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Brønsted Acid Catalyzed Propargylation of 1,3-Dicarbonyl Derivatives. Synthesis of Tetrasubstituted Furans

Roberto Sanz,*,† Delia Miguel,† Alberto Martínez,† Julia M. Álvarez-Gutiérrez,† and Félix Rodríguez‡

Departamento de Química, Área de Química Orgánica, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos, Spain, and Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, C/Julián Clavería, 8, 33006-Oviedo, Spain

rsd@ubu.es

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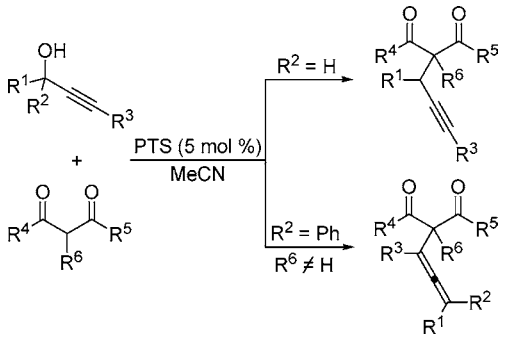
ABSTRACT



Simple Brønsted acids such as *p*-toluenesulfonic acid monohydrate (PTS) efficiently catalyze a direct substitution of the hydroxyl group in propargylic alcohols with 1,3-dicarbonyl compounds. Selective propargylation or allenylation is obtained depending on the nature of the alkynol. Reactions can be performed in air in undried solvents with water being the only side product of the process. By applying this reaction as the key step, a range of interesting polysubstituted furans can easily be synthesized in a one-pot procedure.

The alkylation of 1,3-dicarbonyl compounds represents one of the most useful methodologies for carbon−carbon bond formation. Usually, this process requires the use of a stoichiometric amount of base and an organic halide as the alkylating agent. An alternative approach, via acid-catalyzed addition of active methylenes to alcohols, would provide a more atom-economical process.[1] However, this strategy still remains a major goal of modern organic synthesis.[2]

In this context, we,[3] and others,[4] have been involved in the development of "greener" and cheaper methods for the alkylation of active methylenes, such as 1,3-dicarbonyls, with allylic and benzylic alcohols by using simple Brønsted acids as catalysts. The efficiency of this environmentally friendly methodology led us to explore the scope of such a substitution reaction on propargylic alcohols. Recently, some catalytic methodologies for the direct substitution of propargylic alcohols in the presence of ruthenium,[5] rhenium,[6] gold,[7] or bismuth[8] catalysts have been reported. Nevertheless, the use of 1,3-dicarbonyl compounds as nucleophiles has not been well established in any of these works.[9]

† Universidad de Burgos.
‡ Universidad de Oviedo.

(1) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(2) An interesting direct substitution of allylic and benzylic alcohols by nucleophiles catalyzed by indium trichloride has recently appeared. See: Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793.

(3) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841.

(4) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605.

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Herein, we wish to report that both secondary and tertiary propargylic alcohols undergo efficient and highly regioselective substitution with β-dicarbonyl compounds under Brønsted acid catalysis. This method allows the easy preparation of useful synthetic intermediates for various applications.

Surprisingly, to the best of our knowledge, no reports (general methods) have been described in the literature for the preparation of apparently simple 2-propargylic-1,3-dicarbonyl compounds further substituted at the propargylic position. Our studies started with the reaction between 1,3-diphenyl-2-propyn-1-ol **1a** and several β-dicarbonyl compounds (Figure 1) in analytical grade acetonitrile as solvent,

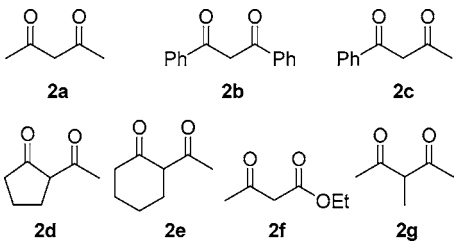


Figure 1. 1,3-Dicarbonyl compounds examined.

