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Indium(III) Chloride: An Efficient Catalyst for the Synthesis of Amidoalkyl Naphthols

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INDIUM(III) CHLORIDE: AN EFFICIENT CATALYST FOR THE SYNTHESIS OF AMIDOALKYL NAPHTHOLS

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Indium chloride was found to be a very efficient catalyst for the synthesis of amidoalkyl naphthols from β-naphthol, aromatic aldehydes, and acetamide/urea under solvent-free conditions using microwave irradiation.

Keywords: Acetamide; amidoalkyl naphthols; aromatic aldehyde; indium(III) chloride; β-naphthol; urea

INTRODUCTION

The development of multicomponent organic synthesis is a very popular area of research in recent years and is acceptable from a "green chemistry" point of view. The major advantages of multicomponent reactions are (i) the use of simple and diverse precursors to construct complex molecules, (ii) a single purification step, requiring less solvents, and (iii) better yields when compared to stepwise reactions. Strecker[1] in 1850 first demonstrated the concept of multicomponent reactions, and the same concept has been subsequently used in both liquid- and solid-phase reactions to construct important structures for pharmaceutical research.

Aminonaphthols are valuable synthetic scaffolds because of their usefulness in the synthesis of organic molecules that exhibit various biological activities including antihypertensive, adrenoceptor blocking, and Ca^{2+} channel blocking activities.[2] This class of compounds can be easily prepared by the reduction of the respective amidonaphthols. Thus, synthesis of amidoalkyl naphthols has received renewed interest, and several catalysts used so far are $HClO_4$-SiO_2,[3] molybdophosphoric acid,[4] PPA-SiO_2,[5] $FeH(SO_4)_2$,[6] $Al(H_2PO_4)_3$,[7] $Sr(OTf)_3$,[8] alumina–sulfuric acid,[9] $NaHSO_4 \cdot H_2O$,[10] $FeCl_3 \cdot SiO_2$,[11] zirconyl(IV) chloride,[12] montmorillonite K10 clay,[13] $Ce(SO_4)_2$,[14] iodine,[15] $K_5CoW_{12}O_4 \cdot 3H_2O$,[16] *p*-toluenesulforic acid (*p*-TSA),[17] sulfamic acid,[18] cation-exchanged resins,[19] and silica-sulfuric acid.[20] Some of these methods suffer from drawbacks including involvement of strong acids, long reaction time, toxic catalysts, and poor yields. Consequently, there is a need to develop protocol for using nontoxic materials with greater yields. Recently, indium

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chloride has attracted much attention because it has emerged as an alternative safe, economical, and air- and moisture-tolerant Lewis acid, which has been used in various organic transformations.

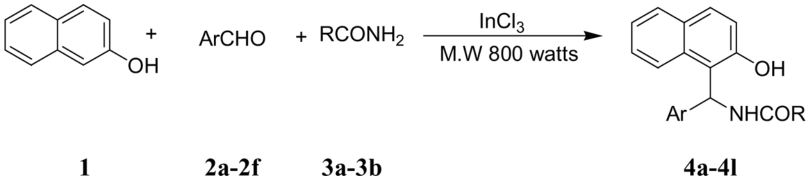
Microwave irradiation (MW) has become an established tool in organic synthesis because of the rate enhancements, greater yields, and often improved selectivity as compared to conventional reaction conditions. In addition, solvent-free MW processes are also clean and efficient, and moreover, reactions using either organic or inorganic solid supports have received increased attention. There are several advantages of performing synthesis in solvent-free media such as (i) short reaction time, (ii) increased safety, (iii) economic advantages because of the absence of solvent, and (iv) environmentally friendly reactions.[21] Herein, we report remarkable catalytic activity of indium chloride in multicomponent synthesis of amidoalkyl naphthols using microwave conditions.

RESULTS AND DISCUSSION

In a preliminary study, the reaction of β-naphthol (1 mmol), 4-nitro benzaldehyde (1 mmol), acetamide (1.2 mmol), and 10 mol% of indium chloride was carried out, in which the corresponding amidoalkylnaphthols were obtained in 75% yield after heating for 90 min. To enhance the rate of the reaction, the same reaction was carried out under microwave irradiation. Gratifyingly, the reaction proceeded smoothly to afford the corresponding amidoalkylnaphthol **4a** in very high yield (95%), which was characterized by both spectral and analytical data and also by comparison with reported values. Upon irradiation in a microwave without $InCl_3$, no reaction occurred. During optimization of the catalyst loading in the reaction, it was observed that 10 mol% of $InCl_3$ is essential to get the greatest yield of the product.

Having this in hand, the scope and limitation of the protocol were investigated. Thus, a variety of aromatic aldehydes having electron-donating as well as electron-withdrawing substituents were used, and in all the cases the corresponding amidoalkylnaphthols were obtained in good yields (Scheme 1; Table 1, entries a–f).

