Fe(OTf)₃-Catalyzed α-Benzylation of Aryl Methyl Ketones with Electrophilic Secondary and Aryl Alcohols

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Abstract: Acid-catalyzed Friedel– Crafts alkylation of 1,3-dicarbonyl compounds with electrophilic alcohols, is known to be an effective C–C bond forming reaction. However, until now, this reaction has not been amenable for α -alkylation of aryl methyl ketones because of the notoriously low nucleophilicities of these compounds. Therefore, α -alkylation of aryl methyl ketone relies on precious metal catalysts and also, the use of primary alcohols is mandatory. In this study, we found that a system composed of a $Fe(OTf)_3$ catalyst and chlorobenzene solvent is sufficient to promote the title Friedel– Crafts reaction by using benzhydrols as electrophiles. 3,4-Dihydro-9-(2-hy-

Keywords: alkylation • aryl methyl ketone • Friedel–Crafts reaction • iron catalysis • three-component reaction

droxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-xanthen-1(2 H)-one was also applicable as an electrophile in this type of benzylation reaction. On the basis of this result, a three-component reaction of salicylaldehyde, dimedone, and aryl methyl ketone was also developed, and this provided an efficient way for the synthesis of densely substituted 4H-chromene derivatives.

Introduction

The past decade has witnessed great strides in developing active reagents and productive catalysts for Friedel–Crafts alkylations, which have experienced a rekindled interest in the synthetic community for the facile construction of the carbon–carbon bond.^[1] Recent enthusiasm of researchers in this area was mostly inspired by the successful use of alcohols as electrophiles;^[2] this avoids the generation of organic or inorganic waste that results from alkyl halide reagents. As for its nucleophile reaction partner, a breakthrough comes from the use of 1,3-dicarbonyl compounds, with which various useful molecules could be prepared by environmentally benign methods (Scheme 1, the upper reaction pathway).^[3] The high reactivity of the 1,3-dicarbonyl com-

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pound could be ascribed to the presence of an equilibrium between this compound and its enol form, which significantly increases the electron density at the C2 position of the molecule, thus activating this substrate.

While the Friedel–Crafts alkylation of 1,3-dicarbonyl compounds has been well investigated, far less attention has been paid to the potential use of a simple ketone as nucleophile in this type of reaction.^[4] Obviously, an obstacle of this chemistry stems from the inherent poor reactivity of a simple ketone. Although some simple ketones can also be transformed into their enol form, which should be more reactive than the ketone form, unfortunately, the equilibrium is thermodynamically unfavorable to afford the enolized ketone. Futhermore, even if the enolized ketone was formed under special reaction conditions, the reactivity is probably still far from sufficient to ensure occurrence of the following α -alkylation.

Aryl methyl ketone is an important ketone derivative, which has often been used in organic transformations. Because of the possible existence of a conjugation effect, aryl methyl ketone showed generally higher reactivity than that of the other simple ketones. With the hope of using a simple ketone as a nucleophile in the Friedel–Crafts α -alkylation, we started, some time ago, a research program on the use of aryl methyl ketones as substrates. Herein, we disclose the successful outcome of this endeavor in which a Friedel– Crafts-type α -alkylation of aryl methyl ketones was realized by using either benzhydrol derivatives or 3,4-dihydro-9-(2hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-Xanthen-1(2 H)-ones as electrophiles (Scheme 1, the bottom reaction pathway).

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Scheme 1. Schematic illustration of our study.

Results and Discussion

Our initial studies started by exploring a suitable catalyst for the title reaction. In initial experiments, benzhydrol 1a and acetophenone 2a were used as substrates in chlorobenzene, and the mixture was heated at 130°C for 4 h in the presence of a catalytic amount of p-toluenesulfonic acid (PTSA; Table 1, entry 1). After the reaction reached completion, a new product was obtained, and the following spectroscopic analysis indicated that it was the expected product, 3a. In the literature, the treatment of acetophenone under Friedel-Crafts alkylation conditions mainly gave the *m*-alkylation product.^[5] Although the yield of the reaction was only 44%, because only the α -alkylation product was obtained, the product isolation was quite straightforward. This result encouraged us to investigate other catalysts with the hope of increasing the reaction yield. As shown in Table 1, when the reaction was carried out at 130 °C in chlorobenzene, Brønsted acids such as sulfuric acid and trifluoromethanesulfonic acid were able to promote the model reaction (Table 1, entries 2 and 3). Phosphomolybdic acid and phosphotungstic acid were ineffective (Table 1, entries 4 and 5). A commonly used Lewis acid, AlCl₃, appeared to be less active, and produced only trace amounts of product after 4 h (Table 1, entry 6). FeCl₃, ZnCl₂, Cu(OTf)₂, Y(OTf)₃, ZrCl₄, BiCl₃, Bi-(OTf)₃, and Sc(OTf)₃ gave slightly better results, but Fe- $(OTf)_3$ showed the highest activity, and afforded **3a** in 60% yield (Table 1, entries 7-15). The effect of solvents on the model reaction was also examined, and DBE and chlorobenzene gave high yields (Table 1, entries 16-20). For safety and economic reasons, we continued the reactions with chlorobenzene. Further investigations revealed that the reaction was also affected by other parameters including the amount of catalyst, substrate ratio, temperature, and reaction time, and the optimal reaction conditions should be 5 mol% of Fe(OTf)₃, **2a/1a** is 3:1, at 130°C, and 4 h (Table 1, entries 21-24). It should be noted that, under acidic conditions, triple condensation of 2a is also possible.

