

Brønsted Acid-Catalyzed Benzylation of 1,3-Dicarbonyl Derivatives

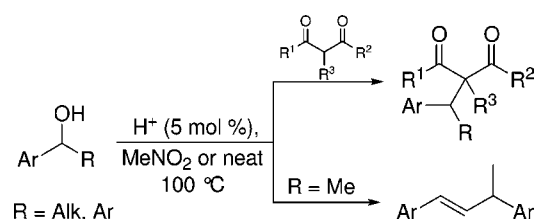
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ABSTRACT



The direct alkylation of 1,3-dicarbonyl compounds with benzylic alcohols is shown to be efficiently catalyzed by simple Brønsted acids such as triflic acid (TfOH) and *p*-toluenesulfonic acid (PTS) to give rise to monoalkylated dicarbonyl derivatives in high yields. In the absence of the nucleophile, substituted alkenes, generated through a formal dimerization reaction, are obtained. The reactions are carried out in air using undried solvents, with water being the only side product of the process.

As one of the most common strategies for the formation of carbon–carbon bonds, the standard protocol for the alkylation of 1,3-dicarbonyl compounds usually requires the usage of a stoichiometric amount of base and an organic halide. Consequently, the development of alternative methods, via acid-catalyzed addition of 1,3-dicarbonyl derivatives to alkenes or alcohols, would provide a more environmentally friendly and atom-economical process.¹ In the last years some metal-catalyzed intramolecular hydroalkylation of alkenes by active methylene compounds have appeared.² In recent years, we³ and others⁴ have reported that simple Brønsted acids, such as *p*-toluenesulfonic acid (PTS) or solid

acids based on montmorillonites are able to catalyze the direct nucleophilic substitution of allylic and benzylic alcohols with a variety of heteroatom- and carbon-centered nucleophiles.⁵

The major issue with proton-catalyzed nucleophilic substitution reactions of alcohols is that the used nucleophile must be less basic than the alcohol, to favor the formation of carbenium ions in the presence of the nucleophile.⁶ In this sense, the acid-catalyzed direct nucleophilic substitution of alcohols by 1,3-dicarbonyl compounds would be a favorable process.⁷

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(2) Pd: (a) Han, X.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem.—Eur. J.* **2004**, *10*, 6333. Au: (b) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884. (c) Nguyen, R.-V.; Yao, X.-Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673.

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(4) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605. Also, a surfactant-type Brønsted acid has been described as a catalyst for nucleophilic substitution of alcohols in water, see: Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 311.

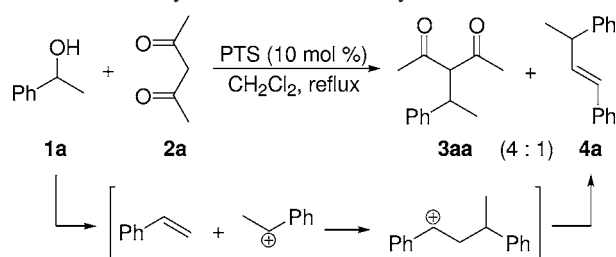
(5) An interesting direct substitution of allylic and benzylic alcohols by nucleophiles catalyzed by InCl₃ has recently appeared: Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793. For an efficient bismuth-catalyzed benzylation of arenes, see: Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033.

(6) For other Brønsted acid-catalyzed reactions, see: (a) Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383. (b) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617.

Herein, we report the use of TfOH as a powerful catalyst for the direct substitution of secondary benzylic alcohols with β -dicarbonyl compounds. While our work was in progress, Rueping et al. reported a similar bismuth-catalyzed reaction.⁸ Surprisingly, these authors state in the paper that TfOH does not show catalytic activity.

The reaction of 1-phenylethanol **1a** with acetylacetone **2a** under PTS-catalysis in CH₂Cl₂ afforded a mixture (ca. 4:1) of the desired alkylated 1,3-diketone **3aa** and 1,3-diphenylbut-1-ene **4a**.^{3a} The formation of the latter might be due to a competitive elimination reaction that would afford styrene. This compound could react with intermediate phenylethyl cation to give, after subsequent elimination of a proton, the alkene **4a** (Scheme 1).⁹

Scheme 1. Brønsted Acid-Catalyzed Reaction of 1-Phenylethanol **1a** with Acetylacetone **2a**



Owing to the great potential of Brønsted acids as easily tunable, economical, and environmentally acceptable catalysts,¹⁰ we investigated the model reaction of **1a** with **2a** by using some Brønsted acids as catalysts under different reaction conditions (Table 1).

