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Practical Preparation of *N*-(1-Alkynyl)sulfonamides and Their Remote Diastereoselective Addition to Aldehydes via Titanation

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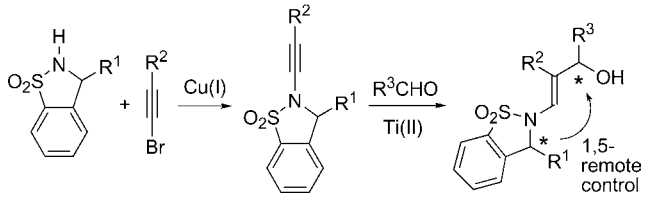
ABSTRACT



Aliphatic and aromatic sulfonamides were alkynylated with 1-bromo-1-alkynes in the catalytic presence of CuI to give *N*-(1-alkynyl)sulfonamides in good to excellent yields. The acetylene–titanium complexes generated from *N*-(1-alkynyl)benzosultams underwent diastereoselective addition to aldehydes.

Acetylene−group 4 metal complexes are versatile and indispensable organometallic reagents in organic synthesis.[1,2] Successful extension of the parent acetylenes to functionalized ones has considerably broadened the utility of these complexes,[1a−c] among which we recently reported the generation of [*N*-(1-alkynyl)sulfonamide]−titanium alkoxide complexes and their regio- and (olefinic) stereoselective coupling with acetylenes or carbonyl compounds.[3] Although their amino group should serve diastereoselective synthesis, such an attempt was somewhat discouraged by the current limited synthesis of the aminoacetylenes via alkynyliodonium salts.[4] Considering the recent progress in the transition metal-catalyzed amination of organic halides,[5,6] particularly the

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(5) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041−2075.

(6) (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. During the course of our study, the following report appeared: (b) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368−2369. However, this paper described that the sulfonamides and sultams are sluggish substrates toward the alkynylation. Furthermore, after the completion of the preparation of this manuscript, alkynylation of a couple of sulfonamides in the presence of a stoichiometric amount of a copper salt was reported: (c) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011−4014.

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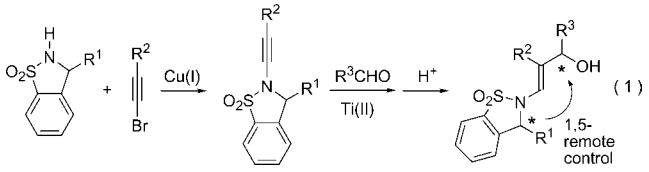
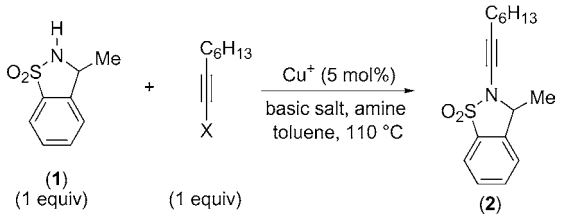
alkynylation of amides by Hsung and co-workers[6b] and that of sulfonamides quite recently reported by Danheiser's group,[6c] we report here our results on a copper-catalyzed preparation of various *N*-(1-alkynyl)sulfonamides from haloacetylenes and sulfonamides and their application along the aforementioned line (eq 1).



(1)

N-Alkynylation of sulfonamides was first investigated by taking benzosultam **1**[7] and a 1-halo-1-octyne as the starting materials under a variety of reaction conditions. The selected variations summarized in Table 1 show that the reaction is

Table 1. Optimum Conditions for the Alkynylation of Benzosultam **1**



(**1**) (1 equiv) (1 equiv) (**2**)

entry	X	Cu^+	basic salt	amine	yield (%)[a]
1	Br	CuI	Cs_2CO_3	$(CH_2NHMe)_2$	68
2	Br	CuI	K_2CO_3	$(CH_2NHMe)_2$	94 (68)
3	Br	CuCN	K_3PO_4	$(CH_2NHMe)_2$	87
4	Br	CuSPh	K_3PO_4	$(CH_2NHMe)_2$	93
5	Br	CuI	K_3PO_4	$(CH_2NH_2)_2$	62
6	Br	CuI	K_3PO_4	$(CH_2NHMe)_2$	97 (79)
7	I	CuI	K_3PO_4	$(CH_2NHMe)_2$	77

[a] Yield determined by ^1H NMR spectroscopy with internal standard. Isolated yield in parentheses.