However, 2a remains unchanged at the end of the reaction, and no triphenylbenzene was detected.^[6]

With the optimized conditions in hand, we probed the scope of the reaction with respect to both the benzhydrol and the aryl methyl ketone components. As evidenced by the results in Scheme 2, benzhydrols with different substituents smoothly reacted with various aryl methyl ketones, and produced the corresponding products in generally moderate to good yields. In general, a methoxy group is necessary in the phenyl ring of the benzhydrol

derivative to afford good yields. However, when this group was introduced into one of the phenyl rings of benzhydrol, an unexpected subtle influence of the substituent group in another phenyl ring was observed. No reaction was observed

Table 1. $\alpha\text{-Benzylation}$ of acetophenone with 1a under different conditions. $^{[a]}$

MeO	OH CI	O catalyst (5 mo solvent, 4	bl %) h MeO	O CI
	1a 2	?a		3a
Entry	Catalyst	Solvent	<i>T</i> [°C]	Yield [%]
1	PTSA	PhCl	130	44
2	H_2SO_4	PhCl	130	31
3	CF ₃ SO ₃ H	PhCl	130	39
4	$H_3PW_{12}O_{40}$	PhCl	130	0
5	H_3PMoO_{40}	PhCl	130	0
6	AlCl ₃	PhCl	130	trace
7	FeCl ₃	PhCl	130	39
8	$ZnCl_2$	PhCl	130	27
9	$Cu(OTf)_2$	PhCl	130	26
10	$Y(OTf)_3$	PhCl	130	20
11	$ZrCl_4$	PhCl	130	30
12	BiCl ₃	PhCl	130	32
13	$Bi(OTf)_3$	PhCl	130	51
14	$Sc(OTf)_3$	PhCl	130	27
15	Fe(OTf) ₃	PhCl	130	60
16	Fe(OTf) ₃	CH ₃ NO ₂	100	0
17	Fe(OTf) ₃	DBE ^[e]	130	54
18	Fe(OTf) ₃	DCE	80	31
19	$Fe(OTf)_3$	1,4-dioxane	100	17
20	Fe(OTf) ₃	-	130	36
21	$Fe(OTf)_3$	PhCl	100	42
22 ^[b]	Fe(OTf) ₃	PhCl	130	59
23 ^[c]	$Fe(OTf)_3$	PhCl	130	59
24 ^[d]	Fe(OTf) ₃	PhCl	130	32

[a] **1a** (0.25 mmol), **2a** (0.75 mmol), solvent (1 mL), catalyst (5 mol%), yields reported are isolated product yields; [b] $Fe(OTf)_3$ (10 mol%); [c] reaction time (6 h); [d] **2a/1a**=1:1; [e] DBE=1,2-Dibromoethane.

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Scheme 2. Substrate scope of $Fe(OTf)_3$ -catalyzed α -benzylation of aryl methyl ketones. [a] Yield of isolated product.

when an electron-withdrawing group, such as nitro, cyano, and ester, was introduced into the second phenyl ring. This can be ascribed to electronic effects. However, strong electron-donating groups, such as methoxy, methyl, and *tert*butyl, proved also to be detrimental for the reaction (see Scheme S1 in the Supporting Information). On the contrary, the benzhydrol derivatives with fluoro, chloro, and bromo functionalities participated readily in the reaction. An unexpected product, 4,4'-dimethoxybenzophenone, was isolated

when 4,4'-dimethoxybenzhydrol was used as the substrate (Scheme 3). In the absence of Fe(OTf)₃, no oxidation product was obtained under identical reaction conditions. As this compound could also be formed under an atmosphere of nitrogen, we therefore speculated that, in this system, 2a is playing a role of an oxidant. As we expected, 4,4'-dimethoxybenzophenone could also be obtained when **2a** was replaced by cyclohexanone (Scheme 3). In fact, this type of Meerwein–Ponndorf–Verley–Oppenauer reaction has been observed when a Lewis acid or Brønsted acid was used as the catalyst.^[7] On the basis of these results, we deduced that the title reaction is not only affected by the electronic effect of the substituent groups, but also influenced by the chemical stability of the alcohol substrate towards oxidation with **2a**. Electron-donating groups in both



Scheme 3. Oxidation of 4,4'-dimethoxybenzhydrol with ketones.

