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A Novel Method for Synthesis of Tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinolines

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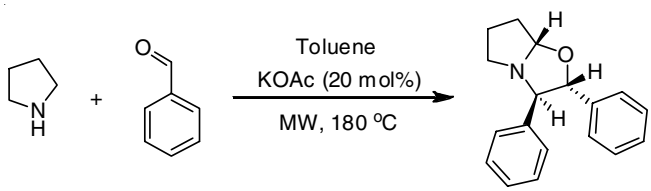
An efficient and direct method for the synthesis of tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinolines is reported. This novel method involves ®T3P mediated *in situ* oxidation of benzyl alcohols to aldehyde followed by acetic acid mediated [3+2] cycloaddition reaction to afford tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinolines in one-pot operation with good to excellent yields. Heterocyclic alcohols also underwent the reaction with tetrahydroquinolines at room temperature.

Keywords: C-H functionalization, ®T3P, [3+2] cycloaddition, Isoquinolines.

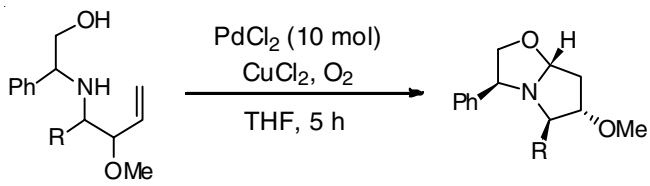
INTRODUCTION

1,3-Oxazolidine core structure is present in a large number of drugs, synthetic complex compounds, natural products, dyes and agrochemicals [1]. These are building blocks for the assembly of nitrogen-containing heterocycles that constituted incredible class of biologically active compounds [2]. Furthermore, they are useful not only as intermediates in organic synthesis but also as effective ligands for metal-catalyzed asymmetric synthesis [3]. Many organic compounds containing 1,3-oxazolidine core showed various biological activities like antitumor, cytotoxic, anti-inflammatory, analgesic properties, *etc*. [4]. They also act as anticonvulsant antibiotic, antibacterial, antifouling, cystic fibrosis transmembrane conductance regulator (CFTR) inhibitor [5], *etc*. Synoxazolidione C extracted from marine organism *Synocium pulmonaria* was found to be antifouling agent against marine bacteria and algae [6]. Linezolid showed antibacterial activity against gram-positive, drug-resistant bacterial infections [7]. Quinocarcin and its analogues are polycyclic tetrahydroisoquinoline alkaloids with remarkable activities against several tumor cell lines [8].

As a consequence, substantial attention has been paid to develop efficient methods for their syntheses. Recently, Ghosal *et al*. [4] reported metal catalyzed conversion of aziridines to oxazolidines through geminal difunctionalization of vinyl arenes. Pyrrolidinooxazolidines were synthesized by cycloaddition reaction between aldehyde and *in situ* generated azomethine ylide from L-proline through decarboxylation method [9,10]. A diastereoselective synthesis of pyrrolidinooxazolidines was achieved by Rahman *et al*. [11] under microwave condition (**Scheme-I**). Alladoum *et al*. [2] demonstrated that unsaturated amino alcohols possessing a dialkylamino function cyclize in the presence of Pd(II) catalyst to afford bicyclic oxazolidines (**Scheme-II**). But all these methods have limitations like use of metal catalyst, low yield, high temperature and drastic conditions.



Scheme-I



Scheme-II

EXPERIMENTAL

General synthesis of 3a-3q: To a solution of alcohol (2 mmol) in DMSO (2 mL), was added at 0 ºC 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 the reaction, the solvent was removed under reduced pressure. The crude product was taken in toluene, was added 3 Å molecular sieves (200 mg), amine **1** (1.0 mmol) 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, (**3a-3q**) which was purified on silica gel using ethyl acetate and petroleum ether.

