Synthetic Methods

DOI: 10.1002/anie.200503936

Copper-Catalyzed Reaction Cascade: Direct Conversion of Alkynes into *N*-Sulfonylazetidin-2-imines**

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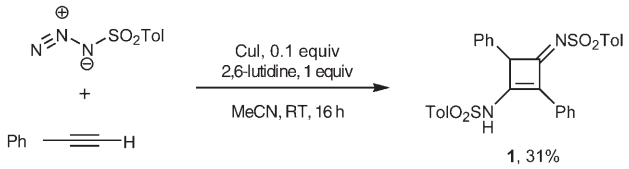
As part of our ongoing research into the discovery and development of highly efficient, versatile reactions,[1] and inspired by the success of the copper-catalyzed 1,3-dipolar cycloaddition reaction between terminal alkynes and azides,[2] we became interested in the unusual reactivity of copper(I) acetylides towards sulfonyl azides. This initially surprising reactivity is illustrated by their conversion into *N*-sufonylamidines when the reaction is conducted in the presence of amines[3] and *N*-acylsulfonamides in the presence of water.[4] Herein, we describe the direct, stereoselective conversion of alkynes to *N*-sulfonylazetidin-2-imines by the initial reaction of copper(I) acetylides with sulfonyl azides, followed, in situ, by the formal [2+2] cycloaddition of a postulated *N*-sulfonylketenimine intermediate with a range of imines.

We began our investigations by looking into the copper(I)-catalyzed reaction of phenylacetylene with *para*-toluenesulfonyl azide. With the expectation of forming the 1-sulfonyl-4-phenyl-1,2,3-triazole, the reaction was carried out in the absence of a nucleophile, under conditions that were known to promote dipolar cycloaddition between alkynes and alkyl or aryl azides.[2a] We were therefore surprised to find that the only isolated product was the cyclobutene derivative **1** (Scheme 1). The results of extensive NMR studies correlate with the proposed structure.

Compound **1** could result from the dimerization of an initially formed toluenesulfonylketenimine intermediate fol-



Scheme 1. Formation of ketenimine dimer **1**. Tol = *p*-tolyl.

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[**] We thank the National Institutes of Health, the National Institute of General Medical Sciences (GM28384), the Skaggs Institute for Chemical Biology, and Pfizer, Inc. for financial support. We also thank Prof. K. B. Sharpless for valuable advice and stimulating discussions.

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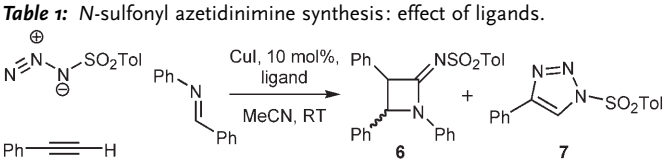
lowed by tautomerization, through a sequence proposed below. Initial cycloaddition of the copper acetylide and sulfonyl azide would give the (1-sulfonyl-4-phenyltriazol-5-yl)copper intermediate **2**. Direct elimination of dinitrogen, as previously reported for a range of 5-lithiated-triazoles,[5] would generate copper alkynamide **3**. Protonation of this species would then furnish the requisite sulfonylketenimine **4** with concomitant liberation of the copper catalyst. Alternatively the cuprated triazole **2** could undergo ring-chain isomerization, which is known to be rapid for electron-deficient triazoles, especially those with an electron-withdrawing group at N-1.[6] This route would give rise to the cuprated diazoimine **5**, which upon loss of dinitrogen and protonation would again generate the *N*-sulfonylketenimine **4** and regenerate the copper catalyst (Scheme 2).

