ORGANIC LETTERS

2011
Vol. 13, No. 21
5728–5731

Copper(I)-Catalyzed Three Component Reaction of Sulfonyl Azide, Alkyne, and Nitrone Cycloaddition/Rearrangement Cascades: A Novel One-Step Synthesis of Imidazolidin-4-ones

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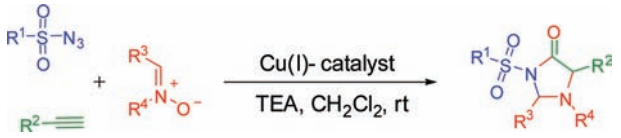
Received August 9, 2011

ABSTRACT



A novel one-pot azide−alkyne/ketenimine−nitrone cycloaddition sequence that is induced by copper(I) and allows the transformation of sulfonyl azides, alkynes, and nitrones to highly substituted imidazolidin-4-ones is described. The corresponding heterogeneous version utilizing Cu(I)-modified zeolites as recyclable heterogeneous catalysts shows marginally improved yield and diastereoselectivity.

In the context of sustainable chemistry, multicomponent cascade reactions have emerged as powerful strategies that allow multiple bond-forming events occurring in a single vessel and, as a consequence, significantly increase resource efficiency for the overall process. Such reactions have not only been sought after for their academic interest but also for their industrial relevance, owing to their high atom economy, selectivity, and low levels of byproduct generation.[1] In biological systems, concurrent cascade processes that integrate a series of individual catalyzed reactions in a continuous process are the most prevalent ones. Cascade processes involving one cycloaddition step are quite common; however, those engaging two or more cycloaddition reactions are rare,[2] especially when transition metals are involved.[3,4] Developing novel cascade reactions combining two cycloaddition steps that achieve the formation of multiple C−C and/or C-heteroatom bonds with stereocontrol and in a single operation is a particularly attractive strategy for the efficient construction of complex molecular architecture.

N-Sulfonylketenimine, a reactive intermediate derived from the Cu-catalyzed cycloaddition of sulfonyl azide and terminal alkyne, has recently been utilized for the synthesis of *N*-sulfonylamidines, amides, *N*-sulfonylazetidin-2-imines, iminocoumarins, and pyrrolines, tetrahydropyrimidines, dihydrofurans, indoles, pyrrolidinones, γ-nitroimidates, indolines, isoquinolines etc.,[5−7] mostly from the groups of Chang[6] and Wang.[7] Despite the advances, the search for unprecedented ketenimine-based multiple cascade reactions

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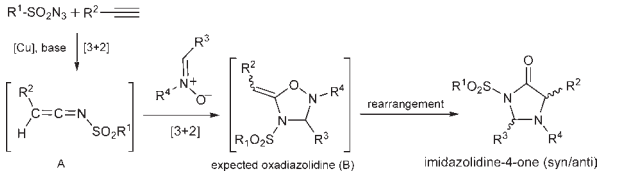
10.1021/ol202164x
Published on Web 10/12/2011

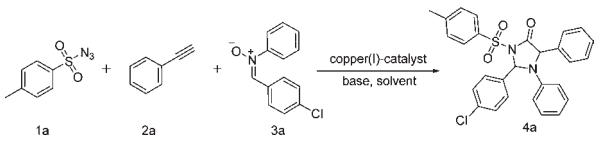
continues. In this context, use of nitrones as coupling partners in [3 + 2] reactions stands out as a powerful method for the construction of stereodefined heterocycles.[8,9] On this basis, we became interested in the possibility of using the above-mentioned *N*-sulfonylketenimine as a suitable dipolarophile to react with nitrones, and in doing so create multiple bonds, rings, and stereocenters in a single transformation. Herein, we report a successful execution of this idea and describe the Cu^{I}-catalyzed azide−alkyne [3 + 2] and ketenimine−nitrone [3 + 2] cycloaddition cascades (Scheme 1). Significantly, the cycloaddition sequence enables quick construction of heavily functionalized imidazolidin-4-ones in high yields with the generation of two new chiral centers with good diastereoselectivity under mild reaction conditions.

