Alkylation of Active Methylenes via Benzhydryl Cations

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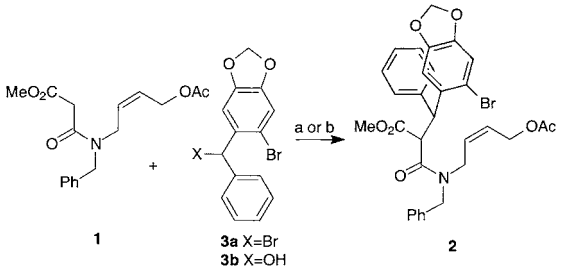
Abstract: The acid mediated reaction between active methylenes and benzhydryl alcohols, or their derivatives, is reported. Ethyl acetoacetate, acetylacetone, and *N*,*N*-dibenzyl-malonamic acid methyl ester are benzhydrylated in quantitative yields in the presence of molar amounts of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at r.t. TMSOTf and H_2SO_4 appear to be equally efficient. Use of benzhydryl acetate in place of the starting free alcohol allows lowering of the Lewis acid to catalytic amounts. A general mechanism for this scarcely studied C-C bond formation is presented. Due to the easier availability of alcohols with respect to halides the method may favorably compare with the more classical halide-based basic conditions.

Key words: boron, carbocations, enols, Lewis acids, benzhydrylation

In the course of our studies toward the synthesis of a lactam analogue of the anticancer agent podophyllotoxin we had to accomplish benzhydrylation of malonamide **1**, so as to obtain the alkylated product **2**. Accordingly, alkylation of the sodium enolate of **1** with benzhydryl bromide **3a** under conventional conditions was undertaken.[1] Rather surprisingly, compound **2** was obtained in a deceiving 16% yield. Further attempts to improve this result constantly met with failure. In the search for more advantageous solutions we serendipitously found that the simple reaction between malonamide **1** and the benzhydryl alcohol **3b** in CH_2Cl_2 at r.t. and in the presence of 2.0 molar equivalents of $BF_3{\cdot}OEt_2$, smoothly gave the desired alkylated product **2** in quantitative yield (Scheme 1).[2]

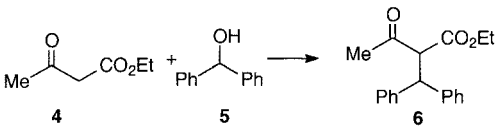


Scheme 1 a) X = Br, NaH, DMF, 0–60 °C, 16%; b) X = OH, CH_2Cl_2, $BF_3{\cdot}OEt_2$ 2.5 equiv, r.t., > 98%.

A perusal into the literature surprisingly indicated that acid-promoted alkylations, although known since a long time, have been only scantly reported,[3,4] and no systematic study had been so far addressed. In this letter we report our preliminary results on the study of such type of alkylation.

We first selected the simple alkylation of ethyl acetoacetate **4** with benzhydryl alcohol **5** as the model reaction. Table 1 shows our results. Quantitative formation of the monoalkylation product **6**[5] was observed in the presence of 1.2 or 2.5 molar equivalents of $BF_3{\cdot}OEt_2$ (entries 1 and 2). On the other hand, sub-stoichiometric amounts of the same Lewis acid did not allow complete alkylation to take place (entries 3 and 4). TMSOTf and H_2SO_4 appeared to be as effective as $BF_3{\cdot}OEt_2$ (entries 5 and 6). Other Lewis acids such as $ZnBr_2$, $MgBr_2{\cdot}OEt_2$, Ti(*i*-PrO)$_4$ were completely ineffective.

