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$Bi(OTf)_3$-catalyzed condensation of 2,2-DMP with aromatic amines: A rapid synthesis of 2,2,4-trimethyl-1,2-dihydroquinolines

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Abstract

Aryl amines undergo smooth coupling with 2,2-dimethoxypropane (2,2-DMP) in the presence of 5 mol% of bismuth triflate under solvent-free conditions to produce 1,2-dihydroquinolines in high yields under mild conditions. However, the condensation of *o*-phenylenediamines with 2,2-DMP gave the corresponding 1,5-benzodiazepines in excellent yields under identical conditions.

Keywords: Aryl amines; Bismuth catalysis; Skraup synthesis; Dihydroquinolines

1,2-Dihydroquinoline derivatives are known to exhibit a wide spectrum of biological activities such as antimalarial [1], antibacterial [2] and anti-inflammatory behavior [3]. In addition, substrates possessing dihydroquinoline motif have been used as lipid peroxidation inhibitors, HMG-CoA reductase inhibitors, ileal bile acid transporter inhibitors and progesterone agonists and antagonists [4] Generally, 1,2-dihydroquinolines are prepared by the condensation of aromatic amines with ketones using a catalytic amount of H_2SO_4 via Skraup's procedure [5]. However, it requires high temperatures, ranging from 145 to 150 °C, under high pressure and long reaction times (2–3 days) [6]. Subsequently, various catalytic systems are explored in search of improved efficiencies [7]. But many of these methods involve the use of expensive reagents and also require microwave irradiation. Since quinoline derivatives are useful and important in the field of drugs and pharmaceuticals, the development of simple, convenient and high yielding protocols is desirable.

Lanthanide triflates are unique Lewis acids that are currently of great interest [8]. The high catalytic activity, low toxicity, moisture and air tolerance, and their recyclability, make the use of lanthanide triflates attractive alternatives to conventional Lewis acids [9]. However, lanthanide triflates are rather expensive and their use in large-scale synthesis is limited. Therefore, cheaper and more efficient catalysts are desirable. In this direction, bismuth triflate has evolved as remarkable Lewis acid catalyst for effecting various organic transformations [10]. Compared to lanthanide triflates, bismuth triflate is cheap and is easy to prepare even on a multi-gram scale, from commercially available bismuth oxide and triflic acid [11]. However, there have been no reports on the use of bismuth triflate for Skraup synthesis.

In this article, we wish to report a novel and improved version of Skraup's procedure for the synthesis of 1,2-dihydroquinolines using a catalytic amount of $Bi(OTf)_3$. Accordingly, treatment of aniline **1** with 2,2-dimethoxypropane **2** in the presence of 5 mol% of $Bi(OTf)_3$ in solvent-free conditions resulted in the formation of 2,2,4-trimethyl-1,2-dihydroquinoline **3a** in 90% yield (Scheme 1).

Similarly, various aromatic amines such as mono-, di- and tri-substituted anilines reacted efficiently with 2,2-DMP to give the corresponding 2,2,4-substituted dihydroquinolines. This method is equally effective for both electron-rich as well as electron-deficient aryl amines (entries **a**–**k**, Table 1). No solvent is required for this reaction. Compared to acetone, the reactions were faster with 2,2-dimethoxypropane. In most cases, high conversions were obtained in short reaction times by using this procedure. Encouraged by the results obtained with aryl amines, we turned our attention towards 1,2-diamines. Thus, treatment of *o*-phenylenediamine with 2,2-dimethoxypropane afforded the corresponding 2,2,4-trimethyl-2,3-dihydro-1*H*-benzo[*b*][1,4] diazepine **4l** in 92% yield (Scheme 2).

