JOC*Note*

A Remarkable Accelerating Effect of Ag-Salt on Intramolecular Cyclization of *o*-(1-Alkynyl)benzenesulfonamides†

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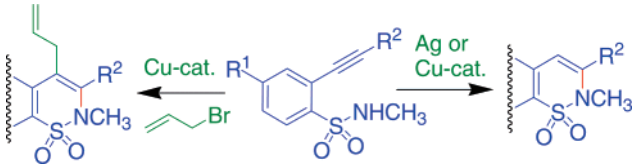

Herein, we report transition metal-catalyzed intramolecular cyclization of *o*-(1-alkynyl)benzenesulfonamides to afford 3-substituted benzothiazines regioselectively via a C−N bond forming reaction and Cu-catalyzed sequential C−N and C−C bond formation leading to the corresponding 3,4-disubstituted derivatives.

Reactions catalyzed by silver and copper salts have attracted remarkable attention in recent years.[1,2] In particular, these salts have been demonstrated to be exceptional and versatile reagents for the formal addition of an X−H bond (where X = O, N) across a C−C triple bond. Thus Cu- or Ag-mediated activation of the triple bond and then prompting the nearest nucleophilic substituent to attack the coordinated alkynyl moiety in an intramolecular fashion offers an attractive and atom-economical route for the synthesis of functionalized heterocycles. For example, furans,[3a] cyclic alkenyl ethers,[3b] benzofurans,[3c] phosphaisocoumarins,[3d] isocoumarins and α-pyrones,[3e] etc. are among the compounds for which highly regioselective syntheses have been demonstrated via Cu-catalyzed reactions. On the other hand, synthesis of 2*H*-1,2-oxaphosphorin 2-oxides,[3f] 5-substituted proline derivatives,[3g] pyrroles,[3h] and other heterocycles[3i,j] has been accomplished via Ag-catalyzed cyclization. But none of these investigations has explored the possibility of accessing benzothiazines (or benzoisothiazoles) via regiocontrolled addition of the sulfonamide moiety toward the triple bond in the presence of a silver or copper salt.

Benzothiazines, a widely studied family of heterocycles, have a privileged framework found in a number of anti-inflammatory agents,[4,5] some of which, particularly oxicams (e.g., Meloxicam, Piroxicam, etc.), have already been marketed. As a consequence of their biological significance, continued effort has been devoted for the development of newer synthetic methods to construct the 2*H*-benzo[*e*][1,2]thiazine ring.[6,7] Recently, a new Pd-mediated one-step synthesis of benzothiazines involving Sonogashira coupling of bromosulfoximine with terminal alkynes has been developed[8] where a substantial number of isomeric 1,2-benzoisothiazoles were isolated as side products. More recently, we have reported a convenient synthesis of benzothiazines that required an additional step to remove the C-4 iodo group.[9a] In this Note, we describe our recent findings on direct and one-step regioselective synthesis of 2*H*-benzo[*e*]-[1,2]thiazine-1,1-dioxides using a transition metal-catalyzed intramolecular cyclization of 2-alkynyl benzenesulfonamide (Scheme 1) addressing several issues, e.g., (i) reactivity of the $-SO_2NH-$ moiety toward transition metal-activated alkynes, (ii) regioselectivity, and (iii) the optimal catalyst system. To the best of our knowledge synthesis of the benzothiazine ring

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(2) The use of copper in the synthesis of an array of heterocycles was first demonstrated by Castro et al., see: (a) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071. (b) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A. M.; Moje, S. W. *J. Am. Chem. Soc.* **1969**, *91*, 6464. This procedure usually requires the use of a stoichiometric amount of the preformed cuprous acetylide and refluxing pyridine.

(3) (a) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (b) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139. (c) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727. (d) Peng, A.-Y.; Ding, Y.-X. *J. Am. Chem. Soc.* **2003**, *125*, 15006. (e) Liang, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2007**, 400. (f) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2005**, *7*, 3299. (g) van Esseveldt, B. C. J.; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791. (h) Agarwal, S.; Knolker, H.-J. *Org. Biomol. Chem.* **2004**, *2*, 3060. (i) Dalla, V.; Pale, P. *New J. Chem.* **1999**, *23*, 803. (j) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 10096.

(4) Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev.* **1982**, *2*, 127.

