

A Facile Access to *N*-Sulfonylimidates and Their Synthetic Utility for the Transformation to Amidines and Amides

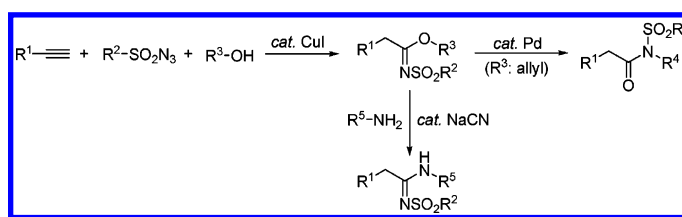
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ABSTRACT



It is shown that *N*-sulfonylimidates can be efficiently prepared by a three-component coupling of terminal alkynes, sulfonyl azides, and alcohols with use of a copper catalyst and an amine base. The reaction is characterized by mild conditions, high selectivity, and tolerance with various functional groups. Facile transformation of imidates to amidines was also achieved by sodium cyanide. Additionally, a protocol for the extremely efficient Pd-catalyzed [3,3]-sigmatropic rearrangement of allylic sulfonimides to *N*-allylic sulfonamides has been developed.

Inspired by nature, synthetic chemists endeavor to develop useful organic transformations with high efficiency and selectivity, wide substrate scope, easy product isolation, and modular approaches under mild conditions.¹ Catalytic multicomponent reactions (MCR) have served as a rapid and effective synthetic approach because they frequently offer complex molecules in a single operation with satisfaction of the criteria mentioned above.² Recently, we have disclosed novel reactivity of sulfonyl azides in Cu-catalyzed coupling reactions with a wide range of terminal alkynes and amines or water to give *N*-sulfonyl amido compounds such as amidines and amides, respectively, under mild conditions.³

Imidates, also known as imidoates, imidic acid esters, or imido esters, are known to be important pharmacophores and useful synthetic building blocks.⁴ Whereas most of the present synthetic approaches take advantage of Pinner-type reactions,⁵ some difficulties are often encountered such as low yields and rather limited substrate scope. As a result, new synthetic methods, especially for the production of functionalized imidates, have been investigated.⁶ Since our MCR protocol for the synthesis of amidines and amides has demonstrated that both single and double carbon–heteroatom

(1) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (b) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (c) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (d) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246. (e) Wangelin, A. J.; Neumann, H.; Gordes, D.; Klaus, S.; Strubing, D.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 4286–4294.

(2) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.

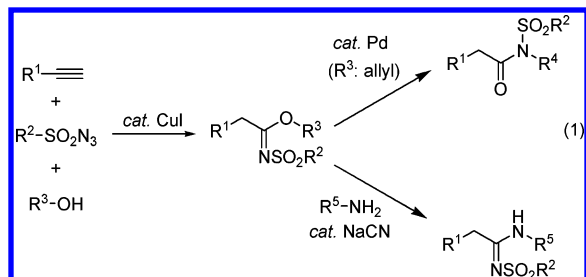
(3) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Soc. Chem.* **2005**, *127*, 2038–2039. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046–16047.

(4) (a) Neilson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley & Sons: London, UK, 1975; Chapter 8. (b) Kantlehner, W. *Synthesis of Iminium Salts, Orthoesters and Related Compounds*. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, pp 485–599. (c) Baindur, N.; Neumeyer, J. L.; Niznik, H. B.; Bozowej, N. H.; Jarvie, K. R.; Seeman, P.; Garlick, R. K.; Miller, J. J., Jr. *J. Med. Chem.* **1988**, *31*, 2069–2071.

(5) (a) Pinner, A.; Klein, F. *Chem. Ber.* **1877**, *10*, 1889–1897. (b) Gavin, D. J.; Mojica, C. A. *Org. Process Res. Dev.* **2001**, *5*, 659–664. (c) For a review, see: Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179–211.

