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Novel Synthesis of Hexahydrochromeno[4,3-*b*]pyrrolo[2,1-*a*]isoquinolines *via* C-H Functionalization

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In present work, an efficient and direct method for the synthesis of hexahydrochromeno[4,3-*b*]pyrrolo[2,1-*a*]isoquinolines is reported. This method involves ®T3P mediated oxidation of alcohols to aldehydes followed by [3+2] cycloaddition to afford hexahydrochromeno[4,3-*b*]-pyrrolo[2,1-*a*]isoquinolines with good yields.

Keywords: C-H Functionalization, ®T3P, [3+2] Cycloaddition, Chromene, Isoquinolines.

INTRODUCTION

Hexahydrochromeno[4,3-*b*]pyrrolo[2,1-*a*]isoquinolines derivatives are structural elements of natural products of great significance for their biological and pharmacological activity, such as acetylcholinesterase inhibitors [1], topoisomerase I inhibitors [2], cytotoxic effect, mitochondrial function inhibitors, proteinkinase inhibitors, multidrug resistance (MDR) reversal activity, HIV I interphase inhibitors, antioxidant activity, anticancerogenic properties [3]. Furthermore, hexahydrochromeno[4,3-*b*]pyrrolo[2,1-*a*]isoquinolines scaffold form the essence structure of large marine alkaloid family Lamellarins (Fig. 1).

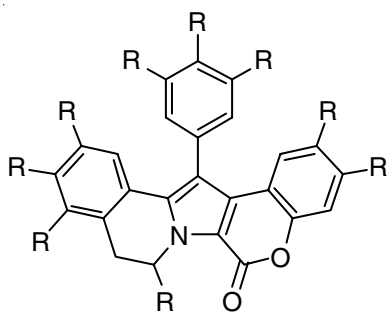


Fig. 1

The [3+2] cycloaddition reaction is a robust method for the synthesis of bicyclic saturated five-membered heterocycles, and consequently, it has been broadly studied by researchers [4]. Formation of fused nitrogen-containing bicyclic systems generally occurs with high regio and stereoselectively by intramolecular [3+2] cycloaddition reactions [5]. Among the methods that are available to generate non-stabilized azomethine ylides most frequently prepared *via* decarboxylative condensation of aldehydes with amino acids such as proline and sarcosine [6]. Majority of examples described in the literature pertain to the synthesis of chromeno[4,3-*b*]pyrrole fused skeletons and only limited reports are available for the synthesis of chromeno [3,4-*b*]pyrroles. Synthesis of chromeno[4,3-*b*]pyrrole *via* deprotonation route was first reported by Confalone and Huie [7]. Intramolecular azomethine ylide cycloaddition reaction for the synthesis of same type of compounds extensively studied by Grigg *et al*. [8]. Synthesis of 1-benzopyrano[3,4-*c*]pyrrolidines by reaction of 3-substituted coumarins with N-alkyl-α-amino acids and aldehydes by Moshkin *et al*. [9]. Intramolecular [3+2] azomethine ylide cycloaddition reaction was the key step in the synthesis of tricyclic core of martinellic acid, which are bradykinin B1 and B2 receptor antagonists [10].

Propylphosphonic anhydride (®T3P) has received much attention as a coupling agent and as a water scavenger [11,12], offering several advantages such as high yields, purity, low toxicity, broad functional group tolerance and easy work-up when compared to traditional reagents. ®T3P was initially employed as peptide coupling agent, dehydrating agent. Its utility was successfully demonstrated in rearrangement reactions, heterocyclic synthesis and C-C bond formation. In continuation

of our work on synthetic applications of ®T3P to the synthesis of heterocyclic compounds [13]. Though, ®T3P has been identified as a mild water scavenger, the wider scope and synthetic utility of this reagent for oxidization and cycloaddition have not been explored. With a need to develop simpler methods for the synthesis of hexahydrochromeno[4,3-*b*]pyrrolo[2,1-*a*]-isoquinolines annulated heterocycles and in continuation of our work on the development of the useful synthetic methodologies [6,13-20], herein we report novel, direct approach for synthesis of hexahydrochromeno[4,3-*b*]pyrrolo[2,1-*a*]-isoquinolines and its analogues. The tandem process involves oxidation of alcohol to aldehyde and intramolecular 1,3-dipolar cycloaddition reaction under mild conditions.

EXPERIMENTAL

All the chemicals were purchased from commercial sources and used as such. Purification of reaction products was carried out by flash column chromatography. IR spectra were recorded by Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ solvent by 400 MHz spectrometer. Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

General synthesis of products 3a-3n: To a solution of alcohol **1** (1.0 mmol) in DMSO (2 mL), was added at 0 ºC propylphosphonic anhydride (®T3P) (1.0 mmol, 50 % solution in ethyl acetate) and the resulting reaction mixture was stirred at room temperature for 1-2 h under nitrogen atmosphere. The reaction was monitored by TLC, after the completion of reaction, the solvent was removed under reduced pressure. The crude product was taken in toluene, amine **2** (1.2 mmol) and acetic acid (0.5 equiv) was added and stirred further for 1-2 h. After completion of the reaction, the mixture was diluted with water (20 mL) and neutralized with 10 % $NaHCO_3$ solution. The product was extracted with ethyl acetate (10 mL) and the combined organic phase was washed with water (10 mL) and brine solution. The organic phase was dried over anhydrous Na_2SO_4. The solvent was dried under reduced pressure to afford a crude product, which was purified on silica gel using ethyl acetate and petroleum ether (**Scheme-I**).

