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# A simple and efficient $FeCl_3$-catalyzed direct alkylation of active methylene compounds with benzylic and allylic alcohols under mild conditions

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**Abstract**—A highly efficient $FeCl_3$-catalyzed alkylation of various active methylene compounds with various benzylic or allylic alcohols under mild conditions has been developed. The reaction was carried out in the presence of a catalytic amount of anhydrous $FeCl_3$ (10 mol %) under reflux in methylene chloride. High to excellent yields were obtained.
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Alkylation of active methylene compounds, such as β-diketones, β-diketoesters and malonic esters is a very important transformation in organic synthesis which has been investigated extensively.[1] Generally, this transformation is carried out using alkyl halides in the presence of a stoichiometric amount of base.[2] Although this method works well even on large scale, often it is associated with significant drawbacks including non-availability of halogenated substrate, toxicity of halogenated substrates, the use of strong base and production of large amounts of salts as by-products. Therefore, the development of a practical and economical process for carbon–carbon bond formation between active methylene compounds and unmodified substrates is an important task. In this regard, carbon–carbon single bond formation between an active methylene compound ($R^1H$) with an alcohol ($R^2OH$) would be an attractive salt-free and atom-economic[3] process with water being the only by-product (Scheme 1). However, little has been explored on direct carbon–carbon bond formation using alcohols.[4–9]

$$R^1H + R^2OH \rightarrow R^1\text{-}R^2 + H_2O$$

**Scheme 1.**

In principle, C–C bond formation by direct substitution of an hydroxyl group is difficult because of its poor leaving group ability. Therefore, a promoter would be required for in situ activation of $R^2OH$ and $R^1H$ for direct C–C bond formation.

A few methods have so far been reported for the reaction of alcohols and active methylene compounds using various transition-metal based reagents, such as palladium[4] in the presence of a base or acid, and equimolar amounts of Cu(I)[5] and Co-salts.[6] Most of these methods only worked well for allylic alcohols, but were not suitable for benzylic alcohols.[4g,6b] Recently, Lewis acid[7,8] and protic acid[9] catalyzed methods have been reported, involving $BF_3{\cdot}OEt_2$,[7] $InCl_3$,[8] formic acid[9a] or H–Montmorillonite.[9b] However, the harsh conditions required, long reaction times, high temperatures, and use of expensive, toxic and moisture sensitive reagents in most of the above methods limit their practical utility in organic synthesis. Therefore, development of a more practical and economical method for direct alkylation of active methylene compounds using alcohols is highly desirable. In recent years, iron(III) chloride[10] has emerged as a powerful Lewis acid catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, iron-salts are inexpensive, easy to handle and are environmentally friendly.

Herein, we report $FeCl_3$ as a catalyst for direct carbon–carbon bond formation between active methylene compounds and various benzylic or allylic alcohols in high

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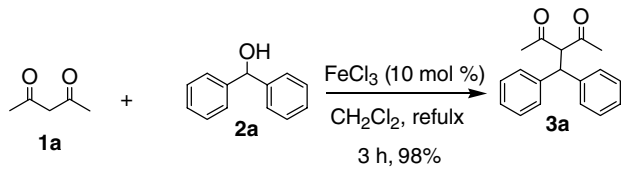