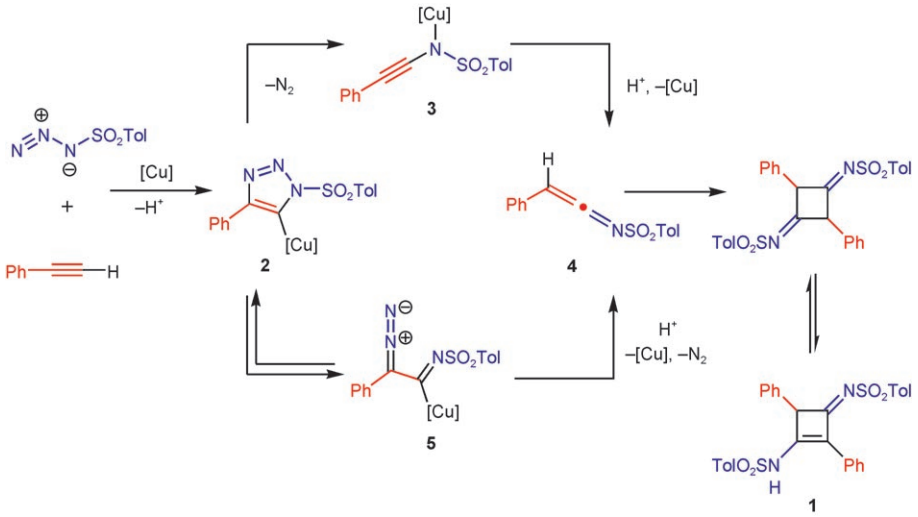
The isolation of **1** was significant in itself, as there are very few reports of ketenimine dimerization and all proceed across at least one of the cumulenic C=N bonds,[7] as opposed to both C=C bonds observed herein. Of greater synthetic interest was

Table 1: *N*-sulfonyl azetidinimine synthesis: effect of ligands.



Entry	Ligand[a]	*t* [h]	*trans*-**6**:*cis*-**6**:**7**[b]
1	2,6-lutidine	3	80:13:7
2	none	16	56:11:33
3	pyridine	3	95:5:0
4	2,6-di-*tert*-butylpyridine	16	45:10:45
6	neocuproine	no reaction	–
7	Et_3N	3	94:6:0
8	TMEDA	3	83:17:0[c]
9	TBTA[d]	< 2	42:58:0

[a] 1 equiv of ligand used. [b] Determined from the ^{1}H NMR spectra of the crude reaction product. [c] The oxidatively coupled di-alkyne was also observed. [d] 0.1 equiv of ligand used. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TBTA = tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.



Scheme 2. Possible mechanistic pathways leading to **1**.

absence of an added ligand and furnished an increased amount of triazole by-product (entry 2). The use of pyridine completely suppressed triazole formation and gave the desired azetidinimine as a 95:5 ratio of isomers in favor of the *trans* product (entry 3). A number of other ligands were screened, but all gave a reduction in the selectivity or the rate of reaction (entries 4–9). Interestingly TBTA,[10] a potent ligand for the Cu^I-catalyzed azide/alkyne cycloaddition, not only increased the rate of azetidinimine formation, but also reversed the selectivity, giving a slight excess of the *cis* isomer (entry 9). The observed dependence of the reaction selectivity upon the additive is not yet fully understood and is the subject of continued investigation. It does however imply that the amine, either itself directly or as a ligand for copper, is involved in promotion of the [2+2] process.

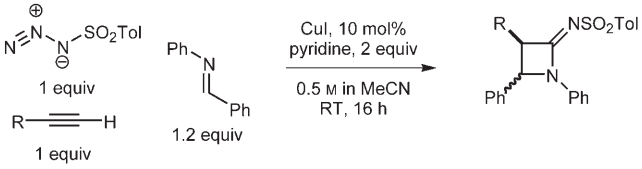
the possibility of capturing the *N*-sulfonylketenimine intermediates by alternative means. Ketenimines with *N*-alkyl or -aryl substituents are considerably less reactive than their oxygen analogues, ketenes, although they are still known to undergo a range of useful transformations,[7a,8] particularly in an intramolecular fashion.[7a] Introduction of an *N*-sulfonyl substituent leads to a marked increase in reactivity. For example, *N*-sulfonylketenimines have been shown by Ghosez and co-workers to readily undergo intermolecular Staudinger-type [2+2] cycloadditions with imines to furnish azetidinimines.[9]

We were pleased to find that carrying out the reaction in the presence of *N*-benzylideneaniline gave the expected azetidinimine product **6** as a 6:1 mixture of the *trans* and *cis* isomers, along with a small amount of the 1,4-disubstituted triazole **7** (Table 1, entry 1). The use of alternative ligands/bases in the reaction gave greatly altered selectivities. For example, the reaction proceeded much more slowly in the