Characterization data

Compound 3a: Colourless solid; yield 68 %; (R_f = 0.8 in hexanes/EtOAc 95:05 v/v). m.p. 142-144 ºC; IR (KBr, ν_{max}, cm^{-1}): 3010, 2850, 1670, 1639, 1608, 1070. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 1.6 Hz, 8.8 Hz, 1H), 7.27-7.23 (comp, 3H), 7.21-7.12 (comp, 9H), 7.11-7.08 (m, 1H), 5.72 (s, 1H), 4.77 (d, *J* = 8.0 Hz, 1H), 3.90 (d, *J* = 6.8 Hz, 1H), 3.06-2.97 (m, 2H), 2.85-2.82 (m, 1H), 2.76-2.71 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 139.6, 135.6, 133.3, 128.8, 128.5, 128.3, 127.7, 127.46. 127.43, 126.9, 126.65, 126.60, 90.4, 87.1, 76.3, 46.7, 28.4; *m/z* (ESI-MS) $[M + H]^+$ Calcd (found): 328.1623 (328.1688).

Compound 3b: Colourless solid; yield 64 %; (R_f = 0.86 in hexanes/EtOAc 80:20 v/v). m.p. 138-140 ºC; IR (KBr, ν_{max}, cm^{-1}): 3018, 2915, 1670, 1629, 1599. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 5.2 Hz, 1H), 7.32-7.26 (m, 2H), 7.22-7.17 (comp, 2H), 7.15-7.10 (m, 5H), 7.06 (d, *J* = 5.2 Hz, 2H), 5.78 (s, 1H), 4.81 (d, *J* = 7.6 Hz, 1H), 3.92 (d, *J* = 7.2 Hz, 1H), 3.13-3.05 (m, 2H), 3.02-2.80 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, CDCl3): δ 137.5, 137.4, 136.9, 136.6, 135.6, 133.5, 129.1, 129.0, 128.6, 127.9, 127.0, 126.7, 126.4, 126.1, 90.2, 87.2, 75.9, 46.5, 28.3, 21.0; *m/z* (ESI-MS) $[M + H]^+$ Calcd (found): 356.1936 (356.1956).

Compound 3c: Colourless solid; yield 70 %; (R_f = 0.88 in hexanes/EtOAc 80:20 v/v). m.p. 148-150 ºC; IR (KBr, ν_{max}, cm^{-1}): 3018, 2902, 2898, 2853, 1673, 1648, 1621, 1070. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (m, 1H), 7.39-7.33 (m, 2H), 7.13 (d, *J* = 7.2 Hz, 4H), 7.28-7.23 (m, 4H), 7.20 7.16 (m, 1H), 5.76 (s, 1H), 4.86 (d, *J* = 7.6 Hz, 1H), 4.02 (d, *J* = 7.2 Hz, 1H), 3.22-3.17 (m, 1H), 3.09-2.95 (m, 2H), 2.87-2.80 (m, 1H), 1.32 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 150.0, 138.3, 138.0, 136.8, 135.6, 133.2, 128.8, 127.9, 126.5, 126.3, 126.0, 125.4, 125.3, 90.3, 86.8, 75.8, 46.9, 31.3, 28.8; *m/z* (ESI-MS) $[M + H]^+$ Calcd (found): 440.2875 (440.2897).

Compound 3d: Colourless solid; yield 60 %; (R_f = 0.65 in hexanes/EtOAc 80:20 v/v). m.p. 124-126 ºC; IR (KBr, ν_{max}, cm^{-1}): 3018, 2850, 1640, 1639, 1622, 1079. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.26-7.13 (comp, 6H), 7.07-7.05 (m, 2H), 6.79 (t, *J* = 6.8 Hz, 2H), 4.92 (s, 1H), 4.62 (d, *J* = 8.4 Hz, 1H), 3.88 (d, *J* = 8.0 Hz, 1H), 2.99 (s, 12H), 2.94-2.89 (m, 2H), 2.58-2.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 130.0, 128.8, 128.5, 128.1, 127.8, 126.8, 126.3, 125.6, 125.0, 112.1, 90.3, 85.1, 70.07, 45.7, 41.8, 29.4. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 401.2389 (401.2381).

