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Palladium-catalyzed multi-component synthesis of steroidal A- and D-ring fused 5,6-disubstituted pyridines under microwave irradiation

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ABSTRACT

The preparation of steroidal A-, D-ring fused 5,6-disubstituted pyridines and nonsteroidal substituted pyridines is described form $Pd(OAc)_2$ catalyzed multi-component reaction of steroidal/nonsteroidal β-halovinyl aldehyde, alkyne and benzylamine in solvent-free condition under microwave irradiation.

1. Introduction

The development of methods for substituted pyridine derivatives is of importance to medicinal chemistry because of its widespread distribution in natural products, pharmaceuticals and synthetic biologically active compounds [1]. Due to the remarkable biological activities of steroids bearing heterocycles, enormous efforts are being made to annelate steroidal moiety with heterocycles such as pyrazole, isoxazole, pyridine, pyran, pyrrole or pyrimidine rings using various synthetic strategies [2–7]. Some of the biologically active steroids fused with heterocycles are shown in Fig. 1. Among annelated heterosteroids, the synthesis of A- and D-ring fused pyridines is drawing particular interest in last decade because of their inherent biological activities [4,6,8–9].

Microwave assisted organic synthesis (MAOS) which has been applied over the last decade as a very efficient tool to accelerate the course of many organic reactions, producing high yields, higher selectivity and lower quantities of side products is recognized as a "green" technology in the field of organic synthesis [10]. In view of the therapeutic importance of heterosteroids and in continuation of our interests in development of newer strategy for A- and D-ring annelated heterosteroids [11], herein we wish to report a solvent-free $Pd(OAc)_2$ catalyzed three component reaction of β-halovinyl aldehyde, alkyne and benzylamine under microwave irradiation for the synthesis of steroidal and nonsteroidal pyridines [Scheme 1].

2. Experimental

2.1. General remarks

Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR-2000 spectrometer on a thin film using chloroform. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (60–120 mesh, Merck Chemicals). All MW reactions were carried out in a Synthos 3000 (Anton Paar) microwave reactor.

2.2. Chemical synthesis

2.2.1. General procedure for the synthesis of steroidal and non-steroidal pyridines from β-bromovinyl aldehydes

Steroidal/nonsteroidal bromo vinyl aldehyde (0.5 mmol), alkyne (0.5 mmol), benzyl amine (0.5 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Na_2CO_3 (1.5 mmol) and neutral alumina (200 mg) were mixed intimately and the mixture was irradiated

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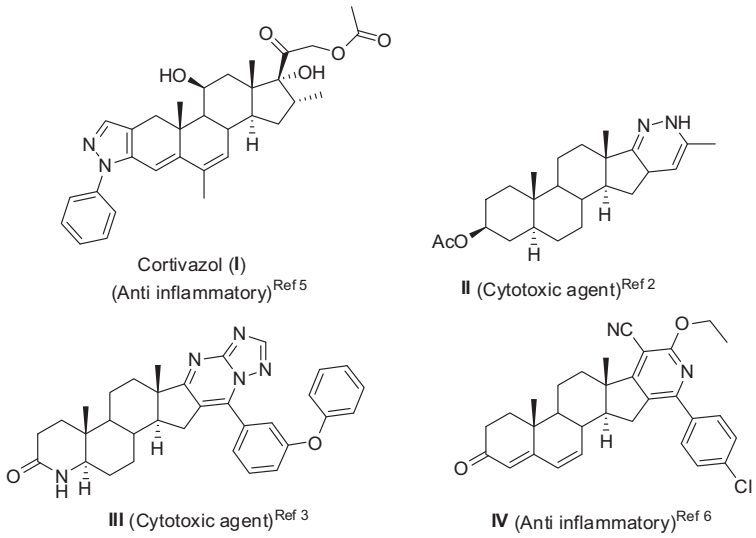
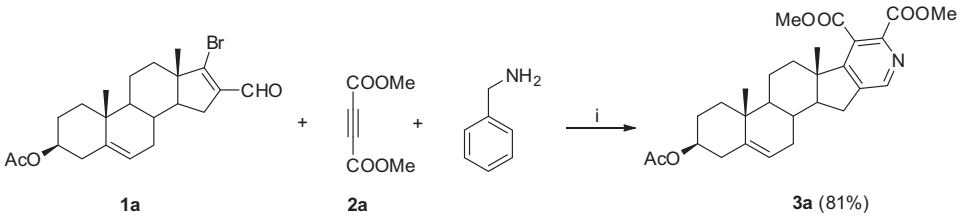


Fig. 1. Examples of biological active heterosteroids (**I**–**IV**).



Scheme 1. Reagents and condition (i) $Pd(OA)_2$, PPh_3, Na_2CO_3, neutral alumina, 10 min, MW.

in a closed vessel in a Synthos 3000 microwave reactor at 600 Watt (140 °C and 12 bar) for 10 min. After 10 min ethylacetate (30 mL) was added to the reaction mixture and it was filtered through whatman filter paper. The residue obtained after removal of ethylacetate layer was purified by silica gel column chromatography using EtOAc/hexane as the eluent to afford the pyridine derivative. The alumina on the filter paper was then dried in vacuo and can be used again for another two times in place of $Pd(OAc)_2$ without substantial loss of the yield of the product.

