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Benzylation of β-dicarbonyl compounds and 4-hydroxycoumarin using TMSOTf catalyst: a simple, mild, and efficient method

Palani Theerthagiri, Appaswami Lalitha *

Department of Chemistry, Periyar University, Salem 636 011, India

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ABSTRACT

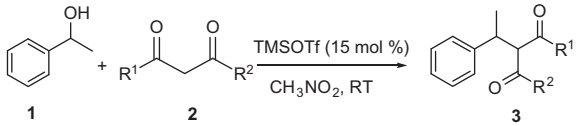
The direct benzylation of 1,3-dicarbonyl compounds and 4-hydroxycoumarin with a wide variety of benzylic alcohols was achieved using trimethylsilyl trifluoromethanesulfonate as an efficient catalyst. The reaction proceeded under very mild conditions at room temperature providing the desired products in good to excellent yields.

The construction of carbon-carbon bonds is one of the fundamental tasks in synthetic organic chemistry.[1] Among the several methods employed to achieve this goal, the alkylation of 1,3-dicarbonyl compounds[2] is found to be one of the best opted. In view of the demand for ecologically valuable processes to avoid large quantities of waste production,[3] the catalytic direct alkylation with unmodified electrophiles such as alcohols, which provides water as the only by-product, would be a suitable alternative. However, the main limitation of this strategy is due to the poor leaving ability of the hydroxyl group. Direct alkylations of 1,3-dicarbonyl compounds with alcohols catalyzed by Pd,[4] Co,[5] Cu,[6] $BF_3{\cdot}OEt_2$,[7] $InCl_3$,[8] InBr,[9] $FeCl_3$,[10] Bi(OTf),[11] Ln(OTf)$_3$ [Ln = La, Yb, Sc, Hf],[12] *p*-toluenesulfonic acid,[13] dodecyl benzene sulfonic acid,[14] molecular iodine,[15] PMA/SiO_2,[16] and $B(C_6F_3)_3$[17] have been reported. Alkylation reactions using metal-triflates as heterogeneous catalysts have also been studied.[11] Inspired by this, we developed a new, mild alkylation of 1,3-dicarbonyl compounds with alcohols, where an organic-triflate could be used as a homogeneous catalyst that leads to reduction of the reaction time and practical difficulties of using the heterogeneous catalyst in large-scale experiments. Trimethylsilyl trifluoromethane sulfonate (TMSOTf) has recently been shown to be a versatile reagent in mediating a wide variety of organic transformations such as aldol and Sakurai allylation,[18] bis-silylation,[19] deprotection,[20] and Baylis–Hillman reaction.[21a] As part of our ongoing research program in the development of new synthetic methods of important organic products,[21b] herein we wish to report the use of TMSOTf as a powerful catalyst for the alkylation of β-dicarbonyl compounds with secondary benzylic alcohols that proceeded in good to excellent yields (Scheme 1).

Initially, the reaction of 1-phenylethanol (**1**) with acetyl acetone (**2a**) in the presence of TMSOTf was selected as a model reaction to develop the optimum reaction conditions. The effect of solvents was investigated and it was observed that the rate of the reaction and the yield were highly influenced by the solvent used which may be attributed to the stability of benzylic carbocation and also the stability of the catalyst in the particular solvent.

The reaction of 1-phenylethanol with acetyl acetone in acetonitrile and dichloroethane afforded the product in only moderate yields. However, the corresponding product was obtained in low yields even after 6 h when toluene or tetrahydrofuran was used as the solvent. The best result was achieved in nitromethane, affording the desired product in 92% yield within 30 min at room temperature.

We then turned our attention to optimize the amount of catalyst. The conversion was very slow at room temperature when



1 2 3

R^1=R^2=Me, **2a**
R^1=Ph; R^2=Me, **2b**
R^1=Me; R^2=OEt, **2c**

Scheme 1. Benzylation of β-dicarbonyl compound.

* Corresponding author. Tel.: +91 427 2345271; fax: +91 427 2345124.
E-mail address: lalitha2531@yahoo.co.in (A. Lalitha).

