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Cycloaddition Reactions of Thiazolium Azomethine Ylides: Application to Pyrrolo[2,1-*b*]thiazoles

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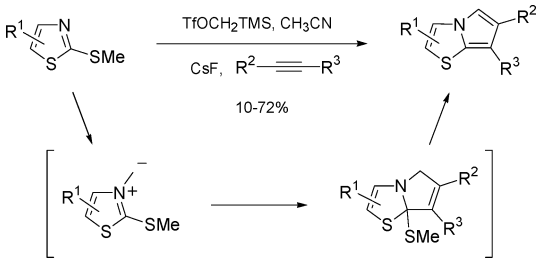
ABSTRACT



Thiazolium azomethine ylides, equipped with a C-2 methanethiol group, participate in an efficient [3 + 2] cycloaddition reaction with acetylene derivatives to yield unique pyrrolo[2,1-*b*]thiazoles. The elimination of the methanethiol leaving group from the cycloadduct has replaced the need for a separate oxidation step and suppresses ring-opening side reactions. Products were obtained in short synthetic sequences to demonstrate their use as a scaffold for compound libraries.

1,3-Dipolar cycloadditions of azomethine ylides are one of the most powerful methods for the construction of five-membered nitrogen heteroaromatic ring systems, both inter- and intramolecularly.[1] Huisgen was first to show that pairing acrylate- or propiolate-derived dipolarophiles with appropriately stabilized azomethine ylides was an effective strategy for the synthesis of pyrroles, pyrrolines, or pyrrolizidines.[2] Vedejs, through a fluoride-induced desilylation of (trimethylsilyl)methylammonium salts, showed that nonstabilized acyclic azomethine ylides could be used to generate pyrroline derivatives.[3]

We envisioned that cyclic azomethine ylides could form a fused 5−5 heteroaromatic system that would comprise the core structural motif for the generation of a diverse library of compounds not previously reported in the literature (Figure 1). Although the pyrrolo[2,1-*b*]thiazole system (Figure 1, Z = S) is not new, and has been prepared by a variety of methods,[4] few patents have been filed with this core scaffold, thereby providing chemical space that is relatively unencumbranced by intellectual property issues. Drug target screening hits from chemical libraries prepared through our novel reaction would not be bound by existing patents.

Early research by Boekelheide with imidazolium azomethine ylides gave initial cycloadducts in which on oxidation (presumably by air) formed the fully aromatic 5−5

(1) For some excellent reviews on azomethine chemistry, see: Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105−1150. Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231−239. Vedejs, E. *Adv. Cycloaddit.* **1988**, *1*, 33−51. Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941−955. Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984; Vol. 2, p 277.

(2) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403−419. Hermann, H.; Huisgen, R.; Mader, H. *J. Am. Chem. Soc.* **1971**, *93*, 1779−1780 and references therein.

(3) Vedejs, E.; Larsen, S.; West, F. G. *J. Org. Chem.* **1985**, *50*, 2170−2174. Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452−6454.

(4) The syntheses of substituted pyrrolo[2,1-*b*]thiazoles is described in the following leading references: Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050−12051. Tverdokhlebov, A. V.; Andrushko, A. P.; Tolmachev, A. A. *Synthesis* **2006**, 1433−1436. Landreau, C.; Janvier, P.; Julienne, K.; Meslin, J. C.; Deniaud, D. *Tetrahedron* **2006**, *62*, 9226−9231. Bedjeguelal, K.; Bienayme, H.; Poigny, S.; Schmitt, Ph.; Tam, E. *QSAR & Comb. Sci.* **2006**, *25*, 504−508. Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075.

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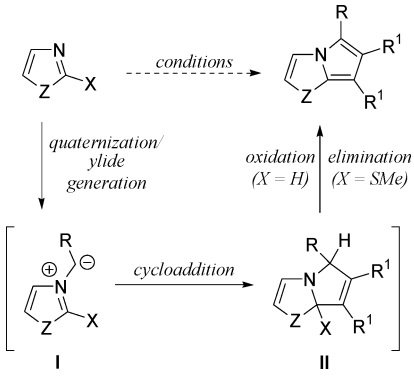


Figure 1. Reaction pathway to the key structural motif.