Reducing the amount of pyridine resulted in a slight reduction in the stereoselectivity, while increasing it to two equivalents gave an even more selective reaction that furnished the azetidinimine with greater than 95:5 selectivity in favor of the *trans* isomer. With regard to the reaction solvent, more polar solvents tended to give reduced *trans*:*cis* selectivity, and less polar solvents generally required longer reaction times. None of those tested, however, were as efficient or resulted in as high a selectivity as acetonitrile. Under the optimal conditions (1 equiv sulfonyl azide, 2 equiv pyridine, 1 equiv alkyne, 1.2 equiv imine, 10 mol% CuI, RT, 16 h), **6** was obtained in 90% yield and in greater than 95% purity by simple dilution of the reaction mixture with 1M HCl and collection of the precipitated product by filtration (Table 2, entry 1).

A brief survey of the scope with regard to the alkyne component revealed that both alkyl and aryl alkynes gave the

Table 2: Synthesis of azetidinimines: scope with respect to the alkyne component.



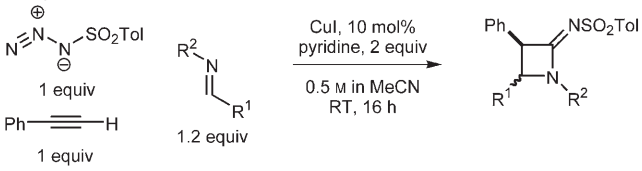
Entry	R	Yield [%][a]	*trans*:*cis*[b]
1	Ph	90	>95:5
2	4-BrC_6H_4	90	>95:5
3	2-$(CF_3)C_6H_4$	79	>95:5
4	4-$(MeO)C_6H_4$	69	90:10
5	3-Pyr	81	>95:5
6	Bn	62	92:8
7	$PhthCH_2$	60	>95:5
8	$CH_2Cl(CH_2)_2$	55	>95:5
9	$MeO_2C(CH_2)_3$	55	>95:5
10	TMS	48	25:75

[a] Yield of the isolated isomeric mixture. [b] Determined from the ^{1}H NMR spectra of the crude reaction product. Bn = benzyl, Phth = phthalimido, TMS = trimethylsilyl.

desired product, generally with high *trans* selectivity (Table 2). The electron-rich (*para*-methoxyphenyl)acetylene (entry 4) and 3-phenyl-1-propyne (entry 6) gave slightly reduced selectivities, and in the case of trimethylsilylacetylene the selectivity was reversed to give a 3:1 *cis*:*trans* ratio of products (entry 10), possibly as the silyl substituent promotes a more concerted [2+2] reaction that leads to a greater amount of the kinetic product. A wide range of functionality was accepted; however incorporation of nucleophilic groups tended to give mixtures of products arising from intra- or intermolecular nucleophilic trapping of the ketenimine intermediate.

We have also examined the scope with regard to the imine and the azide components (Tables 3 and 4, respectively). The reactivity of imines derived from electron-rich or -poor

Table 3: Synthesis of azetidinimines: scope with respect to the imine component.



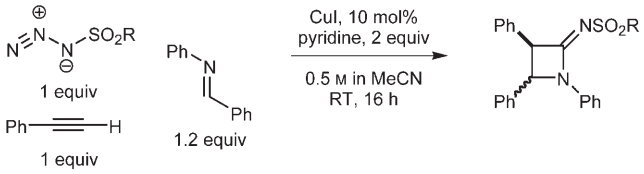
Entry	R^1	R^2	Yield [%][a]	*trans*:*cis*[b]
1	4-FC_6H_4	Ph	87	>95:5
2	4-$(MeO)C_6H_4$	Ph	79	>95:5
3	Ph	Bn	80	89:11
4	Ph	4-$(MeO)C_6H_4$	77	92:8
5	4-$(MeO_2C)C_6H_4$	4-$(MeO)C_6H_4$	73	86:14
6	4-$(TMSC{\equiv}C)C_6H_4$	4-$(MeO)C_6H_4$	65	77:23
7	Ph	SO_2Ph	ca. 5[b]	–
8	EtO_2C	Ph	53	<5:95
9	EtO_2C	4-$(MeO)C_6H_4$	63	<5:95

