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Copper-Catalyzed [4 + 1] Cycloadditions of α,β-Acetylenic Ketones with Diazoacetates to Form Trisubstituted Furans

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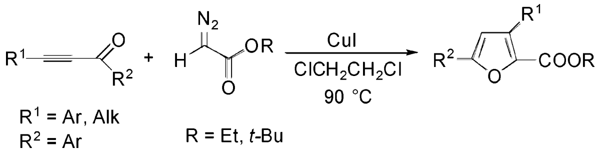


Copper-catalyzed [4 + 1] cycloaddition reaction of α,β-acetylenic ketones with α-diazo esters offers an efficient, direct route to highly substituted furans. The reaction conditions and the scope of the process are examined, and a possible mechanism is proposed.

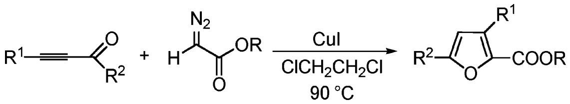
Highly substituted furans play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals[1] but also as useful building blocks for the total synthesis of complicated naturally occurring metabolites,[2] and as versatile starting materials for the preparation of a variety of heterocyclic and acyclic compounds.[3] For this reason, the efficient synthesis of multiply substituted furans continues to attract the interest of synthetic chemists.[4]

Diazo compounds have been extensively employed as a carbene source in organic synthesis.[5] This methodology has gained increasing interest in the past decade because of the use of transition-metal-based catalysts to promote and control the transfer of the CR^1R^2 unit to a plethora of organic substrates.[6]

In 1967, Spencer reported that $CuSO_4$ catalyzes the [4 + 1] cycloaddition of β-methoxy-α,β-unsaturated ketones with ethyl diazoacetate (EDA), leading to furans upon elimination of methanol from the presumed 2,3-dihydrofuran intermediate.[7] Since this pioneering work, there have been several other studies of copper-catalyzed reactions of enones with diazo compounds, but few of these investigations have explored the possibility of direct accessing polysubstituted furans.[8]

As part of our ongoing interest in developing methods for the preparation of highly substituted furans,[9] we herein wish to report for the first time that copper-catalyzed [4 + 1] cycloadditions of α,β-acetylenic ketones with diazoacetates can produce 2,3,5-trisubstituted furans in fair to good yields (Scheme 1).

SCHEME 1



We began the exploration of this cycloaddition process by surveying different potential catalysts[6] and solvents in the presence of 1,3-diphenylprop-2-yn-1-one (**1a**) and EDA (**2a**) (Table 1). Unfortunately, for the cycloaddition reaction of **1a** with EDA, copper(II) salts, such as $CuSO_4$, CuOTf, and $Cu(acac)_2$, were not effective (Table 1, entries 1−3). On the other hand, copper(I) salts were catalytically active in this cycloaddition reaction in 1,2-dichloroethane at 80 °C (entries 4−7). Among the tested copper salts, CuI was found to be the best catalyst, leading to 50% yield of desired polysubstituted furan **3aa** within 12 h at 80 °C (entry 5). In the reaction, starting

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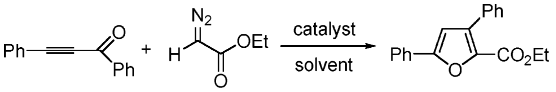
TABLE 1. Effect of Reaction Conditions on the Metal-Catalyzed [4 + 1] Cycloaddition Reaction of 1,3-Diphenylprop-2-yn-1-one (1a) with EDA (2a)[a]