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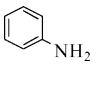
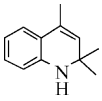
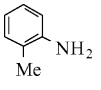
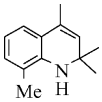
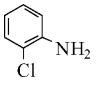
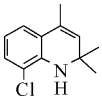
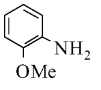
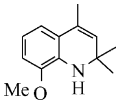
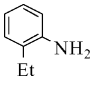
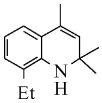
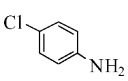
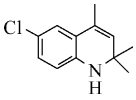
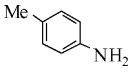
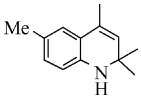
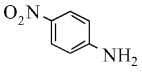
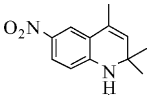
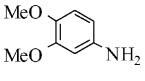
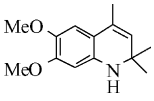
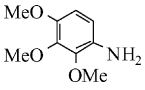
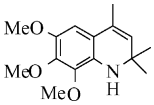
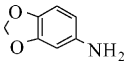
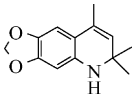
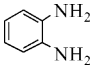
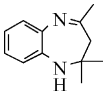
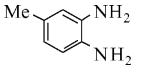
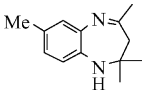
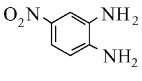
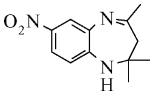
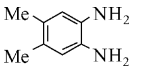
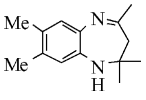
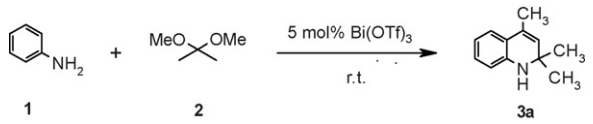
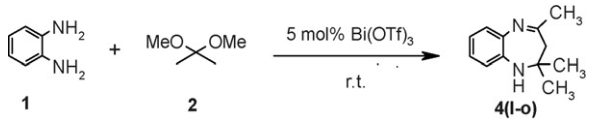
Table 1
$Bi(OTf)_3$-catalyzed synthesis of 1,2-dihydroquinolines and 1,5-benzodiazepines

Entry	Aryl amine **1**	Product[a] **3**	Time (h)	Yield (%)[b]
a			2.0	90
b			2.5	85
c			3.0	83
d			3.5	82
e			2.5	90
f			3.0	89
g			2.0	86
h			4.0	84
i			3.0	82
j			4.0	80
k			3.5	83
l			2.0	92
m			2.5	89[c]
n			4.0	81[c]
o			3.0	87

[a] All products were characterized by ^1H NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] Regioisomeric products were obtained in 1:1 ratio.



Scheme 1.



Scheme 2.

Various substituted *o*-phenylenediamines such as 5-methyl, 5-nitro, and 4,5-dimethyl derivatives underwent smooth condensation with 2,2-dimethoxypropane to afford the respective 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines in high yields (entries **m**, **n** and **o**, Table 1). In all cases, the reactions proceeded rapidly at room temperature with high efficiency. The products were characterized by ^1H, ^{13}C NMR, IR and mass spectroscopic data and also by comparison with authentic samples [7,12]. Unlike reported methods, the present protocol does not require high temperature or drastic conditions to produce dihydroquinolines or benzodiazepines. Among the various metal triflates such as $Cu(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$ and $Ce(OTf)_3$ studied for this transformation, bismuth(III) triflate was found to be the most effective in terms of conversion and reaction rates. In the absence of catalyst, the reaction did not proceed even after long reaction times (8–12 h). The scope and generality of this process is illustrated with respect to various aryl amines and *o*-phenylenediamines and the results are summarized in Table 1 [13].

In conclusion, we have described a novel and efficient version of the Skraup's procedure for the synthesis of dihydroquinolines using bismuth(III) triflate as the novel catalyst. This method not only offers substantial improvements in reaction rates and yields but also avoids the use of hazardous acids and harsh reaction conditions. The method is also useful to the preparation of 1,5-benzodiazepines under extremely mild conditions.