(6) (a) Saluste, C. G.; Whitby, R. J.; Furber, M. *Tetrahedron Lett.* **2001**, *42*, 619–6194. (b) Nakajima, N.; Saito, M.; Kudo, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3579–3588. (c) Kishore, K.; Tetala, R.; Whitby, R. J.; Light, M. E.; Hurthouse, M. B. *Tetrahedron Lett.* **2004**, *45*, 6991–6994. (d) Yadav, V. K.; Babu, K. G. *Eur. J. Org. Chem.* **2005**, 452–456.

bonds are simultaneously generated with high efficiency, we envisioned that imidates could also be readily prepared with the use of alcohols as one part of the reacting components.⁷ We report herein the facile synthesis of *N*-sulfonylimidates and their synthetic utility in the conversion to amidines. A new protocol for the extremely efficient Pd-catalyzed rearrangement of allylic sulfonimides to *N*-allylic sulfonamides also will be described (eq 1).



At the outset of our studies on the optimization for imidate synthesis, we tried a copper-catalyzed three-component reaction of phenylacetylene, *p*-toluenesulfonyl azide, and benzyl alcohol under similar conditions as those applied in the amidine synthesis.^{3a} In contrast to the amidine case, no coupled product was generated in the absence of additional amine bases. Among those examined, a slight excess of triethylamine (1.2 equiv) in CHCl_3 solvent turned out to be most efficient for the formation of imidates. While no conversion was observed without a Cu catalyst, CuI was superior to other copper sources examined.⁸

The generality of the imidate synthesis was next investigated with a range of terminal alkynes, sulfonyl azides, and alcohols under the optimized reaction conditions (Table 1). Primary and secondary alcohols readily participated in the reaction leading to the corresponding imidates in high yields (entries 1–4). Phenol derivatives also work well in this coupling (entries 5 and 6). However, the use of a tertiary alcohol resulted in a sluggish reaction rate and gave a rather low yield, probably due to steric reasons (entry 7). Alcohols bearing various functional groups such as ester, halo, or propargyl internal triple bond moieties were compatible under the reaction conditions (entries 8–10). When a diol was allowed to react, the corresponding bisimide product could be obtained in a high yield (entry 11).

On the other hand, not only arylsulfonyl azides but also alkyl or benzyl variants were equally competent in the coupling reactions (entries 12–15). The efficiency of this process was not significantly affected by the electronic variations of aromatic alkynes (entries 16–18). Note that a broad range of functional groups on alkyne substrates such as heteroaromatic, halo, ether, alkenyl, or ester were tolerated in this transformation (entries 19 and 22–25). It is intriguing that trimethylsilylacetylene can serve as a two-carbon source