[a] Yield of isolated isomeric mixture. [b] Determined from the ^{1}H NMR spectra of the crude reaction product.

aromatic aldehydes appeared to be similar, and equally high selectivities were observed (Table 3, entries 1 and 2). Incorporation of the readily cleavable benzyl (entry 3) or *para*-methoxyphenyl (PMP, entry 4) groups on the nitrogen atom led to slightly reduced selectivities, with PMP being the more selective of the two. The use of more elaborate *N*-PMP imines gave rise to highly functionalized products in good yield, albeit with slightly reduced selectivities (entries 5 and 6). As expected, the electron-deficient benzylidenebenzenesulfonamide (entry 7) did not participate in the reaction, presumably because of the low nucleophilicity of its nitrogen atom. The use of aldimines and ketimines bearing α protons gave rise to alternative modes of reaction; however, imines derived from ethyl glyoxylate gave the desired products with inverted selectivity of <5:95 *trans*:*cis* (entries 8 and 9).

From our initial studies the reaction appears to be amenable to the use of a wide range of sulfonyl azides (Table 4). For example, the desired azetidinimines product

Table 4: Synthesis of azetidinimines: scope with respect to the sulfonyl azide component.

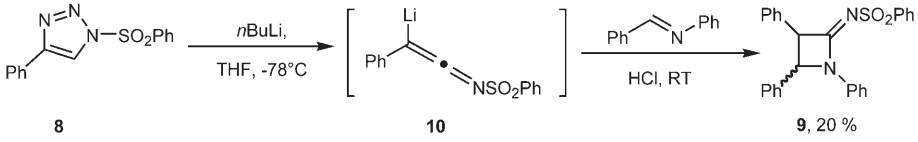


Entry	R	Yield [%][a]	*trans*:*cis*[b]
1	4-$(NO_2)C_6H_4$	63	>95:5
2	4-BrC_6H_4	77	>95:5
3	4-IC_6H_4	76	>95:5
4	Me	68	95:5

[a] Yield of isolated isomeric mixture. [b] Determined from the ^{1}H NMR spectra of the crude reaction product.

bearing a readily cleavable nitrobenzenesulfonyl (nosyl, Ns) group on the imino nitrogen atom was obtained from *p*-nitrobenzenesulfonyl azide with high selectivity (entry 1). The use of *para*-bromobenzenesulfonyl azide and *para*-iodobenzenesulfonyl azide gave equally selective conversion into the expected halogenated products (entries 2 and 3). The reaction also proceeded well when alkylsulfonyl azides were used (entry 4).

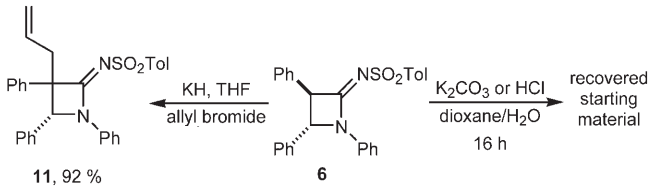
Further support for the proposed mechanism was obtained by conversion of the isolated 1-sulfonyltriazole **8** into the corresponding azetidinimine product **9** (the triazole **8** was isolated as a minor product (17%) from the reaction of benzenesulfonyl azide with phenylacetylene and *N*-benzylideneaniline, carried out in the presence of one equivalent of 2,6-di-*tert*-butylpyridine.[11]) Although **8** was stable when resubjected to the reaction conditions, metalation at the 5-position using *n*BuLi in THF resulted in the immediate extrusion of N_2, even at −78 °C, presumably with formation of the relatively stable metalated ketenimine **10**.[12] Addition of *N*-benzylideneaniline and one equivalent of anhydrous HCl gave rise to the azetidinimine product **9** which could be isolated in 20% yield as an 85:5 mixture of isomers favoring the *cis* product (Scheme 3).



Scheme 3. Conversion of 1-sulfonyl-4-phenyltriazole **8** into azetidinimine **9**.

