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A General and Efficient Iron-Catalyzed Benzylation of 1,3-Dicarbonyl Compounds

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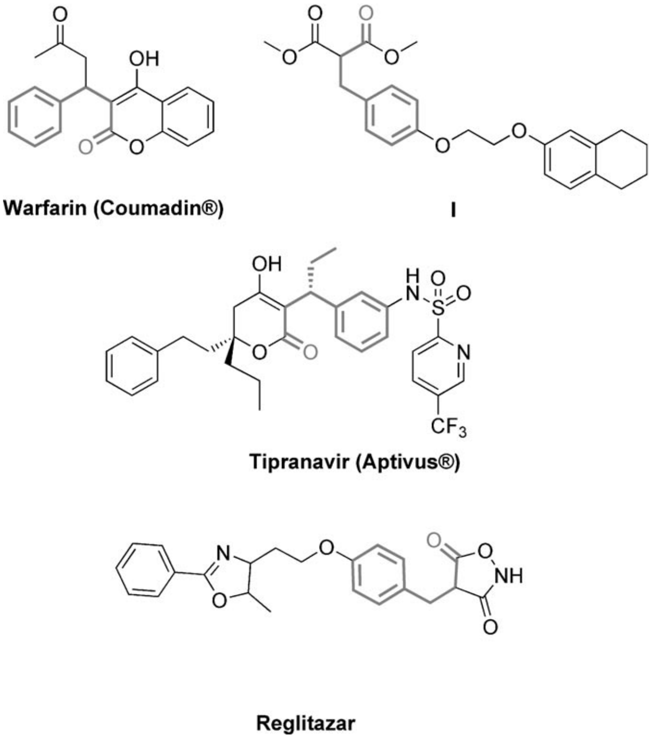
Abstract: Various CH-acidic 1,3-dicarbonyl compounds and methyl 3-acetamidobut-2-enoate react with benzylic alcohols to give the corresponding 2-benzylated products in good to excellent yield. Typically, reactions proceed under mild conditions (50–80 °C; air) in the presence of catalytic amounts of inexpensive iron chloride hexahydrate. The benzylation of 4-hydroxycoumarin gives the pharmaceutically interesting 4-hydroxy-3-(1-phenylethyl)-2*H*-chromen-2-ones. As an example the anticoagulant Phenprocoumon is prepared in one step from commercially available substrates in 94 % yield.

Keywords: anticoagulants; benzylation; C–C coupling; 1,3-dicarbonyl compounds; iron catalysis

Arenes and heteroarenes are of outstanding importance for the pharmaceutical, agrochemical, fine and bulk chemical industries. In general still "classical", well known C–C coupling reactions such as Friedel–Crafts alkylations are used for functionalization of arenes. In spite of their reliability, these methods have significant drawbacks such as drastic reaction conditions, regioselectivity problems, significant amounts of salt by-products etc. Thus, the development of more environmentally friendly transformations of arenes is an actual and important subject of organic chemistry and catalysis.

In this respect we developed novel Friedel–Crafts-type benzylations of arenes utilizing simple benzylic alcohols or acetates under mild conditions with high tolerance towards functional groups (CHO, CO_2R, I, Br, Cl, F etc.).[1] In these reactions various late transition metal salts, and later on simple $FeCl_3{\cdot}6\,H_2O$ led to the corresponding unsymmetrical diarylmethanes in good to excellent yield and regioselectivity. Furthermore, by variation of the electrophilic reagent a 100 %-atom efficient addition of aromatic olefins to arenes was realized.[2]

Based on this work, we became interested in the direct benzylation of 1,3-dicarbonyl compounds with 1-phenylethanol. The resulting structural motif is found in a number of biologically active compounds (Scheme 1). For example, 4-hydroxy-3-(3-oxo-1-phenylbutan-1-yl)-2*H*-chromen-2-one (Warfarin) is known as antagonist of vitamin K and therefore employed as oral anticoagulant. In addition, Tipranavir,[3] an HIV-protease inhibitor, as well as dimethyl 2-{*p*-[2-(5,6,7,8-tetrahydronaphthalen-2-yloxy)ethoxy]benzyl}malo-



Scheme 1. Biologically active compounds with the 3-aryl-1-oxoalkane motif.

