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Zn(II)/Amine-Catalyzed Coupling Reaction of Alkylidenemalonates with Propargyl Alcohol: A One-Pot Synthesis of Methylenetetrahydrofurans

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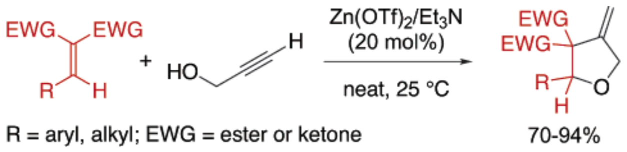
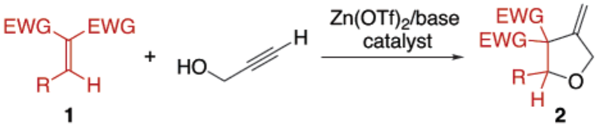
ABSTRACT



A metal-catalyzed tandem 1,4-addition/cyclization between propargyl alcohol and a Michael acceptor, such as alkylidene malonate, has been developed. In the presence of catalytic amounts of zinc triflate [$Zn(OTf)_2$] and triethylamine (Et_3N), various 2-alkylidene-1,3-dicarbonyl compounds reacted with propargyl alcohol to give 3- or 4-methylene tetrahydrofurans in excellent yields.

Owing to their widespread occurrence in nature, as well as their breadth of biological activity, oxygen heterocycles have attracted considerable attention among organic chemists.[1] Among the different methods developed during recent years for constructing highly substituted tetrahydrofurans, free radical[2] and metal-mediated cyclizations[3] have emerged as powerful tools to access this class of compounds. Balme and co-workers recently reported a Li/Pd-mediated approach to highly functionalized 3-methylene tetrahydrofurans from a propargylic alcohol and a Michael acceptor.[4]

During our ongoing research on the carbometalation reaction of metal enolates,[5] we found that zinc and indium salts[5a] catalyze the addition of active methylene compounds to nonactivated alkynes.[6] In this Letter, we report a zinc-catalyzed tandem 1,4-addition/cyclization of 2-alkylidene-1,3-dicarbonyl compounds and propargyl alcohol (eq 1). The reaction possesses the following synthetic features: (1) high yield, (2) mild conditions, (3) simple operation, (4) nontoxic and cheap metal catalyst, (5) no requirement of solvent, and no waste production.



1 2 (1)

Our initial survey of zinc catalysts showed that $Zn(OTf)_2$ is the optimal catalyst in terms of conversion and yield,

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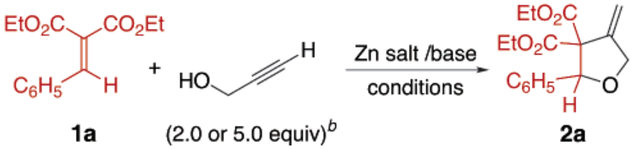
Table 1. Effect of Catalyst, Base, and Solvent on the 1,4-Addition/Cyclization of a Michael Acceptor with Propargyl Alcohol[a]



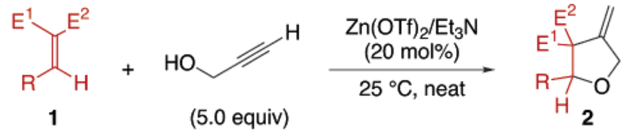
entry	Zn salt	base	conditions temp, time, solvent	% yield[c]
1	$Zn(OTf)_2$	Et_3N	70 °C, 15 h, THF	92
2	$Zn(OTf)_2$	Et_3N	25 °C, 15 h, THF	0
3	$ZnCl_2$	Et_3N	70 °C, 15 h, THF	0
4	$ZnBr_2$	Et_3N	70 °C, 15 h, THF	3[d]
5	ZnI_2	Et_3N	70 °C, 15 h, THF	3[d]
6	Et_2Zn	-	70 °C, 15 h, THF	0
7	$Zn(OTf)_2$	Et_3N	25 °C, 12 h, neat	93
8	$Zn(OTf)_2$ (10 mol%)	Et_3N (10 mol%)	25 °C, 12 h, neat	76[d]
9	$Zn(OTf)_2$	DABCO	25 °C, 12 h, neat	90
10	$Zn(OTf)_2$	DBU	25 °C, 12 h, neat	91
11	$Zn(OTf)_2$	proton sponge	25 °C, 12 h, neat	92

