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BISMUTH NITRATE-CATALYZED MICHAEL REACTIONS OF INDOLES IN WATER

Bimal K. Banik,* Isabella Garcia, and Frances R. Morales

Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, Texas, U.S.A. 78541; Phone: 956-380-8741; Fax: 956-384-5006; E-mail: banik@panam.edu

Abstract – A remarkable and simple bismuth nitrate-catalyzed Michael reaction of indoles with 1,2-unsaturated ketones in water has been developed to reduce the complications that characterize the current standard conditions.

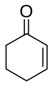
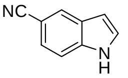
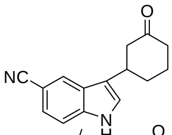
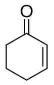
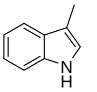
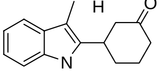
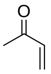
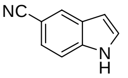
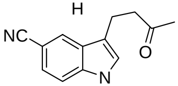
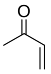
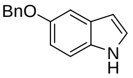
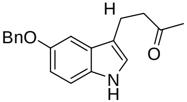
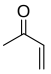
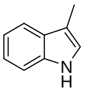
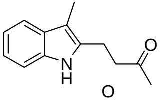
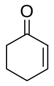
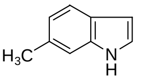
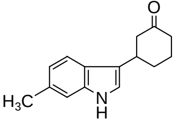
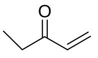
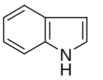
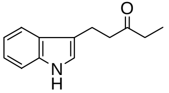
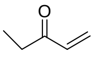
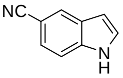
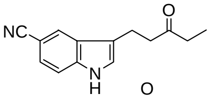
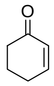
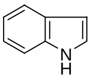
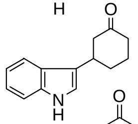
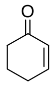
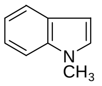
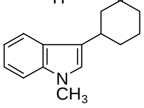
INTRODUCTION

In general, Michael reaction of nucleophiles to unsaturated carbonyl compounds requires basic[1] or acidic conditions.[2] Methods classified as Michael reactions require stoichiometric amounts or excess acids and bases in organic solvents, and side reactions can occur if the reactive partners are sensitive.[3] The main improvement of these reagents is the ability to limit the catalysts used to catalytic amounts.[4] Despite their tremendous success, however, the literature reveals that the success depends on the choice of the catalyst and organic solvent. For example, indium salts are very effective for Michael reactions with indoles[5] and pyrroles,[6] but they are not good promoters in catalyzing a similar reaction with carbamates.[7] In contrast, platinum salts are very effective for this purpose.[7] These reactions were performed in organic solvents. An alternative attractive method using an effective catalyst in aqueous medium would be highly desirable, timely and challenging. This paper describes the development of a simple and environmentally friendly bismuth nitrate pentahydrate-catalyzed Michael reaction of indoles with unsaturated ketones in water. We have been studying reactions mediated by metals or their salts with the aim of developing several biologically active compounds, including anticancer agents[8] and β-lactams.[9] The use of bismuth-derived reagents in several organic transformations has been demonstrated by our group.[10]

RESULTS AND DISCUSSION

Several addition reactions of enones to indoles using Lewis and Bronsted acids have been published.[11] Acid-induced reaction of indoles requires careful control of the acidity to prevent unwanted side reactions, including dimerization and polymerization.[12] Our bismuth nitrate-catalyzed reaction in water has been tested with several indoles and ketones, the results of which have been very encouraging (Table 1). The reactions are efficient, and the products are isolated in high yield. In general, the reactions took place at the 3-position of the indole ring. The reaction produced 2-substituted products when the 3 position is occupied.

Table 1. $Bi(NO)_3 \cdot 5H_2O$- catalyzed Michael reaction of enones with Indoles in water

Entries	Enones	Indoles	Products	% yield
1				78
2				50
3				85
4				80
5				50
6				85
7				55
8				85
9				50
10				50

Catalytic amounts of bismuth nitrate in water were necessary for a complete reaction. The reaction did not proceed at all in the absence of bismuth nitrate. A number of reactions were investigated with bismuth nitrate in varying proportions in water. For example, reaction of indole (1 mmol) with methyl vinyl ketone (1 mmol) was performed with 50 mg, 25 mg, and 5 mg of bismuth nitrate in 1 mL of water for 2 h. It was found that all proportions of bismuth nitrate produced product in excellent yield. Bismuth chloride, scandium triflate, ytterbium triflate and borontrifluoride dietherate proved to be partially effective under identical conditions and did not yield product in good yield**.** Interestingly, the reaction produced products in the absence of water, when the reaction was conducted in more than 2 g scale. However, for very small scale reactions it was difficult to isolate the product in good yield. Mixing of the reactants in a small scale was not adequate and, therefore, bismuth nitrate was not exposed properly to the reactants. This was not the case with gram quantities of the reagents when bismuth nitrate could go into the reactants much more easily.