Table 1. Cu-Catalyzed Three-Component Coupling for the Formation of Imidates^a

| $\text{R}^1\text{—C}\equiv\text{C—H} + \text{R}^2\text{—SO}_2\text{N}_3 + \text{R}^3\text{OH} \xrightarrow[\text{Et}_3\text{N, CHCl}_3, 25^\circ\text{C, 12 h}]{\text{cat. CuI}} \text{R}^1\text{—CH}_2\text{—CH=C(OSO}_2\text{R}^2\text{)—OR}^3$ | | | | |
|---|--|---|---|---------------------------|
| entry | R ¹ | R ² | R ³ | yield [%] ^b |
| 1 | Ph (1a) | 4-MeC ₆ H ₄ (2a) | PhCH ₂ (3a) | 4a 87 |
| 2 | 1a | 2a | 4-BrC ₆ H ₄ CH ₂ | 4b ^c 91 |
| 3 | 1a | 2a | Me | 4c 93 |
| 4 | 1a | 2a | <i>i</i> -Pr | 4d 73 |
| 5 | 1a | 2a | Ph | 4e 61 |
| 6 | 1a | 2a | 4-MeOC ₆ H ₄ | 4f 65 |
| 7 | 1a | 2a | <i>t</i> -Bu | 4g 31 |
| 8 | 1a | 2a | MeO ₂ CCH ₂ | 4h 62 |
| 9 | 1a | 2a | Br(CH ₂) ₃ | 4i 92 |
| 10 | 1a | 2a | CH ₃ C≡CCH ₂ | 4j 68 |
| 11 | 1a | 2a | HO(CH ₂) ₃ | 4k 86 ^d |
| 12 | 1a | Me | 3a | 4l 84 |
| 13 | 1a | TMS—CH ₂ CH ₂ | 3a | 4m 84 |
| 14 | 1a | CH ₃ (CH ₂) ₃ | 3a | 4n 77 |
| 15 | 1a | 4-NO ₂ C ₆ H ₅ CH ₂ | 3a | 4o 37 |
| 16 | 4-CF ₃ C ₆ H ₄ | 2a | 3a | 4p 88 |
| 17 | 4-MeC ₆ H ₄ | 2a | 3a | 4q 89 |
| 18 | 4-MeOC ₆ H ₄ | 2a | 3a | 4r 70 |
| 19 | 3-thienyl | 2a | 3a | 4s 72 |
| 20 | CH ₃ (CH ₂) ₃ | 2a | 3a | 4t 86 |
| 21 | <i>t</i> -Bu | 2a | 3a | 4u 93 |
| 22 | Cl(CH ₂) ₃ | 2a | 3a | 4v 78 |
| 23 | MeOCH ₂ | 2a | 3a | 4w 82 |
| 24 | 1-cyclohexenyl | 2a | 3a | 4x 79 |
| 25 | H ₂ C=CHCH ₂ C-(CO ₂ Et) ₂ CH ₂ | 2a | 3a | 4y 80 |
| 26 | TMS | 2a | 3a | 4z 71 ^e |

^a Alkyne (0.5 mmol), sulfonyl azide (1.2 equiv), alcohol (1.2 equiv), Et₃N (1.2 equiv), and CuI (0.1 equiv) in CHCl_3 (1 mL). ^b Isolated yield. ^c Z-configuration of C=N double bond based on the X-ray crystal analysis (see the Supporting Information). ^d Yield of 1,3-bisimide. ^e Yield of the desilylated imide product.

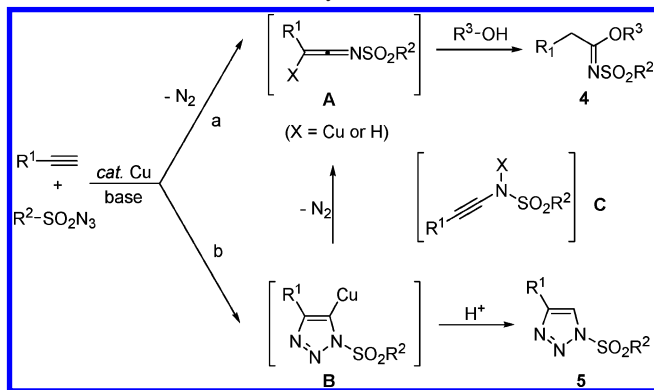
for the formation of acetimide with concomitant desilylation under the reaction conditions (entry 26). Additionally, it should be mentioned that the reaction is readily scaled up with lower amounts of copper catalyst, and pure imide product can be obtained by simple crystallization, thus making this process highly practical.⁸

Since ketenimine species are known to react with alcohols leading to imidates,⁹ it may be reasonable to postulate a ketenimine intermediacy in the present case although a more conclusive description needs further detailed studies. Initial attack of a putative copper acetylide species, generated by the action of 1-alkyne with copper salts, onto a sulfonyl azide may be envisioned to take place leading to a highly reactive ketenimine intermediate or its copper complex (**A**) upon release of N₂ (Scheme 1, pathway a). Alternatively, formation of the ketenimine species may be postulated to take place stepwise (pathway b) via a copper triazole species, which probably forms by the 1,3-dipolar cycloaddition between

