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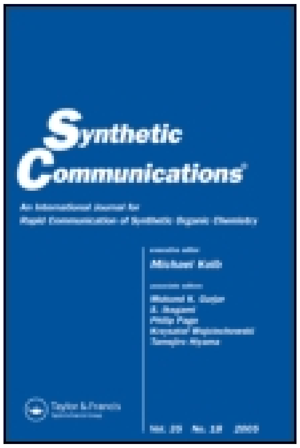

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ONE-POT SYNTHESIS OF TETRAHYDROQUINOLINES CATALYZED BY $Dy(OTf)_3$ IN AQUEOUS SOLUTION

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ONE-POT SYNTHESIS OF TETRAHYDROQUINOLINES CATALYZED BY Dy(OTf)$_3$ IN AQUEOUS SOLUTION

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ABSTRACT

Various 4-substituted-1-methyltetrahydroquinolines are easily accessible from the one-pot condensation reaction of *N*-methylaniline with commercial formaldehyde solution and electron-rich alkenes in the presence of Dy(OTf)$_3$ (1 mol %) under mild conditions at ambient temperature and in the absence of any organic solvents.

Key Words: Tetrahydroquinolines; Dy(OTf)$_3$ catalyst; Aqueous solution reaction

Tetrahydroquinoline derivatives are an important class of natural products, which exhibit both biological and pharmaceutical activities in various fields.[1] In recent years many synthetic methods have been developed for 1,4-disubstituted-1,2,3,4-tetrahydroquinolines.[2] Katritzky and

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Rachwal reported the reactions of *N*-alkyl-*N*-phenyl-1H-benzotriazole-1-methanamines with alkenes, enol ethers and enamines giving the corresponding 4-substituted 1-methyl-1,2,3,4-tetrahydroquinolines in the presence of a catalytic amount of *p*-toluene sulfonic acid in three steps.[3–5] Other methods for the synthesis of tetrahydroquinolines involve ionization of triphenylhexahydro-1,3,5-triazine using $TiCl_4$ as the catalyst;[6,7] reactions of *N*-methyl-*N*-(phenylthiomethyl)aniline with styrene, cyclopentane, *trans*-1-phenylpropene and *cis*-1-phenylpropene catalyzed by $TiCl_4$–PPh_3.[8,9] Recent findings have shown that 7 mol % of dysprosium triflate ($Dy(OTf)_3$) can catalyze the one-pot reaction of benzaldehyde, aniline and endocyclic enamine to afford hexahydropyrrolo[3,2-c]quinolines. However, the use of THF–water (4 : 1) as solvent the yield of product decreased evidently from 91 to 47%.[10] Lanthanide triflate can catalyze the reaction of dienes with in situ formed imines in the presence of $MgSO_4$.[11] None of these methods, however, are as simple and efficient as our high yielding one-pot preparation of tetrahydroquinolines from *N*-methylaniline and commercial formaldehyde solution in the presence of dysprosium triflate (1 mol %) under mild conditions.

Commercial formaldehyde solution, which is an aqueous solution containing 37% formaldehyde and 8–10% methanol, is cheap, easy to handle, and stable even at room temperature.

The reaction of *N*-methylaniline **1** with commercial formaldehyde solution **2** and 2,3-dihydrofuran **3** catalyzed by 1 mol % of $Dy(OTf)_3$ affords tricyclic **4** in 85% yields in 30 min at room temperature in the absence of any organic solvents (Scheme 1). The utility of aqueous reaction is now generally recognized. Aqueous reactions of organic compounds avoid the use of harmful organic solvents and are especially appealing, as they provide an opportunity to develop green chemistry and a safe synthetic process. Although Kobayashi et al have reported that $Ln(OTf)_3$ catalyzed Aldol reaction in aqueous media, in fact the reaction proceeded in co-solvent (THF : water = 4 : 1 to 6 : 1), and the yields were low. When water or THF was used alone, only 18% yield of the product was isolated in 100% water solution.[12]

There is a little effect of the choice of lanthanide triflate catalyst on the outcome of the reaction, although $Dy(OTf)_3$ gives marginally better yields. Other Lewis acid, such as $Zn(OTf)_2$ and $Cu(OTf)_2$, as well as *p*-toluene sulfonic acid can also catalyze this three-component coupling reaction, but the isolated yields of the adducts are obviously lower than the others (Entries 11–13, Table 1).

