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$InCl_3$ catalyzed C–C coupling of aryl alcohols and TosMIC

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Abstract—The $InCl_3$ mediated C–C coupling reaction between aryl alcohols and TosMIC gives the corresponding amides in good to high yields.

Carbon–carbon bond formation under nearly neutral conditions would be a fascinating and a valuable procedure in synthetic organic chemistry.[1,2] There has been a recent increase in activity towards the direct coupling between an alcohol and an active methylene-containing species due to the intrinsic energy saving properties.[2] *p*-Toluenesulfonylmethyl isocyanide[3] (TosMIC) is a versatile, widely applicable reagent that constitutes a densely functionalized building block bearing an active methylene group. Recently, we reported TosMIC mediated synthesis of C-nucleosides[4] as well as its use in diastereoselective Passerini reactions.[5] Apart from the inherent advantage of possessing an isonitrile functionality, the active methylene group of TosMIC is available for secondary reactions through various methods. Owing to these potential uses, we became interested in further expanding the utility of TosMIC. Consequently, a Lewis acid mediated direct C–C coupling was envisaged between TosMIC and aryl alcohols, which would result in α-alkylated TosMIC as products (Fig. 1),[6] however, an N-substituted amide was obtained instead. To the best of our knowledge, this is the first report on the use of an isonitrile in such a mechanistic pathway.[7]

Herein, a novel synthetic protocol is reported which leads to the formation of amides from the corresponding aryl alcohols and TosMIC (Scheme 1). Initially, the coupling reaction was performed between benzhydrol **1** and TosMIC **10** in the presence of $FeCl_3$ (5 mol %) at 80 °C in acetonitrile as solvent to afford amide **1a** in 73% yield

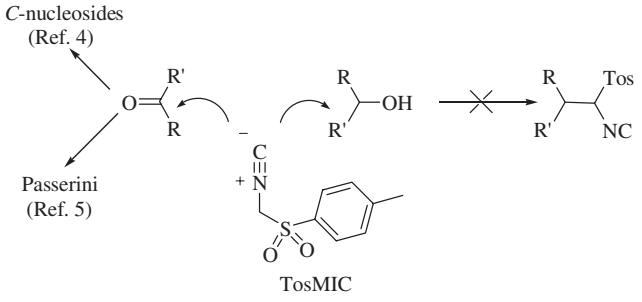
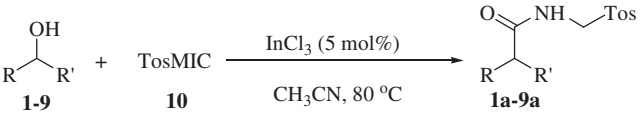


Figure 1.



1-9 **10** **1a-9a**

Scheme 1.

along with the corresponding dimeric ether (9%) as a byproduct. In order to minimize the byproduct formation, different Lewis acids such as $BF_3{\cdot}OEt_2$, $ZrCl_4$, $Sc(OTf)_3$ and $InCl_3$ were screened under similar reaction conditions to afford **1a** and the dimeric ether in varying yields (Table 1).

It was found that when the reaction was carried out using $InCl_3$ as the catalyst, the amide **1a** (92%) was formed in a shorter reaction time (Table 1). Amide **1a** was identified from its spectral data. The ^1H NMR spectrum revealed characteristic methylene protons at δ 4.63 as a doublet ($J = 7.0$ Hz), the aryl methyl at δ 2.44 as a singlet and the benzylic proton at δ 4.76 as a singlet. The

Keywords: Indium chloride; Aryl alcohols; TosMIC; N-Substituted amides.
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Table 1. Coupling reaction of benzhydrol **1** with TosMIC using different catalysts at 80 °C[a]

Entry	Catalyst	Time (h)	Product **1a** (%)
1	$FeCl_3$	8	73 (9)
2	$BF_3{\cdot}OEt_2$	4	76 (7)
3	$ZrCl_4$	6	84 (5)
4	$Sc(OTf)_3$	3	87 (5)
5	$InCl_3$	2	92 (3)

[a] The figure in parenthesis reflects the yields of the dimeric ether.

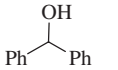
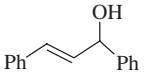
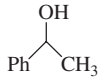
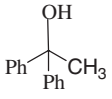
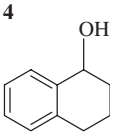
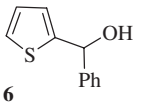
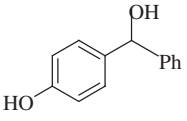
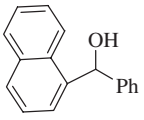
^{13}C NMR spectrum revealed the carbonyl carbon resonating at δ 171.2. This amide product was further supported by the IR spectrum which revealed characteristic stretching frequencies at 3319 and 1675 cm^{-1} due to the –NH and –C=O functional groups, respectively.