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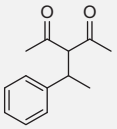
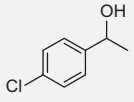
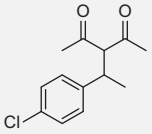
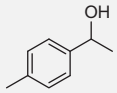
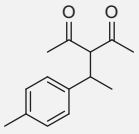
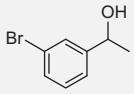
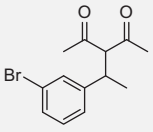
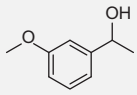
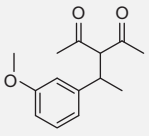
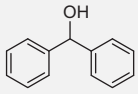
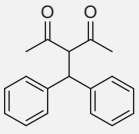
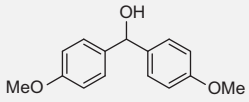
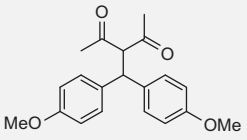
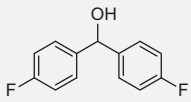
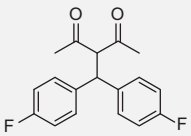
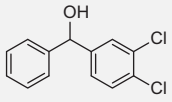
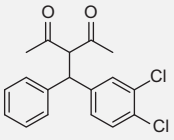
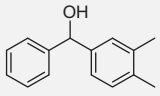
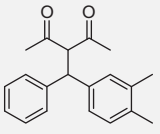
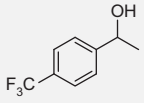
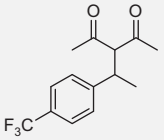
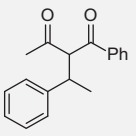
Table 1
TMSOTf-catalyzed alkylation of 1,3-dicarbonyl compounds under the optimum conditions

Entry[a]	Alcohol	Nu-H	Product	Time[b] (h)	Yield[c] (%)
1		**2a**		0.5	85
2		**2a**		0.5	78
3		**2a**		0.5	91
4		**2a**		1.0	67
5		**2a**		0.75	73
6		**2a**		0.5	94
7		**2a**		0.5	96
8		**2a**		0.5	90
9		**2a**		0.75	86
10		**2a**		0.5	88
11		**2a**		1.0	65
12[d]		**2b**		0.5	82

(*continued on next page*)

Table 1 (*continued*)

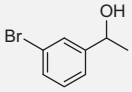
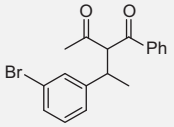
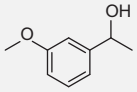
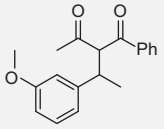
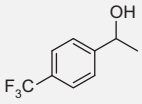
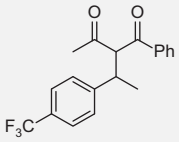
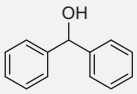
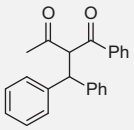
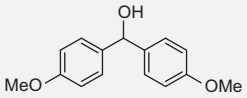
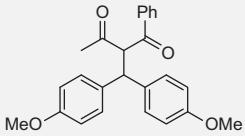
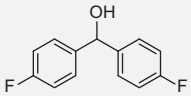
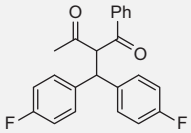
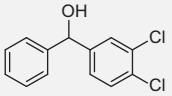
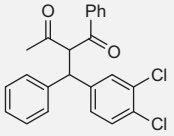
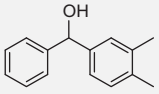
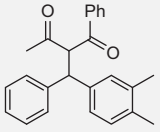
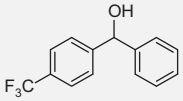
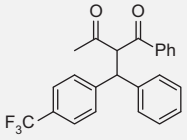
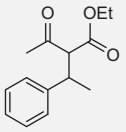
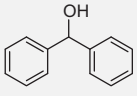
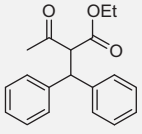
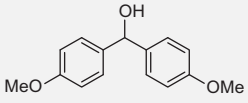
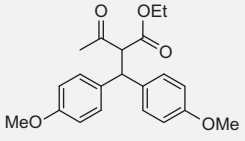
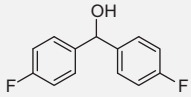
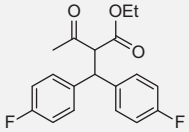
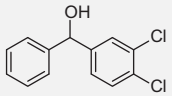
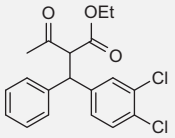
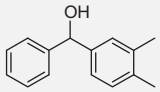
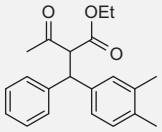
Entry[a]	Alcohol	Nu-H	Product	Time[b] (h)	Yield[c] (%)
13		**2b**		0.5	78
14		**2b**		0.5	71
15		**2b**		1.0	60
16		**2b**		0.5	96
17		**2b**		0.5	94
18		**2b**		0.75	92
19		**2b**		0.5	90
20[d]		**2b**		0.5	87
21		**2b**		1.0	80
22[d]		**2c**		1.0	54
23		**2c**		0.5	65
24		**2c**		0.75	68