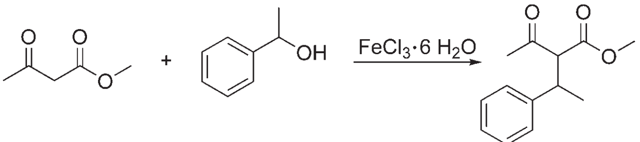
nate (**I**)[4] and Reglitazar, both potential diabetes drugs, include this motif.

Alkylations are typically performed with alkyl halides in the presence of sodium, potassium, or lithium alkoxides,[5] or other strong bases such as KOH, NaOH, NaH,[6] or superbases, e.g., $P[N(Me)CH_2CH_2]_3N$.[7] Obviously, drawbacks of these reactions are the need for a stoichiometric amount of base and the resulting salt waste. Notably, Christoffers et al. developed Fe-catalyzed Michael additions of 1,3-dicarbonyl compounds.[8]

From an environmental point of view the coupling reaction of CH-acidic substrates with alcohols would constitute a significant improvement because water is the only by-product in such reactions. However, only in recent years have examples been reported for milder Lewis acid-catalyzed alkylations of 1,3-dicarbonyl compounds using alcohols as electrophiles.[9]

Noteworthy, Yasuda et al. reported an $InCl_3$-catalyzed reaction of benzylic alcohols with various CH-active methylene compounds. For example, reaction of 1-phenylethanol with acetylacetone yielded 87% of the desired product in the presence of 5 mol% catalyst at 80°C.[10] The same product was obtained by Rueping et al. in 54% yield, when 1 mol% of $Bi(OTf)_3$ was applied at 55°C.[11] Recently, a mixed catalyst system composed of 5 mol% $AuCl_3$ and 7.5 mol% AgOTf has also been employed for the direct addition of acetylacetone to styrene, which gave 89% of 3-(1-phenylethyl)-pentane-2,4-dione at room temperature.[12] Moreover, solid acid catalysts have been described for this addition reaction.[13]

For our investigations, the reaction of methyl 3-oxobutanoate (**1**) with 1-phenylethanol (**2a**) was studied as a model system (Scheme 2).



1 **2a** **3a**

Scheme 2. Reaction of methyl 3-oxobutanoate (**1**) with 1-phenylethanol (**2a**).

An initial catalyst screening with various Brønsted acids (HOAc, HCl, *p*-toluenesulfonic acid etc.) as well as a number of different transition metal salts indicated non-expensive $FeCl_3$·6H_2O as the best catalyst for this model reaction (Table 1).

Table 1. Reaction of methyl 3-oxobutanoate (**1**) with 1-phenylethanol (**2a**).[a]

Entry	Catalyst	**1:2a**	Conversion [%][b]	Yield [%][c]
1[d]	HOAc	-	95	0
2[d]	HCl	-	95	0
3[d]	*p*-TSA	-	99	32
4[d]	$RhCl_3$	-	**100**	**97**
5[d]	$IrCl_3$·nH_2O	-	100	80
6[d]	H_2PtCl_6·6H_2O	-	100	87
7[d]	$BiCl_3$	-	98	7
8[d]	$MesW(CO)_3$	-	92	6
9[d]	$Sc(OTf)_3$	-	**100**	**98**
10[d]	VCl_3	-	76	17
11[d]	$Mn(OAc)_2$·4H_2O	-	93	0
12[d]	$Co(OAc)_2$·4H_2O	-	92	0
13[d]	$NiCl_2$	-	96	0
14[d]	$CuCl_2$·2H_2O	-	**100**	**99**
15[d]	$ZnCl_2$	-	100	59
16[d]	$FeCl_3$·6H_2O	-	**100**	**99**
17	$FeCl_3$·6H_2O	20:1	**100**	**99**
18[e]	$FeCl_3$·6H_2O	20:1	100	48
19[f]	$FeCl_3$·6H_2O	20:1	100	99
20[g]	$FeCl_3$·6H_2O	20:1	100	95
21[h]	$FeCl_3$·6H_2O	20:1	96	66
22	$FeCl_3$·6H_2O	10:1	100	95
23	$FeCl_3$·6H_2O	4:1	**100**	**90**
24	$FeCl_3$·6H_2O	1:1	100	61
25	$FeCl_3$·6H_2O	1:4	100	79
26	$FeCl_3$·6H_2O	1:10	100	51
27	$FeCl_3$·6H_2O	1:20	100	28
28	$RhCl_3$	4:1	100	51
29	$CuCl_2$·2H_2O	4:1	100	6
30	$Sc(OTf)_3$	4:1	100	88
31[g,i,j]	$FeCl_3$·6H_2O	10:1	100	47
32[g,i]	$FeCl_3$·6H_2O	10:1	100	99
33[g,k]	$FeCl_3$·6H_2O	20:1	95	12

