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Diethylene Glycol Serving as Ethyne Equivalent: A Sustainable Approach toward 2,3-Disubstituted Furan

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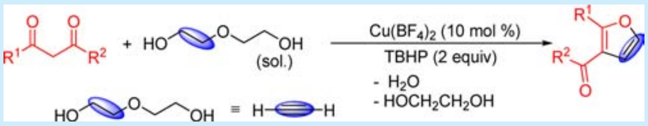
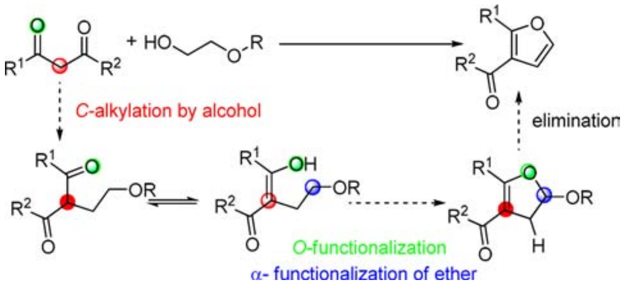
S *Supporting Information*

ABSTRACT: In the presence of *tert*-butyl peroxide (TBHP), the copper-catalyzed annulation of 1,3-dicarbonyl compound with diethylene glycol was developed leading to 2,3-disubstituted furan. Diethylene glycol serves as a cheap and environmentally friendly equivalent of ethyne, with the release of H_2O and alcohol as clean wastes. The procedure involves a sequential *O*- and *C*- functionalization of β-ketoester by diethylene glycol.



Sustainable chemistry is spurring the chemist to develop many important new types of C−C and C−hetero bond-forming reaction using alcohols because these represent renewable starting materials derived from biomass.[1] With these considerations in mind, we recently tested the feasibility of annulating 1,3-ketones with alcohols to construct the framework of furans (Scheme 1), which are ubiquitous natural and synthetic substances.[2]

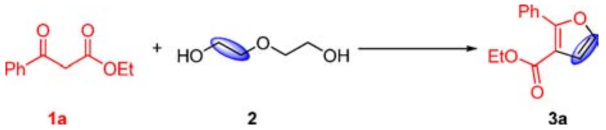
Scheme 1. Design Plan



Conceptually, the procedure may start with the α-alkylation of a 1,3-dicarbonyl compound by the alcohol.[3] Then α-functionalization of the second hydroxy takes place by *O*-functionalization of the 1,3-ketone to construct the framework of a 2*H*-furan.[4] Finally, the elimination of ROH will provide the 2,3-disubstituted furan. During the reaction, the waste is H_2O and ROH. Thus, an alcohol serves as a cheap, safe, reproducible, and environmentally friendly equivalent of ethyne.

Our study started by using the model reaction below. Phenylacetoacetic acid ethyl ester (0.5 mmol) and TBHP (*tert*-butyl hydroperoxide, 70% aqueous, 1.0 mmol) in neat diethylene glycol (1 mL) under N_2 were heated at 120 °C for 5 h. Disappointingly, catalysts such as I_2, Bu_4NI, $FeCl_2$, and $Fe(acac)_2$ all failed to work (Table 1, entries 1−4). To our delight, however, 2-phenyl-3-(ethoxycarbonyl)furan **3a** was isolated in 60% yield by using $Cu(OTf)_2$ as a catalyst (Table

Table 1. Selected Results for Screening the Optimized Reaction Conditions[a]



entry	catalyst	oxidant	solvent	yield[b] (%)
1	I_2	TBHP[c]		<1
2	Bu_4NI	TBHP[c]		<1
3	$FeCl_2$	TBHP[c]		<5
4	$Fe(acac)_2$	TBHP[c]		<1
5	$Cu(OTf)_2$	TBHP[c]		60
6	$Cu(OAc)_2$	TBHP[c]		<1
7	$Cu(NO_3)_2{\cdot}3H_2O$	TBHP[c]		40
8	$Cu(BF_4)_2$[d]	TBHP[c]		64 (71)[e] (62)[e,f] (49)[e,g]
9	$Cu(BF_4)_2$[d]	BPO		50
10	$Cu(BF_4)_2$[d]	DTBP		38
11	$Cu(BF_4)_2$[d]	TBHP[c]	PhCl[h]	37
12	$Cu(BF_4)_2$[d]	TBHP[c]	THF[h]	<5
13	$Cu(BF_4)_2$[d]	TBHP[c]	Cy-H[h]	59
14		TBHP[c]		<5
15	$Cu(BF_4)_2$[d]			<1

[a]Reaction conditions: **1a** (0.5 mmol), catalyst (10 mol %), oxidant (1.0 mmol) (TBHP = *tert*-butyl hydroperoxide, DTBP = di-*tert*-butyl peroxide, BPO = benzoyl peroxide), **2** (1.0 mL), at 120 °C under N_2 for 5 h, sealed tube. [b]Isolated yield. [c]TBHP (70% in water). [d]$Cu(BF_4)_2$ (45% in water). [e]100 °C. [f]Air. [g]O_2. [h]2.0 mL.