1a **2a** **3aa**

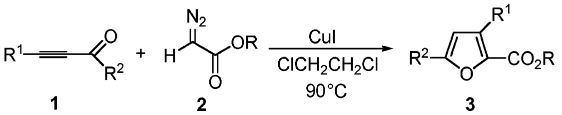
entry	catalyst	solvent	temp (°C)	yield[b] (%)
1	$Cu(acac)_2$	$ClCH_2CH_2Cl$	80	nr[c]
2	$CuSO_4$	$ClCH_2CH_2Cl$	80	nr
3	$Cu(OTf)_2$	$ClCH_2CH_2Cl$	80	nr
4	CuBr	$ClCH_2CH_2Cl$	80	30
5	CuI	$ClCH_2CH_2Cl$	80	50
6	$Cu(PPh_3)_3Br$	$ClCH_2CH_2Cl$	80	25
7	CuCl	$ClCH_2CH_2Cl$	80	37
8	CuI	THF	reflux	nr
9	CuI	CH_3CN	reflux	nr
10	CuI	toluene	80	20
11	CuI	CH_2Cl_2	reflux	nr
12	CuI	$ClCH_2CH_2Cl$	90	57
13	CuI	$ClCH_2CH_2Cl$	60	20
14	CuI	$ClCH_2CH_2Cl$	30	nr
15	CuI[d]	$ClCH_2CH_2Cl$	90	65
16	CuI[e]	$ClCH_2CH_2Cl$	90	18
17	CuI	MeOH	reflux	mixture
18	CuI	C_6H_6	reflux	28
19	$Rh_2(OAc)_4$	$ClCH_2CH_2Cl$	90	0
20	$Co(acac)_2$	$ClCH_2CH_2Cl$	90	0

[a] Reaction conditions: a solution of **2a** (3 equiv) in solvent (2.5 mL) was added via syringe pump over 5 h to a solution of **1a** (1 equiv) and [Cu] (10 mol %) in solvent (2.5 mL) with heating at the indicated temperature. The reaction mixture was stirred for an additional hour. [b] Isolated yields. All data are the average of two runs. [c] No reaction. [d] CuI (20 mol %). [e] CuI (2.5 mol %).

material **1a** was fully consumed and a complicated mixture of unidentified side products was recovered. The solvent effect on the cycloaddition reaction was then studied, and several trends were observed. Solvent plays a crucial role in this catalytic reaction. In all solvents we examined, 1,2-dichloroethane is superior to other solvents. The reactions performed in low polarity solvents such as toluene and benzene proceed in 20 and 28% yields, respectively (entries 10 and 18), but do not afford the desired product in acetonitrile, THF, or CH_2Cl_2 (entries 8, 9, and 11). When the solvent MeOH was employed instead of 1,2-dichloroethane, it gave a complicated mixture (entry 17). Furthermore, other transition metals were also investigated. However, for the cycloaddition reaction of **1a** with EDA, no desired product **3aa** was observed when the catalyst was replaced with $Rh_2(OAc)_4$ or $Co(acac)_2$ (entries 19 and 20).

Encouraged by the elementary results, we also studied the effects of temperature and catalyst loading on the efficiency of the reaction using the same reaction conditions. The studies revealed that the preferred temperature for the reaction was 90 °C, higher temperature had only a minor effect on the product yield, and lower temperature led to long reaction times and lower yields (entries 5, 12, and 13). When the reaction was conducted in 1,2-dichloroethane at 30 °C, no expected product was obtained, even when the reaction time was prolonged to 24 h (entry 14). Further screening demonstrated that the reaction proceeded well with 20 mol % of [CuI] in 1,2-dichloroethane at 90 °C (entry 15, 65% yield). However, the yield decreases to less than 20% after the catalyst loading is reduced to 2.5 mol % (entry 16).

TABLE 2. Scope for the Copper-Catalyzed [4 + 1] Cycloaddition Reaction of α,β-Acetylenic Ketones with Diazo Ester[a]



