Synthesis of Sulfoximidoyl-Substituted Triazoles by Huisgen 1,3-Dipolar Cycloaddition

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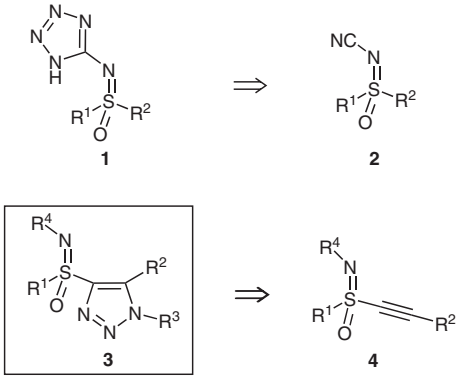
Abstract: The reaction of alkynyl sulfoximines with in situ prepared organic azides in water–dichloromethane under reflux affords sulfoximidoyl-substituted triazoles by Huisgen 1,3-dipolar cycloaddition.

Key words: azide, cycloaddition, Huisgen, sulfoximines, triazole

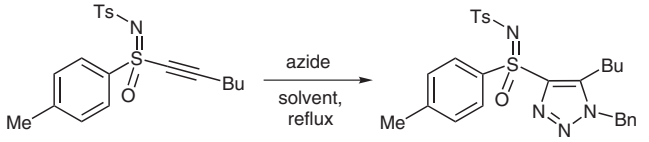
Sulfoximines have been used as chiral auxiliaries,[1] building blocks of pseudopeptides,[2] and chiral ligands.[3] For their synthesis various approaches have been described.[4] Of particular interest are heterocyclic systems, since they might eventually be applied as bioactive compounds with appropriate solubility properties.[5] Recently, we reported on the synthesis of *N*-(1*H*)-tetrazole derivatives **1** starting from *N*-cyano sulfoximines **2**.[6,7] Key step was a metal-catalyzed 1,3-dipolar cycloaddition with sodium azide in the presence of $ZnBr_2$. Realizing the importance of 1,2,3-triazoles as agrochemicals, corrosion inhibitors, dyes, optical brighteners, and pharmaceuticals,[8] we now focused our attention on the synthesis of sulfoximine derivatives **3**, which we envisaged to be accessible by Huisgen 1,3-dipolar cycloaddition reaction between organoazides and sulfoximidoyl alkynes **4** (Scheme 1). The latter compounds have recently been applied as starting materials in regio- and stereoselective copper-catalyzed carbozincation reactions.[9]



Scheme 1 Retrosynthetic approaches towards heterocycles bearing sulfoximidoyl substituents based on 1,3-dipolar cycloadditions

Sulfoximidoyl alkynes **4** were prepared by copper-catalyzed imination of the corresponding sulfoxides with PhI=NTs.[10,11] For the initial screening and optimization, (*N*-tosyl)-tolylhexynyl sulfoximine (**4a**)[12] was chosen as starting material. Albeit in only low yield, the corresponding triazole derivative **3a** was obtained, when mixtures of **4a** and benzyl azide (1.5 equiv) were heated to 100 °C for 3 hours in toluene, water, or a 3:1 mixture of water and dichloromethane (Table 1, entries 1–3). The molecular structure of the product was determined by NMR analysis, and ^{1}H-NOESY spectroscopy confirmed the regioselectivity of the triazole formation.[13] Gratifyingly, a few reaction modifications allowed to significantly

Table 1 Optimization of the Reaction Conditions of the Triazole Synthesis[a]



4a **3a**

Entry	BnBr (equiv)	NaN_3 (equiv)	Solvent	Time (h)	Yield of **3a** (%)[b]
1	BnN_3 (1.5)		Toluene[c]	3	7
2	BnN_3 (1.5)		H_2O	3	31
3	BnN_3 (1.5)		H_2O–CH_2Cl_2[d]	3	19
4	2	1.5	H_2O	3	35
5	2	1.5	H_2O	20	63
6	3	3	H_2O	3	48
7	6	6	H_2O	3	58
8	15	12	H_2O	3	59
9	18	18	H_2O	3	56
10	6	6	H_2O–CH_2Cl_2[d]	3	61
11	15	12	H_2O–CH_2Cl_2[d]	3	68
12	18	18	H_2O–CH_2Cl_2[d]	3	68
13	15	12	H_2O–CH_2Cl_2[d]	8	57
14	24	24	H_2O–CH_2Cl_2[d]	3	67

[a] Reaction conditions: see ref. 14.
[b] Isolated by column chromatography.
[c] Performed at 100 °C.
[d] Ratio of H_2O–CH_2Cl_2 = 3:1.

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increase the yield of **3a**.[14] Thus, finally, performing the reaction in water–dichloromethane with benzyl azide formed in situ from benzyl bromide and sodium azide led to triazole **3a** in 68% yield (Table 1, entry 11).