Compound 3e: Colourless solid; yield 60 %; (R_f = 0.55 in hexanes/EtOAc 85:15 v/v). m.p. 114-116 ºC; IR (KBr, ν_{max}, cm^{-1}): 3015, 2915, 1668, 1629, 1622, 107. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, *J* = 4.0 Hz, 1H), 7.35-7.29 (m, 2H), 7.25 (d, *J* = 8 Hz, 6H), 7.22-7.18 (m, 1H), 7.16 (d, *J* = 8 Hz, 1H), 5.8 (s, 1H), 4.76 (d, *J* = 7.6 Hz, 1H), 3.87 (d, *J* = 7.2 Hz, 1H), 3.10-3.04 (m, 2H), 2.93- 2.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.7, 147.2, 146.9, 135.4, 134.1. 133.5, 133.1, 128.6, 128.5, 128.2, 126.5, 122.1, 120.4, 109.4, 108.1, 107.3, 106.6, 101.0, 100.9, 90.0, 87.3, 75.6, 46.3, 29.0. *m/z* (ESI-MS $[M + H]^+$ calcd (found): 402.1263 (402.1259).

Compound 3f: Colourless solid; yield 80 %; (R_f = 0.55 in hexanes/EtOAc 95:05 v/v). m.p. 140-142 ºC; IR (KBr, ν_{max}, cm^{-1}): 3012, 2852, 1667, 1648, 1633, 1079, 790. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (m, 2H), 7.19-7.16 (m, 2H), 7.09 (s, 1H), 6.92 (s, 1H), 6.82-6.71 (comp, 3H); 6.68 (d, *J* = 3.2 Hz, 1H), 5.94 (s, 4H), 5.76 (s, 1H), 4.71 (d, *J* = 7.6 Hz, 1H), 3.82 (d, *J* = 7.6 Hz, 1H), 3.08 (t, *J* = 6.0, 1H), 2.89-2.84 (m, 2H), 2,74-2.73 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 137.7, 135.4, 133.7, 133.3, 133.2, 128.9, 128.7, 128.6, 128.4, 128.1, 128.0, 127.4, 126.6, 90.4, 86.6, 75.6, 46.4, 28.0; *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 396.0844 (396.0846).

Compound 3g: Colourless solid; yield 65 %; (R_f = 0.50 in hexanes/EtOAc 95:05 v/v). m.p. 132-134 ºC; IR (KBr, ν_{max}, cm^{-1}): 3012, 2895, 1680, 1619, 1611, 1110. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 0.8 Hz, 8.8 Hz, 2H), 7.22-7.18 (m, 4H), 7.12-6.98 (m, 3H), 6.95-6.86 (m, 4H), 5.73 (s, 1H), 4.65 (d, *J* = 7.6Hz, 1H), 3.80 (d, *J* = 7.6 Hz, 1H), 3.02-2.99 (m, 2H), 2.82-2.73 (m, 2H). ^{13}C NMR (100 MHz $CDCl_3$): δ 163.6 (d, J_{C-F} = 72.8 Hz, 1C),161.1 (d, J_{C-F} = 469.6 Hz, 1C), 135.5, 135.4, 134.8, 133.3, 128.8, 128.4, 128.4, 128.1, 128.09, 128.02, 115.6, 115.5, 115.38, 115.31, 90.3, 86.9, 75.5, 46.4, 27.9. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 364.1935 (364.1929.

Compound 3h: Colourless solid; yield 83 %; (R_f = 0.68 in hexanes/EtOAc 90:10 v/v). m.p. 100-102 ºC; IR (KBr, ν_{max}, cm^{-1}): 3018, 2912, 1671, 1629, 1611, 1070, 990, 1118. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 4.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.37- 7.31 (m, 4H), 7.24-7.21 (m, 1H), 5.84 (s, 1H), 4.87 (d, *J* = 7.2 Hz, 1H), 3.0 (d, *J* = 7.0. Hz, 1H), 3.12-3.09 (m, 2H), 3.00 2.92 (m, 1H), 2.88-2.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 143.2, 135.3, 132.7, 130.4, 130.1, 128.5, 128.3, 128.1, 127.4, 126.9, 126.6, 126.2, 125.6, 125.5, 125.3, 122.7, 122.6, 90.7, 86.3, 76.0, 46.6, 28.1. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 464.1371 (464.1381).