Table 1 (*continued*)

Entry[a]	Alcohol	Nu-H	Product	Time[b] (h)	Yield[c] (%)
25		**2c**		1.0	70
26[d]		**2c**		0.5	65
27		**2c**		0.5	62

[a] Alcohol (1 mmol), 1,3-dicarbonyl compound (2 equiv), TMSOTf (15 mol %) at rt.
[b] Reaction monitored by TLC.
[c] Isolated yield.
[d] Mixture of diastereomers (8:2).

5 mol % of TMSOTf was used as catalyst, then it was found that 15 mol % of TMSOTf was the optimum amount for this transformation. Encouraged by these results, we next investigated the scope of the reaction to various alcohols and 1,3-dicarbonyl compounds under these optimized conditions and the results are summarized in Table 1.

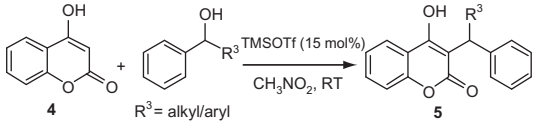
Acetyl acetone with 1-arylethanols in the presence of TMSOTf in nitromethane gave the corresponding benzylated products, in good yields (Table 1). However, the reaction of **2a** with simple benzyl alcohol did not proceed under the optimized conditions, whereas heating at 100 °C yielded only 5–10% of the corresponding benzylated product. However, the reaction of benzoyl acetone (**2b**) and ethylacetoacetate (**2c**) with differently substituted 1-arylethanols proceeded smoothly to give the corresponding products in good yields. The presence of electron-donating substituent in para-position of the benzene ring in 1-phenylethanol can increase the reactivity, while the electron-withdrawing substituent in para-position of benzene ring in 1-phenylethanol seems to have a negative effect on the benzylation reaction (Table 1, entries 2 and 15), whereas, such effects of electron-donating/electron-withdrawing substituent are not observed in diphenylmethanol and the reaction proceeded very smoothly to give the corresponding benzylated products in good yields (Table 1, entries 7–10).

The alkylation of 4-hydroxycoumarin is undoubtedly one of the most important and challenging reactions in organic chemistry as the resulting structures exhibit a wide range of biological activities such as anti-HIV, antibacterial, and cytotoxic.[22] Among the different substituted coumarins, 3-(benzyl)-substituted 4-hydroxycoumarin stands as a significant class of compound due to the frequent existence of such structures in pharmaceutically important compounds.[23] The earlier methods reported for the alkylation of 4-hydroxycoumarin involve organic halides or boronic acids in the presence of Pd catalyst or a base.[24] A few methods that have been reported for the C3-alkylation of 4-hydroxycoumarin so far with alcohols including $Yb(OTf)_3$,[13] strong acids, Amberlite IR-120,[25] and recently molecular iodine[26] require a longer reaction time and high temperatures. Therefore, the development of a new efficient, catalytic method for the direct C3-alkylation of 4-hydroxycoumarin using alcohols is of greater importance and highly desirable. Moreover, the TMSOTf has received much attention as an inexpensive and readily available catalyst due to its moderate Lewis acidity and also it produces only water as a by-product when alcohol is used as alkylating agent. Thus, we report herein a new and simple method for the synthesis of alkyl-substituted 4-hydroxycoumarin from substituted 1-phenylethanols and diphenylmethanols, using only a catalytic amount of TMSOTf (Scheme 2).

Initially, the reaction of 4-hydroxycoumarin (**4**) and diphenylmethanol was chosen as the prototype reaction to develop the optimum reaction conditions (Scheme 2). It was found that treating of alcohols (1 equiv) with 4-hydroxycoumarin in the presence of 15 mol % TMSOTf using nitromethane/dioxane (1:1) as the solvent at room temperature gave the corresponding 3-alkylated 4-hydroxycoumarin (**5a**–**j**) in 91% yield (Table 2).

