# $FeCl_3$/TMSCl: An Effective Catalytic System for the Conjugate Addition of Sodium *p*-Toluenesulfinate to α,β-Enones

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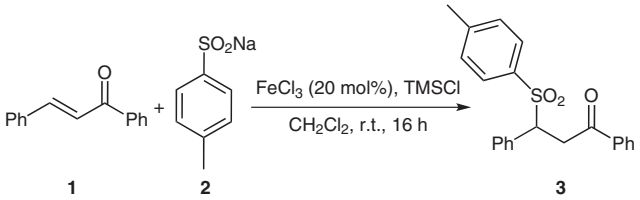
**Abstract:** A new protocol for the β-sulfonation of α,β-unsaturated carbonyl compounds is described. The method employs $FeCl_3$ as catalyst and TMSCl as additive for conjugate addition of sodium *p*-toluenesulfinate to enones.

**Key words:** β-sulfonyl ketones, conjugate addition, α,β-unsaturated carbonyl compounds, iron(III) chloride, trimethylsilyl chloride




**Scheme 1**

The sulfonyl group is a well-established activating moiety introduced in an intermediate molecule for the construction of C–C bonds and other transformations.[1] Recently, the use of sulfones has become a common synthetic methodology in many total syntheses and in the generation of database of functionalized compounds. The ability of the sulfonyl group to stabilize carbanions is one of the best known features of these compounds.[2] They can also act as radical stabilizers[3] and as cationic synthons.[4] Since removal of the sulfonyl group, generally by a reductive process or via a base-promoted β-elimination route,[5] is simple, sulfones have become a very popular tool for organic chemists.

S-Alkylation of sulfinate anions with alkyl halides is a well-established method for the synthesis of aliphatic sulfones.[6] However, the conjugate addition of sulfinate anions has not been investigated, especially with chalcones, as the formed β-sulfonyl ketones are useful for the synthesis of 1,3-diphenylpropan-1-ol and 1-phenylsulfonylcyclopropanes.[7]

Since the pioneering work of Tamura and Kochi,[8] iron salts have emerged as alternative and promising catalysts for many organic transformations, in particular for Michael addition reactions.[9] These methods are distinguished by low cost, ready availability, environmentally benign nature of iron salts, and exceptionally high reaction rates are observed under mild conditions. Encouraged by these results, we envisaged the application of iron catalysts in the conjugate addition of sulfinate nucleophiles with α,β-enones.

Initially, we sought an effective catalytic system for the conjugate addition of sulfinate anion, guided by the template reaction between benzyl acetophenone **1a** and *p*-toluene sulfinate sodium salt **2** (Scheme 1). A range of reaction conditions was studied and some of the results are listed in Table 1.

Among the several Lewis acids screened, $InBr_3$ and $FeCl_3$ gave the product in low yields using acetonitrile as the solvent, whereas all other Lewis acids investigated were ineffective (entries 1–3). Moreover, other solvents such as MeCN, DMF, MeOH, $CH_2Cl_2$, and a mixture of MeCN–$H_2O$ were also ineffective which may be a result of the low solubility of sulfinate salts in organic solvents (entries 4–7). On the other hand, when PEG-400 was used as solvent, due to the increase in the solubility of **2** in the reaction medium, the desired product was obtained in moderate yield (entry 8). Further, to enhance the yield of the product, various additives were added in the presence of 20 mol% $FeCl_3$ in different solvents (entries 9 and 10). The addition of TMSCl as additive in acetonitrile gave the product in 62% yield within 72 hours (entry 9), whereas the reaction in dichloromethane gave the product in 85% yield with a considerable reduction in the reaction time (entry 10). However, TMSCl alone without $FeCl_3$ was ineffective for the reaction. Whereas the addition of TMSOTf as additive, the product was formed in 40% yield. Among the iron sources, $FeCl_3$ and $Fe(acac)_3$ led to the best catalysts and afforded in both cases the conjugate addition product in 85% and 82% yield, respectively (entries 10 and 12). With respect to the catalyst loading, 20 mol% of $FeCl_3$ was found to be optimal. When only 10 mol% of $FeCl_3$ were used, the product was formed in lower yield (51%) and no significant improvement was observed with 30 mol% of the catalyst. Moreover, the effect of temperature on this conjugate addition reaction was also studied. It was found that at 50 °C the reaction was completed within 10 hours, and the corresponding conjugate addition product was isolated in 83% yield. On the other hand, $FeCl_2$ and $FeSO_4$ were not effective for this reaction.