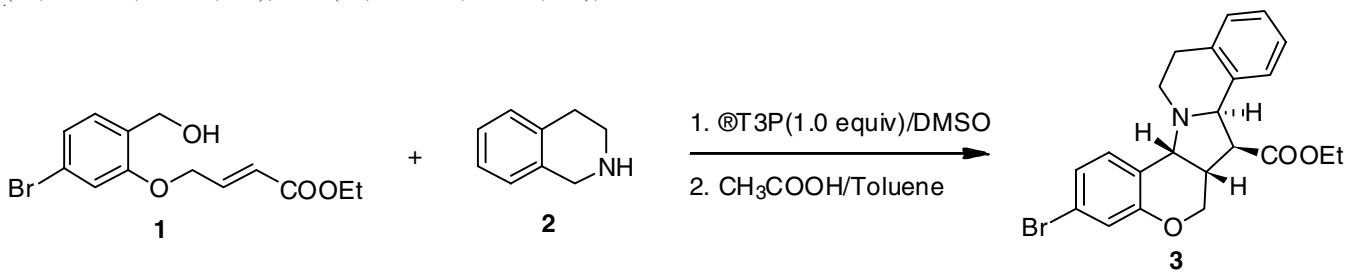
Characterization data

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3a): Colourless solid in 89 % yield; (R_f = 0.31 in hexane/EtOAc 80:20 v/v); m.p.: 149-151 ºC; IR (KBr, ν_{max}, cm^{-1}): 2948, 2927, 2897, 1724, 1483, 1448, 1397, 1224, 1118, 956, 757, 654. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.12-7.00 (4H), 6.94 (t, *J* = 7.5, Hz, 1H), 6.86 (d, *J* = 8.3, Hz, 1H), 4.48-4.41 (2H), 4.32 (dd, *J* = 11.5, 4.0 Hz, 1H), 4.22 (dd, *J* = 11.5, 2.8 Hz, 1H), 3.78 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.65 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.55 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.50-3.45 (m, 1H), 3.30-3.25 (m, 1H), 3.04-2.96 (2H), 2.94-2.87 (m, 1H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 155.9, 135.5, 134.0, 130.5, 128.7, 128.5, 128.0, 126.6, 125.4, 123.1, 121.5, 116.9, 66.3, 62.8, 62.6, 60.7, 52.0, 46.3, 40.9, 30.0, 14.0. (ESI-MS) *m/z* 350.2 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{22}H_{23}NO_3$: C, 75.62 (75.65); H, 6.62 (6.66); N, 4.01 (4.07); O, 13.75 (13.77).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-2,4-dibromo-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3b): Colourless solid in 72 % yield. (R_f = 0.49 in hexane/EtOAc 80:20 v/v); m.p.: 145-147 ºC; IR (KBr, ν_{max}, cm^{-1}): 2977, 2933, 2844, 1728, 1554, 1441, 1382, 1235, 1206, 1178, 852, 742, 647. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.53 (2H), 7.12-7.05 (3H), 7.03 (d, *J* = 7.0 Hz, 1H), 4.46 (dd, *J* = 11.7, 3.5 Hz, 1H), 4.40-4.37 (2H), 4.27 (dd, *J* = 11.7, 2.7 Hz, 1H), 3.78 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.62 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.51 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.45-3.38 (m, 1H), 3.33-3.29 (m, 1H), 3.03-2.94 (2H), 2.90-2.83 (m, 1H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 151.6, 135.2, 134.5, 133.2, 132.2, 128.6, 128.1, 126.8, 126.6, 125.4, 113.5, 111.7, 67.1, 62.8, 60.8, 51.7, 46.3, 40.2, 29.0, 13.9; ESI-MS *m/z* 508.0 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{22}H_{21}Br_2NO_3$: C, 52.16 (52.15); H, 4.20 (4.20); N, 2.70 (2.73); O, 9.40 (9.41); Br, 31.54 (31.55).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-2-methyl-6a,7,7a,12,13, 14a-hexahydro-6*H*-chromeno[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3c): Colourless solid in 66 % yield. (R_f = 0.39 in hexane/EtOAc 80:20 v/v); m.p.: 118-120 ºC; IR (KBr, ν_{max}, cm^{-1}): 2981, 2940, 2843, 1728, 1581, 1382, 1321, 1272, 1043, 912, 818, 754, 575. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 7.10-7.00 (comp, 4H), 6.95 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.75 (app d, *J* = 8.3 Hz, 1H), 4.43 (d, *J* = 9.4 Hz, 1H), 4.39 (d, *J* = 7.2 Hz, 1H), 4.28 (dd, *J* = 11.5, 3.6 Hz, 1H), 4.17 (dd, *J* = 11.5, 2.6 Hz, 1H), 3.77 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.63 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.53 (dd, *J* = 9.3, 6.3 Hz, 1 H), 3.50-3.42 (m, 1H), 3.27 (tt, *J* = 6.4, 3.0 Hz, 1H), 3.04-2.94 (2H), 2.93-2.85 (m, 1H), 2.26 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 153.7, 135.4, 133.9, 130.7, 130.5, 129.4, 128.5, 128.1, 126.5, 125.3, 122.7, 116.6, 66.3, 62.8, 60.6, 52.0, 46.4, 41.0, 29.1, 20.9, 14.0; ESI-MS *m/z* 364.2 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{23}H_{25}NO_3$: C, 76.10 (76.05); H, 6.97 (6.97); N, 3.78 (3.80); O, 13.15 (13.21).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-2-methoxy-6a,7,7a,12,13, 14a-hexahydro-6*H*-chromeno[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3d): Colourless solid in 69 % yield. (R_f = 0.41 in hexane/EtOAc 80:20 v/v); m.p.: 116-118 ºC. IR (KBr, ν_{max}, cm^{-1}): 2982, 2935, 1719, 1498, 1461, 1249, 1259,