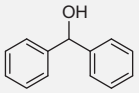
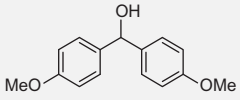
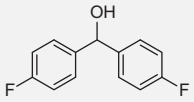
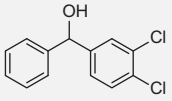
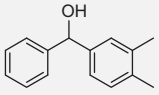
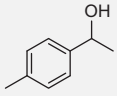
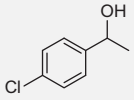
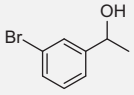
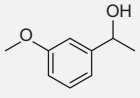
After optimizing the reaction conditions, we applied the procedure to a series of substituted benzylic alcohols and 4-hydroxycoumarin. These results are summarized in Table 2. As shown in Table 2, various diphenylmethanol derivatives were efficiently reacted with 4-hydroxycoumarin and most of them provided the corresponding products in good to excellent yields under the optimized reaction conditions. Whereas, when 1-phenylethanol was used as the alkylating agent, the desired products were isolated in slightly poor yields irrespective of the electron-withdrawing (Table 2, entry 8) or electron-donating (Table 2, entry 10) groups on the phenyl ring.

The plausible mechanism of this reaction can be speculated (Scheme 3) based on the experimental observations. One of the probable routes could be a direct alkylation of **C** with a stabilized carbocation derived from the alcohol. Another probable pathway, we[21b] and others[12a] have previously observed that with a catalytic amount of triflates or other Lewis acids, benzylic alcohols were rapidly converted to dimeric ethers (**A**) by elimination of water. The ether is polarized by triflate to generate the incipient benzylic carbocation, which may act as the alkylating species. The nucleophilic attack of the β-dicarbonyl compound onto the resulting benzyl carbocation produces the final alkylated product after the

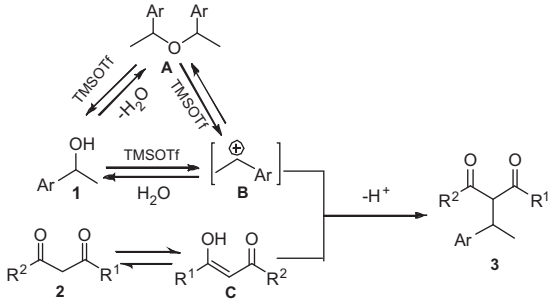


Scheme 2. Benzylation of 4-hydroxycoumarin.

Table 2
TMSOTf-catalyzed alkylation of 4-hydroxycoumarin under the optimum conditions

Entry[a]	Alcohol	Product	Time[b] (h)	Yield[c] (%)
1		**5a**	0.5	91
2		**5b**	0.5	83
3		**5c**	0.5	71
4		**5d**	0.5	81
5		**5e**	0.5	87
6		**5f**	0.5	71
7		**5g**	0.5	60
8		**5h**	0.45	55
9		**5i**	0.5	78
10		**5j**	1.0	50

[a] Alcohol (1 mmol), 4-hydroxycoumarin (1 equiv), TMSOTf (15 mol %) at rt.
[b] Reaction monitored by TLC.
[c] Isolated yield.



Scheme 3. Plausible mechanism for the TMSOTf-catalyzed benzylation.

release of proton. Support for this second mechanism was obtained from the isolation of the symmetric ether at the initial stages (with in 10 min) whose structure was confirmed by NMR and which after appropriate time (mentioned in Table 1) was fully converted to the corresponding alkylated products.

In summary, we have described a simple, convenient, and novel methodology for the direct benzylation of β-dicarbonyl compounds and 4-hydroxycoumarin with various benzylic alcohols as benzylating agents, using TMSOTf as catalyst.[27,28] Operational simplicity and good-to-excellent yields are the key features of this protocol.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.019.

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27. *General experimental procedure for the TMSOTf-catalyzed alkylation of 1,3-dicarbonyl compounds:* To a mixture of alcohol (1 mmol) and 1,3-dicarbonyl-compound (2 mmol) in nitro methane (10 vol), TMSOTf (15 mol %) was added drop wise. The reaction mixture was stirred at room temperature for 30 min. After completion of the reaction (monitored by TLC), water was added and extracted with EtOAc, the organic layer was separated and washed with water, brine and dried over sodium sulfate and concentrated to furnish the desired compound. When necessary, the obtained crude sample was purified by column chromatography.
28. *General experimental procedure for the C3-alkylation of 4-hydroxycoumarins:* To a mixture of 4-hydroxycoumarin (1.0 mmol) and secondary benzyl alcohol (1.2 mmol) in a $MeNO_2$ (10 ml), TMSOTf (0.15 mmol) was added and the reaction mixture was stirred for the given time (see Table 2) at room temperature. After completion of the reaction (monitored by TLC), to the reaction mixture was added water and extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by silica gel column with hexane/ethyl acetate as eluent to afford the corresponding C3-alkylated 4-hydroxycoumarin.