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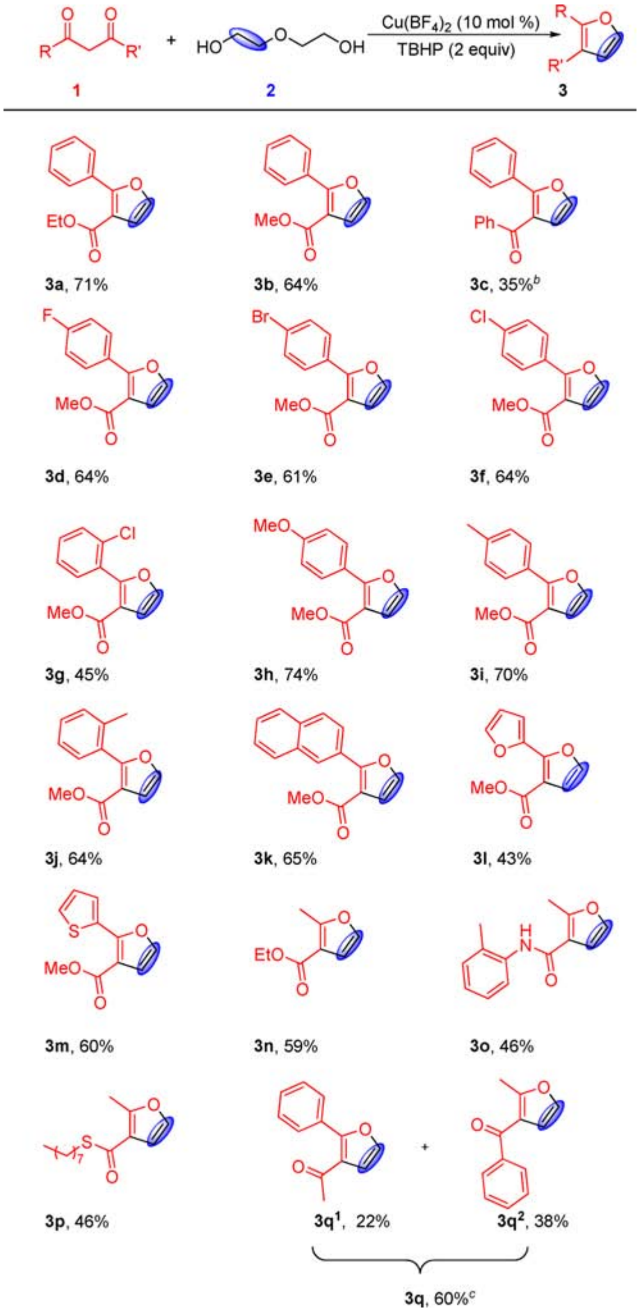
Table 2. Scope of Substrates[a]



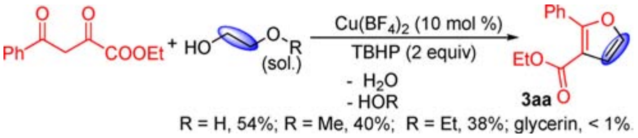
[a]Reaction conditions: **1** (0.5 mmol), Cu(BF$_4$)$_2$ (45% in water, 10 mol %), TBHP (70% in water, 1.0 mmol), **2** (1.0 mL), at 100 °C under N$_2$ for 5 h, sealed tube. [b]26 h. [c]10 h.

1, entry 5). Cu(OAc)$_2$ did not work in the procedure, while Cu(NO$_3$)$_2$·3H$_2$O provided the annulation product in 40% yield (Table 1, entries 6 and 7). Cu(BF$_4$)$_2$ (45% in water) was found to be the best choice producing a 64% yield of **3a** (Table 1, entry 8). The yield could be further increased to 71% by operating at 100 °C (Table 1, entry 8). Conducting the reaction under air or O$_2$ significantly decreased the yield (Table 1, entry 8). BPO (benzoyl peroxide) and DTBP (di-*tert*-butyl peroxide) worked to some extent (Table 1, entries 9 and 10). Solvents such as PhCl, THF, or cyclohexane all decreased the reaction efficiency (Table 1, entries 11−13). No reaction took place in the absence of either copper or peroxide (Table 1, entries 14 and 15).