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phenyl rings of benzhydrol increased not only the reactivity of the alcohol substrate in the S_N 1-type substitution reaction, but also significantly increased the reaction rate of the Oppenauer oxidation. As a result, the α -benzylation of **2a** was affected.

It should be noted that although only moderate yields were obtained in most cases, this system is very promising because of the following considerations: (i) acid-catalyzed Friedel–Crafts α -alkylation of aryl methyl ketone is notoriously difficult owing to the poor reactivity of the ketone; and (ii) although the use of an alcohol as an alkylation reagent in the α -alkylation of aryl methyl ketone has been achieved with the aid of precious metal catalysts, because the catalysis is associated with a "hydrogen-borrowing" mechanism, the use of a primary alcohol is mandatory;^[8] therefore, α -alkylation of aryl methyl ketone with a secondary or tertiary alcohol remains to be a significant challenge.^[9] Our present method thereby offers a complementary system for implementing the title reaction.

The mechanism of the title reaction most likely involves an acid-assisted nucleophilic substitution. However, because Fe(OTf)₃ was used as the catalyst here, catalysis with a hidden Brønsted acid (TfOH generated from Fe(OTf)₃) should be considered.^[10] In fact, TfOH can indeed catalyze our model reaction, although the yield obtained is inferior as compared with that of $Fe(OTf)_3$ (Table 1, entry 3). We have also meticulously investigated the performance of TfOH catalyst in our reaction under different conditions, and it was found that the maximum yield that can be achieved with TfOH is 39% (see Table S1 in the Supporting Information). Interestingly, with TfOH catalyst, the triple condensation product of 2a, triphenylbenzene, in chlorobenzene is formed.^[11] However, this byproduct was not detected when Fe(OTf)₃ was used as the catalyst. In addition, ¹⁹F NMR spectroscopic analysis of the volatiles vacuum transferred from preparative-scale Fe(OTf)₃- and TfOHmediated α -benzylation of **2a** reveals the presence of the TfOH only in the latter reaction (Marks's method to probe the formation of TsOH from metal triflate).^[12] All these results indicated that in the Fe(OTf)₃-mediated α -benzylation, free TfOH is not formed in any significant quantities during the catalytic cycle. Therefore, intervention of TfOH in the catalytic cycle can be ruled out, and Fe(OTf)₃ can be considered as the real catalyst. The mechanism of the α -benzylation of acetophenone might be triggered by activation of benzhydrol by the iron(III) catalyst, and this resulted in formation of a carbonium intermediate. This is followed by nucleophilic attack of the enolized ketone, which leads to formation of the desired product (Scheme 4).^[13] If this mechanism is operative, some other electrophiles that can generate stable carbonium intermediates should be applicable in the α -alkylation of aryl methyl ketones.



Scheme 4. Mechanism of α -benzylation of 1a with 2a.

It is well known that an electrophilic alkylation reaction of benzaldehyde with an aromatic carbon-based nucleophile generally involves formation of a secondary benzyl carbonium intermediate.^[14] However, because the generated intermediate will be preferentially trapped by the reactive aromatic carbon-based nucleophile, a less reactive nucleophile almost has no chance to react with the carbonium ion intermediate. Liu and co-workers^[15] developed an elegant strategy to avoid such problems by using an intramolecular reaction of an aldehyde and nucleophile. However, the generality of this strategy is rather limited. We envisioned that an intermolecular variation of this strategy, if established, will be a huge incentive for us. With the hope of extending our method to perform α -benzylation of aryl methyl ketone, we then examined a three-component reaction of salicylaldehyde, dimedone, and 2a. To our great delight, by using Fe-(OTf)₃ as a catalyst, **6a** was obtained in 56% yield under the optimal reaction conditions (Scheme 5 and see Table S2



Scheme 5. Reaction of salicylaldehyde, dimedone, and 2a.

in the Supporting Information). As shown in Scheme 6, aryl methyl ketones with both electron-donating and electronwithdrawing groups readily participated in the reaction. Some other salicylaldehdyes and 1,3-cyclohexanediones can also be employed in this type of three-component reaction, and a random combination of the three starting materials could give the final products with up to 73 % yield. It should be noted that salicylaldehdye containing an electron-with-drawing group, such as 4-nitrosalicylaldehdye, cannot be used in this type of reaction. Although the yield of the model reaction is not very high under these conditions, considering the fact that synthesis of 6a-type 4H-chromenes has been rarely described, our method thus offers a valuable route to access these molecules.