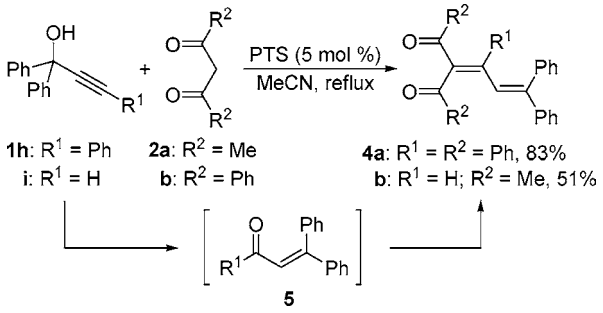
at room temperature under *p*-toluenesulfonic acid monohydrate (PTS) catalysis (5 mol %).[10] As shown in Table 1 (entries 1−6), the process was general with respect to the nature of the 1,3-dicarbonyl derivative **2** employed, and the regioselectivity always completely favored the propargylation reaction of the active methylene or methine compound. Although in general the reactions were run in acetonitrile, it was also possible to carry them out in the absence of solvent using an excess of the 1,3-dicarbonyl compound. In this way, **3aa** could be obtained in 82% yield by treatment of alkynol **1a** with **2a** (5 equiv) and PTS (5 mol %) at room temperature for 8 h (Table 1, entry 1). The effectiveness of the process was evaluated by a gram-scale experiment (15 mmol), which gave **3aa** (4.0 g) in 92% yield (Table 1, entry 1).

We then explored the generality of the reaction by varying the substituents R^1 and R^2 of the propargylic alcohols **1** (Table 1, entries 7−20).

Internal alkynes **1b**−**e** with either an aromatic or heteroaromatic group at the propargylic position (R^1),[11] or with an aromatic, heteroaromatic, or alkyl group at the terminal position (R^2), gave good results allowing the synthesis of propargylated derivatives **3** in high to moderate yields (Table 1, entries 7−16). Moreover, the reactions also proceeded with terminal alkynols such as **1f** and **1g**, though slightly lower yields were obtained in some cases (Table 1, entries 17−20).

We were interested in studying the reactivity of tertiary alkynols. Propargylic alcohols **1h** and **1i** were selected as model compounds and tested as substrates under PTS catalysis with 1,3-diketones **2a** and **2b** (Scheme 1). However,

Scheme 1. Reaction of Diketones **2a** and **2b** with Tertiary Alkynols **1h** and **1i**



the conjugated diene−diones **4a** and **4b** were obtained in these cases as the only isolable compounds. We believe that under the catalytic acid conditions the highly activated tertiary alkynols **1h** and **1i** undergo an isomerization into the corresponding α,β-unsaturated ketone **5a** or aldehyde **5b**, respectively (Meyer−Schuster rearrangement).[12] These carbonyl derivatives undergo aldol-type condensation with diketones **2** to afford the final isolated compounds **4** (Scheme 1).[13]

Interestingly, we found that the presence of a substituent at the active methylene position of β-diketones, such as in **2d**, **2e**, and **2g**, gave rise to substitution reactions with tertiary alkynols **1h** and **1i** (Table 2) under PTS catalysis. However, in these cases, a regioselective allenylation reaction took place affording allene derivatives **6** in moderate to good yields. These results seem to indicate that all these reactions

(5) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem.−Eur. J.* **2005**, *11*, 1433 and references therein.

(6) Ohri, R. V.; Radosevich, A. T.; Hrovat, J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, F. D. *Org. Lett.* **2005**, *7*, 2501 and references therein.

(7) Georgy, M.; Boucard, V.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

(8) Zhan, Z.-p.; Yang, W.-z.; Yang, R.-f.; Yu, J.-l.; Li, J.-p.; Liu, H.-j. *Chem. Commun.* **2006**, 3352.