*2.2.1.1. 3β-Acetoxy-5′,6′-dicarbmethoxy-5-en-androst[16,17-c]pyridine (**3a**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51 (s, 1H), 5.36–5.32 (m, 1H), 4.56–4.50 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 1.97 (s, 3H), 1.10 (s, 3H), 1.01 (s, 3H), 2.84–0.84 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 167.8, 166.8, 165.2, 164.1, 160.2, 146.2, 140.1, 127.1, 121.7, 73.7, 57.1, 53.4, 53.2, 52.7, 49.9, 46.9, 38.1, 36.8, 33.2, 31.4, 30.6, 29.9, 27.7, 21.4, 20.6, 19.3, 17.1. IR ($CHCl_3$, cm^{-1}): 2952, 1733, 1438, 1375, 1251, 755. MS (EI, *m*/*z*): 481.2, 421.2 [M^+–60]. Anal. calcd. for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33; N, 2.91; Found: C, 69.92; H, 7.42; N, 2.83.

*2.2.1.2. 3β-Acetoxy-5′-carbmethoxy-6′-phenyl-5-en-androst[16,17-c] pyridine (**3b**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.61 (s, 1H), 7.71–7.28 (m, 5H), 5.42–5.39 (m, 1H), 4.47–4.42 (m, 1H), 3.65 (s, 3H), 1.99 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 2.80–0.85 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2, 168.8, 160.1, 156.6, 146.2, 140.1, 139.6, 138.0, 128.7, 128.5, 128.3, 124.0, 121.9, 73.6, 57.4, 56.1, 54.7, 52.4, 49.8, 46.8, 40.7, 40.4, 36.7, 36.66, 33.1, 31.4, 30.9, 30.85, 30.6, 21.3, 19.2, 17.0. IR ($CHCl_3$, cm^{-1}): 2923, 1731, 1649, 1048, 1026, 997, 768. MS (EI, *m*/*z*): 439.2 [M-60]. Anal. calcd. for $C_{32}H_{37}NO_4$: C, 76.92; H, 7.46; N, 2.80; Found: C, 76.80; H, 7.32; N, 2.87.

*2.2.1.3. 3β-Acetoxy-5′-carbethoxy-6′-phenyl-5-en-androst[16,17-c]pyridine (**3c**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.46 (s, 1H), 7.54–7.28 (m, 5H), 5.38–5.34 (m, 1H), 4.57–4.52 (m, 1H), 4.10–4.00 (m, 2H), 1.97 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H), 2.79–0.85 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 168.9, 160.4, 156.6, 146.18, 140.2, 139.6, 138.1, 128.8, 128.5, 128.3, 124.0, 121.9, 73.7, 57.5, 56.2, 54.7, 52.2, 49.8, 49.7, 46.8, 40.8, 40.4, 36.7, 33.2, 31.4, 30.9, 30.8, 30.6, 21.5, 19.2, 17.2. IR ($CHCl_3$, cm^{-1}): 2924, 1732, 1650, 1048, 997, 769. MS (EI, *m*/*z*): 453.3 [M-60]. Anal. calcd. for $C_{33}H_{39}NO_4$: C, 77.16; H, 7.65; N, 2.73; Found: C, 77.21; H, 7.69; N, 2.86.

*2.2.1.4. 3β-Acetoxy-5′-trimethylsilyl-6′-phenyl-5-en-androst[16,17-c]pyridine (**3d**).* Yellow solid; m.p. 250–251 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.39 (s, 1H), 7.50–7.28 (m, 5H), 5.40–5.31 (m, 1H), 4.60–4.52 (m, 1H), 2.00 (s, 3H), 1.11 (s, 3H), 1.00 (s, 3H), 2.82–0.83 (m, 17H), 0.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 165.2, 145.1, 139.9, 138.0, 129.5, 127.8, 127.0, 122.2, 73.8, 57.8, 49.7, 48.5, 38.1, 36.9, 36.7, 36.0, 31.5, 31.0, 29.7, 29.4, 27.8, 22.7, 21.4, 21.0, 19.3, 15.9, 14.1, 4.2; IR ($CHCl_3$, cm^{-1}) 2923, 1730, 1649, 1049, 996, 768. MS (EI, *m*/*z*): 453.3 [M-60]. Anal. calcd. for $C_{33}H_{43}NO_2Si$: C, 77.14; H, 8.44; N, 2.73; Found: C, 77.31; H, 8.50; N, 2.89.

*2.2.1.5. 3β-Acetoxy-5′-methyl-6′-phenyl-5-en-androst[16,17-c]pyridine (**3e**).* Yellow solid; m.p. 190–191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.36 (s, 1H), 7.47–7.31 (m, 5H), 5.46–5.39 (m, 1H), 4.65–4.56 (m, 1H), 2.29 (s, 3H), 2.05 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 3.01–0.87 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 160.8, 157.8, 143.2, 141.1, 140.0, 137.0, 129.3 128.0, 127.5, 126.0, 122.1, 73.8, 57.1, 50.9, 49.9, 47.4, 38.1, 36.9, 35.6, 31.5, 30.8, 29.7, 29.4, 27.7, 21.5, 20.9, 19.3, 15.9. IR ($CHCl_3$, cm^{-1}): 2938,

1731, 1373, 1245, 1033, 772. MS (EI, *m*/*z*) 395.2 [M-60]$^+$. Anal. calcd. for $C_{31}H_{37}NO_2$: C, 81.72; H, 8.19; N, 3.07; Found: C, 81.92; H, 8.33; N, 3.27.