At the beginning we employed CH₂Cl₂ as solvent. As shown in Table 1, similar results were obtained by using 2,4-dinitrobenzenesulfonic acid (DNBSA) or PTS as catalysts (entries 1,2). However, the amount of the sideproduct **4a** could be reduced by using TfOH as catalyst (entry 3). The evaluation of different solvents under TfOH-catalysis showed that MeNO₂ was superior, regarding both the yield and selectivity, compared with CH₂Cl₂, MeCN, and toluene (entries 3–6).¹¹ Although no improvements were achieved

(7) For the Lewis acid-mediated direct reaction of alcohols with active methylenes, see: (a) Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823. (b) Liu, J.; Liang, F.; Liu, Q.; Li, B. *Synlett* **2007**, 156.

(8) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Org. Lett.* **2007**, 9, 825.

(9) This product has also been obtained as a byproduct in the metal triflate-catalyzed secondary benzylation of benzylic alcohols with different nucleophiles, see: Noji, M.; Ohno, T.; Fujii, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, 68, 9340.

(10) For recent examples using Brønsted acids as catalysts, see: (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, 8, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiyu, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, 8, 4179. (c) Kampen, D.; List, B. *Synlett* **2006**, 2589. (d) Kumar, R.; Kumar, D.; Chakraborti, A. K. *Synthesis* **2007**, 299.

(11) It should be noted that Rueping et al. reported 0% yield of **3aa** by using similar conditions as those shown in entry 6 of Table 1 (see ref 8). We performed the reaction as follows: TfOH (5 mol %) was added to a mixture of **1a** (3 mmol) and **2a** (3 mmol) in MeNO₂ (3 mL). The reaction was stirred at reflux for 20 min (monitored by GC–MS). The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (hexane/AcOEt, 15:1).

Table 1. Evaluation of Brønsted Acid Catalysts and Conditions for the Nucleophilic Substitution of **1a** with **2a**^a

entry	catalyst	solvent	temp (°C)	time (h)	3aa/4a ratio	yield (%) ^a
1	PTS	CH ₂ Cl ₂	reflux	48	4/1	70
2	DNBSA	CH ₂ Cl ₂	reflux	5	4/1	73
3	TfOH	CH ₂ Cl ₂	reflux	4	9/1	81
4	TfOH	MeCN	reflux	1		0 ^b
5	TfOH	toluene	reflux	0.5	12/1	80
6	TfOH	MeNO ₂	reflux	0.3	13/1	88
7	PTS	MeNO ₂	reflux	17	2.5/1	58
8	DNBSA	MeNO ₂	reflux	5	5/1	76
9	TfOH		100	1	1/0	94
10	none	MeNO ₂	reflux	4		0

^a Isolated yield of **3aa** after column chromatography. ^b *N*-(1-phenylethyl)acetamide was generated through a Ritter-type reaction.

by using other catalysts in MeNO₂ (entries 6–8), we observed that the process could be carried out without solvent, by using an excess of **2a**. Under these conditions, compound **4a** was not detected and **3aa** was isolated in 94% yield (entry 9). Finally, as expected, no reaction took place in the absence of catalyst (entry 10). Consequently, the optimal conditions for the transformation of **1a** and **2a** into **3aa** supposed the use of TfOH as catalyst (5 mol %) without solvent or employing MeNO₂.¹²

Once the best reaction conditions were established, several 1,3-dicarbonyl compounds, including active methylene derivatives **2a–c** as well as active methine ones **2d,e**, were tested (Table 2, entries 1–5). Interestingly, ethyl acetoacetate

Table 2. 1,3-Dicarbonyl Compounds **2** Examined^a

entry	diketone	R ¹	R ²	R ³	product	yield (%) ^a
1	2a	Me	Me	H	3aa	88 (94) ^b
2	2b	Ph	Ph	H	3ab	70
3	2c	Ph	Me	H	3ac	80 ^c
4	2d	Me	–(CH ₂) ₃ –		3ad	76 ^{c,d}
5	2e	Me	Me	Me	3ae	71 ^e
6	2f	Me	OEt	H	3af	61 ^{c,f}

^a Isolated yield after column chromatography. ^b In parenthesis yield obtained in a gram-scale experiment (20 mmol) using **2a** as solvent (3 equiv) and TfOH (3 mol %). ^c Obtained as a ca. 1:1 mixture of diastereoisomers. ^d Carried out in neat **2d** (5 equiv). ^e A total of 10% of the alkene **4a** was also generated. ^f A total of 20% of the alkene **4a** was also generated.

2f also undergoes Brønsted acid-catalyzed alkylation with **1a** under solvent-free conditions, affording the corresponding benzylated β -ketoester **3af** (Table 2, entry 6).¹³

We then explored the generality of the reaction by varying the substituents of the benzylic alcohols **1** (Table 3).