Table 1 Acid-Promoted Alkylation of Ethyl Acetate **4** with Benzhydryl Alcohol **5**



4 **5** **6**

Entry	Promoter	(mol equiv)	Time (h)	**6** (%)
1	$BF_3{\cdot}OEt_2$	2.5	1	> 98
2	$BF_3{\cdot}OEt_2$	1.2	1	> 98
3	$BF_3{\cdot}OEt_2$	0.2	1	40
4	$BF_3{\cdot}OEt_2$	0.01	24	7
5	TMSOTf	1.2	1	> 98
6	H_2SO_4	1	1	> 98

Corollary experiments revealed that when the Lewis acidic promoter was present in sub-stoichiometric amounts, conversion of benzhydryl alcohol **5** into the symmetrical ether[6] **7** took place to a large extent (Scheme 2, a). As expected, such a transformation revealed to be independent of the presence of the active methylene (Scheme 2, b). This result suggested that the symmetrical ether might play a role in the C–C bond formation. Indeed, reaction between ethyl acetoacetate **4** and the symmetrical ether **7** in the presence of either stoichiometric or catalytic amounts of $BF_3{\cdot}OEt_2$ gave rise to adduct **6** in quantitative amounts (Scheme 2, c). Finally, a fourth experiment demonstrated that the desired C–C bond formation could be also obtained in the presence of sub-stoichiometric

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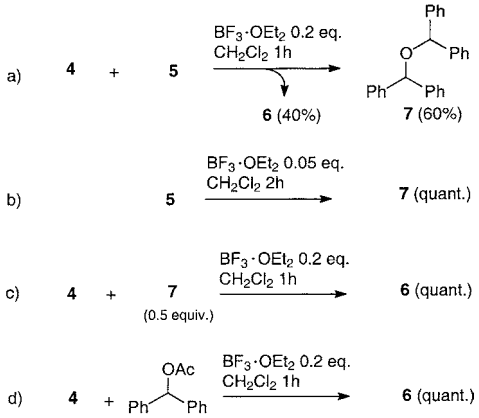
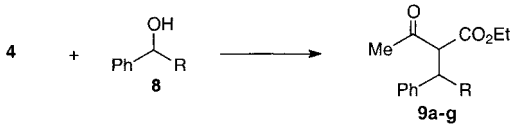
amounts of the promoter by simply using benzhydryl acetate (Scheme 2, d).



Scheme 2

Other differently functionalized benzhydryl alcohols derivatives were next examined as electrophilic partners for ethyl acetoacetate. Table 2 illustrates our results. Electron-rich aryl substituents allowed excellent yields in the alkylation (entries 1 and 7). Conversely, aryl substitutions destabilizing benzhydryl cations were associated to lower yields (entries 2 and 4). In these more difficult cases, higher amounts of the Lewis acid allowed a considerable yield improvement (entry 3). Halide *o*- or *p*-substitution on the benzhydryl alcohol still allowed good coupling yields (entries 5 and 6) Finally, entry 8 indicates that benzyl-type alcohols could also be used in the alkylation, albeit less efficiently.

Table 2 $BF_3{\cdot}OEt_2$-Promoted Benzhydrylation and Benzylation of Ethyl Acetoacetate **4**[a]

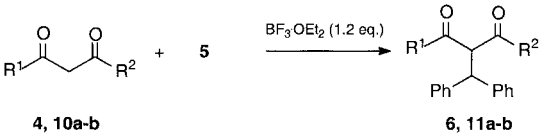


Entry	R	$BF_3{\cdot}OEt_2$	Product	Yield (%)
1	*m*-MeC_6H_4	1.2 equiv	**9a**	> 98
2	*p*-$NO_2C_6H_4$	1.2 equiv	**9b**	13
3	*p*-$NO_2C_6H_4$	2.5 equiv	**9b**	52
4	*m*-$MeOC_6H_4$	1.2 equiv	**9c**	34
5	*o*-Br-C_6H_4	1.2 equiv	**9d**	90
6	*p*-Cl-C_6H_4	1.2 equiv	**9e**	90
7	α-Naphthyl	1.2 equiv	**9f**	> 98
8	Me	1.2 equiv	**9g**	58

[a] All reactions were performed at r.t. for 3 h using a 0.05 M concentration of the benzhydryl alcohol in CH_2Cl_2.