The versatility of the methodology was studied with various substrates. Thus, alcohols **2**–**9**, including an α,β-unsaturated alcohol **2**, a tertiary alcohol **4**, bicyclic benzylalcohol **5**, and heteroaryl benzylalcohol **6** afforded the corresponding amides under standard reaction conditions in good to high yields (75–88%). The corresponding dimeric ethers were isolated in less than 8% yields. All the products were characterized from spectral data (see Table 2).

Amide formation can be rationalized via the plausible mechanism depicted in Figure 2. The ambiphilic reactivity of isonitriles serving both as a nucleophile or an electrophile is well known in the literature[7] and is exploited herein. The Lewis acid initially coordinates ($InCl_3$, Fig. 2) with the alcohol (**A**) due to its greater nucleophilicity,[8] thereby generating an incipient carbocation, to facilitate nucleophilic attack of TosMIC onto **A** resulting in intermediate **B**. Next, the alcohol adds to the more electrophilic isonitrile carbon to generate the corresponding N-substituted acetimidic acid **C**, which tautomerises to the stable N-substituted amide with concomitant regeneration of $InCl_3$.

In conclusion, we have reported a new $InCl_3$ mediated C–C coupling reaction between aryl alcohols and TosMIC to afford the corresponding amides in good to high yields.[9,10] This reaction besides being atom economical in nature is also a novel protocol that paves the way for further exploitation of TosMIC.

Table 2. Coupling reaction between various alcohols and TosMIC under optimized conditions[a]

Entry	Alcohol	Product[b]	Time (h)	Yield[c] (%)
1	 **1**	**1a**	2	92
2	 **2**	**2a**	4	87
3	 **3**	**3a**	8	76
4	 **4**	**4a**	4	85
5	 **5**	**5a**	3	88
6	 **6**	**6a**	4	80
7	 **7**	**7a**	4	76
8	 **8**	**8a**	3	78
9	 **9**	**9a**	6	75

[a] All reactions were conducted as described in the general experimental procedure in the reference section.
[b] All the products were characterized from spectral data.
[c] Isolated yields are after purification by column chromatography.

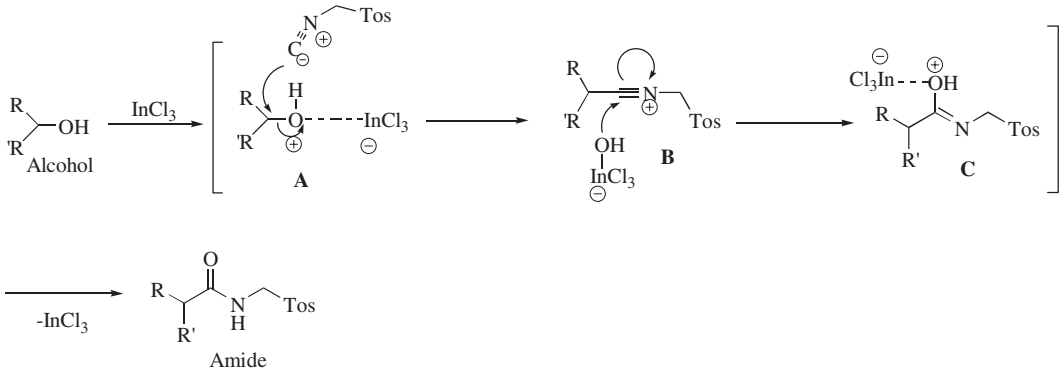


Figure 2. A plausible mechanism.