(9) As known, 1,3-dicarbonyls compounds are good ligands for a broad range of metals. So, we speculate that the complexation between the metal center and the dicarbonyl derivative could inhibit the reaction in some cases. Nevertheless, for the Ru-catalyzed coupling of ketones with terminal alkynols, see: Nishibayashi, Y.; Wakiji, I.; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393.

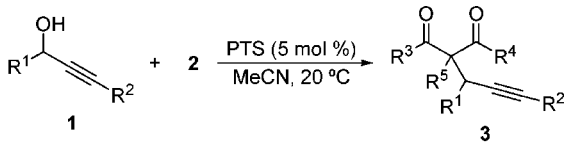
(10) Generally, the reactions are slow at room temperature (1−12 h), whereas at reflux shorter reaction times (0.5−3 h) were required for complete conversions. See Supporting Information for details.

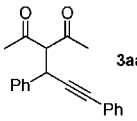
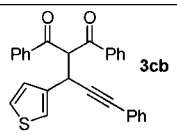
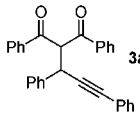
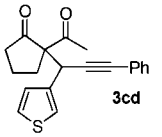
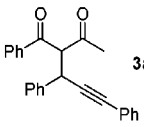
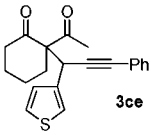
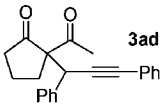
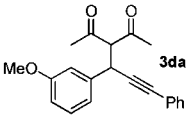
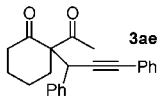
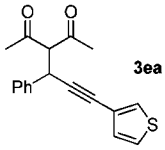
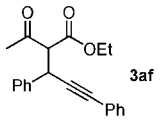
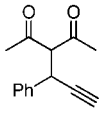
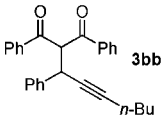
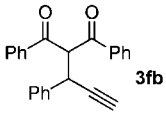
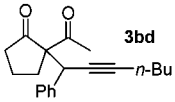
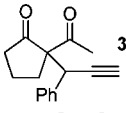
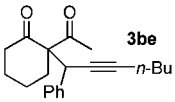
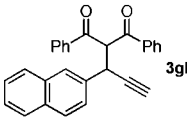
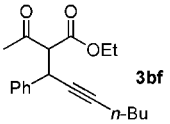
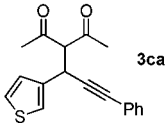
(11) The presence of a cation-stabilizing aryl-type substituent at the propargylic position seems to be necessary for the success of the reaction. An alkyl-substituted propargylic alcohol, such as 1-cyclohexyl-3-phenyl-2-propyn-1-ol, failed to react under the standard conditions.

(12) We have previously observed this Meyer−Schuster rearrangement with these tertiary alkynols and heteroatom-centered nucleophiles: Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383.

(13) Similar tandem isomerization/condensation processes have been reported under ruthenium catalysis: (a) Onodera, G.; Matsumoto, H.; Nishibayashi, Y.; Uemura, S. *Organometallics* **2005**, *24*, 5799. (b) Cadierno, V.; Díez, J.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Adv. Synth. Catal.* **2006**, *348*, 2125. As suggested by a referee, an alternative mechanism may involve allenylation of the diketone followed by isomerization to the conjugated diene.

Table 1. Reactions of Propargylation of β-Dicarbonyl Compounds **2** with Alkynols **1**[a]