Further active methylenes were then tested for benzhydrylation. Thus, submitting of acetylacetone **10a**, or *N*,*N*-dibenzyl-malonamic acid methyl ester **10b**, and benzhydryl alcohol **5** to the above described optimized reaction conditions, furnished the corresponding alkylation products, again in quantitative yield (Table 3).

Table 3 $BF_3{\cdot}OEt_2$-Promoted Alkylation of Aactive Methylenes with Benzhydryl Alcohol[a]



Entry	Nucleophile	R^1	R^2	Product	Time (h)	Yield (%)
1	**4**	Me	OEt	**6**	3	> 98
2	**10a**	Me	Me	**11a**	3	> 98
3	**10b**	Bn_2N	OMe	**11b**	15	> 98

[a] All reactions were performed using a 0.05 M concentration of benzhydryl alcohol in CH_2Cl_2.

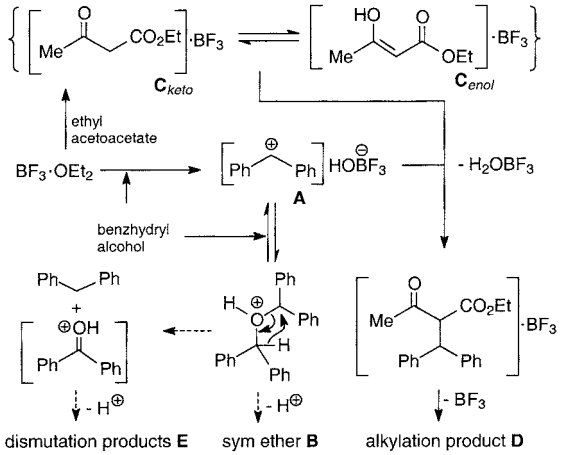
On the other hand, some of the tested active methylenes did not afford the expected alkylation products.[7] In these cases the active methylenes were either recovered unreacted or gave more complex uncharacterized material, whereas the starting benzhydryl alcohol gave either the symmetrical ether **7** or disproportionated to benzophenone and diphenylmethane.[8]

The above results indicate that the reaction is highly dependent on the nature of active methylenes, and not easily rationalizable only on the basis of the nucleophile pK_a value.[9]

The enol form of the nucleophile and the corresponding benzhydryl cation are probably involved in the mechanism of the C-C bond formation. However, the non-innocent role of the Lewis acid on the active methylene must also be taken into account. In order to obtain further information, the ^1H NMR spectrum of ethyl acetoacetate **4** was recorded in the absence and in the presence of $BF_3{\cdot}OEt_2$. As expected, the initial spectrum of pure acetoacetate showed a mixture of the carbonyl and the enol forms, the former tautomer being strongly prevalent. Upon addition of 1.0 molar equivalent of $BF_3{\cdot}OEt_2$, disappearance of the former signals and concomitant generation of two new sets of signals in a 60:40 ratio was detected. These latter peaks have been assigned to the keto and the enol forms, both coordinated to the Lewis acid.[10]

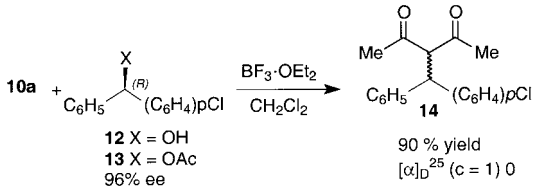
The data so far collected led us to propose the general mechanism shown in Scheme 3. The Lewis acid is expected to play the double role of generating the benzhydryl cation as well as of coordinating,[11] and thereby probably activating, the nucleophile.[12] The thus generated benzhydryl cation **A** can then competitively interact either with the benzhydryl alcohol, to give the symmetrical ether **B**,

or with the (possibly Lewis acid-coordinated) enol form of the active methylene $\mathbf{C}_{enol}$, to give the alkylated product **D**. Since etherification is a reversible process, irreversible alkylation can be normally driven to completion. However, when the rate of C-C bond formation becomes too slow, possibly due to inefficient enolization, acid mediated dismutation to **E** may become the fastest irreversible process, thereby diverting the transitory cation from alkylation.