**Scheme 2.**

**Table 1.** Effect of solvent on the direct alkylation of acetylacetone with benzhydrol in the presence of $FeCl_3$[a]

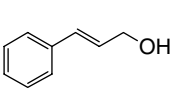
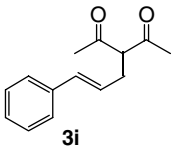
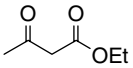
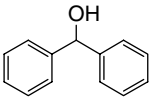
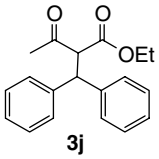
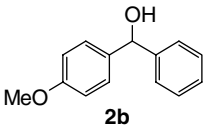
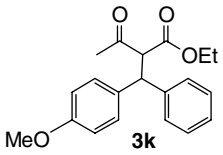
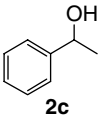
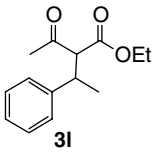
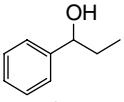
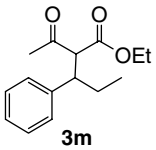
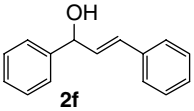
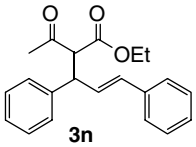
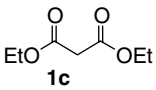
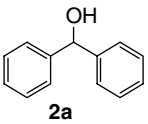
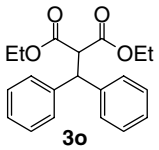
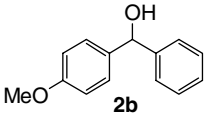
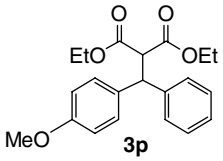
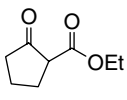
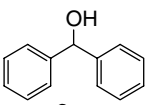
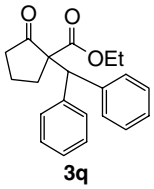
| Entry | Solvent | Time (h) | **3a**[b] (%) |
|---|---|---|---|
| 1 | Dichloromethane | 3 | 98 |
| 2 | Dichloroethane | 3 | 95 |
| 3 | Toluene | 9 | 90 |
| 4 | Tetrahydrofuran | 15 | <10 |
| 5 | Acetonitrile | 10 | 25 |

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), $FeCl_3$ (10 mol %), solvent (3 mL), 45 °C.
[b] Pure isolated yield.

**Table 2.** Alkylation of different active methylene compounds with alcohols in the presence of $FeCl_3$ (10 mol %)[a]

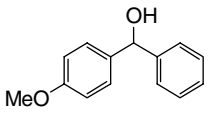
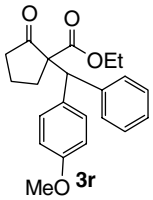
| Entry | Nucleophile | Electrophile | Product | Time (h) | Yield[b] (%) | Ref. |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | **3a** | 3 | 98 | 9a |
| 2 | **1a** | **2b** | **3b** | 4 | 98 | 12 |
| 3 | **1a** | **2c** | **3c** | 5 | 93 | 9b |
| 4 | **1a** | **2d** | **3d** | 6 | 80[c] | 13 |
| 5 | **1a** | **2e** | **3e** | 6 | 88 | 11 |
| 6 | **1a** | **2f** | **3f** | 12 | 82[d] | 8 |
| 7 | **1a** | **2g** | **3g** | 5 | 65[e] | 14 |
| 8 | **1a** | **2h** | **3h** | 6 | 68[e] | 15 |

**Table 2** (*continued*)

| Entry | Nucleophile | Electrophile | Product | Time (h) | Yield[b] (%) | Ref. |
|---|---|---|---|---|---|---|
| 9 | **1a** |  **2i** |  **3i** | 12 | 58[f] | 16 |
| 10 |  **1b** |  **2a** |  **3j** | 4 | 99 | 7 |
| 11 | **1b** |  **2b** |  **3k** | 5 | 98[g] | 11 |
| 12 | **1b** |  **2c** |  **3l** | 5 | 90[g] | 13 |
| 13 | **1b** |  **2e** |  **3m** | 6 | 80[h] | 17 |
| 14 | **1b** |  **2f** |  **3n** | 12 | 72[d] | 9a |
| 15 |  **1c** |  **2a** |  **3o** | 4 | 97 | 18 |
| 16 | **1c** |  **2b** |  **3p** | 5 | 90 | 19 |
| 17 |  **1d** |  **2a** |  **3q** | 5 | 95 | 11 |

(*continued on next page*)

**Table 2** (*continued*)

| Entry | Nucleophile | Electrophile | Product | Time (h) | Yield[b] (%) | Ref. |
|---|---|---|---|---|---|---|
| 18 | **1d** |  **2b** |  **3r** | 5 | 75[i] | 11 |

[a] Reaction conditions: Nucleophile **1** (1 mmol), alcohol **2** (1 mmol), $FeCl_3$ (0.1 mmol), $CH_2Cl_2$ (4 mL), reflux.
[b] The yields refer to pure isolated product characterized by spectral data.
[c] Dichloroethane was used as solvent under reflux.
[d] Toluene was used as solvent at room temperature.
[e] Product existed partly in the enol form.
[f] Compound **2i** (4 mmol), regioisomers ~ 9:1 (GC).
[g] Mixture of diastereoisomers ~ 1:1 ($^1$H NMR).
[h] Mixture of diastereoisomers ~ 2:1 ($^1$H NMR).
[i] Mixture of diastereoisomers ~ 1:1.5 ($^1$H NMR).

yields with complete selectivity under mild reaction conditions.