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[13] *General procedure*. A mixture of the aryl amine (1.0 mmol), 2,2-dimethoxypropane or acetone (3 mmol) and $Bi(OTf)_3$ (5 mol%) was stirred at room temperature for the specified time (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (2 × 10 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate-hexane, 0.5–9.5) afforded pure dihydroquinoline. Spectral data for selected products: **3a**: 2,2,4-trimethyl-1,2-dihydroquinoline: liquid, IR (KBr): ν: 3365, 2960, 1610, 1569, 1485, 705 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 6H), 2.0 (s, 3H), 3.50 (brs, 1H, NH), 5.25 (s, 1H), 6.38 (d, J = 8.1 Hz, 1H), 6.60 (t, J = 7.9 Hz, 1H), 6.90 (t, J = 7.9 Hz, 1H), 7.0 (d, J = 8.1 Hz, 1H). EIMS: *m/z* (%): 173 (M^+, 10), 159 (100). **3b**: 8-Methyl-2,2,4-trimethyl-1,2-dihydroquinoline: liquid, IR (KBr): ν: 3480, 2962, 1615, 1565, 1465, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 6H), 1.98 (s, 3H), 2.1(s,3H), 3.51 (brs, 1H, NH), 5.26 (s, 1H), 6.51 (t, J = 7.9, Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 7.7 Hz, 1H). EIMS: *m/z* (%): 187 (M^+, 7), 172 (100), 155 (42), 141 (95), 98 (7), 55 (35), 43 (60). **3c**: 8-Chloro-2,2,4-trimethyl-1,2-dihydroquinoline: liquid, IR (KBr): ν: 3381, 2966, 1650, 1598, 1486, 771 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 6H), 2.0(s, 3H), 3.50 (brs, 1H, NH), 5.30 (s, 1H), 6.45 (t, J = 7.7 Hz,1H), 6.95 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H). EIMS: *m/z* (%): 207 (M^+, 8), 192 (100), 141 (7). **3d**: 8-Methoxy-2,2,4-trimethyl-1,2-dihydroquinoline: oily liquid, IR (KBr): ν: 3365, 2961, 1581, 1496, 806 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 6H), 1.98 (s, 3H), 3.78 (s, 3H), 3.51 (brs, 1H, NH), 5.27 (s, 1H), 6.51 (t, J = 7.9 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H). EIMS: *m/z* (%): 203 (M^+, 32), 188 (100), 173 (25), 145 (55). **3e**: 8-Ethyl-2,2,4-trimethyl-1,2-dihydroquinoline: oily liquid, IR (KBr): ν: 3428, 2963, 1605, 1567, 1482, 905 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, J = 7.0 Hz, 3H), 1.30 (s, 6H), 2.05 (s, 3H), 2.45 (q, J = 7.0 Hz, 2H), 3.55 (brs, 1H, NH), 5.30 (s, 1H), 6.55 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H). EIMS: *m/z* (%): 201 (M^+, 20), 186 (100), 170 (35), 141 (50), 109 (20), 69 (25), 44 (40). **3f**: 6-Chloro-2,2,4-trimethyl-1,2-dihydroquinoline: oily liquid, IR (KBr): ν: 3381, 2966, 1650, 1598, 1486, 771 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 3H), 2.0 (s, 3H), 3.50 (brs, 1H, NH), 5.49 (s, 1H), 6.48 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 7.08 (s, 1H). EIMS: *m/z* (%): 207 (M^+, 5), 192 (100), 170 (35), 141 (7). **3g**: 6-Methyl-2,2,4-trimethyl-1,2-dihydroquinoline: oily liquid, IR (KBr): ν: 3480, 2962, 1615, 1565, 1465, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.24 (s, 6H), 1.97 (s, 3H), 2.25 (s, 3H) 3.55 (brs, 1H, NH), 5.29 (s, 1H), 6.34 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.86 (s, 1H) EIMS: *m/z* (%):187 (M^+, 7), 172 (100), 155 (42), 141 (95), 98 (7), 55 (35), 43 (60). **3h**: 2,2,4-Trimethyl-6-nitro-1,2-dihydroquinoline: yellow solid, m.p. 137 °C, IR (KBr): ν: 3375, 2945, 1609, 1570, 1485, 1213, 738 