(7) For seminal reports on the Cu-catalyzed cycloaddition between 1-alkynes and alkyl(aryl) azides, see: (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

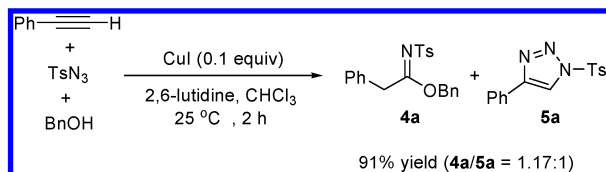
(8) See the Supporting Information for details.

(9) Sauer, R. R.; Van Arnum, S. D. *Phosphorus, Sulfur, Silicon, Relat. Elem.* **2003**, *178*, 2169–2181.

Scheme 1. Postulated Pathways for the Formation of Imidates

copper acetylide and sulfonyl azide in analogy with the explanation by Fokin and Sharpless et al.¹⁰ In this route, the rearrangement may be attributed to be responsible for the ring opening of 1,2,3-triazole (**B**), giving rise to the ketenimine species (**A**) upon release of a N_2 molecule. During the course of the rearrangement, it also can be possible to have an ynamide intermediate species (**C**).¹¹

It was highly interesting to observe that when 2,6-lutidine was employed as an amine base instead of triethylamine, a 1,4-substituted 1,2,3-triazole (**5a**) was also seen to be produced along with imidates (Scheme 2).¹² This observation

Scheme 2

may imply that the suggested key intermediate of ketenimine (**A** in Scheme 1) is likely generated via the triazole adduct (**B**) according to path b. However, the possibility that both pathways a and b are in action competitively at the same time cannot be completely ruled out at present.

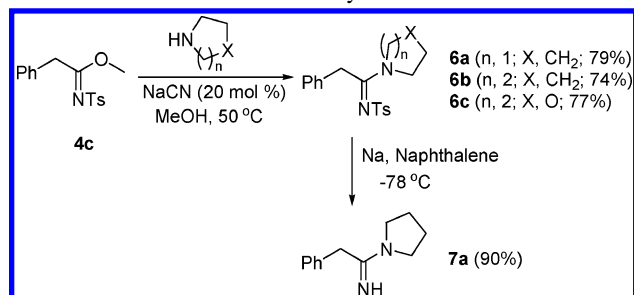
The synthetic utility of imidates was next investigated in the conversion to amidine derivatives. It was immediately

(10) (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216. (b) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210–2215.

(11) We thank one referee for this suggestion. A similar transformation of 5-lithiated triazoles into the corresponding ynamides has been reported: (a) Raap, R. *Can. J. Chem.* **1971**, *49*, 1792–1798. (b) Gilchrist, T. L. *Adv. Heterocycl. Chem.* **1987**, *41*, 41–74.

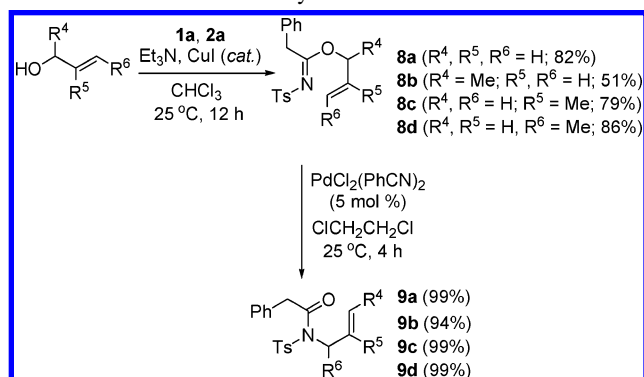
(12) When Et_3N was used as a base, the formation of triazole species was not observed. The difference in the acidity of conjugated ammonium ions between triethylamine and 2,6-lutidine may be attributed to these outcomes. The more acidic 2,6-lutidinium ion [$pK_a(\text{THF})$: 7.2] relative to triethylammonium salt [$pK_a(\text{THF})$: 12.5], formed presumably during the course of generation of copper acetylides, is believed to transfer its proton more readily to the postulated copper triazole species (**B** in Scheme 1) leading to the triazole species **5**. For a reference on the indicated acidity values, see: Rodima, T.; Kaljurand, I.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. *J. Org. Chem.* **2002**, *67*, 1873–1881.