Having determined the optimum reaction conditions, we investigated the generality of this process. As can be seen

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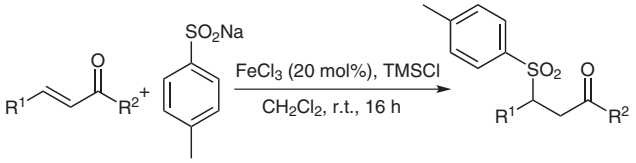
**Table 1** Optimization of the Reaction Conditions for the Conjugate Addition of Sodium Sulfinate **2** to Chalcone **1a**[a]



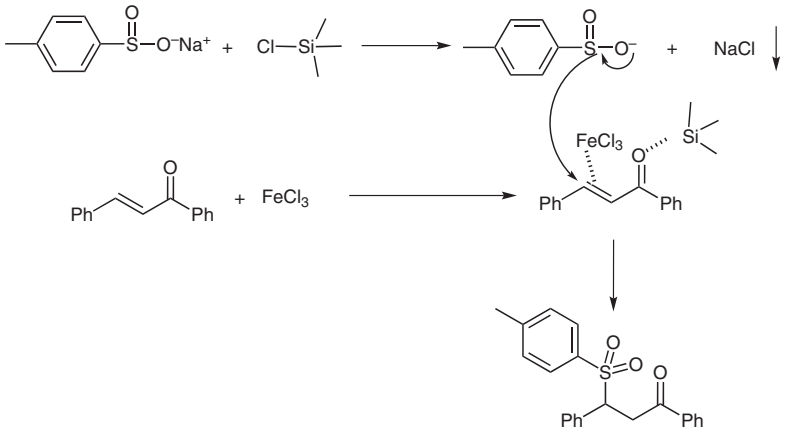

| Entry | Catalyst | Solvent | Additive | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | $InBr_3$ | MeCN | | 72 | 15 |
| 2 | $ZrOCl_2$, $ZrCl_4$, $SmI_2$, $ZnCl_2$, $ZnBr_2$, $BiCl_3$, $CuCl_2$, $Cu(OTf)_2$, $La(OTf)_3$, $Bi(OTf)_3$ | MeCN | | 72 | <10 |
| 3 | $FeCl_3$ | MeCN | – | 72 | 28 |
| 4 | $FeCl_3$ | MeCN–$H_2O$ | – | 72 | 15 |
| 5 | $FeCl_3$ | DMF | – | 72 | 0 |
| 6 | $FeCl_3$ | MeOH | – | 72 | 10 |
| 7 | $FeCl_3$ | $CH_2Cl_2$ | – | 72 | 0 |
| 8 | $FeCl_3$ | PEG 400 | – | 72 | 45 |
| 9 | $FeCl_3$ | MeCN | TMSCl | 72 | 62 |
| 10 | $FeCl_3$ | $CH_2Cl_2$ | TMSCl | 16 | 85, 83[c], 51[d] |
| 11 | $FeCl_3$ | $CH_2Cl_2$ | TMSOTf | 16 | 40 |
| 12 | $Fe(acac)_3$ | $CH_2Cl_2$ | TMSCl | 16 | 82 |
| 13 | $FeSO_4$ | $CH_2Cl_2$ | TMSCl | 16 | 32 |
| 14 | $FeCl_2$ | $CH_2Cl_2$ | TMSCl | 16 | 46 |

