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Copper-Catalyzed Multicomponent Reaction: Synthesis of 4-Arylsulfonylimino-4,5-dihydrofuran Derivatives

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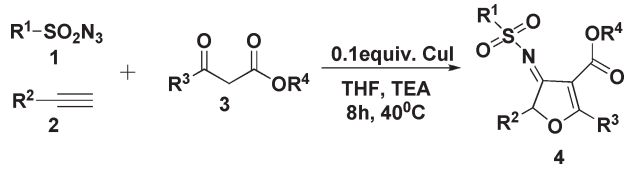

A series of 4-arylsulfonylimino-4,5-dihydrofurans (14 examples) were efficiently synthesized in good to excellent yields by using the copper-catalyzed three-component reaction between sulfonyl azides, phenylacetylene, and β-ketoesters in tetrahydrofuran (THF) at 40 °C for 8 h in the presence of triethylamine (TEA). A plausible mechanism for this process is proposed.

Dihydrofuran and furan derivatives are important heterocyclic compounds commonly found in a wide variety of naturally occurring substances and possessing a multiplicity of biological activities.[1] Among them, 4,5-dihydrofurans belong to an important class of compounds which show a wide range of biological activitaties and form the basic structure of many natural products, such as aflatoxins and so on.[2] The classical syntheses[3] for these compounds include the Diels–Alder reactions, condensations, and cross-coupling reactions. Among those, the metal-catalyzed processes using Pd,[4] Cu,[5] Ag,[6] Au,[7] and Ru[8] metals have been widely used for the synthesis of furan structure, which requires the tedious preparation of alkynones and allenones. On the other hand, the synthesis of highly functionalized dihydrofuran derivatives from simple compounds by using multicomponent reactions (MCRs) remains a challenge. And to the best of our knowledge, 4-arylsulfonylimino-4,5-dihydrofuran has never been reported.

Many MCRs show advantages in atomic economy, environmental friendliness, simplified steps, and efficient use of resources.[9] Among those, the Cu-catalyzed three-component reactions have been extensively used in organic synthesis. Recently, CuI-catalyzed[10] MCRs concerning sulfonyl azides and alkynes have drawn special interest. Chang et al.[11] and Wang's group[12] have used the Cu-catalyzed MCRs of sulfonyl azides and terminal alkynes for the efficient generation of *N*-sulfonylamidines, amides, *N*-sulfonylazetidin-2-imines, iminocoumarins, and 5-arylidene-2-imino-3-pyrrolines, and γ-nitro imidates by using the corresponding amines, water alcohol, imines, salicylaldehyde, aziridine, and nitroolefin as the third component, respectively.

Previously, we have developed an efficient synthesis of the benzoxazoline-amidine using a MCR of sulfonyl azides, alkynes, and Schiffs' base.[13] Herein, we report a novel pathway for the synthesis of highly substituted dihydrofuran

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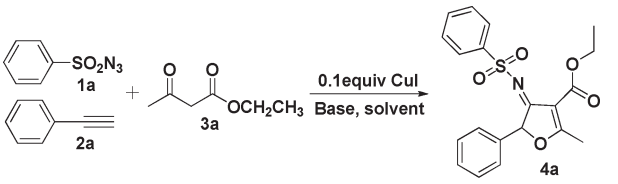
TABLE 1. The Optimal Reaction Conditions of CuI-Catalyzed Three-Component Reactions of Sulfonyl Azides, Phenylacetylene, and β-Ketoesters



entry	base	solvent	temp (°C)	time (h)	yield (%)[a]
1	TEA	THF	r.t.	8	45
2	TEA	THF	40	8	80
3	TEA	THF	60	8	81
4	TEA	THF	80	8	78
5	TEA	CH_2Cl_2	40	8	17
6	TEA	CH_3CN	40	8	70
7	TEA	toluene	40	8	68
8	TEA	DMF	40	8	54
9	pyridine	THF	40	8	51
10	K_3PO_4	THF	40	8	36
11	K_2CO_3	THF	40	8	32
12	TEA	THF	40	4	76
13	TEA	THF	40	6	78
14	TEA	THF	40	10	80

[a]Reaction conditions: **1a** (1.1 mmol), **2a** (1.0 mmol), **3a** (3.0 mmol), CuI (0.1 mmol), and TEA (2.0 mmol), N_2 atmosphere in a sealed tube.

derivatives via CuI-catalyzed three-component reaction with sulfonyl azide, phenylacetylene, and β-ketoester. To the best of our knowledge, no synthetic routes aimed at 4-arylsulfonylimino-4, 5-dihydrofuran derivatives have been reported.