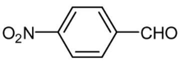
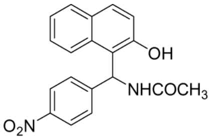
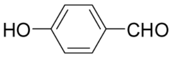
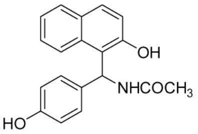
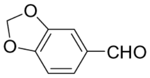
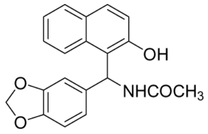
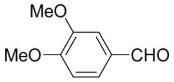
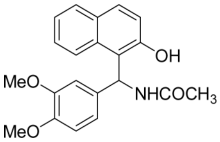
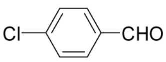
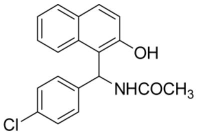
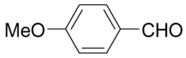
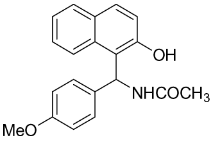
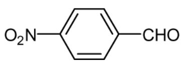
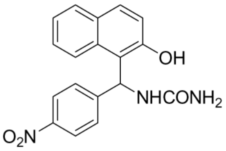
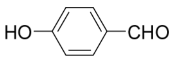
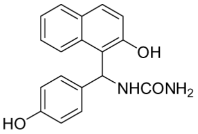
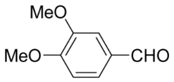
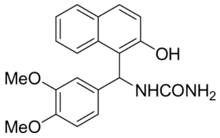
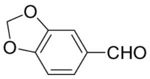
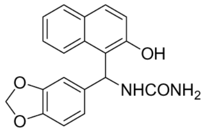
More interestingly, reactions with urea in place of acetamide proceeded smoothly to afford the corresponding hydrazides in excellent yields (Table 1, entries g–l). All the products were characterized by spectroscopic methods. As expected, the aldehydes with electron-withdrawing groups reacted faster than aldehydes having electron-donating groups. We could successfully achieve the synthesis of products **4c, 4g, 4h,** and **4j** using indium chloride in very good yield for the first time.



1 **2a-2f** **3a-3b** **4a-4l**

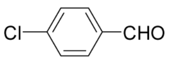
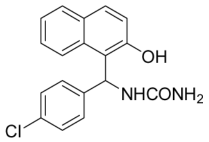
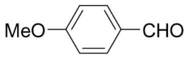
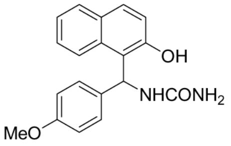
Scheme 1. Indium chloride–catalyzed multicomponent reaction.

Table 1. Indium chloride–catalyzed reaction of β-naphthol, aldehydes, and acetamide or urea using microwaves

Entry	Aldehydes (**2**)	Urea or amide (**3**)	Product (**4**)	Time (min)	Yield (%)
a		NH_2COCH_3		3	95
b		NH_2COCH_3		8	88
c		NH_2COCH_3		7	92
d		NH_2COCH_3		10	89
e		NH_2COCH_3		5	94
f		NH_2COCH_3		8	90
g		NH_2CONH_2		6	93
h		NH_2CONH_2		10	85
i		NH_2CONH_2		13	87
j		NH_2CONH_2		11	89

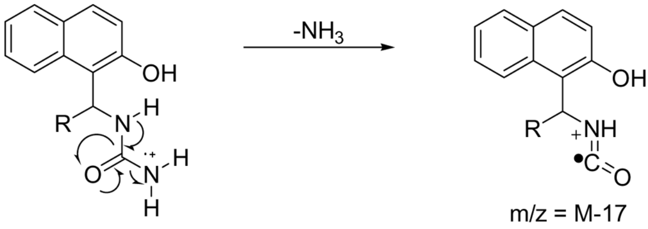
(*Continued*)

Table 1. Continued

Entry	Aldehydes (**2**)	Urea or amide (**3**)	Product (**4**)	Time (min)	Yield (%)
k		NH_2CONH_2		8	91
l		NH_2CONH_2		10	96

It is known that amides undergo α-cleavage next to the carbonyl group in mass spectrometry. The same was observed in the case of products **4g–l**. Because of the instability, the molecular ion peak was not observed in the mass spectrum. The M-17 ion was observed as a peak at the greatest mass because of the loss of ammonia molecule (Scheme 2).

Comparison of yield and time for the reaction using other catalysts under microwave irradiation are shown in Table 2, which clearly indicates that use of indium chloride under microwave conditions is an efficient method for the synthesis of amidoalkyl naphthols.



Scheme 2. Genesis of M-17 ion observed in mass spectrum.

Table 2. Comparison of results for the synthesis of *N*-((2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl) acetamide using various catalysts[3,6,7,10] under microwave irradiation

Entry	Catalyst	Time (min)	Yield (%)
1	$NaHSO_4$	3	89
2	$Al(H_2PO_4)$	3	66
3	$FeHSO_4$	5	96
4	$HClO_4$-SiO_2	12	91
5	$InCl_3$	3	95

CONCLUSION

In summary, we have demonstrated for the first time that indium chloride showed good catalytic activity for three-component condensation of β-naphthol, aromatic aldehydes, and acetamide or urea to furnish amidoalkyl naphthols under solvent-free microwave conditions.