Reactions of *N*-methylaniline and commercial formaldehyde solution with a variety of electron-rich olefins rather than 2,3-dihydrofuran are also examined in the presence of $Dy(OTf)_3$ (1 mol%) at room temperature

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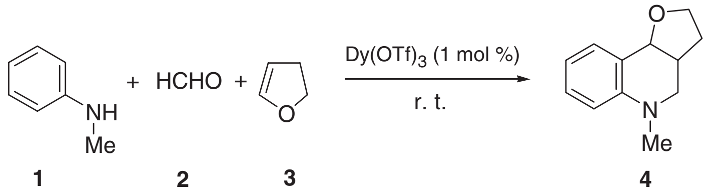
Table 1. One-Pot Synthesis of Furo[3,2-*c*]quinoline Catalyzed by Lewis Acid Catalyst (1 mol %)



Scheme 1.

Entry	Catalyst	Isolated Yield (%)[a]
1	$La(OTf)_3$	82
2	$Pr(OTf)_3$	76
3	$Nd(OTf)_3$	73
4	$Sm(OTf)_3$	78
5	$Gd(OTf)_3$	75
6	$Dy(OTf)_3$	85
7	$Ho(OTf)_3$	76
8	$Yb(OTf)_3$	69
9	$Y(OTf)_3$	77
10	$Sc(OTf)_3$	77
11	$Zn(OTf)_2$	48
12	$Cu(OTf)_2$	57
13	*p*-TsOH	33

and the results are summarized in Table 2. To the most of the substrates, especially the electron-donating alkenes, the reaction could proceed smoothly in the absence of any organic solvents with very short reaction time to afford the desired adduct in good yields. It is noteworthy that this condensation reaction exhibited high atom selectivity, almost all atoms of the substrates transferred to the product expected and no harmful by-product was formed. However, the reactions of styrene and 1-octene with *N*-methylaniline and commercial formaldehyde solution are somewhat difficult.

In summary, we have found a very simple and highly efficient three-component condensation reaction of *N*-methylaniline, commercial formaldehyde solution and electron-rich alkenes for the one-pot synthesis of 1,4-disubstituted-1,2,3,4-quinolines using 1 mol % $Dy(OTf)_3$ as catalyst in the 100% water solution at ambient temperature. The aqueous solution reaction can reduce hazardous pollution and achieve environmental benign organic synthetic process.

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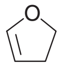
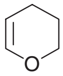
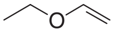
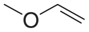
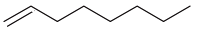
Table 2. Results of the Three-Component Condensation Reactions Catalyzed by $Dy(OTf)_3$ (1 mol%)

Entry	Alkene	Reaction Time (h)	Isolated Yield (%)
1		0.5	85
2		0.5	82
3		2	87
4		2	81
5		5	33
6	PhCH=CH$_2$	5	34

EXPERIMENTAL

General Procedure for the Synthesis of Tetrahydroquinolines

To a mixture of *N*-methylaniline (106 mg, 1 mmol) and commercial formaldehyde solution (82 mg, 1 mmol) was added $Dy(OTf)_3$ (6 mg, 0.01 mmol). After stirred for 5 min, 2,3-dihydrofuran (70 mg, 1 mmol) was added. After stirring for 30 min at room temperature, the reaction was then quenched with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with brine, dried, concentrated in vacuum. The crude product was purified via flash chromatography to afford the desired product furo[3, 2-*c*]quinoline in 85% yield.

Furo[3,2-*c*]quinoline: Colorless oil; ^{1}H-NMR(300 MHz, $CDCl_3$): δ 1.72 (m, 1H), 2.19 (m, 1H); 2.49 (m, 1H); 2.75 (t, $J = 11.0$ Hz, 1H); 2.85 (s, 3H); 2.96 (dd, $J = 5.1$ and 11.2Hz); 3.76 (td, $J = 8.9$ Hz and 6.2 Hz); 3.90 (td, $J = 8.4$ and 5.8 Hz, 1H); 4.56 (d, $J = 5.5$ Hz, 1 H); 6.70 (d, $J = 1.6$ Hz, 1 H); 6.76 (t, $J = 7.7$ Hz, 1 H); 7.17 (td, $J = 7.5$ Hz and 1.6 Hz, 1H); 7.32 (d, $J = 7.5$ Hz, 1H); IR (neat, cm^{-1}): 3068, 3032, 2938, 2866, 2818, 1606, 1576, 1477, 1452, 1430, 1385, 1354, 1298, 1207, 1163, 1141, 1115, 1095, 1059, 1012, 960, 921, 859, 694, 643, 561, 533, 469, 426, 420; MS: 189 (M$^+$, 94.85); 190(M$^+$+1, 24.19); 158 (28.61); 146 (33.16); 145 (27.52); 144

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(100); 131 (13.49); 130 (11.97); Anal. calcd. for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.40. Found C, 76.00; H, 7.63; N, 7.41.