Scheme 3

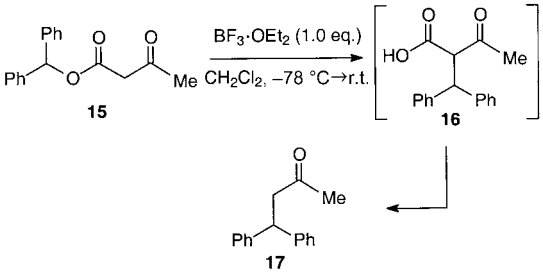
Definitive proof for an S_N1 type substitution mechanism came from alkylation of acetylacetone with (*R*)-*p*-chlorophenyl phenyl methanol **12** (96 ee%)[13] or its acetate ester **13** (Scheme 4). Indeed, isolation of the benzhydrylation product **14** in a completely racemic form confirmed that the C-C bond formation step takes place on the completely ionized electrophilic substrate.



Scheme 4

Finally, a mono-component variant of the above alkylation was developed. In the event, treatment of benzhydryl acetoacetate **15** with $BF_3{\cdot}OEt_2$ (1.0 equiv) in CH_2Cl_2 at –78 °C to r.t. gave rise to the unstable alkylated ketoacid **16** which quantitatively decarboxylated to 4,4-diphenyl-2-oxo-butanone **17** upon standing a few hours in solution. Hence, the above approach may be considered as a novel one-pot acid-promoted acetone benzhydrylation (Scheme 5).

In conclusion, this study shows that some resonance-stabilized methylenes can be smoothly benzhydrylated in very highly yields under non-traditional acidic conditions by reaction with the corresponding benzhydryl alcohols. Benzylation under analogous conditions appears also to



Scheme 5

be possible, albeit less efficient. The ensemble of experiments performed allowed us to propose a general mechanism for such a scarcely studied C–C bond formation. Owing to the simplicity of the experimental conditions and to the easier availability of alcohols with respect to halides, the method may favorably compare with the classical halide-based basic conditions. We believe that the above results may be of interest for the constant development of more and more efficient synthetic methods in organic chemistry.

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References

(1) Valenta, V.; Metys, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1982**, *47*, 984.
(2) Poli, G.; Giambastiani, G. *J. Org. Chem.*, **2002** in press.
(3) (a) Adams, J. T.; Abramovitch, B.; Hauser, C. R. *J. Am. Chem. Soc.* **1943**, *65*, 552. (b) Adams, J. T.; Levine, R.; Hauser, C. R. *Org. Synth., Coll. Vol. 3*; John Wiley and Sons Ltd.: New York, **1955**, 405. (c) Sawicki, E.; Olivero, V. T. *J. Org. Chem.* **1956**, *21*, 183. (d) Crimmins, T. F.; Hauser, C. R. *J. Org. Chem.* **1967**, *32*, 2615. (e) Ohshima, E.; Kumazawa, T.; Obase, H. *Chem. Pharm. Bull.* **1993**, *41*, 36. (f) Gálvez, N.; Molins, E.; Moreno-Mañas, M.; Sebastián, R. M.; Serra, N.; Trepat, E.; Vallribera, A. *J. Heterocyclic Chem.* **2000**, *37*, 895. (g) For a Lewis acid catalyzed intramolecular alkylation of alkene-containing active methylenes see: Reetz, M. T.; Chatziiosifidis, I.; Schwellnus, K. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 687.
(4) For Lewis acid mediated alkylation of silyl enol ethers with S_N1 reactive halides see: (a) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, *23*, 2179. (b) Reetz, M. T.; Hüttenhain, S.; Walz, P.; Löwe, U. *Tetrahedron Lett.* **1979**, *51*, 4971. (c) Reetz, M. T.; Maier, W. F.; Chatziiosifidis, I.; Giannis, A.; Heimbach, H.; Loewe, U. *Chem. Ber.* **1980**, *113*, 3741.
(5) Representative experimental procedure: To a stirred solution of benzhydryl alcohol (202 mg, 1.1 mmol) and ethyl acetoacetate (127 μL, 1 mmol) in CH_2Cl_2 (20 mL) under nitrogen was added $BF_3{\cdot}OEt_2$ (217 μL, 1.2 mmol) at r.t. The mixture was stirred for 1 hour before saturated $NaHCO_3$ solution (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (10 mL). The organic layers were washed with brine (10 mL) dried ($MgSO_4$) and concentrated under reduced pressure. Short column chromatography