Scheme 1. Copper(I)-Catalyzed Azide−Alkyne/Ketenimine−Nitrone Cycloaddition Cascades to Imidazolidin-4-ones



In addition, imidazolidin-4-ones, and compounds of similar structures, constitute a widespread structural motif in natural products and pharmaceuticals.[10] Imidazolidin-4-one derivatives have shown wide range of biological activities,[11] such as antimalarial activity,[12] antiproliferative activity for melanoma,[13] in peptidomimetics,[14] as chiral auxiliaries for the synthesis of amino acids,[15] as an important chiral building block in the total synthesis of natural products,[16] and, most recently, as successful organocatalysts for a variety of asymmetric reactions.[17]

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	solvent	yield (%)[b] (syn/anti)[c]
1	CuI	TEA	DCM	78 (28:72)
2	CuCl	TEA	DCM	71 (27:73)
3	Cu^{I}−Y	TEA	DCM	85 (24:76)
4	Cu/Al-HT	TEA	DCM	trace
5	Cu^{I}−Y	DIPEA	DCM	63
6	Cu^{I}−Y	pyridine	DCM	48
7	Cu^{I}−Y	TEA	THF	60
8	Cu^{I}−Y	TEA	MeCN	52
9	Cu^{I}−Y	TEA	Toluene	49

[a] Reaction conditions: Sulfonyl azide (1 mmol), alkyne (1 mmol), nitrone (1 mmol), TEA (1.2 mmol), catalyst (20 mg), solvent (2 mL), rt, N_2, 3 h. [b] Isolated yield. [c] Diastereomeric ratio (syn/anti) was determined by ^{1}H NMR.

The copper(I)-catalyzed cascade process was standardized with tosyl azide **1a**, phenylacetylene **2a**, and C-4-chlorophenyl-*N*-phenyl nitrone **3a** in the presence of CuI and triethylamine (TEA) under N_2 atmosphere in dichloromethane (DCM). Instead of the anticipated oxadiazolidine (structure B, Schemes 1 and 4), to our surprise, the rearranged product namely imidazolidin-4-one was obtained in

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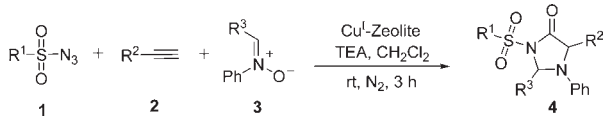
Table 2. Copper(I)-Y Zeolite Catalyzed Cascade Synthesis of Imidazolidin-4-ones[a]



1 2 3 4

entry	R^1	R^2	R^3	yield (%)[b]	(syn/anti)[c]
1	4-MeC_6H_4 (**1a**)	Ph (**2a**)	4-ClC_6H_4 (**3a**)	85	**4a** (24:76)
2	4-ClC_6H_4 (**1b**)	**2a**	**3a**	81	**4b** (14:86)
3	4-BrC_6H_4 (**1c**)	**2a**	**3a**	91	**4c** (13:87)
4	2-naphthyl (**1d**)	**2a**	**3a**	79	**4d** (16:84)
5	Ph (**1e**)	**2a**	**3a**	76	**4e** (26:74)
6	**1a**	4-MeC_6H_4 (**2b**)	**3a**	83	**4f** (13:87)
7	**1a**	1-cyclohexenyl (**2c**)	**3a**	85	**4g** (35:65)
8	**1a**	4-n-pentyl C_6H_4 (**2d**)	**3a**	0	
9	**1a**	**2a**	3-Cl, 4-ClC_6H_3 (**3b**)	82	**4h** (15:85)
10	**1a**	**2a**	Ph (**3c**)	77	**4i** (14:86)
11	**1a**	**2a**	Isovaleraldehyde (**3d**)	0	
12	**1a**	**2a**	4-MeC_6H_4 (**3e**)	88	**4j** (53:47)
13	**1a**	**2a**	4-$OMeC_6H_4$ (**3f**)	85	**4k** (62:38)
14	**1a**	**2a**	4-FC_6H_4 (**3g**)	90	**4l** (18:82)
15	**1a**	**2a**	2-FC_6H_4 (**3h**)	92	**4m** (1:99)
16	**1a**	**2a**	5-Mefurfuryl (**3i**)	84	**4n** (37:63)
17	**1a**	**2a**	3-$NO_2C_6H_4$ (**3j**)	89	**4o** (17:83)
18	**1a**	**2a**	4-$NMe_2C_6H_4$ (**3k**)	73	**4p** (63:37)

[a] Reaction conditions: Sulfonyl azide (1 mmol), alkyne (1 mmol), nitrone (1 mmol), TEA (1.2 mmol), Cu^I-zeolite (20 mg), DCM (3 mL), rt, N_2, 3 h. [b] Isolated yield. [c] Diastereomeric ratio (syn/anti) was determined by ^{1}H NMR.