Pyrano[3,2-*c*]quinoline: Colorless oil; ^{1}H-NMR(300 MHz, $CDCl_3$): δ 1.45 (m, 1H); 1.72–1.95 (m, 3H); 2.15 (m, 1H); 2.90 (s, 3H); 2.93 (dd, $J = 4.0$ and 1.2 Hz), 3.51 (t, $J = 11.1$ Hz, 1 Hz); 3.64 (td, $J = 10.4$ and 2.4 Hz, 1H); 3.92 (m, 1H); 4.40 (d, $J = 3.0$ Hz, 1H); 6.62 (t, $J = 8.3$ Hz, 1H); 6.65 (dd, $J = 1.0$ Hz and 7.4 Hz, 1H); 6.65 (dd, $J = 1.0$ and 7.4 Hz, 1H); 7.12–7.20 (m, 2H); IR (neat, cm^{-1}): 3068, 3028, 2933, 2855, 1607, 1572, 1503, 1478, 1452, 1359, 1322, 1294, 1271, 1245, 1208, 1162, 1141, 1091, 1065, 1052, 1043, 1023, 1002, 977, 934, 911, 884, 865, 850, 746, 727, 703, 663, 642, 574, 541; MS: 203(M$^+$, 48.46); 190 (24.19); 158 (28.61); 146 (33.16); 145 (27.52); 144 (100); 131 (13.49); 130 (11.97); Anal. calcd. for $C_{13}H_{17}NO$: C, 76.84; H, 8.37; N, 6.90; Found C, 76.73; H, 7.93; N, 6.90.

1-Methyl-4-methoxy-1,2,3,4-tetrahydroquinoline: Colorless oil; ^{1}H-NMR (300 MHz, CCl_4): δ: 1.73–2.20 (m, 2H); 2.90 (s, 3H); 3.23 (s, 3H); 3.06–3.57 (m, 2H); 4.03 (t, 1H, $J = 3$ Hz), 6.30–7.23 (m, 4H); IR (neat, cm^{-1}): 3058, 3020, 1600, 1500, 1200, 1090, 742; Anal. calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.21; H, 8.77; N, 7.74.

1-Methyl-4-ethoxy-1,2,3,4-tetrahydroquinoline: Colorless oil; ^{1}H-NMR (300 MHz, CCl_4): δ: 1.15 (t, 3H, $J = 7$ Hz); 1.73–2.11 (m, 2H); 2.88 (s, 1H); 2.96–3.63 (m, 2H); 3.60 (q, 2H, $J = 7.0$ Hz); 4.15 (t, 1H, $J = 3.4$ Hz), 6.30–7.21 (m, 4H); IR (neat, cm^{-1}): 3058, 3020, 1600, 1500, 1325, 1220, 1080, 742; Anal. calcd. for $C_{12}H_{17}NO$: C, 75.37; H, 8.96; N, 7.32. Found: C, 75.03; H, 9.06; N, 7.16.

1-Methyl-4-hexyl-1,2,3,4-tetrahydroquinoline: Colorless oil: ^{1}H-NMR (300 MHz, CCl_4): δ: 0.85 (t, 3H, $J = 4.0$ Hz); 1.07–2.11 (m, 12H); 2.43–2.98 (m, 1H); 2.83 (s, 1H); 2.96–3.63 (m, 2H); 6.23–7.06 (m, 2H); IR (neat, cm^{-1}): 3058, 3020, 1600, 1501, 1320, 742; Anal. calcd. for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 83.01; H, 11.08; N, 5.95

1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinoline: Colorless oil; ^{1}H-NMR (90MHz, CCl_4): δ: 1.94–2.41 (m, 2H); 2.79 (s, 3H); 3.01 (t, 2H, $J = 4.8$ Hz); 3.85 (t, 1H, $J = 5.9$ Hz); 6.15–7.50 (m, 9H); IR (neat, cm^{-1}): 3058, 3019, 1600, 1500, 1320, 740, 700; Anal. calcd. for $C_{16}H_{17}N$: C, 86.06; H, 7.67; N, 6.27. Found: C, 86.01; H, 7.75; N, 6.29.

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