[a] Conditions: catalyst (20 mol%), **1a** (1.0 mmol), **2** (1.5 mmol), additive (1.2 mmol), solvent (3 mL), r.t.
[b] Isolated yield.
[c] The amount of 10 mol% of $FeCl_3$ was used.
[d] Reaction carried out at 45 °C.

from Table 2, a variety of chalcones were sulfonated to give the corresponding products in moderate to excellent yields. Chalcones with electron-donating substituents gave a good yield of products when compared to electron-withdrawing substituents.

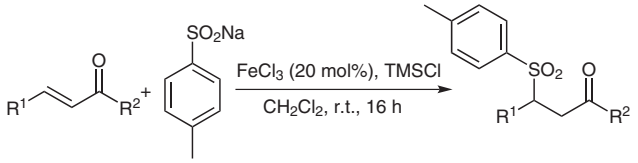
4-Nitro-substituted chalcone gave the product in low yield (entry 5). 4-Hydroxy-and 2-hydroxy-substituted chalcones were equally effective for the reaction (entries 6, 7). The substituent next to the olefinic bond other than phenyl group, that is, furyl group on reaction with **2** gave the corresponding product in moderate yield (entry 11).

To extend the general applicability of this reaction, several cyclic and acyclic enones (e.g., cyclohexenone, cyclopentenone, and methyl vinyl ketone) and enoates (e.g., methyl acrylate) were reacted with *p*-toulene sulfinate sodium salt **2** under optimized conditions, and the results are




**Scheme 2**

**Table 2** $FeCl_3$-Catalyzed Conjugate Addition of **2** to Various α,β-Enones[a]




| Entry | α,β-Enone **1** | | Product[b] | Yield (%)[c] |
|---|---|---|---|---|
| | $R^1$ | $R^2$ | | |
| 1 | Ph | Ph | **3a** | 85 |
| 2 | 4-$BrC_6H_4$ | Ph | **3b** | 78 |
| 3 | 4-$MeC_6H_4$ | Ph | **3c** | 92 |
| 4 | 4-$MeOC_6H_4$ | Ph | **3d** | 90 |
| 5 | 4-$O_2NC_6H_4$ | Ph | **3e** | 54 |
| 6 | Ph | 4-$HOC_6H_4$ | **3f** | 82 |
| 7 | Ph | 2-$HOC_6H_4$ | **3g** | 75 |
| 8 | Ph | Me | **3h** | 90 |
| 9 | Me | Me | **3i** | 72 |
| 10 | Me | H | **3j** | 75 |
| 11 | fur-2-yl | Ph | **3k** | 62 |

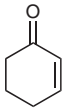
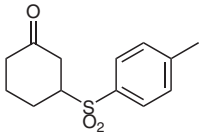
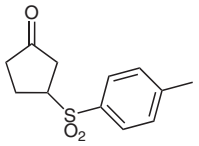
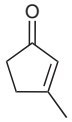
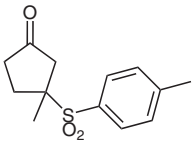
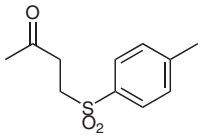
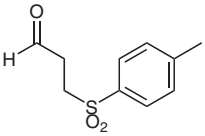
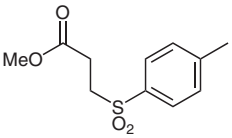
[a] Reaction conditions as exemplified in typical experimental procedure.
[b] All products were characterized by MS, IR, $^1$H NMR, and $^{13}$C NMR spectroscopy.
[c] Isolated yield.

given in Table 3. Among the cyclic enones used in this present study cyclopentenone is more reactive when compared to cyclohexenone, however, the reaction with 3-methyl cyclopentenone proceeded slowly and gave the product in moderate yield (entries 1–3). The reaction of α,β-enones, without any substitution at β-position, gave the corresponding products in good yields (entries 4–6).