[a] *Reaction conditions:* 0.5 mmol **2a**, 10 mol% catalyst, 5 mL CH_3NO_2, 50°C, 20 h.
[b] Conversion of the minor substrate, determined by GC.
[c] GC yield (1:1 ratio of diastereomers).
[d] 5 mL **1**, no CH_3NO_2, 100°C.
[e] Room temperature.
[f] 6 h.
[g] 2 h.
[h] 1 h.
[i] 5 mol% catalyst.
[j] 5 mL CH_2Cl_2 instead of CH_3NO_2.
[k] 1 mol% catalyst.

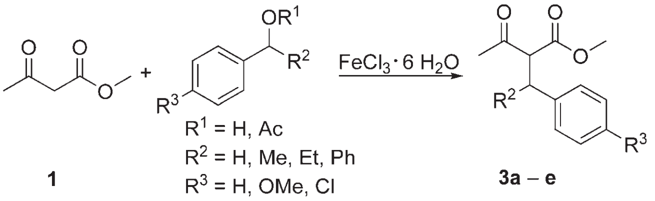
In the presence of catalytic amounts (10 mol%) of Brønsted acids no or only low yields of the benzylated products are obtained (Table 1, entries 1–3). The significant difference between conversion and yield of these reactions is caused by side-reactions of 1-phenylethanol such as elimination to give styrene, oligomerization and polymerization. On the other hand $RhCl_3$, $Sc(OTf)_3$, $CuCl_2$·2H_2O, and $FeCl_3$·6H_2O gave methyl 2-acetyl-3-phenylbutanoate (**3a**) in almost quantitative yield (Table 1, entries 4, 9, 14, 16). In general, best results are obtained when the nucleophile is used as solvent. This is no problem in the case of cheap and readily available substrates such as **1**.

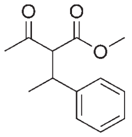
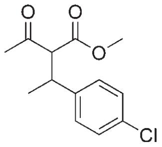
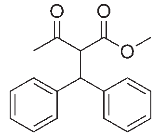
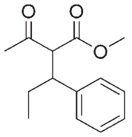
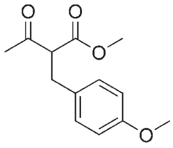
However, if special CH-acidic compounds are to be reacted an additional solvent is advantageous. A screening of solvents for the iron(III) chloride system revealed that dichloromethane and nitromethane are among the most effective ones. This allowed the substrate ratio to be reduced to 4:1 (Table 1, entry 23).

Testing the four best catalyst systems under these more diluted conditions (substrate ratio 4:1), $FeCl_3{\cdot}6H_2O$ was found to be the most productive catalyst (Table 1, entries 23, 28–30). Lower substrate ratios (equimolar or excess of alcohol) led to decreased yields (Table 1, entries 24–27). It is noteworthy that half amount of $FeCl_3{\cdot}6H_2O$ (5 mol%) still catalyzed the model reaction to an excellent yield of 99% employing CH_3NO_2 as solvent (Table 1, entry 32). In comparison CH_2Cl_2 decreased the reactivity to give 47% of **3a** (Table 1, entry 31).