Scheme-I

1156, 1186, 931, 906, 817. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.00 (4H), 6.97 (d, *J* = 3.01 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 1H), 6.74 (dd, *J* = 8.9, 3.0 Hz, 1H), 4.43-4.37 (2H), 4.27 (dd, *J* = 11.5, 3.5 Hz, 1H), 4.16 (dd, *J* = 11.5, 2.5, Hz, 1H), 3.82-3.73 (4H), 3.64 (dq, *J* = 10.8, 7.1, Hz, 1H), 3.53 (dd, *J* = 9.3, 6.3 Hz, 1H), 3.46 (tt, *J* = 8.3, 4.0 Hz, 1H), 3.29-3.25 (m, 1H), 3.04-2.95 (2H), 2.93-2.85 (m, 1H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3, 154.2, 150.0, 135.5, 134.0, 128.6, 128.1, 126.6, 125.4, 123.8, 117.7, 115.3, 114.3, 66.5, 63.2, 62.9, 60.7, 56.0, 52.0, 46.5, 41.1, 29.3, 14.0. ESI-MS *m/z* 380.3 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{23}H_{25}NO_4$: C, 72.82 (72.84); H, 6.63 (6.61); N, 3.63 (3.65); O, 16.82 (16.84).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-2-chloro-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3e): Colourless solid in 75 % yield. (R_f = 0.37 in hexane/ EtOAc 80:20 v/v); m.p.: 150-152 ºC; IR (KBr, ν_{max}, cm^{-1}): 2968, 2935, 1727, 1481, 1456, 1378, 1252, 1218, 1132, 912, 752. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 2.6 Hz, 1H), 7.14-7.03 (4H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 4.42 (d, *J* = 9.4 Hz, 1H), 4.37 (d, *J* = 7.2 Hz, 1H), 4.31 (dd, J = 11.6, 3.6 Hz, 1H), 4.19 (dd, *J* = 11.6, 2.7 Hz, 1H), 3.77 (dq, *J* = 11.0, 7.2 Hz, 1H), 3.63 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.49 (dd, *J* = 9.4, 6.3 Hz, 1H), 3.47-3.40 (m, 1H), 3.27 (tt, *J* = 6.6, 3.1 Hz, 1H), 3.04-2.96 (m, 2H), 2.91-2.83 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 154.4, 135.3, 133.6, 129.9, 128.7, 128.6, 128.0, 126.7, 126.3, 125.4, 124.8, 118.4, 66.3, 62.8, 62.6, 60.7, 51.9, 46.3, 40.5, 29.0, 13.9; ESI-MS *m/z* 384.3 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{22}H_{22}NO_3Cl$: C, 68.70 (68.78); H, 5.63 (5.82); N, 3.60 (3.61); O, 12.52 (12.56); Cl, 9.25 (9.29).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-2-bromo-6a,7,7a,12,13, 14a-hexahydro-6*H*-chromeno[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3f): Colourless solid in 76 % yield. (R_f = 0.35 in hexanes/EtOAc 80:20 v/v); m.p.: 168-170 ºC; IR (KBr, ν_{max}, cm^{-1}): 2975, 2920, 2845, 1719, 1486, 1469, 1412, 1338, 1311, 1232, 1164, 1112, 1032, 892, 761. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 2.3 Hz, 1H), 7.19 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.09-7.04 (m, 1H), 7.02-6.95 (2H), 6.80-6.71 (2H), 4.41 (d, *J* = 9.5 Hz, 1H), 4.01 (dd, *J* = 11.7, 3.2 Hz, 1H), 3.93 (d, *J* = 7.2 Hz, 1H), 3.76-3.66 (2H), 3.61 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.50 (dd, *J* = 9.5, 6.7 Hz, 1H), 3.47-3.40 (m, 1H), 3.08 (ddt, *J* = 9.9, 6.6, 2.9 Hz, 1H), 2.89 (ddd, *J* = 15.4, 10.6, 5.5 Hz, 1H), 2.72-2.62 (2H), 0.78 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 154.9, 135.3, 133.5, 132.9, 131.6, 128.6, 128.0, 126.7, 125.4, 125.3, 118.8, 113.6, 66.3, 62.8, 62.6, 60.7, 51.9, 46.3, 40.5, 29.0, 13.9. ESI-MS *m/z* 429.2 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{22}H_{22}NO_3Br$: C, 61.70 (61.74); H, 5.18 (5.20); N, 3.22 (3.25); O, 11.21 (11.25); Br, 18.65 (18.69).