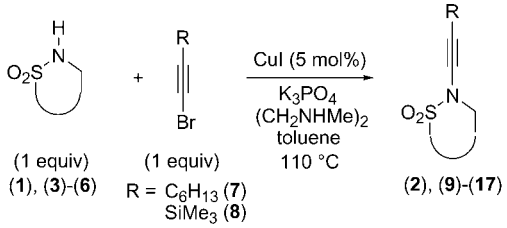
feasible under copper catalysis; and the kind of copper salts appears not to be critical, showing little influence on the product yield (entries 3, 4, and 6). On the other hand, Pd catalysts were totally ineffective. The best yield was obtained in entry 6 with alkynyl bromide rather than iodide (cf. entry 7), with K_3PO_4 rather than K_2CO_3 or Cs_2CO_3 (entries 1 and 2), and with *N*,*N*′-dimethylethylenediamine rather than ethylenediamine (entry 5). Under the optimum conditions, a virtually quantitative yield of **2** was attained.[8]

The generality of this reaction is shown in Table 2. Open-chain sulfonamide **3** was smoothly alkynylated with bromooctyne (**7**) to give **9** (entry 1). This compound was previously prepared via a few inevitable steps, involving (i)

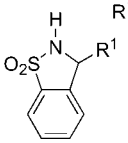
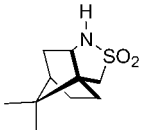
(7) For review, see: Liu, Z.; Takeuchi, Y. *Heterocycles* **2002**, *56*, 693−709. Optically active benzosultams are readily prepared according to this literature.

(8) For details, see the Supporting Information.

Table 2. Preparation of *N*-Alkynylsulfonamides



(1 equiv) (**1**), (**3**)-(**6**) (1 equiv) R = C_6H_{13} (**7**), $SiMe_3$ (**8**) (**2**), (**9**)-(**17**)

entry	starting sulfonamide		bromo-alkyne	product R	product yield (%)
1		(**3**)	**7**	C_6H_{13} (**9**)	93
2		(**3**)	**8**	$SiMe_3$ (**10**)	84
3		R^1 = Me (**1**)	**7**	C_6H_{13} (**2**)	79
4		Me (**1**)	**8**	$SiMe_3$ (**11**)	71
5		Bu (**4**)	**7**	C_6H_{13} (**12**)	84
6		Bu (**4**)	**8**	$SiMe_3$ (**13**)	66
7		*t*-Bu (**5**)[a]	**7**	C_6H_{13} (**14**)[a]	94
8		*t*-Bu (**5**)	**8**	$SiMe_3$ (**15**)	71
9		(**6**)	**7**	C_6H_{13} (**16**)	95
10		(**6**)	**8**	$SiMe_3$ (**17**)	58, 95[b]

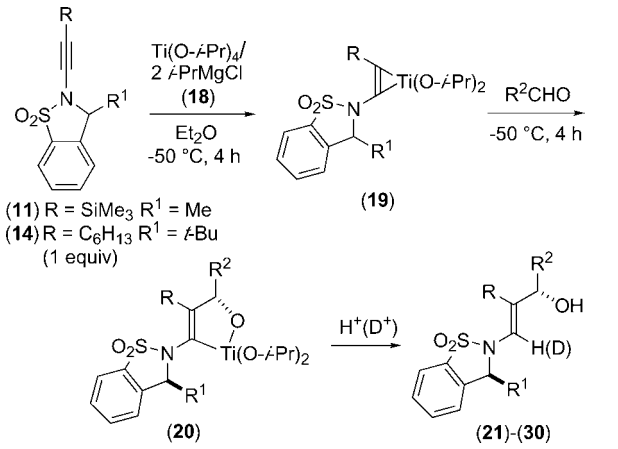
[a] The enantiopurity of (*S*)-**5** (96% ee) was completely preserved in the product (*S*)-**14** (96% ee). [b] **8** (2 equiv) was used.

coupling of (silylethynyl)iodonium salt with *N*-benzyl-*p*-toluenesulfonamide (to give **10**), (ii) desilylation of **10** to the terminal acetylene, and (iii) its alkylation.[3] Thus, the advantage of the one-step synthesis from **3** to **9** is apparent. As the trimethylsilyl group of bromide **8** survived the reaction conditions, *N*-(silylethynyl)sulfonamide **10**, which is a precursor of the versatile terminal acetylene as mentioned above, was also readily prepared by this method (entry 2). Sterically more demanding benzosultams **4** and **5** were alkynylated equally well to afford the desired products (entries 5−8). It is important to note that the enantiopurity of optically active sultam **5** was completely retained in the product (**14**, entry 7). In addition to aromatic sultams **1** and **3**−**5**, an aliphatic counterpart **6**, a useful chiral auxiliary known as Oppolzer's camphorsultam,[9] participated in this coupling reaction to give **16** or **17**. In the latter case, the product yield was improved by the use of excess alkylating agent (entry 10).