For achieving this result, the reagent amounts had to be increased to 15 and 12 equivalents (for BnBr and NaN_3, respectively). Using a larger excess of reagents or extending the reaction time had no impact or even reduced the yield of **3a** (entries 12 and 13, respectively). Without the organic cosolvent (in pure water) the maximal yield of **3a** reached 63% (Table 1, entry 5). Interestingly, this result was achieved with a combination of only 2 equivalents of BnBr and 1.5 equivalents of NaN_3. Entries 4 and 5 in Table 1 reveal that an extended reaction time (20 h) was crucial for the high yield in this case. An increase in the reagent quantity had also benefical effects on the product yield (Table 1, entries 6–9).

For a successful cycloaddition reaction, it was essential to heat the reaction mixture. The cycloaddition did not occur at temperatures below 50 °C, and at 80 °C, the yield of **3a** was only 11% (under the reaction conditions as described in Table 1, entry 11).

Next, the substrate scope of the cycloaddition reaction was examined. As the data in Table 2 (entries 1–4) show, various azides reacted with **4a** analogously, providing the corresponding triazoles (**3b–e**) in moderate yields (of up to 52%). Noteworthy is the fact that also other azides than benzyl azides were applicable. (2-Naphthyl)methyl bromide could not be converted (entry 5).

In reactions between (in situ formed) benzyl azide and various sulfoximines (Table 2, entries 6–9), a strong reactivity dependance on the substitution pattern of the sulfur reagent became apparent. Whereas (*N*-tosyl)-1-hexynylmethylsulfoximine (**4b**) and (*N*-tosyl)-3-methoxypropynyl-phenylsulfoximine (**4c**) reacted well to give the corresponding triazoles **3g** and **3h** in 73% and 51% yield, respectively, (*N*-tosyl)-2-*tert*-butylethynyl-phenylsulfoximine (**4d**) and (*N*-tosyl)-2-phenylethynyl-phenylsulfoximine (**4e**) proved unreactive. Presumably, steric as well as electronic factors hampered their conversion.

In summary, we have developed the synthesis of sulfoximidoyl-substituted triazoles by Huisgen 1,3-dipolar cycloaddition reactions. Starting from alkynyl sulfoximines and organoazides prepared in situ from organobromides and sodium azide, the products can be obtained in yields up to 73% after a short reaction time (3 h). Educts bearing various substituents are tolerated leading to triazole derivatives with potential bioactivities. Our current studies are focused on an expansion of the substrate scope combined with further process optimizations to achieve higher product yields.

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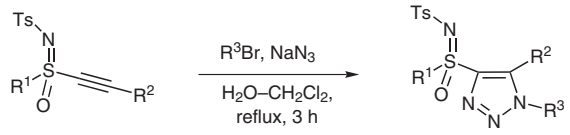
Table 2 Substrate Scope of the Cycloaddition Reaction[a]



4a–e **3b–j**

Entry	R^1	R^2	Sulfoximine	R^3	Product	Yield of **3** (%)
1	4-MeC_6H_4	Bu	**4a**	4-NO_2Bn	**3b**	52
2	4-MeC_6H_4	Bu	**4a**	4-MeOBn	**3c**	41
3	4-MeC_6H_4	Bu	**4a**	$Ph(CH_2)_2$	**3d**	51
4	4-MeC_6H_4	Bu	**4a**	$Ph(CH_2)_3$	**3e**	39
5	4-MeC_6H_4	Bu	**4a**	2-Naphth-CH_2	**3f**	0
6	Me	Bu	**4b**	Bn	**3g**	73
7	Ph	CH_2OMe	**4c**	Bn	**3h**	51[b]
8	Ph	*t*-Bu	**4d**	Bn	**3i**	0
9	Ph	Ph	**4e**	Bn	**3j**	0

[a] *Reaction conditions*: sulfoximine **4** (1.0 equiv), NaN_3 (12.0 equiv), RBr (15.0 equiv) in H_2O–CH_2Cl_2 (3:1) at 100 °C for 3 h.
[b] Determined by NMR.

References and Notes

(1) For selected recent contributions, see: (a) Reggelin, M.; Kuehl, J.; Kaiser, J. P.; Buehle, P. *Synthesis* **2006**, 2224. (b) Rajender, A.; Gais, H.-J. *Org. Lett.* **2007**, *9*, 579. (c) Adrien, A.; Gais, H.-J.; Koehler, F.; Runsink, J.; Raabe, G. *Org. Lett.* **2007**, *9*, 2155.

(2) (a) Bolm, C.; Müller, D.; Dalhoff, C.; Hackenberger, C. P. R.; Weinhold, E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3207. (b) Cho, G. Y.; Okamura, H.; Bolm, C. *J. Org. Chem.* **2005**, *70*, 2346 and references therein.

(3) Reviews: (a) Harmata, M. *Chem. Abstr.* **2003**, *16*, 660. (b) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482.

(4) Reviews: (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (b) Pyne, S. G. *Sulfur Rep.* **1992**, *12*, 57. (c) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (d) Bolm, C. In *Asymmetric Synthesis with Chemical and Biological Methods*; Enders, D.; Jäger, K.-E., Eds.; Wiley-VCH: Weinheim, **2007**, 149.