To shed light on the mechanism, compound **7a** that was synthesized by using salicylaldehyde and dimedone was treated with **2a** in the presence of $Fe(OTf)_3$. In this case, **6a** was obtained in 43 % yield (Scheme 7). It is known that, in the presence of Lewis acid, the dimedone fragment in **7a** is



Scheme 6. Substrate scope of Fe(OTf)₃-catalyzed reaction of salicylaldehyde, dimedone, and aryl methyl ketone. [a] The reaction was conducted in DCE at 80 °C. [b] The molar ratio is 1:1:4. All yields reported are isolated product yields.



Scheme 7. α -Benzylation of 2a with 7a.

removed, thus generating a carbonium intermediate (I).^[16] On the basis of this result, we deduced that the initial event in the three-component reaction is the formation of the carbonium intermediate (I) from salicylaldehyde and dimedone, and this can be quickly trapped by dimedone to form **7a** (Scheme 8). This can be verified by the fact that **7a** could be isolated in 13% yield at the end of the reaction.

Fortunately, the dimedone fragment in 7a is a leaving group in the presence of a Lewis acid. However, owing to the presence of an intramolecular hydrogen bond in 7a, the leaving group ability of dimedone is diminished. 2a might play a key role in the disengagement of the intramolecular hydrogen bond of 7a, thereby ensuring regeneration of the intermediate (I). This reversible alkylation ensures trapping of (I) with 2a to be feasible.

As phenylacetylene could be converted into 2a in the presence of iron catalyst,^[17] we then investigated the feasibility of replacing 2a with phenylacetylene in the three-component reaction. As shown in Scheme 9, in the Fe(OTf)₃/PhCl system, salicylaldehyde and dimedone are able to react smoothly with phenylacetylene derivatives, thereby providing 6a-type products in moderate to good yields. It was also found that, at the end of the synthetic reaction of 6e, 2a was also obtained in 34% yield (with respect to phenylacetylene). Therefore, we suspected that the reactions might proceed according to а hydration/Friedel-Crafts tandem reaction pathway (see Figure S1 in the Supporting Information). It should be noted

that almost the same results were obtained with dried and untreated (wet) chlorobenzene. This result implies that a trace amount of water is sufficient enough to initiate the hydration of alkyne under the present conditions. Because some phenylacetylenes are now cheaper than the corresponding acetophenones, these reactions provided alternative ways to access the target compounds with lower costs. Reaction of benzhydrols and phenylacetylene was also examined, and the formed products retained the triple bond of phenylacetylenes (see Scheme S2 in the Supporting Information), which are in a good agreement with Jiao and co-workers report.^[18]

Conclusions

In summary, we demonstrated that aryl methyl ketone can be used as a nucleophile in Friedel–Crafts-type reactions al-

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Scheme 8. Plausible mechanism of the three-component reaction.



Scheme 9. Reaction of salicylaldehyde, dimedone, and alkynes. [a] Chlorobenzene was purified and dried according to a previously described procedure.^[19]

though its reactivity is notoriously poor. In the optimized system, $Fe(OTf)_3/PhCl$, aryl methyl ketone could react smoothly with benzhydrol, thus providing the corresponding products in moderate to good yields. A new three-component reaction of salicylaldehyde, dimedone, and aryl methyl ketone was also developed, for the first time, and this provided an efficient way for the synthesis of densely substituted 4H-chromene derivatives. Although at the present stage, the yields in these reactions are not very high, the transformation is interesting, and these results served already as a starting point for further investigations, which are currently ongoing in our laboratories.

Experimental Section

A typical procedure for α -benzylation of any methyl ketones

All reactions were conducted in a 10 mL V-type flask equipped with a triangle magnetic stirring bar. In a typical reaction, benzhydrol or xanthene (0.25 mmol) was mixed with an aryl methyl ketone (0.75 mmol) and Fe(OTf)₃ (6.3 mg, 5 mol%) in chlorobenzene (1.5 mL). The mixture was then stirred at 130 °C for 4 h. After the reaction reached completion, the mixture was cooled to room temperature, and the product was obtained

by isolation with preparative TLC. Tests for substrate scope were all performed with an analogous procedure.

A typical procedure for reactions of salicylaldehydes, dimedone, and aryl methyl ketones

reactions were conducted in All a 10 mL V-type flask equipped with a triangle magnetic stirring bar. In a typical reaction, salicylaldehyde (61.1 mg, 0.5 mmol) was mixed with dimedone (70.1 mg, 0.5 mmol) and aryl methyl ketone (1.5 mmol) in chlorobenzene (1.5 mL). The mixture was then stirred at 130°C for 4 h. After the reaction reached completion, the mixture was cooled to room temperature. The desired product was obtained by isolation with preparative TLC. Tests for substrate scope were all performed with an analogous procedure.

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