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-4-methoxy-6a,7,7a,12,13, 14a-hexahydro-6*H*-chromeno[3′,4′:4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3g): Colorless solid in 67% yield (R_f = 0.21 in hexane/EtOAc 80:20 v/v); m.p.: 128-130 ºC; IR (KBr, ν_{max}, cm^{-1}): 2974, 2860, 1737, 1684, 1583, 1479, 1442, 1383, 1304, 1249, 1172, 1027, 946, 801, 758, 649; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09-7.03 (4H), 7.02-6.98 (m, 1H), 6.89 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 4.50-4.40 (3H), 4.25 (dd, *J* = 11.5, 2.7 Hz, 1H), 3.89 (s, 3H), 3.78 (dq, *J* = 10.9, 7.2 Hz, 1H), 3.68-3.56 (2H), 3.50-3.42 (m, 1H), 3.28 (tdd, *J* = 6.6, 3.7, 2.6 Hz, 1H), 3.04-2.93 (2H), 2.93-2.85 (m, 1H) 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 148.3, 145.4, 135.3, 133.8, 128.6, 128.0, 126.6, 125.4, 122.1, 121.0, 110.2, 66.8, 62.8, 62.5, 60.7, 56.1, 51.8, 46.4, 40.8, 29.0, 14.0; m/z (ESI- MS) 380.3 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{23}H_{25}NO_4$: C, 72.82 (72.76); H, 6.60 (6.68); N, 3.60 (3.72); O, 16.88 (16.85).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-9,10-dimethoxy-6a,7,7a, 12, 13,14a-hexahydro-6*H*-chromeno[3′,4′:4,5]-pyrrolo[2,1-*a*]-isoquinoline-7-carboxylate (3h): Colourless solid in 66% yield. (R_f = 0.11 in hexane/EtOAc 80:20 v/v); m.p.: 196-198 ºC; IR (KBr, ν_{max}, cm^{-1}): 2940, 2908, 2841, 1724, 1522, 1464, 1380, 1257, 1244, 1228, 1118, 1017, 872, 761. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.0, Hz, 1H), 6.57 (s, 1H), 6.53 (s, 1H), 4.42 (d, *J* = 7.2 Hz, 1H), 4.38-4.27 (2H), 4.21 (d, *J* = 11.8 Hz, 1H), 3.89-3.81 (4H), 3.78 (s, 3H), 3.68 (dq, *J* = 13.1, 7.2 Hz, 1H), 3.51 (dd, *J* = 9.4, 6.3 Hz, 1H), 3.48-3.41 (m, 1H), 3.33-3.27 (m, 1H), 2.01-2.87 (2H) 2.83-2.76 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3, 155.9, 147.7, 146.9, 130.5, 128.7, 127.5, 125.4, 122.9, 121.6, 116.9, 111.1, 110.9, 66.3, 62.8, 62.7, 60.7, 56.0, 55.9, 51.9, 46.4, 40.9, 28.5, 14.1. ESI-MS *m/z* 410.2 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{24}H_{27}NO_5$: C, 70.40 (70.44); H, 6.60 (6.63); N, 3.44 (3.46); O, 19.52 (19.56).

(6a*R*,7*R*,7a*S*,14a*S*)-ethyl-2,4-dibromo-9,10-dimethoxy-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno[3′,4′:4,5]-pyrrolo[2,1-*a*]-isoquinoline-7-carboxylate (3i): Colourless solid in 72 % yield. (R_f = 0.11 in hexane/EtOAc 80:20 v/v); m.p.: 136-138 ºC. IR (KBr, ν_{max}, cm^{-1}): 2915, 1712, 1518, 1466, 1440, 1239, 1244, 1228, 1133, 1038, 924, 855. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56-7.52 (2H), 6.57 (s, 1H), 6.54 (s, 1H), 4.46 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.37 (d, *J* = 7.1 Hz, 1H), 4.31 (d, *J* = 9.4 Hz, 1H), 4.26 (dd, *J* = 11.8, 2.3, 1H), 3.89-3.81 (4H), 3.79 (s, 3H), 3.67 (dq, *J* = 10.9, 7.2 Hz, 1H), 3.49 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.43-3.37 (m, 1H), 3.34 (tt, *J* = 6.6, 3.0 Hz, 1H), 2.98-2.90 (2H), 2.81-2.72 (m, 1H), 0.97 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 151.7, 147.9, 146.9, 134.5, 132.3, 127.4, 126.7, 124.9, 113.6, 111.7, 111.1, 110.9, 67.2, 63.0, 62.8, 60.9, 56.0, 51.7, 46.5, 40.4, 28.7, 14.4, 14.1. ESI-MS *m/z* 568.2 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{24}H_{25}NO_5Br_2$: C, 50.80 (50.87); H, 4.44 (4.48); N, 2.42 (2.44); O, 14.12 (14.15); Br, 28.10 (28.13).