EXPERIMENTAL

NMR spectra were recorded on a 300-MHz Varian Mercury instrument as δ values in $CDCl_3$ and dimethylsulfoxide (DMSO-d_6) with reference to tetramethylsilane (TMS) as internal standard. Fourier transform–infrared (FT-IR) spectra were recorded on a Shimadzu 8400 instrument. Mass spectra were recorded on a Shimadzu QP 5050 instrument. Elemental analyses were recorded on a Flash E. A. 1112 Thermo Fischer machine. A Domestic microwave oven (LG, 800 W) was used for microwave irradiation.

General Procedure for the Synthesis of Amidoalkyl Naphthols

$InCl_3$ (0.1 mmol, 10 mol%) was added to a mixture of 2-naphthol (1 mmol), aldehydes (1 mmol), and acetamide or urea (1.2 mmol). The mixture was irradiated in a domestic microwave oven at 800 W, and the progress of the reaction was followed by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature, and the residue was purified by column chromatography to afford the pure compound. The products were characterized by their spectral and analytical data and compared with those of the known compounds.

Selected Data

Compound 4c. Yield: 92%, mp 205–206 °C. IR (KBr, ν_{max}): 3365, 3140 (br), 1626, 1510 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.98 (s, 3H), 5.93 (d, 2H, $J = 4.4$), 6.63 (d, 1H, $J = 7.7$), 6.76 (m, 2H), 7.05 (d, 1H, $J = 7.9$), 7.23 (m, 2H), 7.37 (bs, 1H), 7.79 (m, 2H), 7.88 (bs, 1H), 8.45 (d, 1H, $J = 8.2$), 10.0 (bs, 1H). ^{13}C NMR (DMSO-d_6): 22.72, 47.69, 100.69, 106.59, 106.76, 107.75, 118.38, 118.69, 119.03, 122.26, 123.09, 126.21, 128.27, 128.38, 129.06, 132.05, 136.41, 145.32, 146.93, 152.84 and 168.98. MS (GCMS): m/z 335. Anal. calcd. for $C_{20}H_{17}N_2O_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.58; H, 5.05; N, 4.10.

Compound 4g. Yield: 93%, mp 161–162 °C, IR (KBr, ν_{max}): 3468, 3356 (br), 1668, 1602, 1512, 1415 cm^{-1}. ^1H NMR (DMSO-d_6): δ 5.91 (s, 2H), 6.97(s, 2H), 7.19 (d, 1H, $J = 8.5$), 7.28 (t, 1H, $J = 7.1$), 7.38 (m, 3H), 7.80 (m, 3H), 8.12 (d, 2H, $J = 8.8$ Hz), 10.08 (s, 1H). ^{13}C NMR (DMSO-d_6): 48.01, 118.33, 119.12, 122.55, 123.16, 126.84, 128.30, 128.68, 129.53, 131.98, 145.73, 152.90 and 158.44. MS (GCMS): m/z 320 ($M^+ - 17$). Anal. calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 63.91; H, 4.44; N, 12.42.

Compound 4h. Yield: 85%, mp 223–224 °C, IR (KBr, ν_{max}): 3267, 3147 (br), 1718, 1606, 1512, 1402 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 5.95 (d, 1H, $J = 2.4$), 6.68 (m, 3H), 7.07 (m, 3H), 7.24 (d, 1H, $J = 8.8$), 7.36–7.39 (m, 3H), 7.63 (d, 1H, $J = 8.2$), 7.81 (m, 3H), 8.59 (bs, 1H). ^{13}C NMR (DMSO-d_6): 53.34, 114.43, 115.49, 116.80, 123.12, 124.95, 127.19, 128.19, 128.53, 128.87, 129.94, 130.36, 133.39, 147.22, 149.38 and 157.06. MS (GCMS): m/z 291($M^+ - 17$). Anal. calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.03; H, 5.19; N, 9.04.

Compound 4j. Yield: 89%, mp 183–185 °C, IR (KBr, ν_{max}): 3248, 3147 (br), 1749, 1627, 1487, 1228 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.07 (s, 2H), 5.93 (d, 2H, $J = 6.8$), 6.09 (d, 1H, $J = 2.7$), 6.69 (d, 1H, $J = 7.9$), 6.81 (m, 2H), 7.08–7.16 (m, 1H), 7.33 (d, 1H, $J = 8.8$), 7.42–7.49 (m, 2H), 7.76 (d, 1H, $J = 7.7$), 7.94 (m, 2H), 8.77 (s, 1H). ^{13}C NMR (DMSO-d_6): 53.44, 101.11, 107.21, 108.36, 113.82, 116.70, 120.21, 122.96, 124.96, 127.23, 128.46, 128.72, 130.08, 130.24, 136.62, 146.72, 147.18, 147.40 and 149.14. MS (GCMS): m/z 319 ($M^+ - 17$). Anal. calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.76; H, 4.70; N, 8.27.

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