This method suggests that it is not necessary to use large excess of corrosive acid in Michael reaction of indoles with unsaturated ketones. Bismuth nitrate is an inexpensive, commercially available, water soluble and non-toxic solid and therefore, an ideal catalyst for this reaction.

In conclusion, Michael reactions of various indoles have been successfully carried out in the presence of aqueous bismuth nitrate solution with products in excellent yield.[13]

EXPERIMENTAL

Bismuth nitrate (25 mg) in water (1 mL) was added to a mixture of indole (1.00 mmol) and ketone (1.00 mmol). The reaction mixture was then stirred at rt for 2 h. It was then extracted with CH_2Cl_2 (2 x 5 mL), washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), brine solution (10 mL) and dried over Na_2SO_4. The extracts were then concentrated and the crude product was purified using flash chromatography (silica gel, 30% EtOAc-70% hexane) to afford pure compound (50-85%).

The compound characterization data is given below: 3-(5-Cyano-3-indolyl)cyclohexan-1-one (entry 1)**:**[10f]yield 78%; IR (neat): 3324, 2940, 2218, 1698, 1617, 1472, 1429,1344, 1224, 1344, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.92-2.05 (m, 3 H), 2.23-2.30 (m, 1 H), 2.43-2.48 (m, 2 H,CH_2), 2.64-2.68 (m, 1 H, CH), 2.76-2.77 (m, 1 H) 3.43-3.48 (m, 1 H, CH), 7.03 (q, 1 H, ArH), 7.44 (d, 2 H, *J*) 1.2 Hz, ArH), 7.98 (brs, 1 H, ArH), 8.51 (brs, 1 H, NH); ^{13}C NMR (75MHz) δ: 25.0, 32.1, 35.9, 41.8, 48.1, 102.9, 112.6, 120.8, 123.1,125.1, 125.5, 126.4, 138.5, 211.6; Anal. Calcd for $C_{15}H_{14}N_2O$ (238.290): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.47; H, 5.58; N, 11.71.

3-(3-Methyl-2-indolyl)cyclohexan-1-one (entry 2):[10f]yield 50%; IR (neat): 3407, 2940, 1702, 1463, 1344 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89-1.96 (m, 2 H, CH_2), 2.13-2.18 (m, 2H, CH_2), 2.25 (s, 3 H, CH_3), 2.50-2.66 (m, 4 H, 2 x CH_2), 3.38-3.37 (m, 1 H, CH), 6.91-7.16 (m, 2 H, ArH), 7.29-7.32 (m, 1H, ArH), 7.51 (d, *J*) 6 Hz, 1 H, ArH), 7.80 (brs, 1 H, NH); ^{13}CNMR (75 MHz) δ 8.8, 25.8, 31.9, 36.8, 41.7, 47.6, 107.1, 110.8,118.7, 119.7, 121.9, 129.5, 135.5, 136.3, 210.8; Anal. Calcd for $C_{15}H_{17}NO$ (227.307): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.19; H, 7.58; N, 6.01.

4-(5-Cyano-3-indolyl)butan-2-one (entry 3):[10f]yield 85%; mp 108-112 °C; IR (neat) 3338, 2919, 2218, 1706, 1619,1473, 1434, 1359, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.16 (s, 3 H, $COCH_3$), 2.84 (t, *J*) 6 Hz, 2 H, CH_2), 3.02 (t, *J*) 6 Hz, 2 H, CH_2), 7.11-7.12 (m, 1 H, ArH), 7.41-7.42 (m, 2H, ArH), 7.90 (brs, 1 H, ArH), 8.29 (brs, 1 H, NH); ^{13}C NMR(75 MHz) δ: 102.8, 112.4, 116.6, 121.1, 124.1, 124.8, 125.3,127.5, 127.5, 129.2, 131.3, 138.2; Anal. Calcd for $C_{13}H_{12}N_2O$ (212.252): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.29; H, 5.48; N, 13.11.

4-(5-Benzyloxy-3-indolyl)butan-2-one (entry 4):[10f]yield 80%; IR (neat): 3407, 3032, 2915, 1705, 1624, 1582, 1482,1374, 1292, 1197 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.13 (s,3 H, CH_3), 2.78-2.83 (t, *J*) 9 Hz, 2 H, CH_2), 2.97-3.02 (t, *J*) 6 Hz, 2 H, CH_2) 5.12 (s, 2 H, OCH_2), 6.91-6.94 (m, 2 H, ArH), 7.10 (d, *J*) 2.4, 1 H, ArH), 7.22-7.41 (m, 6 H, ArH), 7.48 (m, 2 H, ArH), 7.80 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ: 19.7, 30.4, 44.3, 71.4, 102.8, 112.2, 113.28, 115.3, 122.7, 127.9,128.0, 128.1, 128.9, 131.2, 138.0, 153.5, 209.1; Anal. Calcd for $C_{19}H_{19}NO_2$ (293.366): C, 77.79; H, 6.53; N, 4.77. Found: C, 77.39; H, 6.34; N, 4.61.