To get insight into the mechanism, we performed several experiments to confirm the possibilities of the best reaction system. Although, it is known that TMSCl could activate the carbonyl group by initial interaction with enones,[10] it also activates the sulfinate salt by eliminating NaCl, which precipitates out and facilitate the attack of sulfinate anion to α,β-enone in the presence of transition-metal-based Lewis acid (Scheme 2). The precipitated NaCl was analyzed by XRD and XPS techniques and the presence of $Cl^-$ ion was confirmed by $AgNO_3$ test. The XPS high-resolution narrow scan at 1072 eV and 200 eV are attributed due to Na1s, and Cl2p peak clearly suggest that the precipitate is NaCl. The observed XRD pattern is in consonance with the observations made by XPS.

In conclusion, we have demonstrated that $FeCl_3$ and TMSCl catalytic system effectively promotes the direct β-sulfonation of α,β-unsaturated carbonyl compounds under mild conditions. This $FeCl_3$-catalyzed conjugate addition provides significant advantages as a convenient and an economical method.

**Table 3** $FeCl_3$-Catalyzed Conjugate Addition of **2** to Various Cyclic and Acyclic α,β-enones[a]

| Entry | Substrate | Product[b] | Yield (%)[c] |
|---|---|---|---|
| 1 |  |  **4a** | 72 |
| 2 |  |  **4b** | 63 |
| 3 |  |  **4c** | 56 |
| 4 |  |  **4d** | 81 |
| 5 |  |  **4e** | 83 |
| 6 |  |  **4f** | 65 |

[a] Reaction conditions as exemplified in typical experimental procedure.
[b] All products were characterized by elemental analysis, MS, IR, $^1$H NMR, and $^{13}$C NMR spectroscopy.
[c] Isolated yield.

**Typical Experimental Procedure for Conjugate Addition**

To a solution of chalcone **1** (1.0 mmol), TMSCl (1.2 mmol), and sulfinate sodium salt **2** (1.5 mmol) in $CH_2Cl_2$ (3 mL), $FeCl_3$ (20 mol%) was added. The reaction mixture was stirred at r.t. and monitored by TLC. After completion of the reaction, the reaction mixture was quenched with $NaHCO_3$ (sat. aq). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organics were dried over anhyd $Na_2SO_4$, concentrated in vacuo, and purified by column chromatography on $SiO_2$ to afford the pure product. All products were characterized by MS, IR, $^1$H NMR, and $^{13}$C NMR spectroscopy.

**Representative Spectroscopic Data**

**1,3-Diphenyl-3-(toluene-4-sulfonyl)propan-1-one (3a)**

IR (KBr): ν = 2912, 1648, 1490, 1286, 1136, 808 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.86 (dd, 1 H, $J_1$ = 9.7 Hz, $J_2$ = 18.0 Hz), 4.09 (dd, 1 H, $J_1$ = 3.9 Hz, $J_2$ = 18.0 Hz), 4.81 (dd, 1 H, $J_1$ = 3.9 Hz, $J_2$ = 9.7 Hz), 7.12–7.21 (m, 6 H), 7.37–7.55 (m, 6H), 7.94 (d, 2 H, *J* = 7.8 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.6, 37.0, 66.5, 128.1, 128.4, 128.7, 129.0, 129.4, 129.7, 132.7, 133.6, 134.0, 136.2, 144.7, 194.9 ppm. ESI-MS: *m/z* = 365.1 $[M + 1]^+$, 387.1 $[M + Na]^+$.