The amino-substituted acetylenes obtained above should be useful intermediates for diastereoselective synthesis, which is demonstrated as follows (Table 3): *N*-(Silylethynyl)sultam **11** was first treated with a titanium(II) alkoxide reagent, Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl (**18**),[1] to generate the acetylene−titanium complexe **19**, which was then allowed to react with benzaldehyde to give **21**, after hydrolysis, with virtually complete regio- and olefinic stereoselectivities and with high 1,5-diastereoselectivity (ds = 96:4) in good yield (entry 1).[8]

(9) For review, see: Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241−1250. Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293−318.

Table 3. Remote Diastereoselective Addition of *N*-Alkynylsultams to Aldehydes



entry	sultam	aldehyde R^2	equiv	product	yield (%)	1,5-ds
1	**11**	Ph	0.8	**21**	87 (97% D[a])	96:4[b]
2	**11**	*p*-ClC$_6$H$_4$−	1	**22**	54	96:4
3	**11**	(*E*)-C$_5$H$_{11}$CH=CH−	0.8	**23**	73	94:6
4	**11**	(*E*)-MeCH=CH−	1	**24**	52	95:5
5	**11**	C$_8$H$_{17}$	0.8	**25**	94	88:12
6	**14**	Ph	1	**26**	74	88:12
7	**14**	C$_8$H$_{17}$	1	**27**	62	88:12
8[c]	**14**[d]	*i*-Pr	1	**28**[d]	88 (96% D[a])	93:7
9	**14**	*c*-C$_6$H$_{11}$	0.8	**29**	79	93:7
10	**14**[d]	*t*-Bu	0.8	**30**[d]	93	98:2

[a] Result of deuteriolysis. [b] An isomerically pure sample of **21** could be obtained by recrystallization from hexane−CH_2Cl_2. [c] In this case, a small amount of a regioisomer (less than 4%) was detected and was easily separated from **28** by silica gel chromatography. In other entries, we were unable to identify the regioisomeric product(s). [d] The enantiopurity of (*S*)-**14** (96% ee) was retained in the product **28** (95% ee) or **30** (96% ee).

The excellent level of the remote asymmetric induction (i.e., 1,5-diastereoselectivity) is noteworthy.[10] Other sultams **13**, **15**, and **17** having an *N*-(silylethynyl) group gave the analogous adducts with benzaldehyde in the following yields and diastereoselectivities: 73%, 97:3; 62%, 79:21; and 46%, 84:16, which revealed that sultam **11** is the most suitable one. The structure of **21** was determined by spectroscopic means and appropriate derivatization.[8] The remaining vinyl−titanium bond in the intermediate oxatitanacycle **20**, the presence of which was confirmed by deuteriolysis (entry 1), could be utilized in subsequent transformations. Other aldehydes gave the adducts **22**−**25** in good to excellent diastereoselectivities (entries 2−5). When the same reaction is started with sultams having an *N*-octynyl group, benzosultam **14** with a *tert*-butyl side chain is the substrate of choice and its titanation and subsequent addition to aldehydes afforded the coupling products **26**−**30**, again with exclusive regio- and olefinic stereoselectivities and good to excellent 1,5-diastereoselectivities (entries 6−10). When the reaction was started with chiral alkynylsultam ((*S*)-**14**, 96% ee, prepared in entry 7 of Table 2), the optically active products were obtained without loss of the enantiopurity (entries 8 and 10).

In summary, *N*-alkynylsulfonamides are now conveniently prepared and the titanium complexes of these functionalized acetylenes proved to be a promising organometallic reagent. Further application of the present transformations and the produced amino-substituted allyl alcohols will be reported in due course.

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Supporting Information Available: Experimental procedures, structural determinations, and physical properties of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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