*2.2.1.6. 3β-Acetoxy-5′,6′-diphenyl-5-en-androst[16,17-c]pyridine (**3f**).* Yellow solid; m.p. 225–226 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.55 (s, 1H), 7.29–6.99 (m, 10H), 5.42–5.36 (m, 1H), 4.63–4.55 (m, 1H), 2.03 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 2.82–0.83 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 160.7, 156.3, 144.8, 140.7, 140.0, 137.7, 137.2, 132.1, 131.0, 130.4, 129.8, 127.5, 127.4, 127.0, 126.9, 122.0, 73.8, 57.5, 49.8, 48.0, 47.3, 41.3, 36.6, 32.0, 31.6, 30.8, 29.7, 27.7, 21.4, 20.4, 19.2, 18.2, 14.3, 11.4. IR ($CHCl_3$, cm^{-1}): 2941, 1731, 1374, 1245, 1033, 904, 758, 700. MS (EI, *m*/*z*): 517.3 [M$^+$]. Anal. calcd. for $C_{36}H_{39}NO_2$: C, 83.52; H, 7.59; N, 2.71; Found: C, 83.55; H, 7.67; N, 2.91.

*2.2.1.7. 3β-Acetoxy-5′,6′-n-dipropyl-5-en-androst[16,17-c]pyridine (**3g**).* Red solid; m.p. 154–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.28 (s, 1H), 5.44–5.41 (m, 1H), 4.67–4.55 (m, 1H), 2.05 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H), 2.83–0.85 (m, 31H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 156.9, 139.9, 139.0, 138.1, 133.3, 123.0, 73.7, 56.7, 49.6, 48.3, 38.0, 36.8, 36.7, 36.0, 34.5, 31.4, 30.8, 30.5, 27.7, 25.1, 23.8, 21.5, 21.2, 19.3, 17.2, 14.8, 14.3. IR ($CHCl_3$, cm^{-1}): 2958, 2931, 1732, 1244, 1033, 772. MS (EI, *m*/*z*): 449.3 [M$^+$]. Anal. calcd. for $C_{30}H_{43}NO_2$: C, 80.13; H, 9.64; N, 3.11; Found: C, 80.35; H, 9.74; N, 2.85.

*2.2.1.8. 3β-Acetoxy-6′-(4′′-trifluoromethylphenyl)-5-en-androst[16,17-c]pyridine (**3h**).* Red gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.0 (s, 1H), 8.10–7.18 (m, 5H), 5.43–5.38 (m, 1H), 4.66–4.56 (m, 1H), 2.04 (s, 3H), 1.12 (s, 3H), 1.00 (s, 3H), 2.83–0.85 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.2, 170.5, 153.2, 147.8, 140.0, 134.4, 131.6, 129.2, 126.1, 126.0, 122.0, 120.3, 73.7, 54.8, 51.0, 50.3, 38.1, 36.8, 33.5, 31.3, 30.7, 29.4, 29.2, 21.4, 20.6, 19.2, 15.9, 14.1. IR ($CHCl_3$, cm^{-1}): 2959, 1730, 1030, 774. MS (EI, *m*/*z*): 509.3 [M$^+$]. Anal. calcd. for $C_{31}H_{34}F_3NO_2$: C, 73.06; H, 6.72; N, 2.75; Found: C, 73.31; H, 6.62; N, 2.85.

*2.2.1.9. 3β-Acetoxy-6′-(thiophen-2-yl)-5-en-androst[16,17-c]pyridine (**3i**).* Red solid; m.p. 215–216 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.36 (s, 1H), 7.63 (d, *J* = 4.0 Hz, 1H), 7.58 (d, *J* = 5.0 Hz, 1H), 7.32–7.28 (m, 2H), 5.38–5.34 (m, 1H), 4.61–4.48 (m, 1H), 2.05 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H), 2.83–0.85 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 163.9, 151.9, 145.5, 142.8, 140.0, 136.9, 126.4, 126.0, 122.8, 122.1, 113.3, 73.8, 57.1, 50.4, 45.5, 38.1, 36.9, 36.87, 34.2, 31.6, 30.8, 29.8, 27.7, 21.5, 20.6, 19.4, 18.6. IR ($CHCl_3$, cm^{-1}): 2961, 1731, 772. MS (EI, *m*/*z*): 447.2 [M$^+$]. Anal. calcd. for $C_{28}H_{33}NO_2S$: C, 75.13; H, 7.43; N, 3.13; Found: C, 75.40; H, 7.52; N, 3.04.

