), 36.6 (2C, C10 and C12), 32.3 (C8), 31.0 (C1), 30.6 (C2), 29.0 (C7), 27.5 (C15), 21.2 (C11), 20.2 (CH_3CO_2), 19.2 (C19), 16.3 (C18). Anal. Calcd for $C_{30}H_{36}N_2O_4$: C, 73.74; H, 7.43; N, 5.73. Found: C, 73.68; H, 7.22; N, 5.68.

*2.11. (6bS,8aS,13aS,13bR)-4-Methoxy-8a-methyl-12-phenyl-2,6b,7,8,8a,13,13a,13b-octahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-10-ol (**3ca**)*

Following the general procedure, the title compound **3ca** (84%) was obtained as a white solid. Mp 282–284 °C (methanol); IR (KBr) υ 3411, 2932, 1638, 1559, 1498, 1462, 1378, 1253, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 7.78 (d, J = 6.0 Hz, 2H, aromatic H), 7.53 (m, 3H, aromatic H), 7.22 (d, J = 8.4 Hz, 1H, aromatic C1-H), 6.74 (d, J = 8.4 Hz, 1H, aromatic C2-H), 6.64 (s, 1H, aromatic C4-H), 3.78 (s, 3H, C3-OCH_3), 2.89 (m, 2H, C6-H and C9-H), 2.71 (m, 2H, C15-H), 2.46 (d, J = 12.9 Hz, 1H, C6-H), 2.33 (m, 2H, C11-H and C12-H), 1.96 (m, 1H, C14-H), 1.76 (m, 4H, C7-H, C11–2 and C12-H), 1.44 (m, 1H, C7-H), 1.13 (s, 3H, C18-H); ^{13}C NMR ($CDCl_3$, ppm): 171.7 (C17), 160.6 (pyimidinyl *C*2-OH), 157.5 (C3), 150.2 (pyimidinyl *C*6-Ar), 137.4

Table 1
Preparation of steroidal[17,16-d]pyrimidines (**3aa**–**cc**) promoted by TMSCl.

Entry	**1**	R^1	R^2	R^3	**2**(ArCHO)	R	**3**(product)	Yield (%)
1	**a**	β-OAc	α-H	CH_3	**a**	H	**3aa**	85
2	**a**	β-OAc	α-H	CH_3	**b**	4-F	**3ab**	88
3	**a**	β-OAc	α-H	CH_3	**c**	4-OCH_3	**3ac**	88
4	**a**	β-OAc	α-H	CH_3	**d**	2-NO_2	**3ad**	78
5	**a**	β-OAc	α-H	CH_3	**e**	3-NO_2	**3ae**	81
6	**b**	β-OAc	$\Delta^{5(6)}$	CH_3	**a**	H	**3ba**	83
7	**b**	β-OAc	$\Delta^{5(6)}$	CH_3	**b**	4-F	**3bb**	83
8	**b**	β-OAc	$\Delta^{5(6)}$	CH_3	**c**	4-OCH_3	**3bc**	87
9	**c**	OCH_3	$\Delta^{1,3,5(10)}$-Triene		**a**	H	**3ca**	84
10	**c**	OCH_3	$\Delta^{1,3,5(10)}$-Triene		**c**	4-OCH_3	**3cc**	87

(C5), 132.0 (C10), 131.8 (Ar), 130.8 (Ar), 128.9 (2C, Ar), 128.3 (2C, Ar), 126.0 (C1), 114.6 (C16), 113.8 (C4), 111.4 (C2), 55.1 (Ar)CO*CH*$_3$), 54.0 (C14), 46.9 (C13), 43.9 (C9), 37.5 (C8), 32.5 (C12), 29.4 (C6), 28.6 (C15), 27.2 (C7), 26.0 (C11), 16.7 (C18). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.70; H, 6.72; N, 6.78.

*2.12. (6bS,8aS,13aS,13bR)-4-Methoxy-12-(4-methoxyphenyl)-8a-methyl-2,6b,7,8,8a,13,13a,13b-octahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-d]pyrimidin-10-ol (**3cc**)*