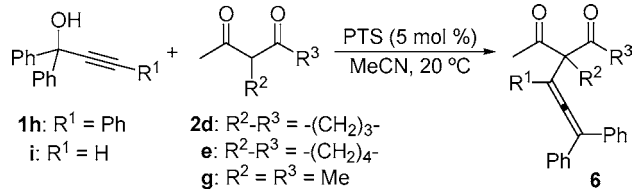


entry	1	R^1	R^2	2	product	yield (%)[b,c]	entry	1	R^1	R^2	2	product	yield (%)[b,c]
1	**1a**	Ph	Ph	**2a**	 **3aa**	88 (82)[d] (92)[e]	12	**1c**	3-Th[g]	Ph	**2b**	 **3cb**	90
2	**1a**	Ph	Ph	**2b**	 **3ab**	93	13	**1c**	3-Th[g]	Ph	**2d**	 **3cd**	89[f,h]
3	**1a**	Ph	Ph	**2c**	 **3ac**	75[f]	14	**1c**	3-Th[g]	Ph	**2e**	 **3ce**	85[f,h]
4	**1a**	Ph	Ph	**2d**	 **3ad**	60[f]	15	**1d**	3-$MeOC_6H_4$	Ph	**2a**	 **3da**	76
5	**1a**	Ph	Ph	**2e**	 **3ae**	66[f]	16	**1e**	Ph	3-Th[g]	**2a**	 **3ea**	64
6	**1a**	Ph	Ph	**2f**	 **3af**	54	17	**1f**	Ph	H	**2a**	 **3fa**	50[i]
7	**1b**	Ph	*n*-Bu	**2b**	 **3bb**	87	18	**1f**	Ph	H	**2b**	 **3fb**	77[i]
8	**1b**	Ph	*n*-Bu	**2d**	 **3bd**	86[f]	19	**1f**	Ph	H	**2d**	 **3fd**	43[f,i]
9	**1b**	Ph	*n*-Bu	**2e**	 **3be**	76[f]	20	**1g**	2-Nf[j]	H	**2b**	 **3gb**	62[i]
10	**1b**	Ph	*n*-Bu	**2f**	 **3bf**	50							
11	**1c**	3-Th[g]	Ph	**2a**	 **3ca**	74							

[a] Reaction conditions: **2** (1 mmol), **1** (1 mmol), PTS (0.05 mmol) in MeCN (5 mL) at room temperature or reflux (see Supporting Information). [b] Isolated yields based on starting alkynols **1**. [c] When it is the case, and unless otherwise stated, the ratio of diastereoisomers was ca. 1:1 (determined by ^{1}H NMR of the crude). [d] Carried out in the absence of solvent. [e] Carried out in a 15 mmol scale. [f] The two diastereoisomers were separated by column chromatography (see Supporting Information). [g] 3-Thienyl. [h] Ca. a 2:1 mixture of diastereoisomers. [i] Run at reflux. [j] 2-Naphthyl.

proceed through the formation of a cationic species, and the regioselectivity of nucleophilic trapping depends on the structure of **1**.[14] The formation of propargylic products such as **3** was highly sensitive to the nature of the starting alcohol, so for tertiary alkynols **1h** and **1i**, an allenyl-type cation was trapped by the nucleophile.

Table 2. Allenylation of Substituted 1,3-Diketones **2d**, **2e**, and **2g** with Tertiary Propargylic Alcohols **1h** and **1i**[a]



1h: R^1 = Ph
i: R^1 = H

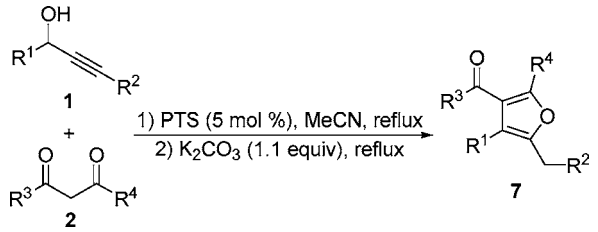
2d: R^2-R^3 = -$(CH_2)_3$-
e: R^2-R^3 = -$(CH_2)_4$-
g: R^2 = R^3 = Me

entry	alkynol	diketone	product	yield (%)[b]
1	**1h**	**2d**	**6a**	68
2	**1h**	**2e**	**6b**	53
3	**1h**	**2g**	**6c**	72
4	**1i**	**2d**	**6d**	61
5	**1i**	**2e**	**6e**	64
6	**1i**	**2g**	**6f**	50

[a] Reaction conditions: alkynol (1 mmol), diketone (1 mmol), PTS (0.05 mmol) in MeCN (5 mL) at room temperature (4 h for **1h** and 24 h for **1i**). [b] Isolated yields based on starting alkynols **1**.