*2.2.1.10. 3β-Acetoxy-6′-(3′,5′-difluorophenyl)-5-en-androst[16,17-c]pyridine (**3j**).* Red solid; m.p. 193–194 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (s, 1H), 7.55–7.47 (m, 2H), 7.42 (s, 1H), 6.86–6.77 (m, 1H), 5.45–5.41 (m, 1H), 4.65–4.57 (m, 1H), 2.05 (s, 3H), 1.12 (s, 3H), 1.00 (s, 3H), 2.82–0.87 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): 170.6, 165.2, 164.3, 161.8, 153.3, 145.8, 143.4, 140.0, 138.5, 122.0, 113.5, 109.9, 109.5, 103.7, 73.8, 57.2, 50.4, 45.6, 38.1, 36.9, 34.1, 31.6, 30.8, 29.8, 27.7, 21.4, 20.6, 19.3, 18.6, 14.1. IR ($CHCl_3$, cm^{-1}): 2957, 2929, 1731, 1243, 1033, 771. MS (EI, *m*/*z*): 417.2 [M-60]$^+$. Anal. calcd. for $C_{30}H_{33}F_2NO_2$: C, 75.45; H, 6.96; N, 2.93; Found: C, 75.69; H, 6.75; N, 2.78.

*2.2.1.11. 3β-Acetoxy-6′-(6′′-methoxynaphthalen-2-yl)-5-en-androst[16,17-c]pyridine (**3k**).* Yellow solid; m.p. 234–235 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.55 (s, 1H), 8.37 (s, 1H), 8.09 (dd, *J* = 8.6 Hz & 1.7 Hz, 1H), 7.85 (d, *J* = 6.3 Hz, 1H), 7.81 (d, *J* = 5.4 Hz, 1H), 7.59 (s, 1H), 7.13–7.19 (m, 2H), 5.45–5.41 (m, 1H), 4.65–4.57 (m, 1H), 3.95 (s, 3H), 2.05 (s, 3H), 1.12 (s, 3H), 1.00 (s, 3H), 2.82–0.87 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 164.0, 158.0, 155.9, 145.6, 140.0, 137.0, 135.3, 134.7, 130.1, 129.0, 127.1, 125.9, 125.4, 122.1, 119.1, 113.5, 105.6, 73.8, 57.2, 55.3, 50.5, 45.6, 38.1, 36.9, 34.2, 31.7, 30.8, 30.2, 29.8, 21.7, 21.4, 20.7, 19.4, 18.7. IR ($CHCl_3$, cm^{-1}): 2958, 2927, 1731, 1242, 1033, 772. MS (EI, *m*/*z*): 461.2 [M-60]$^+$. Anal. calcd. for $C_{35}H_{39}NO_3$: C, 80.58; H, 7.54; N, 2.68; Found: C, 80.62; H, 7.55; N, 2.70.

*2.2.1.12. 5′-Carbmethoxy-6′-phenyl-cholest[2,3-c]pyridine (**3l**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.42 (s, 1H), 7.64–7.27 (m, 5H), 3.64 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 6H), 2.89–0.86 (m, 29H), 0.77 (s, 3H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 153.3, 151.2, 143.4, 139.9, 132.2, 131.0, 128.4, 128.1, 127.6, 56.4, 56.3, 53.6, 52.3, 42.5, 41.2, 39.9, 39.5, 36.2, 35.8, 35.5, 34.7, 29.7, 29.4, 28.2, 28.0, 23.9, 22.9, 22.6, 18.7, 12.0, 11.7. IR ($CHCl_3$, cm^{-1}): 1730, 1457, 1219, 772. MS (EI, *m*/*z*): 555.3 [M$^+$]. Anal. calcd. for $C_{38}H_{53}NO_2$: C, 82.11; H, 9.61; N, 2.52; Found: C, 82.22; H, 9.63; N, 2.43.

*2.2.1.13. 5′-Methyl-6′-phenyl-cholest[2,3-c]pyridine (**3m**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (s, 1H), 7.75–7.19 (m, 5H), 2.17 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 6H), 2.86–0.82 (m, 29H), 0.75 (s, 3H), 0.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.7, 147.6, 144.6, 141.2, 130.6, 129.3, 128.6, 128.3, 128.2, 128.0, 127.4, 56.4, 56.3, 53.7, 42.5, 41.7, 39.5, 36.2, 35.8, 35.6, 34.5, 31.9, 28.3, 28.0, 24.3, 23.9, 22.9, 22.6, 21.2, 18.7, 15.8, 12.0, 11.6. IR ($CHCl_3$, cm^{-1}): 2930, 1676, 1465, 1382, 1261, 1025, 770. MS (EI, *m*/*z*): 510.4 [M$^+$]. Anal. calcd. for $C_{37}H_{53}N$: C, 86.83; H, 10.44; N, 2.74; Found: C, 86.92; H, 10.57; N, 2.81.