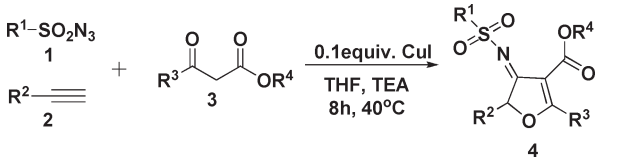
The optimized reaction conditions for our CuI-catalyzed three-component reaction of sulfonyl azide, phenylacetylene, and β-ketoester were obtained with benzenesulfonyl azide **1a**, phenylacetylene **2a**, and ethyl acetoacetate **3a** as the starting materials as shown in Table 1.

Solvent, base, and temperature were found to be able to greatly affect this reaction. Among those, base was found to be critical for this reaction. In the absence of an external base, no reaction was observed. In comparison with K_3PO_4, K_2CO_3, and pyridine, triethylamine (TEA) generally gave better yields. In comparison with commonly used solvents, such as CH_2Cl_2, CH_3CN, DMF, and toluene, THF gave better yields (Table 1, entries 5−11). The increase of the reaction temperature up to 40 °C also brought the increase of the yield (Table 1, entry 2). However, the further increase of the reaction temperature shows little effect on the yield (Table 1, entries 3 and 4). In THF, at 40 °C for 8 h, ethyl 2-methyl-5-phenyl-4-(phenylsulfonylimino)-4,5-dihydrofuran-3-carboxylate **4a** was obtained in 80% yield (Table 1, entry 2). Compound **4a**[14] was unequivocally confirmed by single-crystal analysis as shown in Figure S1 in the SI. Thus, THF was used as solvent, TEA was used as base, and the reaction temperature was set at 40 °C for the rest of the studies.

To test the versatility of this reaction, this optimized reaction condition was applied to the MCRs between various

(14) Crystallographic data for **4a**: space group $P\bar{1}$, a = 10.0868(8) Å, b = 15.8235(13) Å, c = 12.3174(10) Å, α = 90°, β = 99.1310(10)°, γ = 90°, V = 1941.0(3) Å^3, T = 293(2) K, Z = 4. Crystallographic data for compound **4a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-751364. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

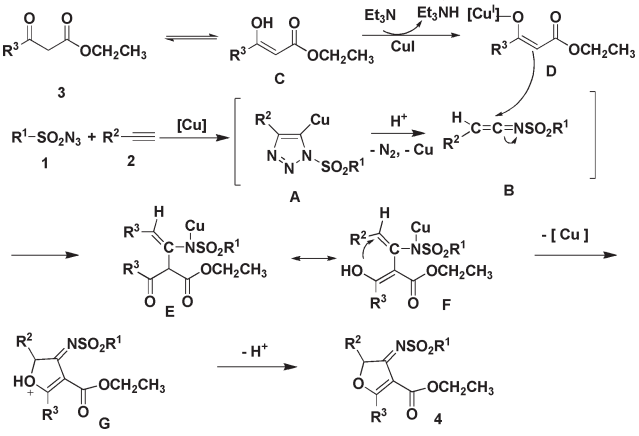
TABLE 2. CuI-Catalyzed Three-Component Reaction for the Formation of 4-Arylsulfonylimino-4,5-dihydrofuran Derivatives[a]



entry	R_1	R_2	R_3	R_4	yield (%) [a]
1	C_6H_5 (**1a**)	C_6H_5	CH_3	C_2H_5 (**3a**)	**4a**, 80
2	*p*-ClC_6H_4 (**1b**)	C_6H_5	CH_3	C_2H_5	**4b**, 82
3	C_6H_5	C_6H_5	CH_3	*n*-C_4H_9 (**3b**)	**4c**, 85
4	*p*-$CH_3C_6H_4$ (**1c**)	C_6H_5	CH_3	*n*-C_4H_9	**4d**, 82
5	*p*-ClC_6H_4	C_6H_5	CH_3	*n*-C_4H_9	**4e**, 87
6	C_6H_5	C_6H_5	C_6H_5	C_2H_5 (**3c**)	**4f**, 78
7	*p*-$CH_3C_6H_4$	C_6H_5	C_6H_5	C_2H_5	**4g**, 75
8	*p*-ClC_6H_4	C_6H_5	C_6H_5	C_2H_5	**4h**, 80
9	C_6H_5	C_6H_5	CH_3	$C_6H_5CH_2$ (**3d**)	**4i**, 75
10	*p*-$CH_3C_6H_4$	C_6H_5	CH_3	*n*-C_5H_{11} (**3e**)	**4j**, 82
11	C_6H_5	C_6H_5	CH_3	*n*-C_5H_{11}	**4k**, 84
12	*p*-ClC_6H_4	C_6H_5	CH_3	*n*-C_5H_{11}	**4*l***, 88
13	C_6H_5	C_6H_5	CH_3	*n*-C_7H_{15} (**3f**)	**4m**, 85
14	*p*-$CH_3C_6H_4$	C_6H_5	CH_3	*n*-C_7H_{15}	**4n**, 88
15	C_6H_5	*p*-$CH_3C_6H_4$	CH_3	C_2H_5	0
16	C_6H_5	*p*-$CH_3OC_6H_4$	CH_3	C_2H_5	0
17	C_6H_5	*n*-C_5H_{11}	CH_3	C_2H_5	0

[a]Reaction conditions: sulfonyl azide (1.1 mmol), phenylacetylene (1.0 mmol), β-ketoester (3.0 mmol), CuI (0.1 mmol), and TEA (2.0 mmol), N_2 atmosphere, 40 °C, 8 h in a sealed tube.