Compound 3i: Colourless solid; yield 82 %; (R_f = 0.58 in hexanes/EtOAc 85:15 v/v). m.p. 136-138 ºC; IR (KBr, ν_{max}, cm^{-1}): 3012, 2912, 1684, 1643, 1611, 1530, 1311, 1180. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 3H), 7.41 (d, *J* = 8.20 Hz, 2H), 7.33 (t, *J* = 4.4 Hz, 2H), 7.24- 7.22 (m, 1H), 5.84 (s, 1H), 4.89 (d, *J* = 7.6 Hz, 1H), 4.04 (d, *J* = 6.8 Hz, 1H), 3.12-3.08 (m, 2H), 3.00-2.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

147.8, 147.7, 147.2, 146.3, 135.2, 132.3, 128.5, 128.4, 128.1, 127.90, 127.92, 127.4, 126.8, 124.0, 123.9, 91.0, 85.8, 76.0, 46.8, 28.2. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 418.1325 (418.1333).

Compound 3j: Colourless solid; yield 78 %; (R_f = 0.85 in hexanes/EtOAc 95:05 v/v). m.p. 138-140 ºC; IR (KBr, ν_{max}, cm^{-1}): 3014, 2910, 1658, 1612, 1112. 710, 738. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.2 Hz, 1H), 7.55-7.51 (m, 3H), 7.44 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.33-7.28 (m, 2H), 7.26-7.18 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 5.92 (s, 1H), 5.45 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 3.19-3.07 (m, 1H), 2.91-2.87 (m, 1H), 2.83 (t, *J* = 3.2 Hz, 1H), 2.79 (t, *J* = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 139.5, 135.4, 132.96, 132.90, 132.5, 129.0, 128.9, 128.8, 128.6, 128.4, 128.1, 128.0, 127.7, 127.6, 126.5, 124.8, 122.8, 90.5, 83.5, 74.9, 46.9, 28.6. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 472.9735 (472.9727).

Compound 3k: Colourless solid; yield 69 %; (R_f = 0.66 in hexanes/EtOAc 80:20 v/v). m.p. 134-136 ºC; IR (KBr, ν_{max}, cm^{-1}): 3018, 2902, 1658, 1659, 1090, 690. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 2 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.48-7.46 (m, 1H), 7.33-7.25 (m, 4H), 7.21-7.19 (m, 1H), 6.66 (d, *J* = 8.4 Hz, 2H), 5.66 (s, 1H), 5.15 (d, *J* = 6.8 Hz, 1H), 4.36 (d, *J* = 7.2 Hz, 1H), 3.53 (s, 3H), 3.44 (s, 3H), 3.22-3.19 (m, 1H), 3.05-3.02 (m, 2H), 2.84- 2.80 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 156.2, 135.7, 132.3, 131.0, 130.6, 130.3, 130.2, 130.1, 128.9, 128.2, 128.0, 126.3, 112.99, 112.97, 111.8, 111.6, 90.1, 79.2, 70.5, 55.3, 54.9, 47.4, 29.6. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 546.0024 (546.0018).

Compound 3l: Yellow solid; yield 63 %; (R_f = 0.75 in hexanes/EtOAc 80:20 v/v). m.p. 120-122 ºC; IR (KBr, ν_{max}, cm^{-1}): 3014, 2912, 1668, 1638, 1612, 1080. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.8 Hz, 1H), 7.21-7.13 (m, 4H), 7.12-7.08 (m, 1H), 6.95 (d, *J* = 3.2 Hz, 1H), 6.90 (m, 1H), 6.85 (t, *J* = 4.8 Hz, 2H), 5.66 (s, 1H), 5.14 (d, *J* = 6.8 Hz, 1H), 4.30 (d, *J* = 6.4 Hz, 1H), 3.20-3.13 (m , 1H), 3.08-3.03 (m ,1H), 2.95-2.87 (m, 1H), 2.78-2.72 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 135.5, 132.4, 128.9, 128.7, 128.1, 127.9, 127.3, 126.3, 125.7, 125.4, 124.6, 124.0, 123.9, 90.3, 83.0, 72.9, 47.0, 28.7. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 340.0752 (340.0750).