Acknowledgements

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9. *General experimental procedure*: A solution of alcohol (1.0 mmol), TosMIC (1.0 mmol) and $InCl_3$ (0.05 mmol) in acetonitrile (2.0 mL) was stirred at 80 °C for 2–8 h until complete conversion of the alcohol was observed (tlc). The resulting solution was partitioned between an equimolar ratio of diethyl ether and water (30 mL, 1:1), the organic layer separated and then the aqueous layer was washed with ether (2×20 mL).The combined organic layers were washed with brine, dried (Na_2SO_4), evaporated in vacuo and the residue thus obtained was purified by column chromatography (silica gel 60–120 mesh, EtOAc:*n*-hexane, 2.5:7.5) to afford amides **1a**–**9a** in 75–92% yields.
10. *Spectral data of selected compounds*: Compound **1a**: white solid; mp: 145–148 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.61$ (d, 2H, $J = 7.0$ Hz, Ar-H), 7.29–7.18 (m, 8H, Ar-H), 7.10–7.05 (m, 4H, Ar-H), 6.59 (br s, 1H, NH), 4.76 (s, 1H, benzylic), 4.63 (d, 2H, $J = 7.0$ Hz, CH_2), 2.44 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.2$, 145.2, 138.3, 135.3, 133.4, 129.8, 128.6, 127.3, 80.7, 60.1, 58.2, 29.6, 21.7. IR (KBr): 3319, 2924, 2854, 1745, 1675, 1141 cm^{-1}. ESI: $m/z = 380$ [M^++1], 402 [M^++23]. Anal. Calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69. Found: C, 69.70; H, 5.42; N, 3.65. Compound **2a**: white solid; mp: 158–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (d, 2H, $J = 6.7$ Hz, Ar-H), 7.29–7.12 (m, 12H, Ar-H), 6.39–6.35 (m, 3H, NH, olefin), 4.60 (d, 2H, $J = 6.0$ Hz, CH_2), 4.17 (d, 1H, $J = 5.2$, benzylic), 2.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.3$, 145.2, 133.3, 132.9, 129.8, 128.8, 128.7, 128.4, 128.0, 127.7, 127.5, 126.7, 126.3, 60.1, 56.0, 21.5. ESI: $m/z = 405$ [M^++1]. Anal. Calcd for $C_{24}H_{23}NO_3S$: C, 71.08; H, 5.72; N, 3.45. Found: C, 71.12; H, 5.62; N, 3.38. Compound **4a**: white solid; mp: 155–160 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.62$ (d, 2H, $J = 8.9$ Hz, Ar-H), 7.31–7.21 (m, 8H, Ar-H), 7.06–7.02 (m, 4H, Ar-H), 6.15 (t, 1H, $J = 6.7$ Hz, NH), 4.61 (d, 2H, $J = 6.7$ Hz, CH_2), 2.48 (s, 3H, CH_3), 1.79 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 174.3$, 145.2, 143.7, 133.8, 129.8, 128.7, 128.5, 128.2, 127.9, 127.2, 127.0, 60.2, 56.8, 26.9, 21.6. ESI: $m/z = 416$ [M^++23]. Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 70.11; H, 6.05; N, 3.52. Compound **5a**: white solid; mp: 160–165 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.71$ (d, 2H, $J = 7.7$ Hz, Ar-H), 7.31 (d, 2H, $J = 7.7$ Hz, Ar-H), 7.24 (s, 2H, Ar-H), 7.20–7.11 (m, 2H, Ar-H), 6.94 (d, 1H, $J = 6.9$ Hz, NH), 5.96 (br s, 1H, benzylic), 4.59 (br s, 2H, CH_2), 2.83–2.73 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.05–2.02 (m, 2H, CH_2), 1.83–1.61 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.1$, 145.3, 137.8, 133.8, 132.5, 129.8, 128.7, 127.6, 126.2, 60.1, 47.4, 46.5, 30.0, 29.6, 28.9, 27.0, 21.7, 20.1, 19.8. ESI: $m/z = 344$ [M^++1]. Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08. Found: C, 66.75; H, 6.05; N, 4.03. Compound **6a**: white solid; mp: 128–132 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.61$ (d, 2H, $J = 8.0$ Hz, Ar-H), 7.38 (t, 1H, $J = 6.5$ Hz, NH), 7.20–7.08 (m, 8H, Ar-H), 6.84 (dd, 1H, $J = 3.6$, 5.1 Hz, Ar-H), 6.75 (d, 1H, $J = 3.6$ Hz, Ar-H), 4.98 (s, 1H, benzylic), 4.60 (dd, 2H, $J = 2.1$, 7.3 Hz, CH_2), 2.37 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.5$, 145.2, 140.7, 138.3, 133.2, 129.8, 128.6, 128.4, 128.2, 127.6, 127.1, 126.5, 126.0, 125.5, 124.6, 60.2, 53.4, 47.5, 29.6, 21.6. ESI: m/z 386 [M^++1]. Anal. Calcd for $C_{20}H_{19}NO_3S_2$: C, 62.31; H, 4.97; N, 3.63. Found: C, 62.15; H, 5.12; N, 3.59.