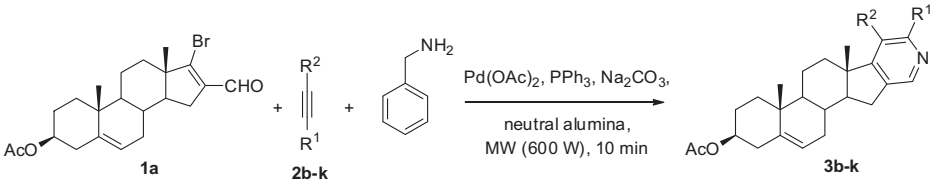
*2.2.1.14. 5′,6′-Diphenyl-cholest[2,3-c]pyridine (**3n**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.33 (s, 1H), 7.45–6.90 (m, 10H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 6H), 2.88–0.85 (m, 29H), 0.77 (s, 3H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 147.8, 144.5, 141.2, 141.0, 130.6, 129.4, 128.7, 128.3, 128.2, 127.4, 56.6, 56.3, 53.7, 42.6, 41.7, 39.5, 36.2, 35.8, 35.8, 34.5, 31.9, 28.3, 24.3, 23.8, 22.9, 22.6, 21.2, 18.7, 15.9, 12.0, 11.7. IR ($CHCl_3$, cm^{-1}): 2931, 1677, 1465, 1383, 1263, 1025, 770. MS (EI, *m*/*z*): 572.4 [M$^+$]. Anal. calcd. for $C_{42}H_{55}N$: C, 87.90; H, 9.66; N, 2.44; Found: C, 87.81; H, 9.50; N, 2.73.

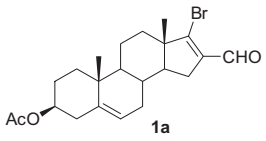
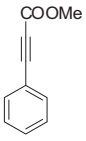
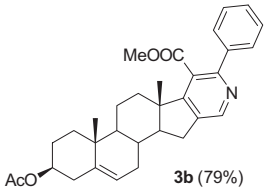
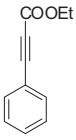
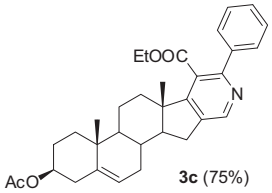
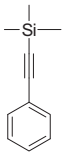
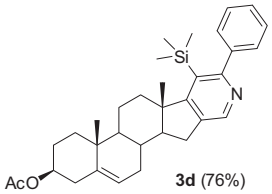
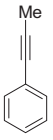
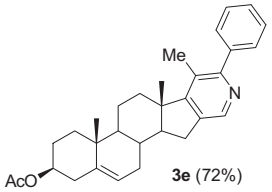
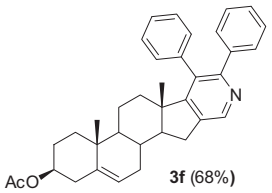
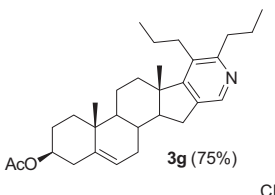
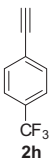
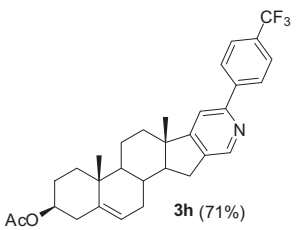
*2.2.1.15. 5′,6′-Di-n-propyl-cholest[2,3-c]pyridine (**3o**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (s, 1H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 6H), 2.87–0.85 (m, 43H), 0.77 (s, 3H), 0.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.0, 146.2, 146.1, 133.8, 130.6, 57.0, 56.3, 53.6, 42.5, 41.6, 39.5, 36.2, 35.8, 34.4, 29.7, 28.9, 28.2, 28.0, 23.8, 23.5, 22.9, 22.6, 18.7, 14.8, 14.4, 12.0, 11.5. IR ($CHCl_3$, cm^{-1}): 2932, 1677, 1463, 1263, 1025, 768. MS (EI, *m*/*z*): 505.4 [M$^+$]. Anal. calcd. for $C_{36}H_{59}N$: C, 85.48; H, 11.76; N, 2.77; Found: C, 85.54; H, 11.89; N, 2.90.

*2.2.1.16. 5′,6′-Dicarbmethoxy-cholest[2,3-c]pyridine (**3p**).* Yellow gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.35 (s, 1H), 3.74 (s, 3H), 3.59 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 6H), 2.89–0.82 (m, 29H), 0.77 (s, 3H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 168.1, 165.3, 164.6, 151.9, 151.0, 140.1, 56.2, 53.7, 52.8, 52.7, 51.9, 51.1, 42.4, 40.9, 39.5, 35.8, 34.6, 31.4, 30.4, 30.3, 29.7, 28.0, 23.8, 22.8, 22.5, 18.7, 12.0, 11.7. IR ($CHCl_3$, cm^{-1}): 2952, 1740, 1594, 1435, 1259, 1049. MS (EI, *m*/*z*): 537.3 [M$^+$]. Anal. calcd. for $C_{34}H_{51}NO_4$: C, 75.94; H, 9.56; N, 2.60; Found: C, 76.12; H, 9.52; N, 2.73.

*2.2.1.17. 6′-Carbethoxy-cholest[2,3-c]pyridine (**3q**).* Red gum; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.54 (s, 1H), 7.75 (s, 1H), 4.38 (q, *J* = 7.14 Hz, 2H), 0.96 (t, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H),

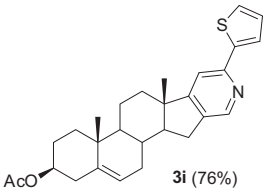
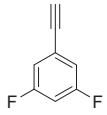
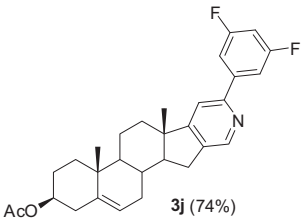
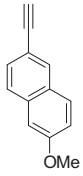
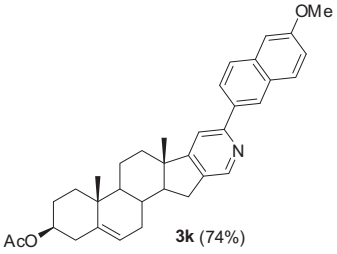
Table 1
Synthesis of steroidal D-ring fused substituted pyridines.