Compound 3m: Colourless solid; yield 71 %; (R_f = 0.40 in hexanes/EtOAc 90:10 v/v). m.p. 162-164 ºC; IR (KBr, ν_{max}, cm^{-1}): 3021, 2918, 1670, 1648, 1621, 1070, 658, 748. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.50 (m, 2H), 7.46- 7.41 (m, 3H), 7.35-7.29 (m, 5H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 6.4, 11.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 2.8 Hz, 1H), 4.99 (d, *J* = 8.8 Hz 1H), 3.84 (dd, *J* = 8.1 Hz, 1H), 3.84 (s, 3H), 3.15-3.09 (m, 1H), 2.87-2.78 (m, 2H), 2.59-2.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 146.0, 137.7, 136.3, 135.3, 131.7, 131.2,130.4, 130.3, 130.2, 129.8, 129.0, 128.3, 127.8, 127.7, 121.9, 121.8, 113.3, 112.2, 112.1, 96.1, 87.0, 72.2, 55.2, 41.1, 29.6; *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 592.0232 (592.0236).

Compound 3n: Colourless solid; yield 45 %; (R_f = 0.40 in hexanes/EtOAc 80:20 v/v). m.p. 104-106 ºC; IR (KBr, ν_{max}, cm^{-1}): 3394, 2998, 2934, 1685, 1604, 1054. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.14 (m, 6H), 7.11-7.08 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.96 (s, 1H), 6.84 (s, 1H), 4.85 (d, *J* = 12.4 Hz, 1H), 3.9 (d, *J* = 12, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.05-3.0 (m, 2H), 2.94-2.84 (m, 2H), 1.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.8, 136.4, 135.7, 134.4, 134.2, 127.9, 127.7, 127.6, 127.4, 127.1, 127.0, 126.4, 125.6, 90.4, 86.6, 75.6, 55.3, 46.9, 28.5, 21.2. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 467.1420 (468.1413).

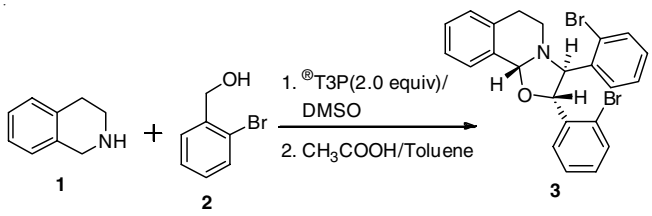
Compound 3o: Colourless solid; yield 65 %; (R_f = 0.36 in hexanes/EtOAc 80:20 v/v). m.p. 144-146 ºC; IR (KBr, ν_{max}, cm^{-1}): 3358, 3018, 2912, 1660, 1638, 1621, 1078. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.38-7.28 (m, 7H), 7.25-7.14 (m, 6H), 7.12-7.09 (m, 1H), 7.01 (dd, *J* = 2.0 Hz, 8 Hz, 1H), 6.22 (s, 1H), 5.01 (d, *J* = 7.6 Hz, 1H), 4.02 (d, *J* = 8.2 Hz, 1H), 3.24 (q, *J* = 4.4 Hz, 2H) 2.88-2.86 (m, 1H), 2.68-2.64 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 137.9, 136.6, 131.9, 128.6, 128.3, 128.0, 127.9, 127.2, 127.1, 126.8, 126.6, 126.59, 126.54, 122.5, 119.6, 119.5, 118.9, 111.4, 109.8, 88.5, 86.8, 71.4, 43.9, 29.7. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 367.1732 (367.1748).

Compound 3p: Colourless solid; yield 73 %; (R_f = 0.36 in hexanes/EtOAc 80:20 v/v). m.p. 154-156 ºC; IR (KBr, ν_{max}, cm^{-1}): 3348, 3010, 2914, 1674, 1645, 1621, 1514, 1318, 1079. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 8.22 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* =8.4 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.48-7.39 (m, 3H), 7.29- 7.24 (m, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 4.99 (d, *J* = 7.6 Hz, 1H), 4.06 (d, *J* = 5.6 Hz, 1H), 3.28-3.23 (m, 1H), 3.16-3.13 (m, 1H), 2.88-2.80 (m, 1H), 2.72-2.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 147.8, 145.5, 144.7, 136.8, 130.6, 128.7, 128.4, 128.2, 127.3, 126.5, 126.2, 124.1, 123.7, 123.2, 120.0, 119.1, 111.5, 86.9, 71.0, 44.13, 29.6. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 406.1199 (406.1191).