With the optimized parameters (5 mol% $FeCl_3{\cdot}6H_2O$, substate ratio 4:1, CH_3NO_2 as solvent, 50 °C, 2 h) we focused on the reactivity of different electrophiles (Table 2). 1-Phenylethyl acetate reacted comparably to 1-phenylethanol yielding 99% of **3a** (Table 2, entry 2). A chloro substituent in *para*-position of the benzylic alcohol had only a slight influence on the reactivity. Thus, 1-(4-chlorophenyl)-ethanol gave 82% of the corresponding coupling product **3b** (Table 2, entry 3). Diphenylmethanol as well is an excellent electrophile, which yielded 99% of methyl 2-benzhydryl-3-oxobutanoate (**3c**, Table 2, entry 4). A moderate yield of 60% of **3d** was obtained from the reaction of **1** with 1-phenylpropan-1-ol (Table 2, entry 6). In the presence of benzyl alcohol, acetate, and carbonate only low yields are observed due to the decreased stability of the carbocation intermediate. However, the more electron-rich 4-methoxy-substituted benzyl alcohol reacted with an improved yield of **3e** (44 and 66%, respectively, Table 2, entries 7 and 8). For products **3a**, **3b**, and **3d** a diastereo-

Table 2. Variation of the electrophilic reagent in the benzylation reaction of methyl 3-oxobutanoate.[a]



Entry	Product		R^1	mol% $FeCl_3$	Electrophile:**1**	*T* [°C]	Conv. [%][b]	Yield [%][c]
1		**3a**	H	5	1:4	50	100	98
2			Ac	5	1:4	50	100	99
3		**3b**	H	5	1:4	50	100	82
4		**3c**	H	5	1:4	50	100	99
5		**3d**	H	5	1:4	50	100	51
6			H	10	1:10	80	100	60[d]
7		**3e**	H	5	1:4	50	100	44
8			Ac	5	1:4	50	100	66

[a] *Reaction conditions:* 0.5 mmol electrophile, 2 mL CH_3NO_2, 4 h.

[b] Conversion of the electrophile, determined by GC.

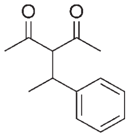
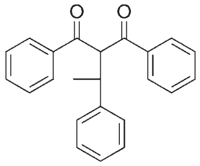
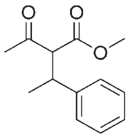
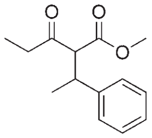
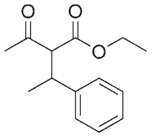
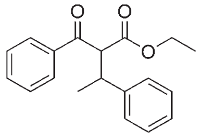
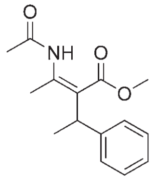
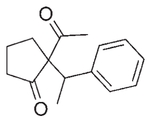
[c] GC yield.

[d] 5 mL CH_3NO_2, 20 h.

meric ratio of approximately 1:1 is observed by GC analysis.

Next, we set out to study the scope and limitation of the nucleophilic coupling partner in more detail. As shown in Table 3, a number of different 1,3-dicarbonyl compounds have been reacted with 1-phenylethanol. Acetylacetone is benzylated quantitatively under optimized conditions within four hours (**4a**, Table 3, entry 1). Dibenzoylmethane as well is employed successfully and yielded the benzylated product **4b** almost quantitatively (99%, Table 3, entry 2). Comparable to our standard substrate **1**, methyl 3-oxovalerate also reacted smoothly resulting in the analogous products **4c** in 95% yield (Table 3, entry 4). Similarly, 97% of product **4d** is obtained in the benzylation reaction of ethyl 3-oxobutanoate (Table 3, entry 5). This result proved a higher activity of $FeCl_3$ compared to $InCl_3$, which only yielded 46% of the diastereomeric products in this reaction.[10] Interestingly, also cyclic 1,3-diketones can be employed in this $FeCl_3$-catalyzed benzylation (Table 3, entry 8).[14]

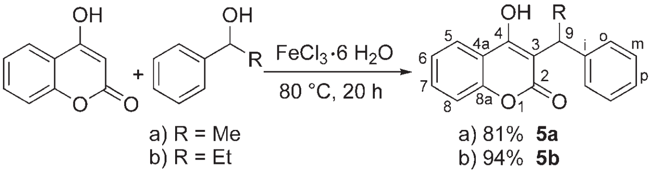
Table 3. Benzylation of different 1,3-dicarbonyl compounds with 1-phenylethanol.[a]