**3-(4-Bromophenyl)-1-phenyl-3-(toluene-4-sulfonyl)propan-1-one (3b)**

IR (KBr): ν = 2884, 1671, 1341, 1332, 1152, 1064, 810 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.78 (dd, 1 H, $J_1$ = 9.3 Hz, $J_2$ = 18.0 Hz), 4.05 (dd, 1 H, $J_1$ = 3.9 Hz, $J_2$ = 18.0 Hz), 4.77 (dd, 1 H, $J_1$ = 3.9 Hz, $J_2$ = 9.3 Hz), 7.10–7.24 (m, 7 H), 7.37 (d, 2 H, *J* = 8.5 Hz), 7.57 (d, 2 H, *J* = 8.5 Hz), 7.82 (d, 2 H, *J* = 8.5 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.5, 37.1, 65.9, 121.3, 127.4, 128.3, 128.7, 128.8, 129.2, 130.0, 130.6, 131.2, 133.2, 133.5, 144.7, 198.3 ppm. ESI-MS: *m/z* = 455 $[M + 1]^+$, 467 $[M + Na]^+$.

**4-(Toluene-4-sulfonyl)pentan-2-one (3i)**

IR (KBr): ν = 2924, 1710, 1596, 1455, 1282, 1134, 1080, 812, 658 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3 H), 2.47 (s, 3 H), 2.82 (dd, 1 H, $J_1$ = 9.2 Hz, $J_2$ = 17.6 Hz), 3.21 (dd, 1 H, $J_1$ = 3.8 Hz, $J_2$ = 17.6 Hz), 3.61–3.66 (m, 1 H), 7.34 (d, 2 H, *J* = 8.1 Hz), 7.70 (d, 2 H, *J* = 8.1 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 18.9, 21.4, 29.0, 45.8, 64.1, 129.6, 130.1, 131.2, 145.1, 206.8 ppm. LC-MS: *m/z* = 263 $[M + Na]^+$.

**3-(Toluene-4-sulfonyl)cyclohexanone (4a)**

IR (KBr): ν = 3053, 2948, 1703, 1529, 1428, 1424, 1260, 1127, 818, 556 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.54–1.97 (m, 2 H), 2.15–2.36 (m, 4 H), 2.47 (s, 3 H), 2.53 (d, 2 H, *J* = 7.3 Hz), 3.19–3.34 (m, 1 H), 7.36 (d, 2 H, *J* = 8.1), 7.72 (d, 2 H, *J* = 8.1) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.4, 23.3, 23.7, 40.3 (2 C), 62.2, 128.8, 129.9, 133.4, 145.1, 206.3 ppm. ESI-MS: *m/z* = 252 $[M^+]$, 275 $[M + Na]^+$.

**3-(Toluene-4-sulfonyl)cyclopentanone (4b)**

IR (neat): ν = 2923, 1748, 1596, 1403, 1295, 1144, 1086, 816, 582 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.15–2.26 (m, 2 H), 2.35–2.44 (m, 3 H), 2.48 (s, 3 H), 2.59 (dd, 1 H, $J_1$ = 7.5 Hz, $J_2$ = 18.1 Hz), 3.63–3.73 (m, 1 H), 7.36 (d, 2 H, *J* = 8.3 Hz), 7.75 (d, 2 H, *J* = 8.3 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.7, 23.2, 36.9, 38.6, 60.6, 128.4, 130.0, 134.2, 145.2, 212.8 ppm. LC-MS: *m/z* = 251 $[M + Na]^+$.

**4-(Toluene-4-sulfonyl)butan-2-one (4d)**

IR (neat): ν = 2922, 1716, 1597, 1445, 1304, 1271, 1144, 1088, 524 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3 H), 2.46 (s, 3 H), 2.90 (t, 2 H, *J* = 7.5 Hz), 3.28 (t, 2 H, *J* = 7.5 Hz), 7.35 (d, 2 H, *J* = 8.3 Hz), 7.76 (d, 2 H, *J* = 8.3 Hz) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 21.5, 29.8, 35.9, 50.5, 127.9, 129.9,135.7, 144.8, 203.8 ppm. LC-MS: *m/z* = 249 $[M + Na]^+$.

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