Compound 3q: Colourless solid; yield 74 %; (R_f = 0.30 in hexanes/EtOAc 80:20 v/v). m.p. 152-154 ºC; IR (KBr, ν_{max}, cm^{-1}): 3340, 3014, 2914, 1659, 1657, 1622, 1110, 680, 710. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.43-7.37 (m, 3H), 7.26 (t, *J* = 10.4 Hz, 2H), 7.18-7.22 (m, 3H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.23 (s, 1H), 5.52 (d, *J* = 7.2 Hz, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 3.25-3.21 (m, 1H), 3.15-3.12 (m, 1H), 2.93-2.86 (m, 1H), 2.70-2.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 132.8, 132.4, 131.4, 129.4, 129.2, 128.9, 127.8, 127.7, 125.2, 122.9, 122.6, 119.6, 119.1, 111.4, 110.5, 86.8, 85.5, 69.3, 44.3, 29.6, 18.0. *m/z* (ESI-MS) $[M + H]^+$ calcd (found): 524.9922 (524.9914).

RESULTS AND DISCUSSION

Propylphosphonic anhydride (®T3P) has received increased attention as a coupling agent and dehydrating agent, offering several advantages such as high yields, purity, low toxicity, broad functional group tolerance and easy work-up when compared to traditional reagents [12-14]. In continuation of our work on synthetic applications of (®T3P) in heterocyclic compounds and development of the useful synthetic methodologies [12,15-20], herein we report novel, tandem approach for the synthesis of tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinoline and its analogues. The tandem process involves DMSO mediated oxidation of alcohols followed by intermolecular [3 + 2] cycloadditions of azomethineylides under mild conditions (**Scheme-III**).



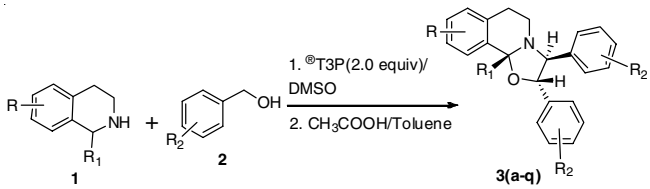
Scheme-III

Initially, 2-bromobenzyl alcohol was oxidized to 2-bromobenzaldehyde using ®T3P and DMSO at room temperature [15]. The reaction of 2-bromobenzaldehyde (crude) was carried out with tetrahydroisoquinoline (THIQ) in the absence of acetic acid and toluene as a solvent, the 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 35 % yield (Table-1, entry 2). Upon increasing the amount of acetic acid 20, 30, 40 and 50 mol % the yield of products **3** were increased (Table-1, entries 3-6).

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	35
3	20	Toluene	24	RT	37
4	30	Toluene	12	RT	54
5	40	Toluene	6	RT	63
6	50	Toluene	6	RT	81
7	100	Toluene	6	RT	77
8	150	Toluene	6	RT	74
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

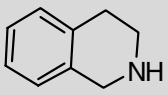
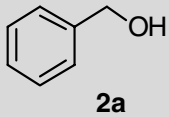
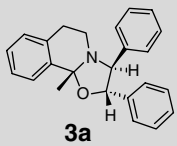
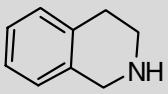
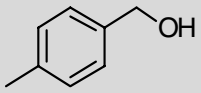
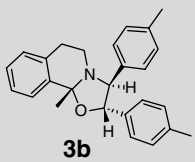
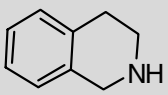
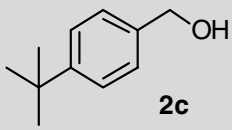
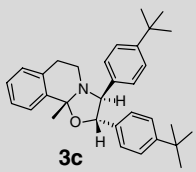
Further increase in the amount of acetic acid to 1.0 and 1.5 equiv, no significant improvement in the yield was observed (Table-1, entries 7 and 8). The effect of temperature was also tested, when temperature was increased to 40 , 50 and 60 ºC, no significant improvement in the yields were observed (Table-1, entries 9-11). Later we screened a number of solvents *viz*., THF, EtOAc, DMF, ethanol and CH_3CN found that toluene was preferred as a solvent. We also screened other molecular sieves like 3 and 4 Å but no significant difference was observed finally, it was found that the 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 5). Under the above optimized reaction conditions, the efficiency and versatility of this newly developed methodology, reactions of THIQs with a range of benzaldehyde derived from differently substituted benzylalcohol were evaluated **(Scheme-IV)**. In all cases, products (**3a-3q**) were obtained in good yields at room temperature.