4-(3-Methyl-2-indolyl)butan-2-one (entry 5):[10f]yield 50%; IR (neat): 3407, 2400, 1714, 1605, 1455, 1360, 1166 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.16 (s, 3 H, CH_3), 2.23 (s, 3 H,CH_3), 2.82 (t, *J*) 6.6 Hz, 2 H, CH_2), 2.98 (t, *J*) 6.6 Hz, 2 H,CH_2), 7.05-7.11 (m, 2 H, ArH), 7.25-7.27 (m, 1 H, ArH), 7.45-7.48 (d, *J*) 9 Hz, 1 H, ArH), 8.29 (brs, 1 H, NH); ^{13}C NMR (75 MHz) δ 8.7, 19.7, 30.4, 44.0, 107.0, 110.7, 118.4, 119.2,121.5, 129.3, 134.6, 135.5, 209.7; Anal. Calcd for $C_{13}H_{15}NO$ (201.269): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.39; H, 7.59; N, 6.71.

3-(6-Methyl-3-indolyl)cyclohexan-1-one (entry 6): yield 55%; IR (neat): 3325, 2940, 1695, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42-1.98 (m, 4 H), 2.20 (s, 3 H), 2.19-2.60 (m, 5 H), 6.82 (d, J= 6 Hz, 1 H), 7.01 (s, 1 H), 7.2 (s, 1 H), 7.35 (d, J= 6 Hz, 1 H), 7.85 (s, 1 H); Anal. Calcd for $C_{15}H_{17}NO$ (227): C, 79.29; H, 7.48; N, 6.16. Found: C, 79.01; H, 7.15; N, 5.98.

3-Indolylpent-3-one (entry 7): yield 85%; IR (neat): 3330, 2920, 1710, 1615, 1475 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (t, 3 H, CH_3), 2.32 (q, 2 H, CH_2), 2.85 (q, 2 H, CH_2), 3.15 (q, 2 H, CH_2), 7.12-7.65 (m, 5 H, ArH), 8.00 (s, 1 H, NH); Anal. Calcd for $C_{13}H_{15}ON$ (201.13): C, 77.62; H, 7.45; N, 6.96. Found: C, 77.41; H, 7.28; N, 7.01.

(5-Cyano-3-indolyl)pentan-3-one (entry 8): yield 85%; IR (neat): 3400, 2950, 1705, 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (t, 3 H, CH_3), 2.40 (q, 2 H, CH_2), 2.80 (t, 2 H, CH_2), 3.12 (t, 2 H, CH_2), 7.10 (s, 1 H, ArH), 7.25-7.45 (m, 2 H, ArH), 7.80 (s, 1 H, ArH), 9.20 (s, 1 H, NH); Anal. Calcd for $C_{14}H_{14}N_2O$ (226.14): C, 74.35; H, 6.19; N, 12.38. Found: C, 74.11; H, 6.30; N, 12.00.

3-Indolylcyclohexan-1-one (entry 9): yield 50%; IR (neat): 3330, 2950, 1698, 1470 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30-1.55 (m, 4 H, CH_2), 1.60-1.70 (m, 1 H, CH), 2.30 (t, 2 H, CH_2), 2.60 (t, 2 H, CH_2), 6.95-7.45 (m, 5 H, ArH), 7.70 (d, 1 H, ArH), 7.85 (s, 1 H, NH); Anal. Calcd for $C_{14}H_{15}NO$ (231.14): C, 72.74; H, 6.48; N, 6.05. Found: C, 72.51; H, 6.30; N, 5.89.

(N-Methyl-3-indolyl)cyclohexan-1-one (entry 10): yield 50%; IR (neat): 3320, 2945, 1700, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.75-1.80 (m, 4 H, CH_2), 1.81-1.85 (m, 1 H, CH) 2.20 (t, 2 H, CH_2), 2.50 (t, 2 H, CH_2), 3.82 (s, 3 H, N-CH_3), 6.90 (s, 3 H, ArH), 6.92 (d, ArH, 1 H), 7.22 (d, 1 H, ArH), 7.38 (d, ArH, 1 H), 7.38 (d, 1 H, ArH); Anal. Calcd for $C_{15}H_{17}NO$ (227.15): C, 79.15; H, 7.48; N, 6.16. Found: C, 79.15; H, 7.43; N, 6.01.

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