(5) Lazer, E. S.; Miao, C. K.; Cywin, C. L.; Sorcek, R.; Wong, H.-C.; Meng, Z.; Potocki, I.; Hoermann, M.; Snow, R. J.; Tschantz, M. A.; Kelly, T. A.; McNeil, D. W.; Coutts, S. J.; Churchill, L.; Graham, A. G.; David, E.; Grob, P. M.; Engel, W.; Meier, H.; Trummlitz, G. *J. Med. Chem.* **1997**, *40*, 980 and references cited therein.

(6) Layman, W. J., Jr.; Greenwood, T. D.; Downey, A. L.; Wolfe, J. F. *J. Org. Chem.* **2005**, *70*, 9147.

(7) (a) Sianesi, E.; Redaelli, R.; Magistretti, M. J.; Massarani, E. *J. Med. Chem.* **1973**, *16*, 1133. (b) Lombardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1971**, *14*, 973. (c) Catsoulacos, P. *J. Heterocycl. Chem.* **1971**, *8*, 947. (d) Hauser, C. R.; Wantanabe, H.; Mao, C.-L.; Barnish, I. T. *J. Org. Chem.* **1969**, *34*, 919.

(8) Harmata, M.; Rayanil, K.-o.; Gomes, M. G.; Zheng, P.; Calkins, N. L.; Kim, S.-Y.; Fan, Y.; Bumbu, V.; Lee, D. R.; Wacharasindhu, S.; Hong, X. *Org. Lett.* **2005**, *7*, 143.

(9) Because of its cheap availability and high catalytic activity, Pd/C has been used in Sonogashira coupling by us and several other groups, see for example: (a) Barange, D. K.; Batchu, V. R.; Gorja, D.; Pattabiraman, V. R.; Tatini, L. K.; Babu, J. M.; Pal, M. *Tetrahedron* **2007**, *63*, 1775. (b) Batchu, V. R.; Subramanian, V.; Parasuraman, K.; Swamy, N. K.; Kumar, S.; Pal, M. *Tetrahedron* **2005**, *61*, 9869. (c) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778. (d) Pal, M.; Batchu, V. R.; Swamy, N. K.; Padakanti, S. *Tetrahedron Lett.* **2006**, *47*, 3923. (e) For a review, see: Yin, L. X.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. On several occasions it has been observed that the use of Pd/C provided normal Sonogashira products where homogenous palladium catalysts either failed or yielded unexpected products, see for example: (f) Yin, L.; Erdmann, F.; Liebscher, J. *J. Heterocycl. Chem.* **2005**, *42*, 1369. (g) Marrison, L. R.; Dickinson, J. M.; Ahmed, R.; Fairlamb, I. J. *Tetrahedron Lett.* **2002**, *43*, 8853. (h) Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, 1976.

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SCHEME 1. Intramolecular Cyclization of 2-Alkynyl Benzenesulfonamide

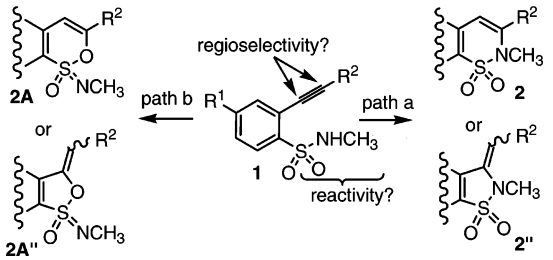
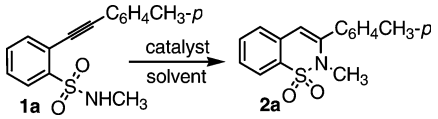


TABLE 1. Transition Metal Mediated Cyclization of *N*-Methyl-2-*p*-tolylethynyl Benzenesulfonamide 1a[a]



entry	catalyst	solvent	time (h)	temp (°C)	yield (%)[b]
1	CuI	DMF	8	130−140	78
2	no CuI	DMF	8	130−140	
3	CuCl	DMF	8	130−140	54
4	CuBr	DMF	8	130−140	60
5	$AgNO_3$	DMF	2	80	81
6	AgF	DMF	0.5	80	80
7	$AgSbF_6$	DMF	5	80	82
8	$AgSbF_6$	EtOH	3	80	85
9	$AgSbF_6 + Et_3N$[c]	EtOH	5 min	80	89