For our initial studies we chose to explore the anhydrous $FeCl_3$-catalyzed alkylation of acetylacetone (**1a**) with benzhydrol (**2a**) due to its high acidity (Scheme 2). The reaction was carried out in the presence of a catalytic amount of anhydrous $FeCl_3$ (10 mol %) in dichloromethane under reflux. The alkylated product was obtained in high yield with excellent regioselectivity under mild conditions without exclusion of air or moisture.

The reaction yield depended on the solvent used (Table 1). Dichloromethane and dichloroethane were found to be the most effective solvents in terms of time and yield. The yield was lower with coordinating solvents such as tetrahydrofuran and acetonitrile. Benzene and toluene were also effective solvents, but the reactions were sluggish compared to dichloromethane and dichloroethane. Thus, we decided to use low boiling dichloromethane as the solvent for this transformation.

Having established the reaction conditions, we further explored the generality and efficiency of the $FeCl_3$-catalyzed direct alkylation of various active methylene compounds such as a β-diketone, acyclic and cyclic β-ketoesters and a β-diester with benzylic and allylic alcohols. In general, the reaction proceeded smoothly for all cases in very good to excellent yields within a very short period of time with complete selectivity. The results are summarized in Table 2.

This procedure worked well with cyclic β-ketoester **1d** (Table 2, entries 17 and 18), a reaction which has not previously been reported by other Lewis acid mediated reactions.[8,9] Both electron rich and electron poor benzyl alcohols (Table 2, entries 2, 4, 11 and 15) underwent smooth conversion to the desired products with excellent yields. Alcohols sensitive to acid catalyzed dehydration also tolerated this method (Table 2, entries 3, 4, 5, 12 and 13). Surprisingly this method gave good yields with primary benzylic alcohols (Table 2, entries 7, 8 and 9). This reaction has not been reported using $InCl_3$[8] and only ether formation was reported using H–Montmorillonite.[9a] Various functional groups that coordinate to the Lewis acid, such as ether, ester, ketone, chloride and dioxymethylene remained unaffected under the reaction conditions. No side product was isolated in any of the reactions. Acetophenone did not react using this method. Moreover, both secondary and primary allylic alcohols reacted smoothly to give the desired product in high to moderate yields (Table 2, entries 6, 9 and 14). Although the primary allylic alcohol **2i** (Table 2, entry 9) initially reacted in a low yield, a higher loading of **2i** (4 mmol) improved the yield up to 58% (Table 2, entry 9). Allylic alkylation is an important transformation, and various metal-complex catalyzed[4–6,20] processes have been reported so far. However, many of these reactions have been performed with activated nucleophiles or with acylated allyl alcohols.

Thus, the present method has potential for direct alkylation of active methylene compounds with varieties of benzylic and allylic alcohols with complete selectivity[2] without the use of acids or base and toxic organohalides. Compared to $InCl_3$ (80 °C for 16 h) and H–Montmorillonite (100–150 °C for 3 h) our method works under mild conditions. Although the exact mechanism is not known at this stage, presumably the reaction proceeds due to complexation of both electrophile and nucleophile simultaneously with $FeCl_3$. Further investigation on the elucidation of the mechanism and scope of this reaction are currently underway in our laboratory.

In conclusion, we have developed a new, efficient and highly atom-economical method for direct benzylation and allylation of active methylene compounds with various benzyl and allyl alcohols.