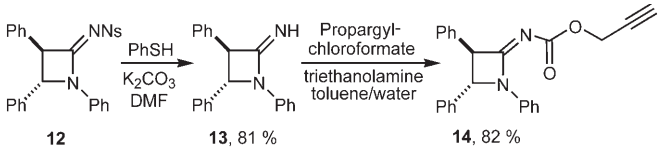
The sulfonyl azetidinimne products described above can be viewed as β-lactam analogues, and as such they have potential applications as therapeutic agents.[13] They are highly stable under acidic conditions: the starting material was quantitatively recovered after stirring in HCl (2 M, dioxane/water) overnight. Moderately basic conditions (K_2CO_3 in dioxane/water) did not cause any degredation either. However, prolonged exposure to KOH under similar conditions led to various hydrolysis products.

The stability of azetidinimines to a wide range of reaction conditions makes them valuable synthetic intermediates. Several examples of their selective functionalization (see below) illustrate their synthetic utility. Thus, deprotonation of **6** with KH followed by quenching with allyl bromide furnished **11** in 92% yield as a single diastereomer, presumably that with the *cis* configuration (Scheme 4).



Scheme 4. Acid/base stability and allylation of **6**.

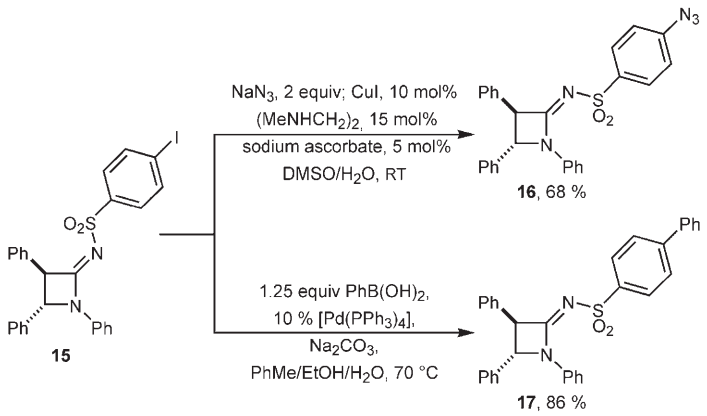
Cleavage of the *p*-Ns group[14] from **12** furnished the NH imine **13** which reacts readily with activated carbonyl compounds. For example, carbamate **14** was obtained in 66% yield over the two steps (Scheme 5).



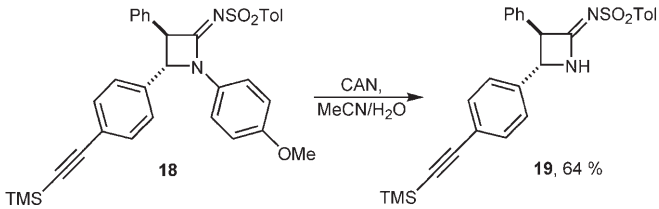
Scheme 5. Cleavage of the *p*-nitrobenzenesulfonyl (Ns) group and formation of a carbamate.

Aryl halide functionality can be easily converted into a range of alternative products. As an example, iodide **15** was converted into azide **16** by copper-catalyzed azidation,[15] or to the biaryl derivative **17** by using a Suzuki coupling with a boronic acid (Scheme 6).[16] 1*H*-Azetidinimines, such as **19**, are easily accessible from *N*-1-PMP derivatives (**18**) by treatment with ceric ammonium nitrate (CAN) (Scheme 7).[17]

In summary, we have developed an experimentally simple catalytic procedure for the highly selective conversion of alkynes into *N*-sulfonylazetidin-2-imines under mild conditions. This three component process is thought to proceed through the initial reaction of in situ generated copper(I) acetylides with sulfonyl azides to give transient (1-sulfonyltriazolyl)copper intermediates which, upon extrusion of dinitrogen, generate *N*-sulfonylketenimines. The azetidinimine products are remarkably stable to a wide range of reaction conditions and readily undergo further functionalization. This newly discovered reaction sequence rapidly constructs densely functionalized azetidine derivatives from readily available terminal alkynes in just one simple step and should prove useful for exploring the utility of these four-membered heterocycles.



Scheme 6. Further functionalization of **15**.



Scheme 7. Cleavage of the *N*-1-PMP group.

Received: November 7, 2005
Published online: March 29, 2006

Keywords: alkynes · azides · cycloaddition · homogeneous catalysis · small ring systems

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