[a] The reaction was performed by the addition of **1a** (1 mmol) to a mixture of $Zn(OTf)_2$ (20 mol %), a base (20 mol %), and propargyl alcohol under the conditions described in the text unless otherwise noted. [b] Two equivalents of propargyl alcohol was used in entries 1−6, and 5 equiv of propargyl alcohol was used in entries 7−11. [c] Isolated yield. [d] NMR yield determined with 1,1,2,2-tetrachloroethane as an internal standard.

whereas an elevated temperature was required to achieve reasonable reaction rate (entries 1 and 2, Table 1). Thus, a mixture of olefin **1a** and propargyl alcohol (1:2 mole ratio) was refluxed in THF in the presence of 20 mol % $Zn(OTf)_2$ and 20 mol % Et_3N to give the desired product **2a** in 92% yield. On the other hand, the use of $ZnCl_2$, $ZnBr_2$, ZnI_2, and Et_2Zn resulted in low yield or no reaction (entries 3−6).

In the course of the optimization study, we eventually found that the reaction takes place around room temperature in the absence of solvent (entries 7−11).[7] Although the use of a large excess of propargyl alcohol (5 equiv) is required to achieve smooth conversion of the substrate, unreacted propargyl alcohol can be recovered quantitatively. Reduction of the amount of the catalyst slowed the reaction (entry 8). As shown in entries 9−11, any common base gave the desired product in equally good yield.[8] We thus used the $Zn(OTf)_2/Et_3N$ catalyst system for further investigation.[9]

Table 2. Reaction of Propargyl Alcohol with Various Michael Acceptors[a]



entry	olefin (E^1, E^2, R)	product	% yield[b]
1	**1a** (CO_2Et, CO_2Et, C_6H_5)	**2a**	93
2	**1b** (CO_2Et, CO_2Et, 4-MeC_6H_4)	**2b**	90
3	**1c** (CO_2Et, CO_2Et, 4-ClC_6H_4)	**2c**	90[c]
4	**1d** (CO_2Et, CO_2Et, 4-BrC_6H_4)	**2d**	93[c]
5	**1e** (CO_2Me, CO_2Me, C_6H_5)	**2e**	88
6	**1f** (CO_2Me, CO_2Me, 4-ClC_6H_4)	**2f**	91[c]
7	**1g** (CO_2Et, CO_2Et, C_9H_{19})	**2g**	94
8	**1h** (CO_2Et, CO_2Et, *i*-C_3H_7)	**2h**	90
9	**1i** (COMe, COMe, 4-$CH_3C_6H_4$)	**2i**	70[d]
10	(*Z*)-**1j** (COMe, CO_2Et, 4-$CH_3C_6H_4$)[e]	**2j**	84[f]
11	(*E*)-**1j** (CO_2Et, COMe, 4-$CH_3C_6H_4$)	**2j**	86[f]

[a] The reaction was carried out on a 1-mmol scale under the conditions described in ref 8 (25 °C, 12 h) unless otherwise noted. [b] Isolated yield. [c] The reaction time was 9 h. [d] The reaction time was 48 h at 0 °C. [e] A single geometrical isomer was used. [f] A mixture of diastereomers (*cis*/*trans* = 1: 2) was obtained.

Having identified the best conditions, we explored the scope of the reaction, and the results are summarized in Table 2.[10] With a variety of benzylidene malonate derivatives, the present reaction generates 4-methylenetetrahydrofurans with good yields. As shown in entries 1−4 in Table 2, both electron-rich and -poor benzylidene derivatives gave the products **2a**−**d** in similar yields, while the electron-deficient substrates (**1c** and **1d**) showed reactivity slightly higher than that of the electron-rich substrate (**1b**) (entries 3 and 4 vs 2, Table 2). Methyl esters (**1e**, **1f**, and **1h**) take part in the reaction without ester exchange reaction (entries 5, 6, and 8 in Table 2).

Alkylidene malonates possessing a primary or secondary alkyl side chain (**1g** and **1h**) also reacted with propargyl alcohol to give 3-methylene tetrahydrofurans (**2g** and **2h**) in 94% and 90% yields, respectively (entries 7 and 8 in Table 2). While the reaction involving a 1,3-diketone substrate was not very clean at room temperature because of unidentified side reactions, the desired product was obtained more cleanly in 70% yield at 0 °C (entry 9). The 2-alkylidene-3-oxobutanoic acid ester **1j** was found to be more reactive than the diester substrates, and the desired product was obtained in good yields after 3 h at 25 °C (entries 10 and 11, Table 2). It should be noted that the reactions starting from *E* and

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(6) Selected examples of the addition of a carbonyl compound or related enolate species to unactivated alkynes or alkenes: (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527. (b) Karoyan, P.; Quancard, J.; Vaissermann, J.; Chassaing, G. *J. Org. Chem.* **2003**, *68*, 2256−2265. (c)Arisawa, M.; Akamatsu, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 789−790. (d) Lorthiois, E.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1997**, *38*, 89−94. (e) Kitagawa, O.; Suzuki, T.; Inoue, T.: Watanabe, Y., Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470, (f) Tsukada, N.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2477−2480.