Entry	Product		mol% $FeCl_3$	**2a**:nucleophile	T [°C]	t [h]	Conv. [%][b]	Yield [%][c]
1		**4a**	5	1:4	50	4	100	99[d]
2		**4b**	5	1:4	50	4	100	99
3		**3a**	5	1:4	50	4	100	98
4		**4c**	5	1:4	50	4	100	95
5		**4d**	5	1:4	50	4	100	97
6		**4e**	10	10:1	100	20	100	99[e]
7		**4f**	10	1:4	100	20	100	38[e]
8		**4g**	5	1:4	50	4	100	77

[a] Reaction conditions: 0.5 mmol **2a**, 2 mL CH_3NO_2.
[b] GC conversion of **2a**.
[c] GC yield of benzylated products (1:1 ratio of diastereomers).
[d] Isolated yield: 97%.
[e] 5 mL CH_3NO_2, 0.5 mmol 1-phenylethyl acetate.

To our delight dehydro-β-amino acid derivatives can be benzylated to a reasonable extent in the presence of $FeCl_3{\cdot}6\,H_2O$. Hence, methyl 3-acetamidobut-2-enoate in the reaction with 1-phenylethanol (**2a**) yielded 38% of the corresponding product **4f** (Table 3, entry 7). To the best of our knowledge these are the first benzylations involving this class of enamides.

Finally, the benzylation of 4-hydroxycoumarin to give 4-hydroxy-3-(1-arylalkyl)-2*H*-chromen-2-ones was investigated. The resulting products constitute important building blocks for potentially new pharmaceuticals, especially anticoagulants. Actual examples of this class of compounds are Warfarin (Coumadin®) and Phenprocoumon (Marcumar®, Falithrom®, Phenpro Ratiopharm®). Furthermore, this motif is widely present in rodenticides such as Bromadiolon and Difenacoum.[15] Indeed, the reaction of 4-hydroxycoumarin with 1-phenylethanol (**2a**) proceeded with 81% yield of the desired product **5a**. The benzylation with 1-phenyl-1-propanol was even more successful yielding Phenprocoumon (**5b**) in excellent 94% yield (Scheme 3).[16]



Scheme 3. Benzylation of 4-hydroxycoumarin – synthesis of Phenprocoumon (**5b**).

In summary, we have developed novel catalysts for convenient and effective benzylations of 1,3-dicarbonyl compounds and similar substrates. Best results have been obtained employing $FeCl_3{\cdot}6\,H_2O$ as a non-expensive and disposable catalyst. When applying benzylic alcohols as electrophiles, water is the only by-product in these reactions and excellent product yields under mild reaction conditions (50 °C, 4 h) are achieved. The usefullness of this procedure is shown by a one-step synthesis of Phenprocoumon, a current pharmaceutical drug.

Experimental Section

General Remarks

All reactions were performed in ACE pressure tubes. Unless specified, commercial solvents were used directly without further purification. Column chromatography was carried out with silica gel (230–400 mesh ASTM) from Merck. ^{1}H NMR spectra (300 and 500 MHz) and ^{13}C NMR spectra (76 and 126 MHz) were recorded on Bruker spectrometers AVANCE 300 and AVANCE 500, respectively. The calibration of spectra was carried out on solvent signals ($CDCl_3$: δ $^1H = 7.25$, δ $^{13}C = 77.0$; acetone-d_6: δ $^1H = 2.05$, δ $^{13}C = 29.8$).

IR spectra are taken as nujol mulls (using KBr plates) or KBr pellets or as capillary films. MS were obtained on an AMD 402/3 (EI, 70 eV). HR-MS analyses were recorded on a high resolution magnetic sector spectrometer. GC analyses were performed on an HP 6890 equipped with an HP-5 capillary column ($l = 30$ m, $d = 250$ μm) and an FID detector. Quantitative GC analyses were referenced to decane as internal standard.

Representative Procedure

In a pressure tube, catalyst (5 mol%, 0.025 mmol), 1-phenylethanol (0.5 mmol), and methyl 3-oxobutanoate (2 mmol) were dissolved in 2 mL CH_3NO_2. After stirring for 4 h at 50 °C decane (50 μL) was added as internal GC standard. Aliquots were taken from the reaction mixture and subjected to GC analyses for determination of yield and conversion. For product isolation, the reaction was quenched with water followed by extraction with dichloromethane. The combined organic layers were dried over $MgSO_4$ and the solvents were distilled off. Then, the product was purified by column chromatography (*n*-heptane/ethyl acetate, 1:1).

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