system, however in low yields (Figure 1, Z = NR^2, X = H).[5] Wang published similar work with benzimidazoles where the addition of CrO_3 as an oxidant afforded the desired compound with modest to good success.[6] In our hands, multiple reaction conditions with imidazole derivatives did not provide the desired system or gave very low yields (Figure 1, Z = NR^2, X = H).[7]

A potential pitfall in this chemistry was the oxidation of the cycloadduct intermediate to the aromatic final product (Figure 1, X = H). Slow aromatization appears to compete with ring-opening reactions due to the ring strain of the fused 5−5 system.[8] An elimination reaction rather than a formal oxidation would be a better alternative to achieve this final transformation. The addition of a leaving group at C-2 would replace the need for an oxidation step as elimination to a fully aromatic ring system would be thermodynamically favored. This strategy was employed by Vedejs and Padwa in alicyclic and acyclic azomethine ylide examples.[9]

Clean quaternization of 2-methylthio-1,3-thiazole (**1**) occurred with $TMSCH_2OTf$ as monitored by ^1H NMR experiments, and after optimization of reaction conditions[10] the cycloadduct **2** was obtained in 66% yield (entry 1, Table 1). The methylmercaptan eliminated from the initial cycloadduct was trapped by excess DMAD present in the reaction mixture to give dimethyl 2-methylthiomaleate, which was isolated. Our attempts to apply these reaction conditions to 1-benzyl-2-methylthioimidazole (Figure 1, Z = NCH_2Ph, X = SCH_3) to form the analogous pyrrolo[1,2-*a*]imidazole were unsuccessful. The reaction of 1-benzyl-2-methylthioimidazole with $TMSCH_2OTf$ in CD_3CN was monitored by NMR, and in 1−2 h at room temperature the quaternary species was

(5) Boekelheide, V.; Fedoruk, J. *J. Am. Chem. Soc.* **1968**, *90*, 3830−3834.

(6) Wang, B.; Hu, J.; Zhang, X.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2000**, *37*, 1533−1537.

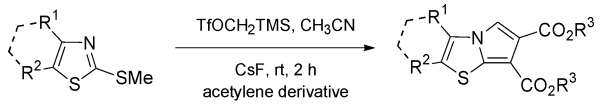
(7) Extensive experimentation with imidazole derivatives under a variety of conditions (solvent, time, temperature, different substrates such as 1-benzylimidazole, 1-methylimidazole, acetylene derivatives, and oxidants) led to little or no desired products being isolated.

(8) Padwa, A.; Chiacchio, U.; Venkatramanan, M. K. *Chem. Commun.* **1985**, 1108.

(9) Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773−4774. Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314−3322.

(10) For details of the optimized protocol, see the Supporting Information.

Table 1. 1,3-Dipolar Cycloaddition of Thiazolium Azomethine Ylides with Acetylene Dicarboxylates



1 **2-12**

entry[a]	R^1 =	R^2 =	R^3 =	prdt	yield[b] (%)
1	H	H	Me	**2**	66
2	H	H	Et	**3**	58
3	H	H	*t*-Bu	**4**	72
4	H	Ph	Me	**5**	37
5	H	3,5-dimethylphenyl	Me	**6**	35
6	H	2-methoxyphenyl	Me	**7**	10
7	H	Br	Me	**8**	0
8	benzo		*t*-Bu	**9**	34
9	2-methoxybenzo		Me	**10**	30
10	Ph	H	*t*-Bu	**11**	10
11	*t*-Bu	H	Me	**12**	0

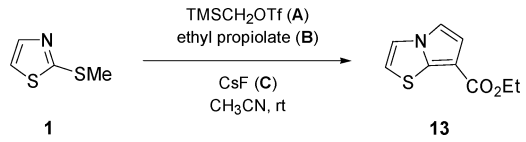
[a] Inverse addition used with 1.4 equiv of CsF, 4.0 equiv of dimethylacetylene dicarboxylate in CH_3CN at ambient temperature for 2 h. For exact conditions, see the Supporting Information. [b] Isolated yields.

cleanly formed. However, the reaction of the imidazolium ylide with dimethyl acetylenedicarboxylate gave a dark reaction mixture that contained multiple spots by TLC.