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 6H), 2.05 (s, 3H), 4.35 (brs, 1H, NH), 5.40 (s, 1H), 6.30 (d, J = 8.1 Hz, 1H), 7.90–7.95 (m, 2H). EIMS: *m/z* (%): 218 (M^+, 10), 204 (100), 158 (90). **3i**: 6,7-Dimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline: oily liquid, IR (KBr): ν: 3359, 2962, 1716, 1615, 1458, 1355, 1278, 1143, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 6H), 2.10 (s, 3H), 3.91 (s, 6H), 3.55 (brs, 1H, NH), 5.10 (s, 1H), 6.11 (s, 1H), 6.65 (s, 1H). EIMS: *m/z* (%): 233 (M^+, 8), 218 (100), 202 (35), 175 (15), 145 (8). **3j**: 6,7,8-Trimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline: oily liquid, IR (KBr): ν: 3344, 2970, 1641, 1606, 1462, 1366, 1261, 1196, 730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (s, 6H), 2.19 (s, 3H), 3.55 (brs, 1H, NH), 3.80 (s, 9H), 5.18 (s, 1H), 5.85 (s, 1H). EIMS: *m/z* (%): 264 (M^+, 7), 248 (100), 218 (40), 188 (8), 147 (10). **3k**: 6,7-(Methylenedioxy)-2,2,4-trimethyl-1,2-dihydroquinoline: oily liquid, IR (KBr): ν: 3375, 2963, 1610, 1501, 1479, 1383, 1254, 1195, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 6H), 2.2 (s, 3H), 3.55 (brs, 1H, NH), 5.80 (s, 1H), 6.15 (s, 2H), 6.7 (s, 2H). EIMS: *m/z* (%): 217 (M^+, 7), 202 (100), 101 (6). **4l**: 2,2,4-Trimethyl-2,3-dihydro-1*H*-1,5diazapine: solid, m.p. 137–138 °C; IR (KBr): ν_{max}: 3345, 1635, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 6H), 2.20 (s, 2H), 2.32 (s, 3H), 6.60–6.68 (d, J = 7.8 Hz, 1H), 6.90–7.0 (m, 2H), 7.10–7.15 (d, J = 7.8 Hz, 1H). ^{13}C NMR (Proton decoupled, 75 MHz, $CDCl_3$): δ 29.7, 30.4, 44.9, 68.3, 121.6, 122.0, 125.4, 126.7, 137.8, 140.6, 172.3. EIMS: *m/z* (%): 188 (M^+, 30), 173 (100), 132 (70), 77 (15), 41 (35). **4m**: 2,2,4-Trimethyl-2,3-dihydro-8-methyl-1*H*-1,5diazapine: solid, m.p. 127–129 °C; IR (KBr): ν_{max}: 3325, 1665, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 6H), 2.19 (s, 2H), 2.23 (s, 3H), 2.80 (s, 3H), 6.65–6.75 (s, 1H), 6.70–6.80 (d, J = 7.8 Hz 1H),6.95–7.0 (d, J = 7.8 Hz, 1H). ^{13}C NMR (Proton decoupled, 75 MHz, $CDCl_3$): δ 20.9, 29.6, 30.4, 30.8, 45.8, 67.0, 122.6, 126.6, 127.0, 131.8, 136.7, 138.1, 174.3. EIMS: *m/z* (%): 202 (M^+, 40), 187 (100), 146 (70), 77 (15), 41 (20). **4n**: 2,2,4-Tri-methyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine: pale yellow solid, m.p. 113–114 °C; IR (KBr): ν_{max}: 3280, 1645, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 6H), 2.95 (s, 3H), 3.20 (s, 2H), 7.15–7.20 (s, 1H), 8.0–8.15 (m, 1H), 8.75–8.80 (m, 1H); ^{13}C NMR (Proton decoupled, 75 MHz, $CDCl_3$): δ 29.9, 30.0, 30.2, 45.6, 60.8, 118.3, 121.2, 126.2, 132.4, 137.9, 145.2, 170.7; EIMS: *m/z* (%): 233 (M^+, 30), 218 (100), 177 (48), 172 (48), 131 (30), 90 (40), 63 (45). **4o**: 2,2,4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine: yellow solid, m.p. 112–114 °C; IR (KBr): ν_{max}: 3290, 1635, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 6H), 2.19 (s, 3H), 2.20 (s, 3H) 2.22 (s, 2H), 2.34 (s, 3H), 2.80 (brs, NH, 1H), 6.52 (s, 1H), 6.39 (s, 1H). ^{13}C NMR (Proton decoupled, 75 MHz, $CDCl_3$): δ 18.9, 19.1, 29.8, 30.3, 30.4, 45.3, 67.7, 122.8, 127.8, 129.9, 133.6, 135.5, 138.4, 171.3. EIMS: *m/z* (%): 216 (M^+, 20), 201 (60), 161 (30), 145 (15), 97 (17), 71 (50), 43 (100).