(5) For a selection of recent patents emphasizing this point, see: (a) Luecking, U.; Krüger, M.; Jautelat, R.; Siemeister, G. WO 037800 A1, **2005**; Schering AG. (b) Luecking, U.; Siemeister, G.; Jautelat, R. WO 099974 A1, **2006**; Schering AG. (c) Luecking, U.; Nguyen, D.; von Bonin, A.; von Ahsen, O.; Krueger, M.; Briem, H.; Kettschau, H.; Prien, O.; Mengel, A.; Krolikiewicz, K.; Boemer, U.; Bothe, U.; Hartung, I. WO 071455 A1, **2007**; Schering AG. (d) Luecking, U. EP 1 710 246 A1, **2006**; Schering AG. (e) Luecking, U.; Bader, B.; Siemeister, G. EP 1 803 723 A1, **2007**; Bayer Schering Pharma. (f) Shetty, S. J.; Patel, G. D.; Lohray, B. B.; Lohray, V. B.; Chakrabarti, G.; Chatterjee, A.; Jain, M. J.; Patel, P. R. WO 077574 A2, **2007**; Cadila Healthcare Limited. (g) Zhu, Y.; Rogers, R. B.; Huang, Y. X. US 228027 A1, **2005**; Dow Agroscience. (h) Jeanguenat, A.; O'Sullivan, A. C. WO 032462 A1, **2006**; Syngenta. (i) Jeanguenat, A.; O'Sullivan, A. C. WO 061200 A1, **2006**; Syngenta. (j) Plant, A.; Boehmer, J. E.; Peace, A. L. WO 037945 A1, **2006**; Syngenta. (k) Kajita, S.; Ohmura, H.; Akashi, M.; Kojima, S.; Satoh, A.; Tomida, K. WO 052849, **2004**; Nippon Soda Co., Ltd.

(6) Garcia Mancheño, O.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349.

(7) Garcia Mancheño, O.; Bistri, O.; Bolm, C. *Org. Lett.* **2007**, *9*, 3809.

(8) For regioselective syntheses and applications of triazoles, see: (a) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford UK, **1996**, 121. (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1730. Reviews: (c) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. (d) Lutz, J. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1018.

(9) Sklute, G.; Bolm, C.; Marek, I. *Org. Lett.* **2007**, *9*, 1259.

(10) (a) Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116. (b) Leca, D.; Song, K.; Amatore, M.; Fensterbank, L.; Lacote, E.; Malacria, M. *Chem. Eur. J.* **2004**, *10*, 906.

(11) For recently developed alternative imination protocols, see: (a) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305. (b) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983. (c) Cho, G. Y.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 8007. (d) Refs 6 and 7.

(12) In the reactions reported here, racemic sulfoximines were used.

(13) The interactions between the benzylic hydrogens and the hydrogens of the alkyl or alkoxy chain in the ^{1}H-NOESY spectra also confirmed the molecular structures of triazole derivatives **3b–e**,**g**,**h**. Although present in the crude product mixtures, the other regioisomers (triazoles **5**) could never be obtained in pure form (Figure 1).

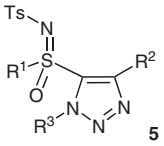


Figure 1

(14) **General Procedure for the Cycloaddition Reaction**

Under vigorous stirring a mixture of NaN_3 (12 equiv) and the corresponding bromide (15 equiv) was heated to reflux in H_2O (0.7 M) for 1 h. Then, a solution of sulfoximine **4** (1 equiv) in CH_2Cl_2 (0.08 M) was added dropwise. After 3 h at 100 °C under reflux and stirring, the product was extracted with CH_2Cl_2 and purified by flash column chromatography. As representative example, the analytical data for 1-benzyl-5-butyl-4-(*N*-tosyl)-(4-methylphenylsulfonimidoyl)-1*H*-1,2,3-triazole (**3a**) obtained from the reaction of sulfoximine **4a** with benzyl azide are given. Colorless oil (68%); chromatography: EtOAc–pentane (1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.0 Hz, 3 H), 1.21–1.29 (m, 4 H), 2.37 (s, 3 H), 2.41 (s, 3 H), 2.76–2.85 (m, 1 H), 2.93–3.02 (m, 1 H), 5.44 (d, *J* = 15.5 Hz, 1 H), 5.49 (d, *J* = 15.5 Hz, 1 H), 7.14–7.18 (m, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.31–7.35 (m, 5 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.98 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 21.5 (CH_3), 21.7 (CH_3), 22.7 (CH_2), 23.0 (CH_2), 30.5 (CH_2), 52.5 (CH_2), 126.5 (CH), 127.2 (CH), 128.2 (CH), 128.7 (CH), 129.0 (2 × CH), 129.9 (CH), 133.5 (C), 135.2 (C), 140.4 (C), 141.4 (C), 141.9 (C), 142.6 (C), 145.4 (C). IR ($CHCl_3$): ν = 2959 (m), 1454 (m), 1318 (m), 1243 (m), 1096 (s), 1018 (m), 757 (s), 540 (m). MS (CI): *m/z* (relative intensity) = 523 (6) [M + H]$^+$. Anal. Calcd for $C_{27}H_{30}N_4S_2O_3$: C, 62.04; H, 5.79; N, 10.72. Found: C, 62.06; H, 5.81; N, 11.14.