Applying our inverse addition conditions[10] to substituted thiazoles provided pyrrolothiazoles **3**−**11**. Substitution at C-5 (entries 4−7) provided lower yields of the cycloadduct as compared with the unsubstituted thiazoles. Substituents that reduced the thiazole nitrogen electron density (cf. entries 7−9) or that increased steric hindrance at the thiazole nitrogen (cf. entries 8−11) all gave low yields (10−34%) or none of the desired product.

When ethyl propiolate was used as the dipolarophile in this cycloaddition reaction (Table 2), CsF was added to the preformed azolium species and then alkyne added in one portion, only a 32% isolated yield of **13** was obtained (entry 1). The other regioisomer was observed as a ∼5% unseparable impurity in the reaction mixture for all examples. However, when the azolium species and alkyne were added dropwise via an additional funnel to a stirred solution of CsF, the yield was increased to 53% (entry 2). Using this "inverse addition" method, modification of the ethyl propiolate stoichiometry (1−10 equiv), the reaction concentration (0.05−1 M), the temperature (rt to −5 °C), or the addition of CuI, all had no effect on the isolated yield. Substituting tetramethylammonium fluoride (TMAF) for CsF (entry 3) or varying the equivalents of $TMSCH_2OTf$ (entry 4) reduced the yield. TBAF gave even poorer results, presumably due to traces of water present. The best yield was obtained when the preformed thiazolium salt, combined with 1.5 equiv of ethyl propiolate in acetonitrile, was added at room temperature over 1 h to a stirred solution of CsF and 1.5 equiv of ethyl propiolate in acetonitrile (entry 6). After workup and purification, a 69% isolated yield of the pyrrolo[2,1-*b*]-thiazole **13** was obtained on a 15 mmol reaction scale.[10,11]

Table 2. Optimization of Reaction Conditions with Ethyl Propiolate



1 13

entry[a]	**A** (equiv)	**B** (equiv)	**C** (equiv)	yield[b] (%)
1[c]	1.05	4.0	1.4	32
2	1.05	4.0	1.4	53
3[d]	1.05	4.0	1.4	19
4	2.0	4.0	2.0	32
5[e]	1.05	4.0	1.4	48
6[f]	1.05	3.0	1.4	69

[a] Reactions were run with inverse addition over 2 h at 0.1 M in acetonitrile at rt. [b] Isolated yields. All crude products contained ~5% of the other regioisomer. [c] No inverse addition. [d] TMAF was used in place of CsF. [e] Azolium plus alkyne added to CsF. [f] Half alkyne with azolium and half alkyne with CsF.

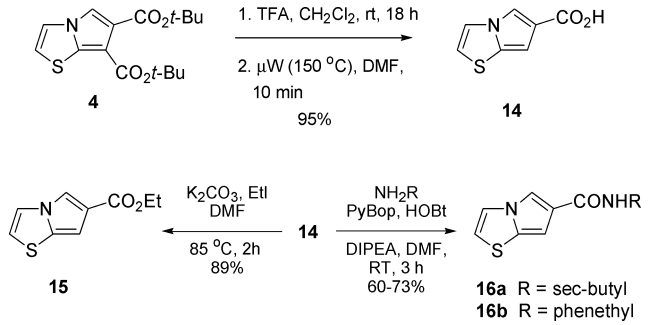
Under these inverse addition conditions, we postulate that as the thiazolium species is added to the CsF/ethyl propiolate solution, the ylide **I** is rapidly formed under dilute reaction conditions, but in the presense of higher concentrations of ethyl propiolate which facilitates the formation of the initial cycloadduct **II** (Z = S, R = H, X = SCH_3). These inverse addition conditions would serve to minimize the dimerization of the ylide **I** or the condensation of the ylide **I** to the thiazolium precursor; side reactions that are well-known for reactive dipoles.[12]

The use of other unsymmetrical acetylenes with this cycloaddition was investigated. 3-Butyne-2-one, ethynyl *p*-tolyl sulfone, and *N*-phenyl-2-propynamide[13] gave low-yielding, complex mixtures that were difficult to purify. Phenylacetylene and *N*-phenylmaleimide provided total decomposition of the reaction mixture.