1 **2** **3**

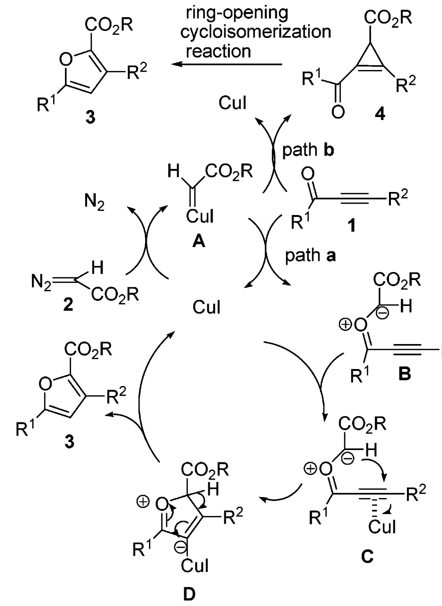
entry	substrate **1**	diazo ester **2**	product **3**	yield[b] (%)
1	**1a** (R^1 = Ph, R^2 = Ph)	**2a** (R= Et)	**3aa**	65
2	**1b** (R^1 = Ph, R^2 = 4-MeC_6H_4)	**2a**	**3ba**	66
3	**1c** (R^1 = Ph, R^2 = 4-ClC_6H_4)	**2a**	**3ca**	53
4	**1d** (R^1 = Ph, R^2 = 3-MeC_6H_4)	**2a**	**3da**	50
5	**1e** (R^1 = Ph, R^2 = 3-BrC_6H_4)	**2a**	**3ea**	35
6	**1f** (R^1 = Ph, R^2 = 2-ClC_6H_4)	**2a**	**3fa**	28
7	**1g** (R^1 = Ph, R^2 = 4-FC_6H_4)	**2a**	**3ga**	54
8	**1h** (R^1 = Ph, R^2 = 3,5-DiMeC_6H_3)	**2a**	**3ha**	70
9	**1i** (R^1 = 4-BrC_6H_4, R^2 = 4-MeC_6H_4)	**2a**	**3ia**	60
10	**1j** (R^1 = 4-BrC_6H_4, R^2 = 3,5-DiMeC_6H_3)	**2a**	**3ja**	81
11	**1k** (R^1 = Ph, R^2 = 2-$MeOC_6H_4$)	**2a**	**3ka**	62
12	**1l** (R^1 = n-C_5H_{11}, R^2 = 4-$MeOC_6H_4$)	**2a**	**3la**	46
13	**1m** (R^1 = 3-BrC_6H_4, R^2 = 4-MeC_6H_4)	**2a**	**3ma**	62
14	**1a** (R^1 = Ph, R^2 = Ph)	**2b** (R = *t*-Bu)	**3ab**	56
15	**1b** (R^1 = Ph, R^2 = 4-MeC_6H_4)	**2b**	**3bb**	57
16	**1c** (R^1 = Ph, R^2 = 4-ClC_6H_4)	**2b**	**3cb**	52

[a] Reaction conditions: a solution of diazo ester **2** (3 equiv) in $ClCH_2CH_2Cl$ (2.5 mL) was added via syringe pump over 5 h to a solution of α,β-acetylenic ketone **1** (1 equiv) and CuI (20 mol %) in $ClCH_2CH_2Cl$ (5 mL) with heating at 90 °C. The reaction was continued for about 5 h. [b] Isolated yields.

We next examined other α,β-acetylenic ketones to clarify the scope of this reaction. The results are listed in Table 2. α,β-Acetylenic ketones bearing either electron-rich or electron-withdrawing substituents reacted smoothly to give highly substituted furans in fair to good yields. When R^1 or R^2 was a phenyl with electron-donating groups such as OMe or Me, the yields of **3** were higher than those substrates with electron-withdrawing groups such as Br, Cl, or F (Table 2, entries 2 vs 3, 7 and 11 vs 6, and 4 vs 5). An α,β-acetylenic ketone that bears an alkyl group can also react with **2a** to afford the corresponding trisubstituted furan (entry 12). The position of a substituent on the α,β-acetylenic ketone also influences the yield of the reaction. *para*-Substituted α,β-acetylenic ketones usually give higher yields than do *meta*- or *ortho*-substituted ones (entries 2 vs 4 and 3 vs 6), but the reason for the negative effect of these substituents is unclear.

Various α-diazo esters were then utilized in the reaction. The cycloaddition reactions of *tert*-butyl diazoacetate yielded the corresponding products (entries 14−16), showing that the size of the R group of the diazo ester has a negligible effect on the reaction. In most of these reactions, small amounts of fumarate and malcate, the homocoupling products of diazo

SCHEME 2



compound, were observed. The prior decomposition of diazo compounds is a common reason for reduced yields involving carbenoids.[10]

We also conceived to extend the cycloaddition reaction to other diazo compounds. However, when the above reaction conditions were applied to CH_2N_2, TMS/diazomethane, $PhCHN_2$, and 1-(α-diazoglycyl)piperidine, the expected cycloaddition products were not obtained. Diazo compound decomposition occurred rapidly to give a complex mixture.