Following the general procedure, the title compound **3cc** (87%) was obtained as a white solid. Mp 240–242 °C (methanol); IR (KBr) υ 3413, 2933, 1632, 1608, 1563, 1513, 1461, 1376, 1256, 1181 cm^{-1}; ^{1}H NMR (dimethyl sulphoxide (DMSO)-d_6, ppm): 11.44 (brs, 1H, pyimidinyl C2-*OH*), 7.57 (d, *J* = 8.4 Hz, 2H, aromatic H), 7.07 (d, *J* = 8.7 Hz, 1H, aromatic C2-H), 7.97 (d, *J* = 8.4 Hz, 2H, aromatic H), 6.58 (d, *J* = 8.7 Hz, 1H, aromatic C1-H), 6.52 (s, 1H, aromatic C4-H), 3.73 (s, 3H, *CH*$_3$OAr), 3.58 (s, 3H, C3-O*CH*$_3$), 0.92 (s, 3H, C18-H); ^{13}C NMR (DMSO-d_6, ppm):172.8 (C17), 161.6 ((Ar)*C*OCH$_3$), 161.2 (pyimidinyl *C*2-OH), 159.2 (pyimidinyl *C*6-Ar), 157.2 (C3), 137.4 (C5), 132.2 (C10), 131.9 (Ar), 130.2 (2C, Ar), 128.0 (C1), 126.1 (Ar), 114.1 (2C, C16 and Ar), 113.7 (C4), 111.6 (C2), 55.5 ((Ar)CO*CH*$_3$), 55.0 ((Ar)CO*CH*$_3$), 53.4 (C14), 46.3 (C13), 43.6 (C9), 37.3 (C8), 32.5 (C12), 29.1 (C6), 28.1 (C15), 26.8 (C7), 25.8 (C11), 16.8 (C18). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.82; H, 6.73; N, 6.36

3. Results and discussion

The reaction was initially studied with (3β,5α)-3-acetyloxyandrosterone, urea and benzaldehyde, which were selected as suitable substrates for reaction development in various promoters or catalysts and various solvents. At the outset, various promoters or catalysts (HCl, $FeCl_3$, $ZnCl_2$, ZnO, *p*-toluene sulphonic acid (PTSA) and TMSCl) and solvents (DMF, DMSO, ACN, and DMF + ACN) were screened. To our delight, we observed the formation of the desired product, **3aa** (Table 2), when the reaction was carried out using steroid (1.0 mmol), benzaldehyde (1.5 mmol), urea (2.0 mmol) and DMF (10 ml) in the presence of various promoters or catalysts (0.10 mmol or 2.0 mmol) under 90 °C for 12 h.

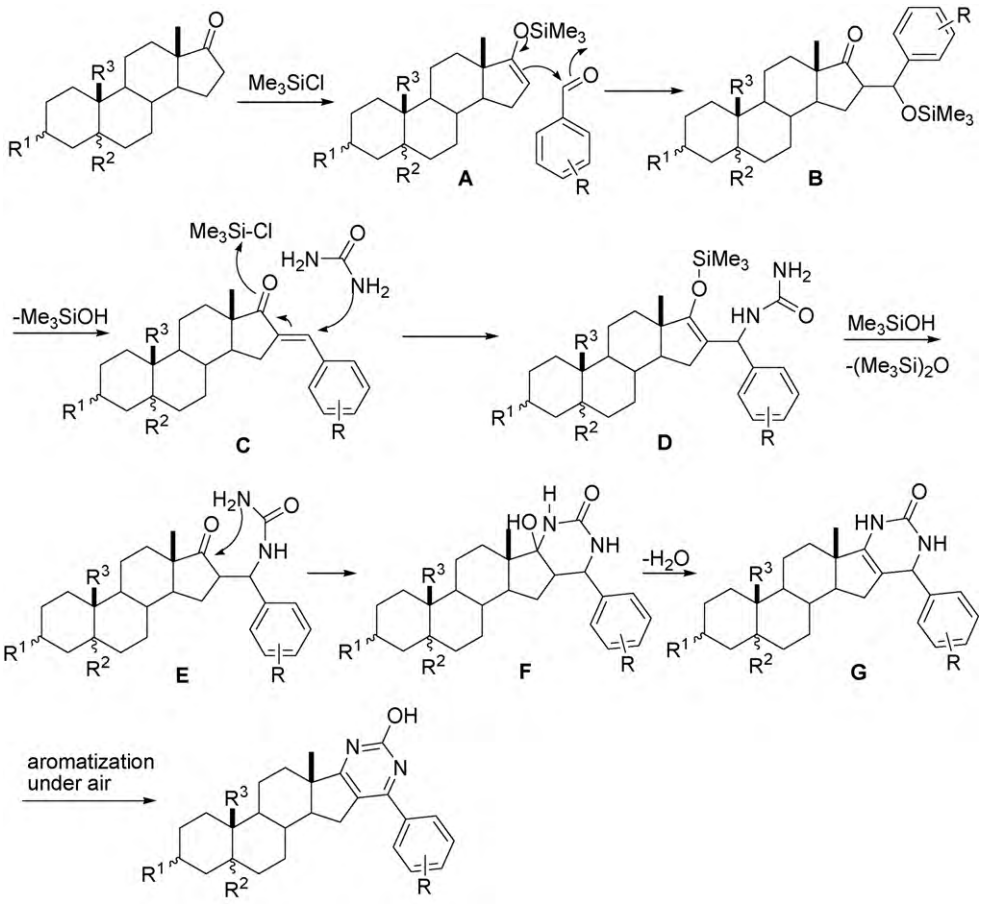
A comparison of the methods using TMSCl as a promoters (Table 2, entry 6, 71% in yield), with selected other promoters such as HCl, PTSA and other Lewis acids ($FeCl_3$ and $ZnCl_2$) or ZnO (Table 2, entry 1, 68% in yield; entry 2, 36% in yield; entry 3, 65% in yield; entry 4, 57% in yield; entry 5, 10% in yield, respectively) that were examined is assembled in Table 2 to demonstrate that the method using TMSCl as a promoter is indeed superior to several of the other protocols. When the catalytic amount of HCl or PTSA or $FeCl_3$ or TMSCl was used in the reaction, a low yield of product 3aa was obtained. Thus, TMSCl was found to be the better choice as a promoter for this reaction. Next, solvent, time and the amount of TMSCl were varied. First, the solvent in the preparation of steroidal[17,16-d]pyrimidines (**3aa**) was varied. Among the solvents tested (Table 2, entries 6–9), the mixed solvent DMF/ACN gave the best result. The result showed that DMF/ACN gave the product **3aa** in 73%. In the second set of experiments, the model reaction in DMF/ACN was carried out by varied reaction temperature. After some experimentation, it was found that the model reaction using a reaction temperature of about 90 °C produced the corresponding compound **3aa** in excellent yield. Furthermore, the reaction time and the catalyst concentration could be reduced to 12 h and two equivalents, respectively (Table 2, entry 1, 85%).