Table 3. Reactions of Secondary Benzylic Alcohols **1** with Diketones **2a** and **2b**^a

1 **2a**: R² = Me
2b: R² = Ph **3**

entry	alcohol	Ar	R ¹	diketone	product	yield (%) ^b
1	1b	4-BrC ₆ H ₄	Me	2a	3ba	89
2	1c	4-PhC ₆ H ₄	Me	2a	3ca	88
3	1d	4-ClC ₆ H ₄	Me	2a	3da	82
4	1e	2-BrC ₆ H ₄	Me	2a	3ea	72 ^c
5	1f	3-BrC ₆ H ₄	Me	2a	3fa	70
6	1g	2-Nf ^d	Me	2a	3ga	90
7	1h	Ph	Pr	2a	3ha	70 ^e
8	1i	4-ClC ₆ H ₄	Bu	2a	3ia	58 ^f
9	1j	4-BrC ₆ H ₄	Et	2a	3ja	57 ^g
10	1e	2-BrC ₆ H ₄	Me	2b	3eb	81 ^c
11	1k	Ph	CH=CH ₂	2b	3kb ^h	53 ^c

^a Reaction conditions: alcohol (3 mmol), diketone (15 mmol for **2a** or 3 mmol for **2b**), TfOH (0.15 mmol) in MeNO₂ (3 mL for **2b**) at 100 °C. ^b Isolated yield after column chromatography. ^c Carried out in MeNO₂. ^d 2-Nf: 2-naphthyl. ^e 1-Phenyl-1-butene was obtained in 20% yield. ^f 1-(4-Chlorophenyl)-1-pentene was obtained in 30% yield. ^g 1-(4-Bromophenyl)-1-propene was obtained in 35% yield. ^h The linear styrene derivative which corresponds to an S_N2'-type process was obtained.

Functionalized 1-arylethanols **1b–g** gave high yields of 3-alkylated-2,4-pentanediones **3ba–3ga** in neat **2a** (entries 1–6). Interestingly, benzylic alcohols **1h–j** substituted with ethyl, propyl, or butyl groups were appropriate starting materials (entries 7–9). Moreover, dibenzoylmethane **2b** also yielded high yields of the alkylated products with different benzylic alcohols by performing the reactions in MeNO₂ as solvent (entries 10–11).

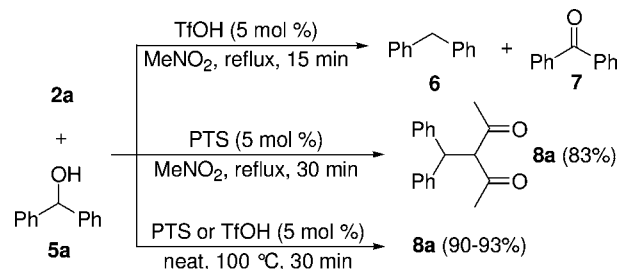
Interestingly, when we tried the reaction of **2a** with benzhydrol **5a** under the standard conditions (TfOH as catalyst in MeNO₂), we isolated an equimolecular mixture of diphenylmethane **6** and benzophenone **7** (Scheme 2).¹⁴ Surprisingly, the use of PTS instead of TfOH gave rise to the alkylated diketone **8a** in 83% yield. Moreover, the reaction of **5a** in neat **2a** afforded **8a** in 90–93% yield irrespective of using PTS or TfOH-catalysis (Scheme 2).

(12) The use of other solvents like DMF and DMSO did not afford any substitution products. In THF, only bis(1-phenyl-ethyl) ether was obtained.

(13) The TfOH-catalyzed reaction of **1a** with **2d** or **2f** in MeNO₂ gave rise to low yields of **3ad** or **3af**, respectively.

(14) Some examples of disproportionation of benzhydrols in acidic media are mentioned in the literature. See, for instance: (a) Bartlett, P. D.; McCollum, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 1441. (b) Harig, M.; Neumann, B.; Stammer, H.-G.; Kuck, D. *Eur. J. Org. Chem.* **2004**, 2381. (c) L'Hermite, N.; Giraud, A.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron* **2006**, *62*, 11994.

Scheme 2. Brønsted Acid-Catalyzed Reactions of Benzhydrol **5a**



Different diarylcarbinols **5** were tested in their acid-catalyzed substitution with **2a** and **2f** under solvent-free conditions, and excellent yields of the corresponding alkylated β -dicarbonyl derivatives **8** were obtained in short reaction times, even when strong electron-withdrawing groups are present in the starting alcohol **5** (Table 4).