Entry	β-Bromovinyl aldehyde (**1a**)	Alkyne (**2b-k**)	Pyridine derivatives (% Yield)[a]
1			
	1a	**2b**	**3b** (79%)
2	**1a**		
		2c	**3c** (75%)
3	**1a**		
		2d	**3d** (76%)
4	**1a**		
		2e	**3e** (72%)
5	**1a**		
		2f	**3f** (68%)
6	**1a**		
		2g	**3g** (75%)
7	**1a**		
		2h	**3h** (71%)

(*continued on next page*)

Table 1 (*continued*)

Entry	β-Bromovinyl aldehyde (**1a**)	Alkyne (**2b-k**)	Pyridine derivatives (% Yield)[a]
8	**1a**	 **2i**	 **3i** (76%)
9	**1a**	 **2j**	 **3j** (74%)
10	**1a**	 **2k**	 **3k** (74%)

[a] Yield of the isolated product.

0.88 (d, J = 6.4 Hz, 6H), 2.90–0.86 (m, 29H), 0.78 (s, 3H), 0.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 151.0, 146.2, 136.7, 128.4, 125.0, 61.7, 56.3, 56.2, 53.6, 42.4, 39.5, 36.2, 35.8, 35.5, 35.0, 30.0, 28.2, 28.0, 23.8, 22.8, 22.6, 21.2, 18.7, 14.4, 14.1, 12.0, 11.6. IR ($CHCl_3$, cm^{-1}): 2928, 2869, 1725, 1255, 772. MS (EI, m/z): 493.3 [M^+]. Anal. calcd. for $C_{33}H_{51}NO_2$: C, 80.27; H, 10.41; N, 2.84; Found: C, 80.28; H, 10.48; N, 2.97.

*2.2.1.18. 8-Methoxy-1,2-diphenyl-5,6-dihydrobenzo[f]isoquinoline (**3r**).* Red liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.51 (s, 1H), 7.30–6.95 (m, 11H), 6.63 (dd, J = 8.3 Hz & 2.9 Hz, 1H), 6.22 (d, J = 2.7 Hz, 1H), 3.07 (s, 3H), 2.82–2.77 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.6, 157.2, 147.1, 141.8, 140.5, 139.1, 133.1, 132.5, 132.4, 131.2, 129.7, 128.6, 127.6, 127.1, 116.1, 113.7, 54.7, 29.7, 27.2. MS (EI, m/z): 363.1 [M^+]. IR ($CHCl_3$, cm^{-1}): 2933, 1670, 1462, 1262, 768. Anal. calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.85; Found: C, 86.07; H, 5.90; N, 3.96.

*2.2.1.19. 2,3,4-Triphenylpyridine (**3s**).* Red solid; m.p. 188–190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.70 (s, 1H), 7.33 (d, J = 5.0 Hz, 1H), 7.45–6.79 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.4, 149.9, 148.2, 140.7, 139.3, 137.7, 134.4, 131.4, 129.9, 129.7, 129.3, 128.4, 128.2, 127.9, 127.7, 127.6, 127.4, 126.7, 123.7. IR ($CHCl_3$, cm^{-1}): 2959, 1576, 1491, 1074. Anal. calcd. for $C_{23}H_{17}N$: C, 89.87; H, 5.57; N, 4.56; Found: C, 89.98; H, 5.41; N, 4.40.

3. Results and discussion

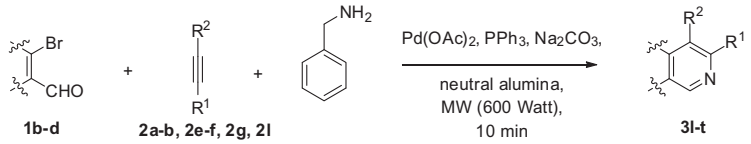
The palladium and nickel catalyzed annulation processes which found a range of applications in organic synthesis were used to synthesize many nitrogen heterocycles including substituted pyridines [12]. Although these methods are highly useful, they have some disadvantages such as stepwise synthesis of *tert*-butylimines followed by coupling reactions of imine intermediates with alkynes, long reaction time, and low yield of the annulated products with terminal mono-substituted acetylenes [13].