After the optimal reaction conditions were identified, we studied the scope of the 1,3-dicarbonyl compounds that could be used, as shown in Table 2. As expected, all substrates reacted smoothly under the standard procedure. Importantly, the reaction was not limited to phenylacetoacetic acid ester, as ketone, amide, and thioester analogues all worked under the standard procedure. For example, **3c**, **3o**, **3p**, and **3q** were isolated in 35%, 46%, 46%, and 60% yields, respectively. The presence of bromo and chloro groups in the phenyl ring of phenylacetoacetic acid ester appeared to be tolerated well. These provide handles for further functionalization. The methyl in the *ortho*- position of the phenyl had no effect on the reaction since **3j** was isolated in 64% yield. Notably, heteroarylacetoacetic acid esters took part in the annulation reaction, providing **3l** and **3m** in 43% and 60% yields, respectively. Acetoacetic acid ethyl ester proved to be a good reaction partner with a 59% yield of isolated **3n**. In the case of 1-phenylbutane-1,3-dione, two isomers were isolated in a ratio of 1.7:1 and a total yield of 60%.

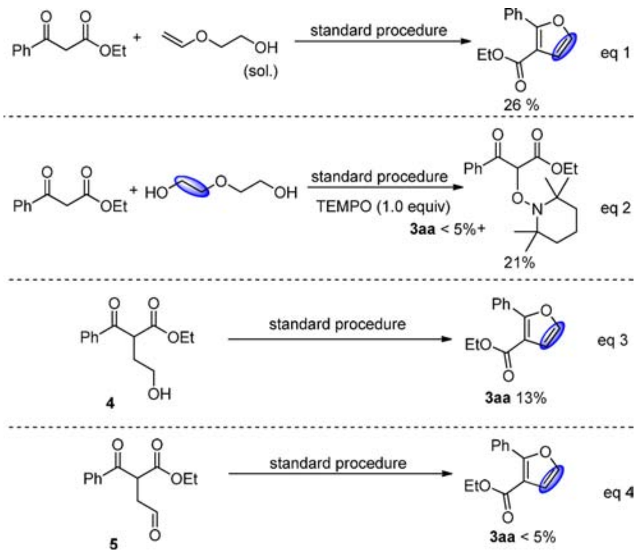
Notably, ethylene glycol, 2-methoxyethanol, and ethyl ether also served as equivalents of ethyne, providing the annulation products in 54%, 40%, and 38% yields, respectively (Scheme 2). However, glycerin failed to work in this procedure.

Scheme 2. Scope of Glycol and Its Derivatives



To obtain insights into the mechanism, more experiments were conducted. Recently, vinyl acetate and its analogues could serve as an ethyne equivalent in the annulation reactions.[5] Thus, we subjected 2-(vinyloxy)ethanol to the standard procedure. However, the annulation product was only isolated in 26% yield, which ruled out the possibility of having a vinyl alcohol ether as a reaction intermediate (eq 1, Scheme 3). Moreover, adding the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) inhibited the reaction, and the

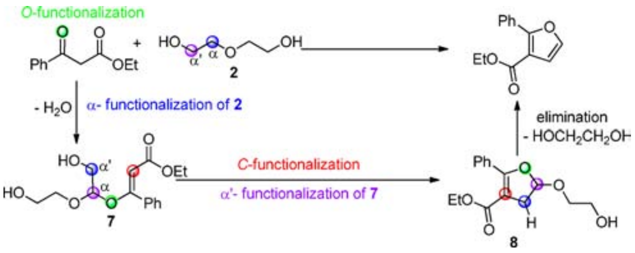
Scheme 3. Preliminary Mechanism Study



adduct of TEMPO radical with β-ketoester was isolated, indicating that a radical pathway may be involved in this transformation (eq 2). The potential intermediates **4** and **5** were prepared and subjected to the standard procedure. However, the yield of **3aa** was quite low (eqs 3 and 4). Thus, the path described in Scheme 1 was not possible.

On the basis of these experimental results, the tentative pathway of these reactions is outlined in Scheme 4. In step 1, the α-functionalization of the substrate **2** takes place at the O atom in the β-ketoester to produce intermediate **7**, along with the loss of 1 equiv of H_2O. In this case, a radical pathway may be involved as confirmed by the radical scavenger experiment, and copper took part in the single-electron-transferring (SET) process to fulfill this transformation.[6] After that, the C-functionalization occurs at the α'-position of intermediate **7** to afford intermediate **8**. Finally, the elimination of 1 equiv of $HOCH_2CH_2OH$ in intermediate **8** constructs the framework of furan.

Scheme 4. Plausible Reaction Pathway



In conclusion, a copper-catalyzed annulation of 1,3-dicarbonyl compound with diethylene glycol was developed, leading to 2,3-disubstituted furans. The procedure features the application of alcohols as renewable starting materials. Thus, it represents a sustainable pathway to access 2,3-disubstituted furans.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures along with copies of spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01521.

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Notes

The authors declare no competing financial interest.

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