(hexane/EtOAc = 8:2) afforded quantitatively ethyl 2-benzhydryl-3-oxo-butanoate. ^{1}H NMR ($CDCl_3$, 400 MHz): δ(ppm) 7.5–7.1 (m, 10 H, H), 4.81 (d, 1 H, ^3J = 12.3 Hz), 4.58 (d, 1 H, ^3J = 12.3 Hz), 4.01 (q, 2 H, ^3J = 7.1 Hz), 2.12 (s, 3 H), 1.02 (t, 3 H, 7.1). ^{13}C NMR: δ(ppm) 201.7, 167.6, 141.5, 141.2, 128.8–126.8, 65.2, 61.4, 50.8, 30.0, 13.7.

(6) For a recent application of BF_3·OEt_2 mediated symmetrical ether synthesis see: Díaz, D. D.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 9993.

(7) Experiments with dimethyl malonate, methyl phenylsulfonyl acetate and bis-phenylsulfonylmethane gave back the unreacted methylene plus benzhydryl alcohol dismutation. Meldrum's acid gave an alkylated/transesterified product. Ethyl malononitrile gave a complex mixture.

(8) (a) Gautert, P.; El-Ghammarti, S.; Legrand, A.; Couturier, D.; Rigo, B. *Synth. Commun.* **1996**, *26*, 707. (b) Balfe, M. P.; Kenyon, J.; Thain, E. M. *J. Chem. Soc.* **1952**, 790. (c) Burton, H.; Cheesman, G. W. H. *J. Chem. Soc.* **1953**, 986. (d) Bartlett, P.; McCollum, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 1441.

(9) (a) Giambastiani, G.; Poli, G. *J. Org. Chem.* **1998**, *63*, 9608. (b) Tamaru, Y.; Horino, Y.; Araki, M.; Tanaka, S.; Kimura, M. *Tetrahedron Lett.* **2000**, *41*, 5705.

(10) ^{1}H NMR ($CDCl_3$, 400 MHz): coordinated keto form δ = 4.17 (q, ^3J = 7 Hz, 2 H), 3.38 (br s, 2 H); 2.24 (br s, 3 H), 1.26 (t, ^3J = 7 Hz, 3 H); coordinated enol form δ = 11,98 (s, 1 H), 5.32 (s, 1 H), 4.47 (q, ^3J = 7 Hz, 2 H), 2.14 (s, 3 H), 1.38 (t, ^3J = 7 Hz, 3 H).

(11) For an example of complexation between BF_3·OEt_2 and tetronic derivatives during acylations see: (a) Jones, R. F.; Peterson, G. E. *Tetrahedron Lett.* **1983**, *24*, 4757. (b) Jones, R. F.; Begley, M. J.; Peterson, G. E.; Sumaria, S. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1959.

(12) For examples of active methylene enolization by means of metal salts see: (a) Moreno-Mañas, M.; Marquet, J.; Vallribera, A. *Tetrahedron* **1996**, *52*, 3377. (b) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553. (c) Christoffers, J. *Chem. Commun.* **1997**, 943. (d) Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259. (e) Bartoli, G.; Bosco, M.; Bellucci, M. C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* **1999**, 617.

(13) (a) Bolm, C.; Muniz, K. *Chem. Commun.* **1999**, 1295. (b) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3465. (c) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem. Int. Ed.* **2001**, *40*, 1488.