Thus, with these results in hand, the optimised procedure includes the application of one equivalent of the steroid-17-one (**1a**–**c**) with one-and-a-half equivalents of aromatic aldehyde (**2a**–**e**) and a twofold excess of urea in DMF/ACN in the presence of two equivalents of TMSCl under air and requires the reaction mixture to be initially maintained at room temperature, and then at 90 °C for 12 h. The desired steroidal[17,16-d]pyrimidines(**3aa**–**cc**) were obtained in good yields (Scheme 1). Evidently, a sequence of reactions involving Biginelli-like condensation took place during formation of the product. This may be concluded from the fact that when condensation of steroid-17-one and benzaldehyde was carried out, 16-benzylidene-steroid-17-one was isolated as the product, thereby indicating that a condensation reaction is the first step in this three-component process. The proposed mechanism of this novel ring formation is depicted in Scheme 2. The silyl enol ether A is initially generated by TMSCl. A β-siloxy ketone B is preformed by nucleophilic addition reaction of the aldehyde with the silyl enol ether A; expectedly, the siloxy substituent plays the role of the leaving group, followed by subsequent elimination of trimethylsilyl alcohol to give the ketone C and Michael addition reaction with urea promoted by TMSCl to yield the new silyl enol ether D. Next, the silyl enol ether D isomerises ketone E quickly.

Table 2
Various promoter/catalysts and solvents effect on reaction.[a,b].

Entry	Promoter/catalyst	Solvent	Yields[c] (%)
1	HCl	DMF	62[a] 68[b]
2	PTSA	DMF	28[a] 36[b]
3	$FeCl_3$	DMF	52[a] 65[b]
4	$ZnCl_2$	DMF	57[b]
5	ZnO	DMF	10[b]
6	TMSCl	DMF	47[a] 71[b]
7	TMSCl	DMSO	66[b]
8	TMSCl	ACN	48[b]
9	TMSCl	DMF/ACN	73[b]
10	TMSCl	DMF/ACN	85[d]

[a] Steroid (1 mmol), urea (2.0 mmol), benzaldehyde (1.5 mmol), catalyst (0.10 mmol), solvent (10 ml); reflux for ACN, 90 °C for DMSO, DMF and DMF/ACN (6/12 ml); 12 h.
[b] Besides the amount of promoter/catalysts was changed to 1 mmol, other reaction conditions were the same as above conditions.
[c] Isolated yields.
[d] Two equivalents of TMSCl were used in the reaction.



Scheme 2. Proposed mechanism of pyrimidine formation.

Then, as the key step, the nitrogen of urea within the 17-ketone moiety of steroidal skeleton forms the six-membered heteroring F in an intramolecular cyclisation reaction. Subsequently, water is eliminated from compound F, giving the dihydropyrimidine compound G. Finally, aromatisation occurs under air that leads to the steroidal[17,16-d]pyrimidines (**3aa**–**cc**) [19]. The air oxygen apparently acts as an effective oxidant for the aromatisation of the dihydropyrimidine [19]. In general, unsaturated pyrimidinol compounds are difficult to oxidise. Here, the aromatisation of dihydropyridinones with aromatic groups was promoted by "HCl" generated from TMSCl. However, the aromatisation took a long time.

In conclusion, some steroidal[17,16-d]pyrimidines as potentially biologically active pentacyclic heterosteroids were synthesised through an one-pot multicomponent Biginelli-like condensation of steroid-17-ones, urea and aromatic aldehydes promoted by TMSCl under mild conditions. The methodology also provides a facile strategy for D-ring steroidal[17,16-d]pyrimidines with a substitution at 2′-position.

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