(6b*S*,14b*S*,15*R*,15a*R*)-ethyl-3,5-dibromo-1,6b,8,9,9a, 14,14a,14b,15,15a-decahydrochromeno[3′,4′:2,3]-indolizino[8,7-*b*]indole-15-carboxylate (3j): Yellow solid in 58 % yield. (R_f = 0.30 in hexane/EtOAc 80:20 v/v); m.p.: 178-180 ºC; IR (KBr, ν_{max}, cm^{-1}): 2975, 2920, 1719, 1486, 1442, 1311, 1232, 1032, 833, 760. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 2.3 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.81 (d, *J* = 7.7 Hz, 1H), 4.52 (dd, *J* = 11.7, 2.7 Hz, 1H), 4.31 (d, *J* = 8.9 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.03 (dd, *J* = 11.6, 3.1 Hz, 1H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.51-3.40 (m, 1H), 3.16-3.06 (2H) 3.02-2.97 (m, 1H), 2.80-2.71 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 152.4, 136.3, 134.4, 131.6, 130.8, 129.1, 126.9, 122.4, 119.7, 118.5, 114.0, 112.6, 111.1, 111.0, 68.8, 61.8, 59.4, 56.7, 48.6, 45.2, 39.7, 17.6, 14.3; ESI-MS *m/z* 547.0 [M

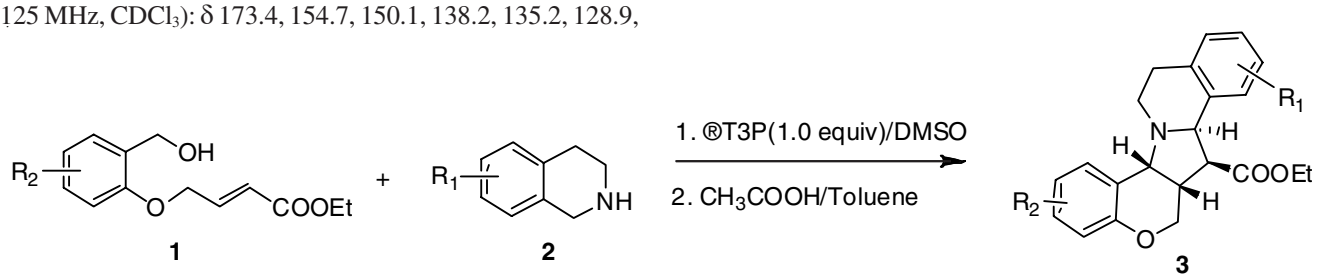
+ H]$^+$. Elemental anal. calcd. (found) % for $C_{24}H_{24}N_2O_3Br_2$: C, 52.50 (52.54); H, 4.44 (4.48); N, 5.10 (5.16); O, 8.66 (8.70); Br, 29.10 (29.13).

(6a*R*,7*R*,7a*S*,13a*S*)-ethyl-2,4-dibromo-6,6a,7,7a,12,13a-hexahydrochromeno[3',4':4,5]pyrrolo[2,1-*a*]isoindole-7-carboxylate (3k): White solid in 68 % yield. (R_f = 0.47 in hexane/EtOAc 80:20 v/v); m.p.: 140-142 ºC. IR (KBr, ν_{max}, cm^{-1}): 2982, 2947, 2871, 1720, 1474, 1459, 1449, 1378, 1289, 1182, 1164, 1134, 1017, 941, 855, 747, 683, 630, 550, 442. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.53 (2H), 7.29-7.16 (3H), 7.13 (d, *J* = 7.3 Hz, 1H), 5.01 (d, *J* = 8.6 Hz, 1H), 4.64 (d, *J* = 13.6 Hz, 1H), 4.42-4.28 (3H), 4.23 (dd, *J* = 11.5, 6.5 Hz, 1H) 3.88 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.76 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.35 (dd, *J* = 8.7, 6.1 Hz, 1H), 3.19-3.07 (m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{13}C (NMR (75 MHz, $CDCl_3$): δ 171.7, 150.1, 140.4, 138.1, 134.3, 132.0, 128.2, 127.0, 123.4, 122.4, 113.4, 111.7, 71.3, 66.1, 62.9, 61.0, 60.8, 50.3, 40.2, 13.9. ESI-MS *m/z* 494.1 [M + H]$^+$. Elemental anal. calcd. (found) % for $C_{21}H_{19}NO_3Br_2$: C, 51.10 (51.12); H, 3.90 (3.93); N, 2.80 (2.81); O, 9.72 (9.75); Br, 32.38 (32.37).