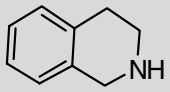
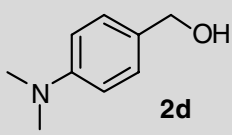
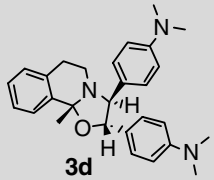
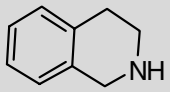
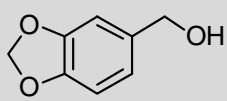
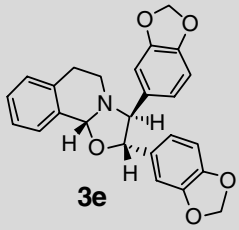
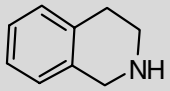
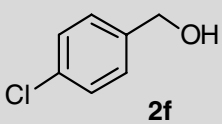
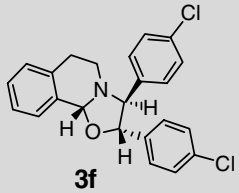
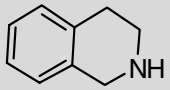
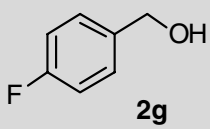
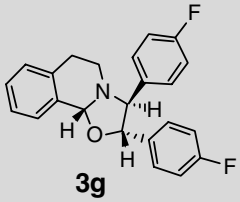
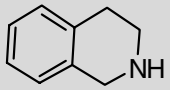
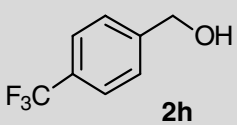
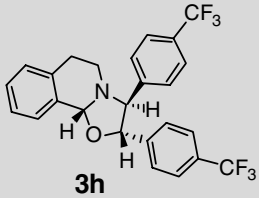
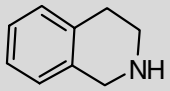
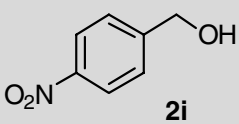
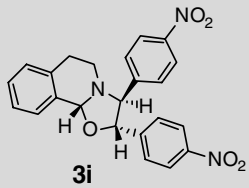
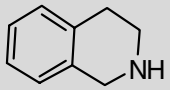
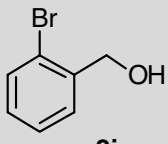
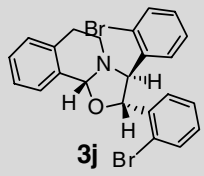
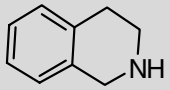
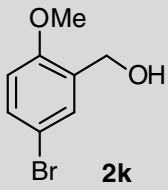
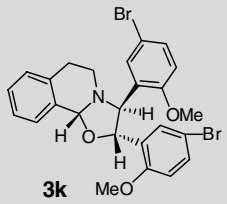
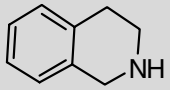
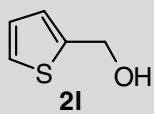
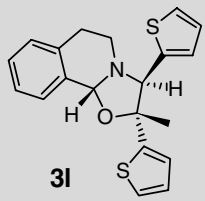