78% yield (syn/anti ratio 28:72) after 3 h (Table 1, entry 1), while lesser yield of product was obtained in the case of CuCl (entry 2). However, our interest in heterogeneous catalysis[18] on the use of zeolites as solid supports/catalysts, a well-known approach to increase reactivity and selectivity, prompted us to use Cu(I)-modified zeolites, which were prepared according to a reported solid-state exchange procedure[19] and were characterized by powder XRD, XPS, EDX and HR-TEM (see Supporting Information). This cascade reaction proceeds quite efficiently with Cu^I-modified zeolites with higher yields and selectivity. In comparison with DIPEA and pyridine, TEA generally gave better yields. Besides DCM, other solvents such as MeCN, THF and toluene were also used and no significant improvement was observed (entries 5–9). The structure and stereochemistry of the product was unambiguously confirmed by single crystal X-ray analysis (see Supporting Information), which are in accordance with the ^{1}H NMR, and ^{13}C NM R spectra. Thus, the optimal conditions for this copper-catalyzed cascade process are use of Cu^I-modified zeolite as a catalyst and TEA as base in DCM under N_2 atmosphere for 3 h (entry 3).

A useful feature of this cascade reaction is that the building blocks can be readily varied. After initial catalyst and base and solvent screening, the reaction is also successfully extended to different combinations of azides, alkynes and nitrones. As depicted in Table 2, this reaction works very well for a wide range of substrates with good yields and selectivity. Among the various sulfonyl azides, electron-withdrawing groups (−Cl) as well as electron-donating groups (−CH_3) provided high yields. Phenylacetylene (**3a**) was highly reactive, usually giving high yields of adducts depending on the coreacting azide and nitrone (entries 1–6, and 14). *p*-Tolylacetylene and 1-ethynylcyclohexene were as effective as phenylacetylene (**3a**), giving the expected adducts in high yields. Among the nitrones, aryl- and heteroaryl aldehyde derived nitrones (entries 9, 10 and 12–18) are generally well tolerated in the cascade reactions. An interesting correlation between electronic effects of substituents in the aryl ring of nitrone and diastereoselectivity is noticed. In the case of electron-withdrawing groups, the anti isomer was obtained as the major product (entries 1–7, 9, 10, 14, 15, and 17). In fact, with 2-fluorobenzaldehyde derived nitrone, the anti isomer was formed almost exclusively (see Supporting Information). In contrast, the yield of the syn isomer is significantly enhanced with electron donating groups (entries 13 and 18).

While the present method has been shown to be effective for the synthesis of imidazolidin-4-ones from nitrones that bear an *N*-phenyl group, it was also of interest to study the reactivity of *N*-alkyl-substituted nitrone **5** (Scheme 2). Accordingly, 1-benzylimidazolidin-4-ones **4q** and **4r** were synthesized starting from *C*-phenyl-*N*-benzylnitrone, phenylacetelyne, tosyl azide and benzenesulfonyl azide with syn-isomer as

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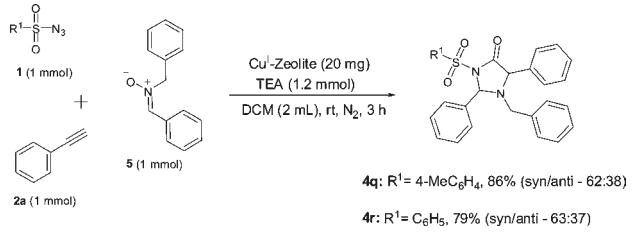
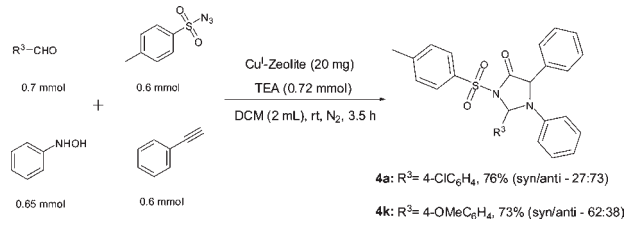
major product (as evident from proton NMR). The structure with syn-orientation was unambiguously confirmed by single crystal (after repeated recrystallizations) X-ray analysis.