(6a*R*,7*R*,7a*R*,14a*R*)-ethyl 7a-phenyl-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3l): Colourless solid in 70 % yield. (R_f = 0.62 in hexane/EtOAc 80:20 v/v); m.p.: 173-175 ºC. IR (KBr, ν_{max}, cm^{-1}): 2982, 2967, 2938, 1728, 1485, 1455, 1317, 1210, 1031, 746, 703, 573. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.16-7.09 (2H), 7.06 (d, *J* = 7.3 Hz, 1H), 7.04-6.91 (3H), 6.83 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.62 (dd, *J* = 9.9, 3.9 Hz, 1H), 4.08 (dd, *J* = 11.4, 9.9 Hz, 1H), 3.89-3.73 (4H), 3.46-3.32 (2H), 3.31-3.21 (m, 1H), 3.07-2.98 (m, 1H), 2.81 (dt, *J* = 15.6, 2.5 Hz, 1H), 1.03 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 154.7, 150.1, 138.2, 135.2, 128.9, 128.6, 128.3, 127.4, 127.2, 127.0, 126.2, 125.7, 122.3, 120.2, 116.8, 79.2, 70.1, 62.7, 61.1, 58.6, 42.6, 40.1, 30.3, 14.0. ESI-MS *m/z* 426.2 [M + H]$^+$. Elemental anal. calcd. (found) % for $C_{28}H_{27}NO_3$: C, 79.02 (79.06); H, 6.46 (6.44); N, 3.32 (3.34); O, 11.30 (11.31).

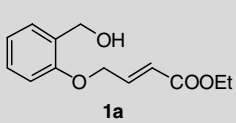
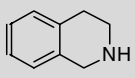
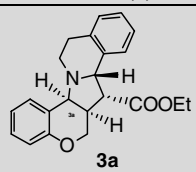
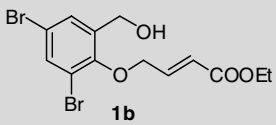
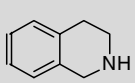
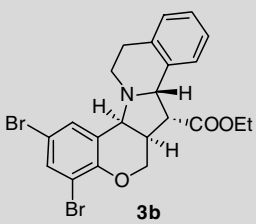
(6a*R*,7*R*,7a*R*,14a*S*)-ethyl 2,4dibromo-9,10-dimethoxy-7a-phenyl-6a,7,7a,12,13,14a-hexahydro-6*H*-chromeno-[3',4':4,5]pyrrolo[2,1-*a*]isoquinoline-7-carboxylate (3m): White solid in 64 % yield. (R_f = 0.30 in hexane/EtOAc 80:20 v/v); m.p.: 222-224 ºC; IR (KBr, ν_{max}, cm^{-1}): 2975, 2920, 1719, 1486, 1442, 1311, 1252, 1164, 1032, 833, 760. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.53-7.50 (m, 1H), 7.43-7.40 (m, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.58 (s, 1H), 6.53 (s, 1H), 4.75 (dd, *J* = 10.1, 4.0 Hz, 1H), 4.12 (t, *J* = 10.4 Hz, 1H), 3.89 (dq, *J* = 11.0, 7.2 Hz, 1H), 3.82-3.78 (5H), 3.74 (dq, *J* = 11.1, 7.2 Hz, 1H), 3.68 (s, 3H), 3.41-3.31 (m, 1H), 3.30-3.25 (m, 1H), 3.23-3.14 (m, 1H), 3.02-2.95 (m, 1H), 2.75-2.68 (m, 1H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1; 150.7, 149.6, 147.5, 146.8, 134.2, 129.4, 129.0, 128.8, 127.5, 127.2(3), 127.1(7), 125.4, 112.3, 112.2, 111.8, 110.8, 79.2, 71.0, 62.3, 61.4, 57.8, 56.0, 55.9, 41.9, 40.2, 29.7, 14.1; ESI-MS *m/z* 643.9 [M + H]$^+$. Elemental anal. calcd. (found) % for $C_{30}H_{29}NO_5Br_2$: C, 56.00 (56.06); H, 4.56 (4.59); N, 2.12 (2.15); O, 12.30 (12.38); Br, 24. 75 (24.79).