Having successfully developed an efficient propargylation of β-dicarbonyl compounds, we finally turned our attention to the application of this methodology to the synthesis of highly substituted furans.[15] It should be remarked that the development of routes that allow the facile assembly of substituted furans under mild conditions from simple readily available starting materials remains an important objective.[16] Although there are many reports in the literature about the cyclization of alkynes with enolizable β-dicarbonyls mainly under transition metals or base catalysis,[17] most of them give rise to 2,3,5-trisubstituted furans[18] due to the difficulty in accessing 2-propynyl-1,3-dicarbonyl compounds substituted at the propargylic position. So, reaction of alkynols **1** with β-dicarbonyl derivatives **2** and a catalytic amount of PTS followed by addition of potassium carbonate allows the synthesis of functionalized furans **7** in moderate to good yields (Table 3). Thus, a straightforward one-pot procedure

Table 3. Application of the Propargylation of 1,3-Dicarbonyls to the Synthesis of Functionalized Furans **7**



entry	**1**	R^1	R^2	**2**	R^3	R^4	product	yield (%)[a]
1	**1a**	Ph	Ph	**2a**	Me	Me	**7a**	70
2	**1a**	Ph	Ph	**2b**	Ph	Ph	**7b**	75
3	**1a**	Ph	Ph	**2f**	OEt	Me	**7c**	45
4	**1b**	Ph	*n*-Bu	**2a**	Me	Me	**7d**	52
5	**1c**	3-Th[b]	Ph	**2a**	Me	Me	**7e**	78

[a] Isolated yields based on starting alkynols **1**. [b] 3-Thienyl.

for the synthesis of tetrasubstituted furans has been developed from simple starting materials, using only a catalytic amount of a Brønsted acid and an inorganic base.

In summary, we have presented the first examples of Brønsted acid catalyzed nucleophilic substitution of propargylic alcohols with active methylene and methine 1,3-dicarbonyl compounds. The protocol is operationally simple and generates only H_2O as a side product. In many cases, due to the easier availability of alcohols with respect to halides, the method may favorably compete with the more classical halide-based methodologies under basic conditions. Moreover, we have developed a simple strategy for the synthesis of polysubstituted furans by using the Brønsted acid catalyzed nucleophilic substitution as the key step.

Acknowledgment. We gratefully thank Junta de Castilla y León (BU012A06) and Ministerio de Educación y Ciencia (MEC) and FEDER (CTQ2004-08077-C02-02/BQU) for financial support. D.M. and A.M. thank MEC for FPU predoctoral fellowships. J.M.A.-G. and F. R. are grateful to MEC and the Fondo Social Europeo ("Ramón y Cajal" contracts).

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

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(14) A similar tendency was observed in the Lewis acid catalyzed nucleophilic substitution of propargylic silyl ethers: Ishikawa, T.; Aikawa, T.; Mori, Y.; Satio, S. *Org. Lett.* **2003**, *5*, 51 and references therein. As suggested by a referee, an alternative mechanism for the formation of the allenyl derivatives may involve initial capture of the propargylic cation by the enol form of the 1,3-diketone and subsequent Claisen rearrangement of the propargylic enol ether. However, we have never observed O-alkylated products in any of the reactions.

(15) These compounds play an important role as structural elements of many natural and pharmaceutically important substances: Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Elsevier: Oxford, 1997; Vol. 2, pp 395−436.

(16) For recent reviews about the synthesis of polysubstituted furans, see: (a) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850. (b) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076.

(17) See, for instance: (a) Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037. (b) Wipf, P.; Soth, M. J. *Org. Lett.* **2002**, *4*, 1787. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Tetrahedron* **2003**, *59*, 4661. (d) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679.

(18) For alternative syntheses of tetrasubstituted furans, see, for instance: (a) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (b) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645. (c) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (d) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (e) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.