Scheme 2. Copper(I)-Catalyzed Cascade Synthesis of Imidazolidin-4-ones from *N*-Benzylnitrones



This methodology was also extended to an one-pot sequential synthesis of imidazolidin-4-ones. To begin with, 4-chlorobenzaldehyde and phenylhydroxylamine were allowed to react in the presence of Cu^{I}-zeolite for 30 min. After the complete consumption of hydroxylamine (from TLC), tosyl azide, TEA and phenylacetylene were added. The overall process proceeded smoothly to afford the corresponding imidazolidin-4-one in slightly lower yields (Scheme 3). Meanwhile, the recovery and reuse of Cu^{I}-zeolite were also investigated, and the recovered catalyst exhibited a good activity up to 4 consecutive cycles (see Supporting Information).

Scheme 3. Copper(I)-Catalyzed One-Pot Synthesis of Imidazolidin-4-one from an Aldehyde, Phenylhydroxylamine, Tosyl Azide, and Phenylacetylene



A plausible mechanistic pathway for the present reaction cascade is depicted in Scheme 4. Sulfonyl azide **1** reacted readily with the terminal alkyne **2** in the presence of Cu^{I}–Y and Et_3N to give a ketenimine intermediate **A**, which then underwent a formal [3 + 2] cycloaddition with nitrone **3** to offer the oxadiazolidine **B** intermediate. Subsequent N–O cleavage[20] followed by diradical recombination generated diastereomeric mixtures of product **4**.

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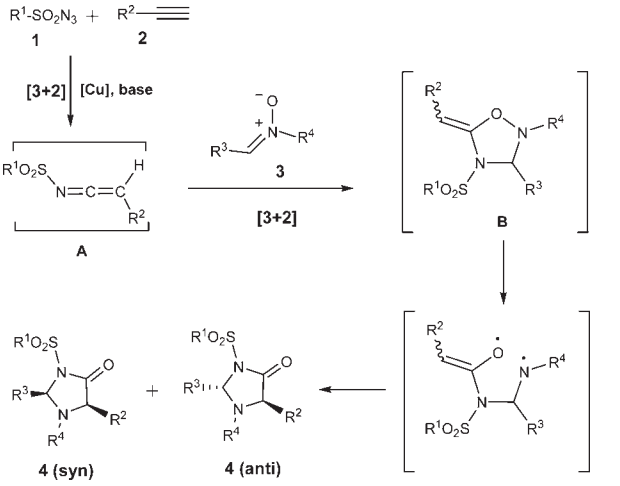
Scheme 4. Proposed Mechanistic Pathway



In conclusion, we have described a novel cascade reaction of nitrones with sulfonyl azides and alkynes mediated by copper(I) for the one-step synthesis of a diverse range of imidazolidin-4-ones. This reaction proceeds via sulfonyl azide–alkyne/ketenimine–nitrone double cycloaddition sequences, which are normally rare. The reported protocol involves nitrone as the cycloaddition partner, which was significant in itself, as the addition proceeds across C=N bonds of *N*-sulfonyketenimines, where additions to C=C bonds are most common. The use of a copper(I)-Y zeolite as a heterogeneous Cu(I) source allows for fast and simple isolation of the reaction products by simple filtration in addition to other advantages such as recyclability and minimization of metallic waste. Detailed studies on the mechanism and applications of nitrile oxides and nitrile imines as dipoles are underway.

Acknowledgment. We thank Department of Science and Technology (DST), New Delhi for financing under FIST and IRPHA facility.

Supporting Information Available. Experimental procedure, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products, and X-ray data for compound **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.