found that methyl imidates were readily transformed to the corresponding amidines upon the reaction with amines in the presence of catalytic amounts of NaCN (Scheme 3).¹³

Scheme 3. Conversion of Imidates to Amidines and *N*-Desulfonylation

Subsequent *N*-desulfonylation of amidines was successfully achieved with sodium naphthalide. Since the MCR protocol developed by us for the synthesis of amidines often affords rather low yields with some cyclic amine component, this indirect route would be a facile complementary pathway for specific types of amidines.¹⁴

We also briefly surveyed a catalytic [3,3]-sigmatropic rearrangement of allylic sulfonimidates to *N*-allylic sulfonamides¹⁵ as this type of conversion has been frequently applied as a key step in total synthesis.¹⁶ Since we succeeded in setting up an effective MCR for a series of allylic imidates using allyl alcohols, the subsequent rearrangement was investigated using a range of transition metal catalysts.⁸ We were pleased to find that $[PdCl_2(PhCN)_2]$ readily catalyzes the transformation under very mild conditions to furnish the corresponding allylic amides in excellent yields (Scheme 4).

Scheme 4. Pd-Catalyzed Rearrangement of Allylic Imidates to *N*-Allylic Amides

The scope of the rearrangement turned out to be wide enough to cover a range of substituted allylic imidates (**8b–d**). When an internal allylic sulfonimidate (e.g., **8d**) was subjected to

(13) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652–15653.

the conditions, an *N*-allylic sulfonamide bearing a substituent at the α -position (**9d**) was isolated in almost quantitative yield. To the best of our knowledge, this represents the first example in which *N*-allylic sulfonamides can be obtained by a catalytic rearrangement with such an extremely high efficiency.

In summary, it is shown that *N*-sulfonylimidates can be prepared highly efficiently by a three-component coupling of terminal alkynes, sulfonyl azides, and alcohols by the

action of a copper catalyst in the presence of an amine base. The process appears to provide high efficiency and selectivity, very mild conditions, a wide substrate scope, and high tolerance with diverse functional groups. Facile transformation of imidates to amidines was readily achieved with the help of NaCN as a catalyst. Additionally, a protocol for the extremely efficient Pd-catalyzed [3,3]-sigmatropic rearrangement of allylic sulfonimidates to *N*-allylic sulfonamides has been developed.

(14) For example, a reaction of phenylacetylene, *p*-toluenesulfonyl azide, and morpholine provided the corresponding amidine **6c** in a poor 19% yield under the previously described conditions (ref 3a).

(15) For the rearrangement of allylic acyl(aryl)imidates, see: (a) Overman, L. E. *J. Am. Chem. Soc.* **1978**, *98*, 2901–2910. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224. (c) Hollis, T. K.; Overman, L. E. *J. Organomet. Chem.* **1999**, *576*, 290–299. For a recent report on the rearrangement of allylic phosphorimidates, see: (d) Chen, B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5364–5365.

(16) For selected examples, see: (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829–4837. (b) Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Fukuda, Y.; Isobe, M. *Tetrahedron* **2001**, *57*, 3875–3883. (c) Kim, S.; Lee, T.; Lee, E.; Lee, J.; Fan, G.-j.; Lee, S. K.; Kim, D. *J. Org. Chem.* **2004**, *67*, 3144–3149.

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Supporting Information Available: Experimental details plus ¹H and ¹³C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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