(7) Other solvents were examined for the reaction of **1a** with propargyl alcohol under the conditions described in parentheses: **2a** was obtained in 43% yield (CH_2Cl_2, reflux, 15 h), 27% yield (methanol, reflux, 15 h), 42% yield (toluene, 80 °C, 15 h).

(8) Similar results were obtained with NaH and BuLi as base: **2a** was obtained in 77% yield (THF, reflux, 15 h) and in 99% yield (THF, reflux, 15 h).

(9) We have examined in vain this reaction in the presence of a variety of Lewis acids, such as $Mg(OTf)_2$, $In(OTf)_3$, $Cu(OTf)_2$, $Sn(OTf)_2$, $Yb(OTf)_3$.

(10) **Typical Procedure.** $Zn(OTf)_2$ (73 mg, 0.2 mmol) was placed in a dry Schlenk tube and dried in vacuo (0.05 mmHg) for 1 h with gentle heating (90−100 °C). The reaction vessel was allowed to cool to room temperature and filled with dry nitrogen. Propargyl alcohol (0.30 mL, 5 mmol) and triethylamine (29 μL, 0.2 mmol) were added sequentially. After stirring at 25 °C for 10 min, **1a** (0.25 g, 1 mmol) was added to the clear colorless solution. After 12 h **1a** was consumed completely.The reaction mixture was filtered through a plug of silica gel eluted by Et_2O. After removal of solvent, purification with silica gel chromatography gave **2a** as a colorless liquid (0.28 g, 93% yield).

Z geometrical isomers of **1j** gave the tetrahydrofuran **2j** as a diastereomixture of an identical ratio (1:2). We observed the isomerization of the starting olefins (*Z*)-**1j** and (*E*)-**1j** under the reaction conditions, which suggests the reversibility of the first 1,4-addition step.[11]

On the basis of the experimental results, we offer a mechanistic rationale for the present catalytic coupling reaction in Figure 1.[12] First, zinc alkoxide **A** forms by the reaction of propargyl alcohol with Et_3N and $Zn(OTf)_2$, and the resulting zinc alkoxide adds to the Michael acceptor **1**. The zinc enolate intermediate **B** must be reactive enough to undergo cyclization quickly, since we could never observe the initial 1,4-adduct. On the other hand, the reverse 1,4-addition must be even faster that the cyclization, and overall the equilibrium of the first stage favors the starting material side (vide supra). The intramolecular carbozincation of **B** followed by the protonation of alkenylzinc intermediate **C** furnishes the tetrahydrofuran product and regenerates the zinc alkoxide **A**.

In summary, we have developed a new synthesis of a series of 3-methylene tetrahydrofurans from propargyl alcohol and a variety of Michael acceptors. The present reaction proceeds under mild conditions and gives a variety of substituted 3-methylene tetrahydrofurans.

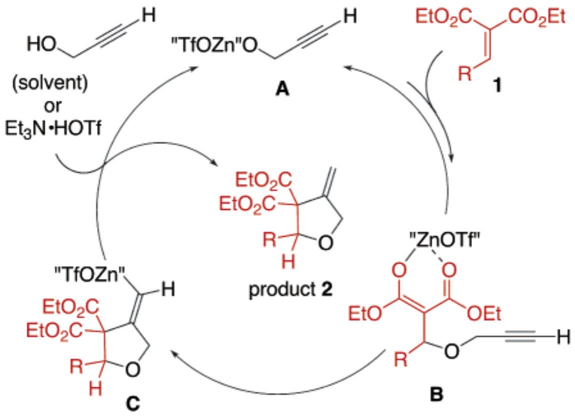

Figure 1. Possible catalytic cycle consisting of sequential 1,4-addition and carbozincation of zinc enolate to the terminal alkyne.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Judging from the ^1H NMR analyses of the aliquots of the reaction mixture in the course of the addition/cyclization reaction, the isomerization of **1j** is much faster than the production of **2j** under the reaction conditions. The assignment of the stereochemistry of the compounds was reported in ref 4a.

[12] “ZnOTf” is a possible counter cation, and it could be solvated by propargyl alcohol in the reaction system.