Table 4. Reactions of Benzhydryl Alcohols **5** with β -Dicarbonyl Compounds **2a** and **2f**^a

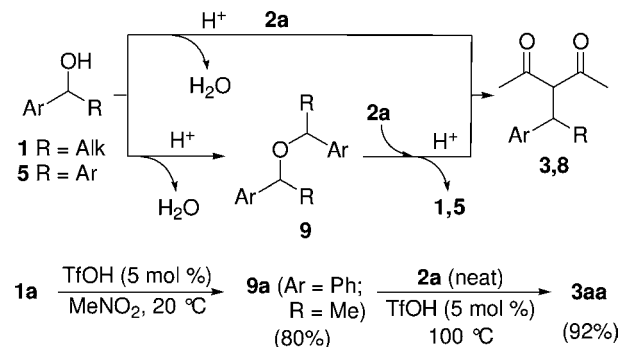
5 **2a**: R = Me
2f: R = OEt **8**

entry	alcohol	Ar ¹	Ar ²	R	product	yield (%) ^b
1	5b	4-ClC ₆ H ₄	Ph	Me	8b	91
2	5c	4-NO ₂ C ₆ H ₄	Ph	Me	8c	88
3	5d	4-BrC ₆ H ₄	Ph	Me	8d	87
4	5e	4-FC ₆ H ₄	4-FC ₆ H ₄	Me	8e	96
5	5f	4-ClC ₆ H ₄	4-ClC ₆ H ₄	Me	8f	95
6	5a	Ph	Ph	OEt	8g	84

^a Reaction conditions: alcohol (3 mmol), **2a** or **2f** (15 mmol), PTS or TfOH (0.15 mmol) at 100 °C. ^b Isolated yield after column chromatography.

Scheme 3 shows plausible mechanisms for the Brønsted acid-catalyzed reaction of secondary benzylic alcohols **1** and

Scheme 3. Plausible Pathways for the Catalyzed Reaction



5 with **2a**. One of them could be a direct alkylation of **2a** with a stabilized carbocation derived from the alcohol (Scheme 3). Another probable pathway, at least for less bulky carbocations, is a fast condensation of the starting alcohol to the corresponding symmetric ether **9**. Then, alkylation of the dimeric ether by **2a** takes place, affording the substitution products **3** and **8** and releasing starting alcohol.¹⁵ Support for this second mechanism was found in the reaction of **1a** with TfOH as catalyst in MeNO₂ at room temperature. Under these reaction conditions, dimerization to give bis(1-phenylethyl) ether **9a** was observed. Moreover, reaction of isolated **9a** in neat **2a** at 100 °C in the presence of a catalytic amount of the Brønsted acid led to the formation of the alkylated 1,3-diketone **3aa** in almost quantitative yield (Scheme 3).

Finally, we turned our attention to the alkene derivative **4a**, which was obtained as a side-product in low yield in the reaction of **1a** with **2a** under Brønsted acid-catalysis (see Scheme 1 and Table 1). As said before, this compound formally comes from the dimerization of styrene, and this process, that is, the dimerization of vinylarenes, is an interesting reaction. As far as we know, this kind of reaction has previously been carried out under palladium-catalysis.¹⁶ So, we envisaged that a metal-free alternative for the dimerization of vinylarenes could be achieved by the reaction of 1-arylethanol derivatives **1** under Brønsted acid-catalysis in the absence of any external nucleophile. Gratifyingly, 1,3-diarylbut-1-ene derivatives **4** were easily obtained in moderate yields¹⁷ when a solution of **1** in MeNO₂ was refluxed in the presence of a catalytic amount of TfOH (Table 5).

In summary, we have shown that simple Brønsted acids such as TfOH and PTS are efficient catalysts for the direct nucleophilic substitution of benzylic alcohols with active methylene and methine 1,3-dicarbonyl compounds. This metal-free method, which can be carried out without solvent

Table 5. Formation of 1,3-Diarylbut-1-ene Derivatives **4** from 1-Arylethanol **1** under Brønsted Acid Catalysis^a

entry	alcohol	Ar	product	yield (%) ^a
1	1a	Ph	4a	43
2	1b	4-BrC ₆ H ₄	4b	55
3	1d	4-ClC ₆ H ₄	4d	67
4	1e	2-BrC ₆ H ₄	4e	45
5	1f	3-BrC ₆ H ₄	4f	52

^a Isolated yield after column chromatography.

and gives water as the only side product, represents a clean and environmentally friendly alternative to the classical halide-based strategies under basic conditions or to the already established use of metallic catalysts. The results here presented clearly demonstrate that Brønsted acids are appropriate catalysts for the direct hydroxy substitution of benzylic alcohols. So, the possibility of in situ formation of a small amounts of Brønsted acids in related catalytic reactions with metallic Lewis acids should be taken into consideration.

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Supporting Information Available: Experimental procedures and characterization data for compounds; copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) This type of reaction course has also been proposed by different authors, see ref 5 and 9.

(16) (a) Tsuchimoto, T.; Kamiyama, S.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 852. (b) Kabalka, G. W.; Dong, G.; Venkataiah, B. *Tetrahedron Lett.* **2004**, 45, 2775.

(17) Moderate yields are probably a reflection of the high tendency of the final products to polymerize under the workup or purification conditions.