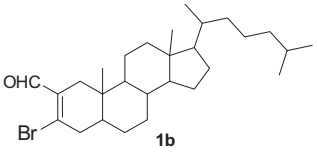
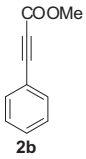
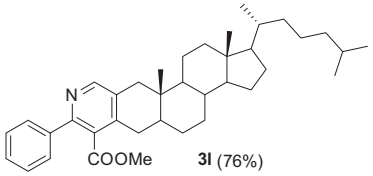
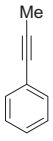
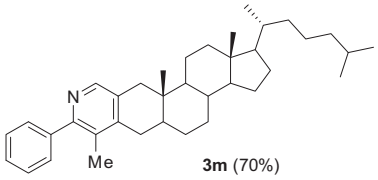
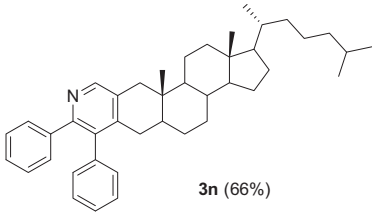
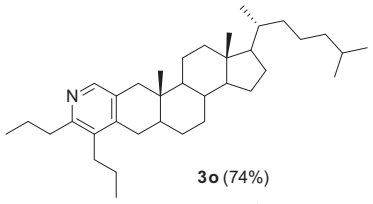
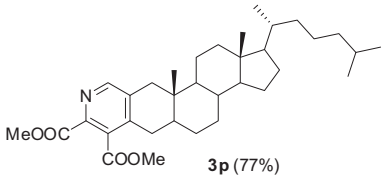
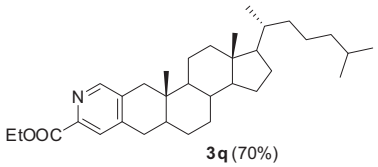
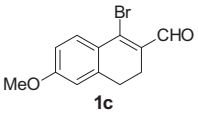
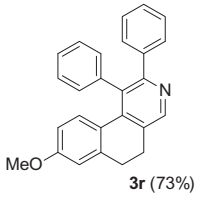
Miller described the first synthesis of steroidal heterocycles containing a pyridine ring using high temperature and multistep reaction strategy [14] which was followed by three-steps synthesis by Chelucci and co-workers through pyridoannelation of *N,N*-dimethylhydrazones with bromoethyl-1,3-dioxolane [15]. Moreover, Abbiati et al., developed one method to synthesize steroidal pyridines from corresponding carbonyl compounds by using Gold(III) salts as a catalyst [8]. Recently, Yan et al., reported Cu(II) salt-mediated synthesis of steroidal[3,4-*b*]pyridines from 3-keto steroids and propargylamine using Cu(II) salt as the catalyst with very low yield (6–51%) and limited substrate scope [4]. We also reported synthesis of steroidal A ring fused chloropyridines by refluxing a mixture of steroidal enamides with Vilsmeier reagent in DMF [16] as well as Lewis acid catalyzed synthesis of steroidal 4,6-diarylpyridines from steroidal 1,5-dicarbonyl compounds under microwave-irradiation [11]. However these existing syntheses led to steroidal pyridines with no diversity at 5,6-position of the pyridine ring. To the best of our knowledge, there is no report focusing on the synthesis of steroidal 5,6-disubstituted pyridines in the literature.

The starting material steroidal β-bromovinyl aldehyde **1a** was synthesized from commercially available 3-acetoxy-androst-5-en-17-one by treatment with Vilsmeier reagent prepared from PBr_3 and DMF [17]. Another steroidal β-bromovinyl aldehyde **1b** was synthesized starting from commercially available 5α-cholestan-3-one by reacting with Vilsmeier reagent under refluxing chloroform [17]. Similarly, other nonsteroidal β-bromovinyl aldehydes **1c-d** were synthesized by using the same procedure. Then, a mixture of steroidal β-bromovinyl aldehyde **1a** (1.0 equivalent), benzylamine (1.1 equivalent), dimethylacetylene dicarboxylate (1.0 equivalent), palladium acetate (5 mol%), triphenylphosphine (1.0 equivalent), Na_2CO_3 (3.0 equivalent) and neutral alumina (200 mg) was irradiated in a closed vessel in a Synthos 3000 microwave reactor at 600 Watt (140 °C and 12 bar) for 10 min which

afforded compound 3β-acetoxy-5′,6′-dicarbmethoxy-5-en-androst[16,17-*c*]pyridine (**3a**, Scheme 1) in excellent yield (81%). It was observed that the alumina used in this reaction, where the Pd catalyst was trapped can be reused for another two times without losing the yield of 3a to a great extent (1st recycle, yield of **3a** = 73%, 2nd recycle, yield of **3a** = 56%). Instead of benzyl amine

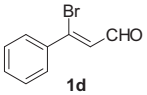
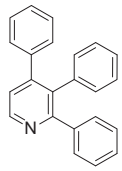
Table 2
Synthesis of steroidal A-ring fused substituted pyridines and nonsteroidal pyridines.