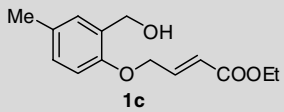
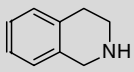
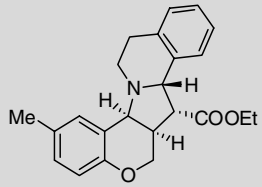
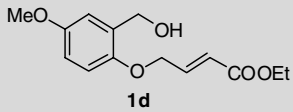
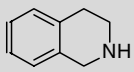
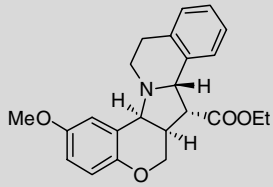
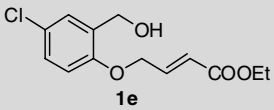
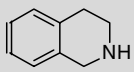
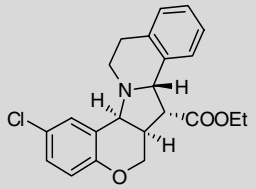
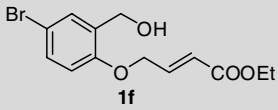
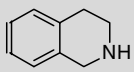
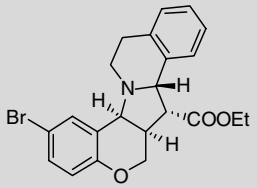
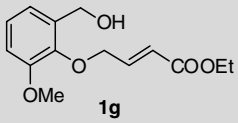
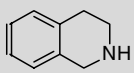
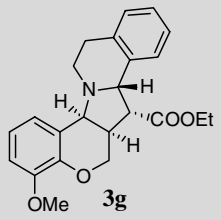
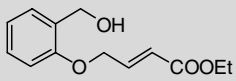
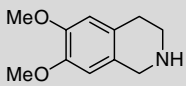
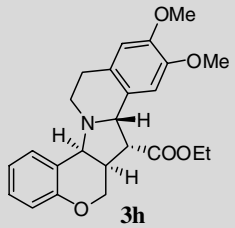
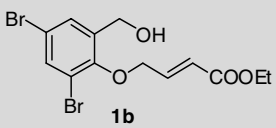
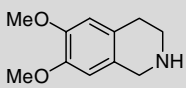
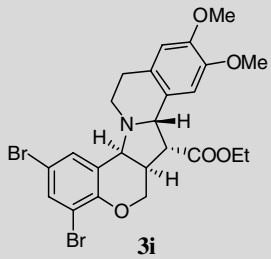
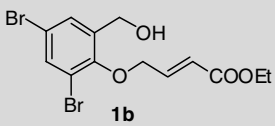
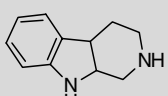
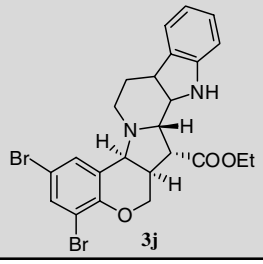
(6b*S*,14b*S*,15*R*,15a*R*)-ethyl-3,5-dibromo-14b-(4-chlorophenyl)-1,6b,8,9,14,14b,15,15a-octahydrochromeno[3′,4′:2,3]indolizino[8,7-*b*]indole-15-carboxylate (3n): Colourless solid in 65 % yield; (R_f = 0.35 in hexane/EtOAc 80:20 v/v); m.p.: 168-170 ºC. IR (KBr, ν_{max}, cm^{-1}): 3060, 2975, 2845, 1719, 1469, 1486, 1338, 1240, 1220, 1164, 1073, 1061, 911, 862, 686. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.7 Hz, 2H), 7.61 (s, 1H), 7.59-7.56 (m, 1H), 7.54-7.51 (m, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* =

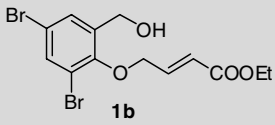
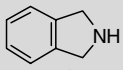
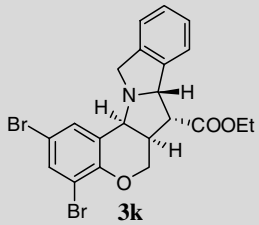
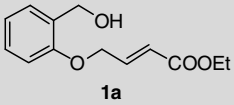
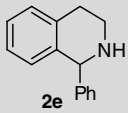
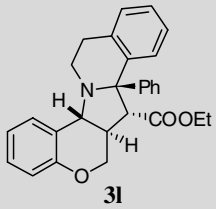
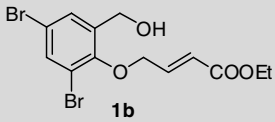
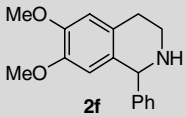
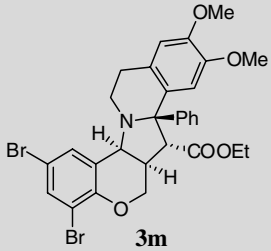
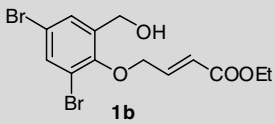
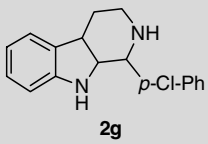
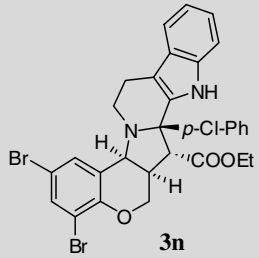


Scheme-II

TABLE-2
SUBSTRATE SCOPE FOR [3 + 2] CYCLOADDITION REACTIONS

Entry	Substrate (1)	Substrate (2)	Product (3)	Yield (%)
1	 **1a**	 **2a**	 **3a**	89
2	 **1b**	 **2a**	 **3b**	72