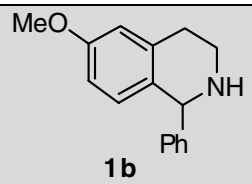
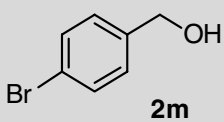
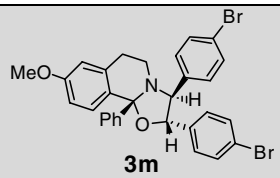
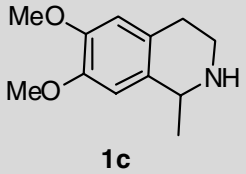
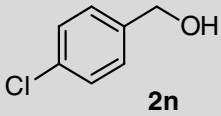
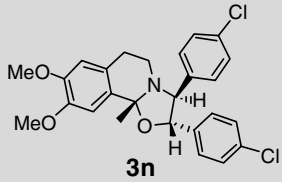
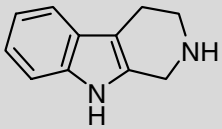
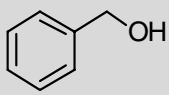
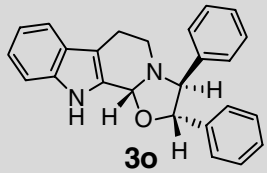
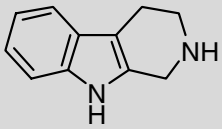
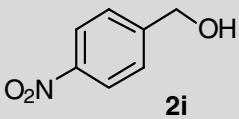
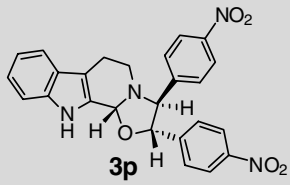
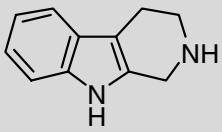
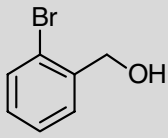
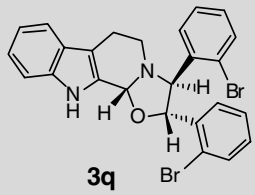
Scheme-IV

Using optimized reaction conditions we studied the general substrate scope of the reaction (Table-2). A number of benzaldehyde derived from benzyl alcohols efficiently reacted with THIQs to afford the corresponding products under the optimized reaction conditions (**3a-3q**). Benzyl alcohols bearing halogens such as -F, -Cl, -Br, CF_3 and a strong electron withdrawing group like $-NO_2$ were underwent the title reaction to form desired products in good yields (**3f-3j**). Even disubstituted benzyl alcohols successfully formed the product without diminishing the yield compound **3k**. Piperonal and heterocyclic benzyl alcohol like thiophen-2-yl-methanol also underwent

TABLE-2
SUBSTRATE SCOPE FOR THE [3 + 2] CYCLOADDITION REACTION

Entry	Substrate 1	Substrate 2	Product 3	Yield (%)
1	 **1a**	 **2a**	 **3a**	68
2	 **1a**	 **2b**	 **3b**	64
3	 **1a**	 **2c**	 **3c**	70

4	 **1a**	 **2d**	 **3d**	61
5	 **1a**	 **2e**	 **3e**	63
6	 **1a**	 **2f**	 **3f**	80
7	 **1a**	 **2g**	 **3g**	65
8	 **1a**	 **2h**	 **3h**	83
9	 **1a**	 **2i**	 **3i**	82
10	 **1a**	 **2j**	 **3j**	78
11	 **1a**	 **2k**	 **3k**	69
12	 **1a**	 **2l**	 **3l**	63

13	 **1b**	 **2m**	 **3m**	71
14	 **1c**	 **2n**	 **3n**	45
15	 **1d**	 **2a**	 **3o**	65
16	 **1d**	 **2i**	 **3p**	72
17	 **1d**	 **2j**	 **3q**	74

the reaction to give the desired products **3e** and **3l**, respectively in good yields. The scope of the reaction was successfully extended to other substrates such as trypoline and sterically demanding 1-alkyl THIQ, 1-aryl THIQ and 1-aryl-trypoline which also underwent the title reaction under equally mild conditions (**3m-3q**).

Conclusion

A novel and direct method is developed for the synthesis of tetrahydro-2*H*-oxazolo[2,3-*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 tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinolines. The products were characterized by spectroscopic techniques.

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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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