SCHEME 1. Possible Mechanistic Pathway Leading to the Highly Substituted Dihydrofurans 4



sulfonyl azides **1**, phenylacetylene **2**, and β-ketoester **3** as summarized in Table 2. Among various sulfonyl azides **1** investigated (Table 2, entries 1, 2, and 4), molecules with either electron-withdrawing groups (−Cl) or electron-donating groups ($-CH_3$) attached all provided high yields. Among various β-ketoester **3** investigated, when R_3 was an alkyl group, it often gave higher yields (Table 2, entries 5, 12, and 14). On the other hand, when R_3 was a phenyl group, it often gave slightly lower yields (Table 2, entries 6−8). The reaction was also limited to β-ketoesters. Use of β-dicarbonyl compounds as substrates did not afford the desired products. In comparison with phenylacetylene, when the substituted phenylacetylene and aliphatic terminal alkyne, such as *p*-methylphenylacetylene, *p*-methoxyphenylacetylene, and *n*-heptylacetylene,

were used for this reaction, no desired product was obtained (Table 2, entries 15−17).

A plausible mechanism for this three-component domino-like process is shown in Scheme 1. First, in the presence of CuI, sulfonyl azide **1** reacts with the alkyne **2** to form the ketenimine species **A**. Protonation of **A** leads to the formation of the highly reactive ketenimine **B**, which is quickly attacked by nucleophile **D** to generate the intermediate **E**. The subsequent intramolecular nucleophilic addition of dihydrofuran **F** followed by deprotonation generates 4,5-dihydrofuran **4**.

In conclusion, an efficient copper-catalyzed three-component reaction for the generation of a series of highly substituted dihydrofurans has been developed. The method provides an alternative synthetic route for the synthesis of 4-arylsulfonylimino-4,5-dihydrofuran derivatives in excellent yields.

Experimental Section

General Procedure for the Synthesis of 4-Arylsulfonylimino-4,5-dihydrofuran Derivatives. To a stirred mixture of CuI (19.1 mg, 0.1 mmol), benzenesulfonyl azide (219 mg, 1.2 mmol), phenylacetylene (102 mg, 1 mmol), and ethyl acetoacetate (309 mg, 3.0 mmol) in anhydrous THF (5 mL) was slowly added TEA (2 mL) via syringe under an N_2 atmosphere at 40 °C. The reaction mixture was stirred for 8 h in a sealed tube. Solvent was reduced under vacuum, then extracted with CH_2Cl_2 (3 × 10 mL). Organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (200−300 mesh) with ethyl acetate and petroleum ether (1:10−1:15) as eluting solvent to give the desired product.

Ethyl 4-(phenylsulfonylimino)-2-methyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (4a): white solid (80%), mp 136 °C; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.93 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.45−7.50 (m, 1H), 7.28−7.37 (m, 5H), 6.90 (s, 1H), 3.96 (q, J = 7.0 Hz, 2H), 2.47 (s, 3H), 1.20 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0, 156.8, 147.5, 138.6, 132.8, 128.8, 128.5, 128.2, 127.8, 125.4, 117.0, 111.4, 60.4, 14.3, 14.1 ppm; IR (KBr) ν 3234, 2974, 2904, 1689, 1627, 1585, 1571, 1492, 1440, 1406, 1382, 1342, 1327, 1251, 1230, 1174, 1136, 1101, 1016, 910, 866, 785, 767, 746, 694 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{19}NO_5S + H]^+$ 386.1062, found 386.1061.

Ethyl 4-(4-chlorophenylsulfonylimino)-2-methyl-5-phenyl-4,5-dihydrofuran-3-carboxylate (4b): white solid (82%), mp 147 °C; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.87 (d, J = 7.0 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.55−7.36 (m, 5H), 6.91 (s, 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 1.24 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ 163.2, 156.9, 147.8, 139.4, 137.1, 129.4, 128.7, 128.6, 128.3, 128.2, 125.5, 116.8, 60.6, 14.4, 14.1 ppm; IR (KBr) ν 3286, 3242, 2980, 2956, 2937, 2378, 2347, 1730, 1676, 1625, 1585, 1571, 1475, 1415, 1328, 1230, 1170, 1087, 1072, 831, 756, 696 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H1_8ClNO_5S + H]^+$ 420.0672, found 420.0675.

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products, and crystallographic information files for compound **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.