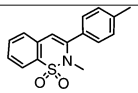
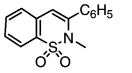
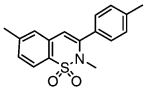
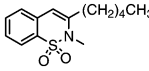
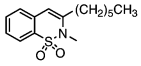
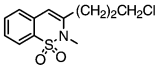
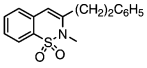
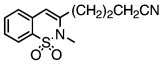
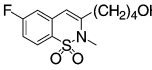
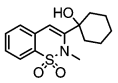
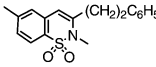
[a] All the reactions were carried out with **1a** with 15 mol % catalyst. [b] Isolated yields. [c] 3 equiv of Et_3N was used.

by using this strategy (path a, Scheme 1) has not been disclosed earlier.

The key starting alkynes **1** required for our synthesis were readily prepared via the Pd/C-mediated coupling[9] of *o*-halobenzenesulfonamide with terminal alkynes in 85−97% yield.[9a,10a]

Initially, we examined the intramolecular cyclization of *N*-methyl-2-*p*-tolylethynyl benzenesulfonamide (**1a**) in the presence of Cu-catalysts (Table 1). After assessing a number of solvents (e.g., toluene, THF, 1,4-dioxane, acetonitrile, DMF, and DMSO), a combination of DMF-CuI was found to be optimum. Under this condition the best yield of **2a** [R_1 = H, $R_2 = -C_6H_4CH_3$-*p*] was achieved when the reaction was carried out at 130−140 °C for 8 h in the presence of 15 mol % of CuI (entry 1, Table 1). No product was detected in the absence of Cu-salt (entry 2, Table 1) and the use of other Cu-catalysts (e.g., CuCl and CuBr) afforded **2a** albeit in moderate yields (entries 3 and 4, Table 1). To accelerate the rate of cyclization we then assessed other transition metal catalysts. The use of silver salts, e.g., $AgNO_3$, AgF, and $AgSbF_6$, reduced the reaction time and temperature significantly without affecting the product yields (entries 5−7, Table 1). However, the best result was obtained by using $AgSbF_6$ in combination with Et_3N in ethanol that reduced the reaction time remarkably affording **2a** in 89% yield (entry 9, Table 1). With use of these optimized reaction conditions,[10b] $AgSbF_6$-mediated electrophilic cyclization of other alkynes (**1b**−**k**) was carried out and the results are summarized in Table 2. As indicated, intramolecular cyclization of **1** afforded

TABLE 2. Synthesis of 2*H*-1,2-Benzothiazine 1,1-Dioxides via $AgSbF_6$-Mediated Cyclization[a]

entry	Alkyne **1** (R^1 & R^2)	Product **2**		%Yield[b]
1	H, $C_6H_4CH_3$-*p* (**1a**)		**2a**	89
2	H, C_6H_5 (**1b**)		**2b**	91
3	CH_3, $C_6H_4CH_3$-*p* (**1c**)		**2c**	85
4	H, $(CH_2)_4CH_3$ (**1d**)		**2d**	87
5	H, $(CH_2)_5CH_3$ (**1e**)		**2e**	89
6	H, $(CH_2)_2CH_2Cl$ (**1f**)		**2f**	90
7	H, $CH_2CH_2C_6H_5$ (**1g**)		**2g**	91
8	H, $(CH_2)_2CH_2CN$ (**1h**)		**2h**	93
9	F, $(CH_2)_3CH_2OH$ (**1i**)		**2i**	90
10	H,  (**1j**)		**2j**	92
11	CH_3, $CH_2CH_2C_6H_5$ (**1k**)		**2k**	90

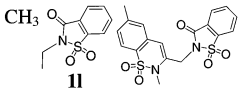
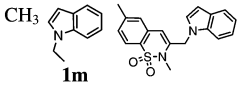
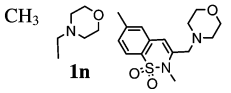
[a] All the reactions were carried out at 80 °C with 15 mol % of $AgSbF_6$ and Et_3N (3 equiv) in EtOH for 5 min. [b] Isolated yields.