3	 **1c**	 **2a**	 **3c**	66
4	 **1d**	 **2a**	 **3d**	69
5	 **1e**	 **2a**	 **3e**	75
6	 **1f**	 **2a**	 **3f**	76
7	 **1g**	 **2a**	 **3g**	67
8	 **1a**	 **2b**	 **3h**	66
9	 **1b**	 **2b**	 **3i**	72
10	 **1b**	 **2c**	 **3j**	58

11	 **1b**	 **2d**	 **3k**	68
12	 **1a**	 **2e**	 **3l**	70
13	 **1b**	 **2f**	 **3m**	64
14	 **1b**	 **2g**	 **3n**	65

8.2 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 4.74 (dd, *J* = 10.0, 3.9 Hz, 1H), 4.08 (t, *J* = 10.6 Hz, 1H), 3.99-3.88 (3H), 3.59 (d, *J* = 10.0 Hz, 1H), 3.53 (td, J = 10.8, 3.3 Hz, 1H), 3.50-3.44 (m, 1H), 3.04-2.82 (3H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCCl_3$): δ 172.1, 150.7, 146.2, 136.8, 134.5, 133.6, 132.3, 129.4, 129.1, 127.9, 126.1, 124.9, 122.6, 119.8, 118.9, 112.6, 112.0, 111.3, 110.9, 75.7, 70.8, 62.1, 61.9, 58.2, 41.9, 40.4, 21.4, 14.1. ESI-MS *m/z* 657.0 $[M + H]^+$. Elemental anal. calcd. (found) % for $C_{30}H_{26}N_2O_3Br_2$: C, 56.60 (56.58); H, 4.18 (4.18); N, 4.66 (4.63); O, 8.70 (8.68); Br, 25.86 (25.84).

RESULTS AND DISCUSSION

Initially, the reaction of aldehyde (crude) was carried out with tetrahydroisoquinoline (THIQ) in the absence of acetic acid and toluene as a solvent, desired product **3** was obtained in trace amount (Table-1, entry 1). Later we carried out the reaction of aldehyde (crude) with THIQ in the presence of 10 mol % acetic acid product **3** was obtained in 33 % yield (Table -1, entry 2). Upon increasing the amount of acetic acid 20, 30, 40 and 50 mol %, the yield of the products **3** were increased (Table-1, entries 3 to 6). Further increase in the amount of acetic acid to 1.0 and 1.5 equiv, no significant improvement in the yield was observed (Table-1, entries 7 and 8). The effect of the temperature was also tested, when the temperature was increased to 40, 50 and 60 ºC, no significant improvement in the yield was observed (Table-1, entries 9, 10 and 11).

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS

No.	CH_3COOH (mol %)	Solvent	Time (h)	Temp. (°C)	Yield (%)
1	–	Toluene	24	Reflux	Trace
2	10	Toluene	24	RT	33
3	20	Toluene	24	RT	37
4	30	Toluene	12	RT	56
5	40	Toluene	6	RT	62
6	50	Toluene	6	RT	82
7	100	Toluene	6	RT	79
8	150	Toluene	6	RT	78
9	50	Toluene	6	40	67
10	50	Toluene	6	50	66
11	50	Toluene	6	60	66
12	50	THF	24	RT	35
13	50	EtOAc	24	RT	25
14	50	DMF	24	RT	55
15	50	Ethanol	24	RT	10
16	50	CH_3CN	24	RT	48

Later on, we screened a number of solvents *viz*., THF, EtOAc, DMF, ethanol and CH_3CN found that toluene was the preferred solvent. The other molecular sieves like 4Å and 5Å were also screened but no significant difference was observed finally, it

is found that reactions with aldehyde (crude, 1.0 mmol) and tetrahydroisoquinoline (1.0 mmol) in the presence of acetic acid at room temperature for 6 h was ideal (Table-1, entry 6). Under the above optimized reaction conditions, the efficiency and versatility of this newly developed methodology, reactions of tetrahydroisoquinolines (THIQs) with a range of alcohol derived from differently substituted salicylalcohol were evaluated (**Scheme-II** and Table-2).

In all cases, products were obtained in good yields at room temperature (products 3a-3n). Importantly, other benzylic amines including 6,7-dimethoxy-THIQ, tryptoline, isoindoline, also underwent the title reaction under equally mild conditions. Interestingly, even sterically demanding 1-aryl THIQ′s and a 1-aryl-tryptoline readily participated in the reaction sequence to generate polycyclic amines containing tetra substituted carbon centers.

Conclusion

In conclusion, a novel and direct method is developed for the synthesis of hexahydrochromeno[4,3-*b*]pyrrolo[2,1-*a*]-isoquinolines in good yields, starting directly from a variety of alcohols and various tetrahydroisoquinolines. The protocol involves ®T3P mediated oxidation of alcohols to aldehydes followed by [3+2] cycloaddition to afford hexahydrochromeno-[4,3-*b*]pyrrolo[2,1-*a*]isoquinolines.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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