Although the NMR spectroscopic data support the formation of 2,3,5-trisubstituted furans **3**, the structure was unambiguously secured by an X-ray crystal structure analysis of compound **3aa**.[11]

Two mechanisms are plausible for the copper-catalyzed cycloaddition reaction (Scheme 2). In one (path **a**), first, the diazo ester **2** reacts with CuI to give the copper-stabilized carbene complex **A**.[5−7] Next, exposure of an α,β-acetylenic ketone **1** to a carbenoid **A** produced a carbonyl ylide **B**.[8a,12] Then, coordination of copper to the triple bond of the carbonyl ylide **B** (intermediate **C**) would make it subject to intramolecular nucleophilic attack to produce a zwitterion **D**. The latter undergoes a subsequent proton transfer to afford furan **3** with simultaneous regeneration of the CuI catalyst. An alternative mechanism is also possible (Scheme 2, path **b**). The copper-stabilized carbene complex **A** directly reacts with the triple bond to produce cyclopropenyl ketone **4**, then the CuI-catalyzed ring-opening cycloisomerization reaction of cyclopropenyl ketone **4** affords furan **3** and regenerates the catalyst CuI.[13] The mechanism illustrated in path **a** appears more likely since formation of carbonyl ylide **B** is very easy.[10b]

In conclusion, we have described the first examples of copper-catalyzed [4 + 1] cycloadditions of α,β-acetylenic ketones with diazo esters. This new method furnished synthetically useful, highly substituted furan derivatives in a direct, one-flask process with good efficiency and regioselectivity. Current studies are focused on further exploration of the substrate scope and synthetic utility of this methodology.

Experimental Section

Using 3ga as an Example. To a solution of α,β-acetylenic ketone (**1g**, 0.5 mmol) and CuI (0.1 mmol) in $ClCH_2CH_2Cl$ (5 mL) heated at 90 °C under argon was added a solution of a EDA (1.5 mmol) in $ClCH_2CH_2Cl$ via syringe pump over 5 h. Next, the reaction was heated at 90 °C with stirring for 5 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water and saturated brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography on silica gel to afford **3ga** (ethyl 5-(4-fluorophenyl)-3-phenylfuran-2-carboxylate): colorless crystals; mp 101−102 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82−7.78 (m, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.43−7.40 (m, 3H), 7.13 (dd, J = 8.4, 8.8 Hz, 2H), 6.78 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 163.17 (d, $^1J(CF) = 246$ Hz), 159.14, 154.91, 138.17, 136.45, 132.06, 129.31, 128.29, 127.97, 126.84 (d, $^3J(CF) = 8$ Hz), 125.73, 115.97 (d, $^2J(CF) = 21$ Hz), 109.08, 60.75, 14.17; IR (film) ν 2930, 1764 1709, 1641, 1545, 1492, 1453, 1419, 1390, 1231, 1178, 1110, 1023, 761, 695 cm^{-1}. Anal. Calcd for $C_{19}H_{15}FO_3$: C, 73.54; H, 4.87. Found: C, 73.59; H, 4.95. For characterization data of other compounds, see the Supporting Information.

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Supporting Information Available: Typical experimental procedure and spectral data of all products, and single-crystal X-ray crystallographic data for compound **3aa** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Crystal data for **3aa**: $C_{19}H_{16}O_3$, triclinic space group H-M $P\bar{1}$, MW = 292.32, $T = 294(2)$ K, wavelength 0.71073 Å, $a = 7.2161(12)$ Å, $b = 8.5279(13)$ Å, $c = 12.8078(19)$ Å, $\alpha = 76.386(7)°$, $\beta = 87.519(7)°$, $\gamma = 81.803(7)°$, $\upsilon = 758.2(2)$ Å^3, $Z = 2$, $D_{calcd} = 1.280$ mg/m^3, absorption coefficient = 0.086 mm^{-1}, $F(000) = 308$, crystal size 0.29 × 0.25 × 0.20 mm^3, reflections collected 4099, independent reflections 2777 [R(int) = 0.0167], refinement method, full-matrix least-squares on F^2, goodness-of-fit on $F^2 = 1.061$, Final R indices [$I > 2\sigma(I)$], $R_1 = 0.0408$, $wR_2 = 0.1010$, R indices (all data) $R_1 = 0.0577$, $wR_2 = 0.1128$, extinction coefficient = 0.023(4), largest diff. peak and hole 0.154 and −0.149 e·Å^{-3}.

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