a variety of 2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides **2** in good to excellent yields (85−93%). Substituents such as aryl (entries 1−3, Table 2) and alkyl (entries 4−11, Table 2) at the acetylenic end were well tolerated under the condition studied. The scope of Cu-catalyzed cyclization for the synthesis of **2** was also examined by using the optimized condition (e.g., entry 1, Table 1) and an array of benzothiazines were synthesized in good yields (Table 3).[11a] To demonstrate the flexibility of this methodology and to permit further structural elaboration of the benzothiazine ring, we carried out the Cu-mediated intramolecular cyclization of **1c** and **1e** in the presence of allyl bromide separately.[11b] To our delight, this one-pot reaction afforded 4-allyl-substituted benzothiazines **3a**,**b** via sequential C−N and

(10) (a) The required sulfonamide was prepared from the corresponding sulfonyl chloride according to the known procedure (see the Supporting Information). (b) While all the reactions were carried out with 15 mol % of the catalyst an attempt to reduce the catalyst loading without changing the other reaction conditions, however, resulted in lowering of product yields.

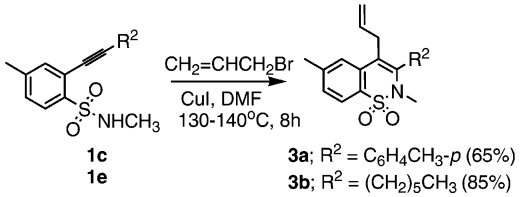
(11) (a) Notably, the reaction of **1*l*** and **1m** with AgSbF6 was investigated, which afforded a mixture of unidentified products and therefore remained inconclusive. (b) For a similar type of reaction of *o*-ethynylphenylphosphonic acid monoesters with allyl bromide, see: Wei, P.; Ding, Y.-X. *Synlett* **2005**, 599.

TABLE 3. Synthesis of 2*H*-1,2-Benzothiazine 1,1-Dioxides via CuI-Mediated Cyclization[a]

Entry	Alkyne **1** (R^1 & R^2)	Product **2**	%Yield[b]
1	**1c**	**2c**	75
2	**1f**	**2f**	60
3	**1k**	**2k**	85
4	 **1l**	**2l**	80
5	 **1m**	**2m**	75
6	 **1n**	**2n**	70

[a] All the reactions were carried out at 130−140 °C with 15 mol % of CuI in DMF for 8 h. [b] Isolated yields.

SCHEME 2



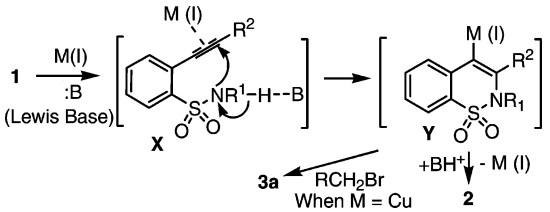
C−C bond forming reaction under copper-catalysis (Scheme 2). Thus, 2-alkynyl benzenesulfonamide can be regarded as a useful precursor for the construction of the diversity-based benzothiazine ring.

The present Ag- and Cu-mediated cyclization of **1** showed very high selectivity for the six-membered ring formed as a result of "*6-endo-dig*" ring closure.[12] No isomeric five-membered-ring product was detected under the condition employed. This unique selectivity is different from that of palladium-catalyzed coupling-cyclization of bromosulfoximines with terminal alkynes where a substantial quantity of five-membered-ring product was formed following a *5-exo-dig* cyclization.[8] While the reasons for these observations are not very clear, a possible explanation is that the longer S−N bond length perhaps favored endo ring closure due to the less geometric constraint. Nevertheless, structures of all the compounds synthesized, i.e., **2** and **3**, were confirmed by spectral data and this was supported by the molecular structure of **2k** and **3a** being confirmed by X-ray analysis (see the Supporting Information).

A plausible mechanism for the formation of **2** is shown in Scheme 3. In the presence of Ag or Cu catalyst the reaction proceeds via activation of the triple bond of **1** by coordination to the transition metal salt to form the π-complex **X**. In the absence of Et_3N, a Lewis base such as DMF (or EtOH) can form a S−N−H···O═C (or S−N−H···HOEt) hydrogen bond, which can enhance the nucleophilicity of the sulfonamide nitrogen. Regioselective nucleophilic attack of the sulfonamide group to the metal-coordinated triple bond through its nitrogen

(12) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

SCHEME 3. Proposed Mechanism for the Formation of Benzothiazines



in an endo dig fashion provides the metal−vinyl species **Y**, which upon subsequent in situ protonation regenerates the catalyst producing the benzothiazine **2**. Et_3N, being a stronger base, can enhance the nucleophilicity of the sulfonamide group thereby reducing the reaction time significantly. In the presence of allyl halides the vinylcopper species **Y** (M = Cu) undergoes in situ allylation to give the product **3**. The observation that benzothiazine **2c** does not afford the compound **3a** when treated with allyl bromide in the presence of CuI under the same reaction condition supports the intermediacy of vinylcopper species **Y** during formation of **3**.