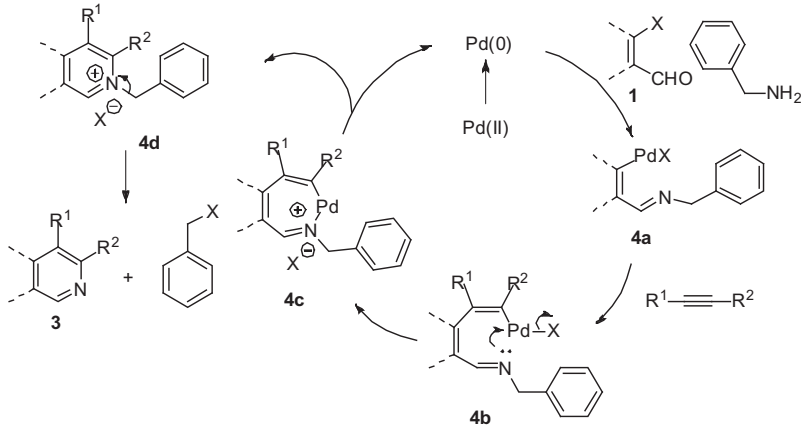
Entry	β-Bromovinyl aldehyde (**1b-d**)	Alkyne	Pyridine derivatives (% Yield)[a]
1			
	OHC, Br, **1b**	COOMe, **2b**	N, COOMe, **3l** (76%)
2	**1b**		
		Me, **2e**	N, Me, **3m** (70%)
3	**1b**		
		2f	N, **3n** (66%)
4	**1b**		
		2g	N, **3o** (74%)
5	**1b**		
		COOMe, COOMe, **2a**	N, MeOOC, COOMe, **3p** (77%)
6	**1b**		
		COOMe, **2l**	N, EtOOC, **3q** (70%)
7			
	Br, CHO, MeO, **1c**	**2f**	N, MeO, **3r** (73%)

(*continued on next page*)

Table 2 (*continued*)

Entry	β-Bromovinyl aldehyde (**1b-d**)	Alkyne	Pyridine derivatives (% Yield)[a]
8	 **1d**	 **2f**	 **3s** (77%)

[a] Yield of the isolated product.



Scheme 2. Plausible mechanism of Pd-mediated formation of compound **3**.

when we tried some other (Table 1) amine such as *tert*-butylamine to perform the reaction of **1a** with dimethylacetylene dicarboxylate we obtained decreased yield (48%) of compound **3a** which could be due the lower boiling point of *tert*-buylamine. We also observed that reducing the quantity of $Pd(OAc)_2$ from 5 mol% to 2.5 mol% decreased the yield of **3a** to 65% while increase of catalyst loading to 10 mol% did not affect the yield of **3a** at all. Although there is the possibility of formation of product **3a** in the three component reaction in absence of Pd catalyst also, via a Diels Alder reaction between the benzylimine of β-bromovinyl aldehyde (**1a**) with alkyne **2a**, followed by elimination of benzyl group as benzyl bromide, our efforts to obtain **3a** in absence of the Pd catalyst met with failure (Table 2). After having the product **3a** in hand it was identified from spectroscopic and analytical data. The ^{1}H NMR of compound **3a** exhibited a characteristic aromatic singlet signal at δ 8.51 and two singlet signals at δ 3.90 and δ 3.88 for two ester methyl groups. The ^{13}C NMR spectrum of **3a** showed signals for five aromatic carbons of pyridine, two steroidal B-ring olefinic carbons and three ester carbonyls at δ 170.5, 167.8, 166.8, 165.2, 164.1, 160.2, 146.2, 140.1, 127.1 and 121.7. The EI mass spectra of compound **3a** exhibited molecular ion peaks at *m*/*z* 481.2 and 421.2 [M^+–60].

Similarly, microwave reactions of steroidal β-bromovinyl aldehyde **1a** with alkynes **2b-k** and steroidal β-bromovinyl aldehyde **1b** with alkynes **2a-b**, **2e-f**, **2g**, **2l** afforded steroidal D-ring fused substituted pyridines **3b-k** and steroidal A-ring fused substituted pyridines **3l-q** respectively in high yields (Tables 1 and 2). In addition, the reaction of non-steroidal β-bromovinyl aldehydes **1c** and **1d** with alkyne **2f** yielded non-steroidal pyridine derivatives **3r** (73%) and **3s** (77%) under the same reaction condition. It was noteworthy to observe that in all the reactions of β-bromovinyl aldehydes with substituted alkynes and benzylamine under the above reaction condition afforded only one regioisomer of the pyridine derivative as shown in Tables 1 and 2.

Based on our findings and literature information, we propose a mechanism for this palladium-catalyzed iminoannulation chemistry which is shown in Scheme 2 [18,19]. Oxidative addition of the vinylic halide group of **1** to Pd(0) and reaction of aldehyde group of **1** with benzylamine produces an organopalladium imine intermediate **4a**. Literature on similar alkyne annulations chemistry shows that Pd of **4a** adds to the more hindered end of the alkyne to provide vinylic palladium intermediate **4b** which accounts for the regioselectivity of the final pyridine derivatives [19]. Intramolecular reaction of vinylic palladium with the benzyl imine of intermediate **4b** produces a seven-membered palladacyclic ammonium salt **4c** which on subsequent reductive elimination produces a benzylpyridinium salt **4d** and regenerates Pd(0). The fragmentation of the benzyl group of **4d** to relieve the strain resulting from interaction of benzyl group with the substituent present in the *ortho*-position of the pyridine ring leads to the formation of compound **3** as well as benzyl halide.

In conclusion, a solvent free multi-component reaction condition for the synthesis steroidal A-, D-ring fused 5,6-disubstituted pyridines and nonsteroidal substituted pyridines was developed using $Pd(OAc)_2$ as the catalyst under microwave irradiation. A wide variety of alkyl-, aryl- and ester-substituted alkynes undergo this highly regioselective reaction to give good yields of pyridine derivatives.

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