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11. *Representative experimental procedure*: To a stirred solution of benzhydrol **2a** (184 mg, 1 mmol) and acetyl acetone **2a** (100 mg, 1 mmol) in dry dichloromethane (4 mL) was added anhydrous $FeCl_3$ (16 mg, 0.1 mmol). The mixture was refluxed for 3 h and concentrated under reduced pressure and then the residue was purified by silica gel column chromatography to afford 3-benzhydryl pentane 2,3-dione **3a** as a white solid (261 mg, 0.98 mmol); mp 115 °C (lit. 115 °C);[9a] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.00 (s, 6H), 4.71–4.83 (m, 2H), 7.16–7.20 (m, 2H), 7.26–7.30 (m, 8H).
    The spectral data for unknown compounds are given below:
    Compound **3e** (entry 5): IR (neat) 2966, 1726, 1967 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.69 (t, $J = 7.3$ Hz, 3H), 1.44–1.60 (m, 2H), 1.81 (s, 3H), 2.27 (s, 3H), 3.30–3.39 (m, 1H), 4.10 (d, $J = 11.6$ Hz, 1H), 7.13–7.31 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 11.68, 27.64, 29.74, 29.94, 47.74, 76.26, 127.11, 128.35, 128.75, 140.60, 203.47, 203.75; HRMS: *m*/*z* calcd for $C_{14}H_{18}O_2Na$: 241.1204; found, 241.1218.
    Compound **3k** (entry 11): Mixture of diastereoisomers: IR (neat) 1743, 1714, 1512, 1251 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.98–1.06 (m, 3H), 2.09 (s, 3H), 3.74 (s, 3H), 3.94–4.03 (m, 2H), 4.47 (d, $J = 12.2$ Hz, 1H), 4.72 (d, $J = 12.2$ Hz, 1H), 6.80 (d, $J = 8.6$ Hz, 2H), 7.12–7.22 (m, 7H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.84, 13.92, 30.02, 30.10, 50.20, 50.25, 55.24, 55.26, 61.53, 61.57, 65.45, 65.52, 114.06, 114.29, 126.82, 126.94, 127.66, 127.76, 127.95, 128.67, 128.80, 128.91, 133.40, 133.81, 141.70, 141.98, 158.44, 158.48, 167.82, 201.96, 202.11; HRMS: *m*/*z* calcd for $C_{20}H_{22}O_4Na$: 349.1416; found, 349.1404.
    Compound **3q** (entry 17): IR (neat) 2979, 1749, 1718 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.84 (t, $J = 7.10$ Hz, 2H), 1.45–1.49 (m, 1H), 1.66–1.89 (m, 2H), 2.20–2.30 (m, 2H), 3.03–3.07 (m, 1H), 3.84–4.01 (m, 2H), 5.25 (s, 1H), 7.07–7.28 (m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.86, 20.14, 29.84, 38.91, 55.38, 62.06, 66.52, 126.89, 127.20, 128.69, 128.78, 128.44, 129.30, 130.56, 140.76, 141.68, 169.12, 214.36; HRMS: *m*/*z* calcd for $C_{21}H_{22}O_3Na$: 345.1470; found, 345.1467.
    Compound **3r** (entry 18): Mixture of diastereoisomers: IR (neat) 2962, 1751, 1718, 1512 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.81–0.92 (m, 3H), 1.47–1.54 (m, 1H), 1.70–1.90 (m, 2H), 2.21–2.31 (m, 2H), 3.00–3.10 (m, 1H), 3.74 (s, 1.8H), 3.77 (s, 1.2H), 3.85–4.00 (m, 2H), 5.19 (s, 0.4H), 5.21 (s, 0.6H), 6.72–6.82 (m, 2H), 6.98–7.10 (m, 2H), 7.17–7.29 (m, 5H), $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.54, 13.68, 19.81, 19.87, 29.40, 29.42, 38.64, 38.65, 54.29, 55.20, 55.25, 54.35, 61.71, 61.75, 66.30, 66.40, 113.70, 113.77, 126.46, 128.33, 126.79, 128.44, 128.84, 130.04, 130.12, 131.24, 132.50, 133.32, 140.73, 141.65, 158.18, 158.36, 168.82, 168.84, 214.16, 214.30; HRMS: *m*/*z* calcd for $C_{22}H_{24}O_4Na$: 375.1570; found, 375.1572.
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