In conclusion, we have developed a simple strategy for the intramolecular cyclization of 2-alkynyl benzensulfonamide to afford 2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides directly with high regioselectivity and good yields. The reaction proceeds via C−N bond forming reaction in the presence of Ag- or Cu-catalyst. The major appealing attributes of this single-step process include atom economy, functional group tolerance, efficiency, and generality. Since the earlier methodology[9a] developed by us requires an additional step involving the removal of C-4 iodo group the present method thus compares favorably with the previously reported strategies and should find applications in the short synthesis of benzothiazine-based anti-inflammatory agents.

Experimental Section

General Procedure for the Preparation of 1. A mixture of 2-iodo-*N*-methyl bezenesulfonamide (0.925 mmol), 10% Pd/C (0.027 g, 0.029 mmol), PPh_3 (0.029 g, 0.11 mmol), CuI (0.010 g, 0.05 mmol), and triethylamine (0.279 g, 0.385 mL, 2.77 mmol) in acetonitrile (15 mL) was stirred at 25 °C for 30 min under nitrogen. To this mixture was added appropriate terminal alkyne (2.77 mmol) slowly with stirring. The reaction mixture was then stirred at 80 °C for 10 h, cooled to room temperature, diluted with EtOAc (50 mL), and filtered through celite. The filtrate was collected and concentrated under vacuum. The residue was purified by column chromatography (SiO_2) to afford the desired product. Analytical data for **1a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (dd, J = 7.8 and 1.0 Hz, 1H), 7.70 (dd, J = 7.8 and 1.4 Hz, 1H), 7.57−7.20 (m, 6H), 5.08 (br s, NH, 1H), 2.61 (d, J = 5.9 Hz, 3H), 2.39 (s, 3H); IR (cm^{-1}, $CHCl_3$) 3346, 2214, 1467, 1330, 1166; *m*/*z* (ES mass) 286 (M + 1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 139.9, 139.2, 133.9, 132.2, 131.6, 129.7, 129.4, 128.2, 122.4, 120.8, 118.7, 111.5, 97.8, 85.1, 29.5, 21.6; elemental analysis found C 67.39, H 5.28, N 4.87; $C_{16}H_{15}NO_2S$ requires C 67.34, H 5.30, N 4.91.

Typical Procedure for the Preparation of 2a. To a mixture of **1a** (0.27 g, 0.94 mmol) and triethylamine (0.28 g, 0.39 mL, 2.8 mmol) in ethanol (5.4 mL) was added $AgSbF_6$ (0.048 g, 0.14 mmol) and the mixture was stirred at 80 °C for 5 min. After completion of the reaction (indicated by TLC), the mixture was filtered through celite and washed with EtOAc (3 × 10 mL). The filtrate was collected and concentrated under vacuum. The residue was purified by column chromatography (SiO_2) to afford the desired product as a white solid (0.24 g, 89%); mp 119−120 °C; ^{1}H NMR ($CDCl_3$,

400 MHz) δ 7.90 (dd, J = 7.7 and 0.6 Hz, 1H), 7.63−7.26 (m, 7H), 6.69 (s, 1H), 3.01 (s, 3H), 2.41 (s, 3H); IR (cm^{-1}, $CHCl_3$) 1346, 1184; *m*/*z* (ES mass) 286 (M + 1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 144.7, 140.1, 132.9, 132.1, 131.7, 131.3, 129.6 (2C), 128.0 (2C), 127.6, 127.5, 122.4, 111.5, 35.7, 21.3; elemental analysis found C 67.39, H 5.29, N 4.63; $C_{16}H_{15}NO_2S$ requires C 67.34, H 5.30, N 4.91.

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Supporting Information Available: Experimental procedures, characterization for all new compounds, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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