In an ab initio study, full optimizations of the reactants, which included the ylides **I** (Z = NMe and S, R = H, X = SMe), dimethyl acetylene dicarboxylate, and methyl propiolate, was carried out using the density functional B3LYP, at the 6-31++g(2d,p) level of theory. The results indicate that the cycloaddition reaction is charge or orbital controlled. This confirms that the reaction is a Sustmann Type 1 1,3-dipolar cycloaddition reaction, where the dominant frontier molecular orbital interaction is between the dipole HOMO and the dipolarophile LUMO.[14] The similar HOMO−LUMO gap energies as well as similar orbital coefficients predict that the cycloaddition reactions of both the imidazolium ylide (**I**, Z = NMe) and thiazolium ylide (**I**, Z = S) should occur. In fact, the imidazolium reaction is slightly more favored than the thiazolium case. These results imply that the low yields with the imidazolium ylide result from an adduct ring-opening reaction to byproducts. Since C−N bonds are shorter than the C−S bonds, the imidazolium ylide cycloadduct (**II**, Z = NMe) would have more ring strain than the thiazolium ylide cycloadduct (**II**, Z = S), thereby favoring ring opening of **II** (Z = NMe) instead of MeSH elimination to aromatize to form the fused 5−5 system. The molecular orbital coefficients and atomic charges of the methyl propiolate LUMO and the thiazolium ylide HOMO predict the observed regioselectivity in the formation of the cycloaddition product **13**.[15]

Manipulation of these cycloadducts **4** and **13** was then undertaken to enable the preparation of diverse compound libraries (Scheme 1). Cycloadduct **4** was treated with trifluoroacetic acid, concentrated, and without purification was placed into a microwave reactor (150 °C) for 10 min in DMF to provide the 6-substituted monoacid **14** in very high yields. Ester formation with EtI and K_2CO_3 provided the 6-ethyl ester **15**. Alternatively, the monoacid **14** could be coupled with amines to provide amides **16a** and **16b** in good yield.

Scheme 1. Manipulation of the Pyrrolo[2,1-*b*]thiazole Core



We now had in place efficient synthetic schemes to prepare both ethyl ester regiosiomers (**13** and **15**) for further experimentation. We found that NBS bromination of **13** gave the best yield and isolated purity of the 6-bromo-pyrrolo-[2,1-*b*]thiazole. This bromide could be isolated by column chromatography, however in lower yield, and on standing at room temperature the compound decomposed overnight. Bromination of the ethyl ester **15** provided a complex mixture of regioisomers and purification proved extremely difficult. Other halogenation protocols resulted in little to no desired products being detected.[16]

The crude product from the NBS bromination of **13** following aqueous workup and concentration was immediately reacted with arylboronic acids in the Suzuki

(11) The ^{1}H NMR coupling of the aromatic signals of the pyrrolo[2,1-*b*]thiazole **13** support the structural assignment. For details of the coupling constant assignments for **13** and ^{1}H-NMR spectra, see the Supporting Information.

(12) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984; Vols. 1 and 2.

(13) For synthesis, see: Coppola, G. M.; Damon, R. E. *Synth. Commun.* **1993**, *23*, 2003−2010.

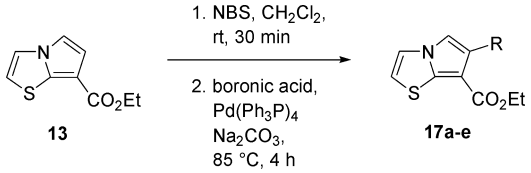
(14) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717−2720. Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569−593. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909.

(15) See the Supporting Information for details on the ab initio calculations, the FMO correlation diagrams, and the HOMO−LUMO orbital coefficient diagrams.

(16) Other iodination conditions (I_2 and AgO_2CCF_3, NIS, for example) and bromination conditions (Br_2, Br_2 and acetic acid, for example) provided little to no desired compound.

reaction to provide the 6-aryl pyrrolo[2,1-*b*]thiazoles **17a**−**e** in good overall yields for two steps (Table 3). Both electron-rich (**17c**) and electron-poor (**17b** and **17d**) boronic acids gave similar results in the Suzuki coupling with the brominated pyrrolo[2,1-*b*]thiazole **13**. In addition, 3-pyridinylboronic acid underwent successful coupling to give compound **17e**. These products were stable and could be stored with ease. Other electrophilic aromatic substitution reactions such as Friedel−Crafts acylation of **13** or **15** led to significant decomposition or products that were obtained in very low yield.

Table 3. Bromination/Suzuki Coupling of Cycloadduct **13**

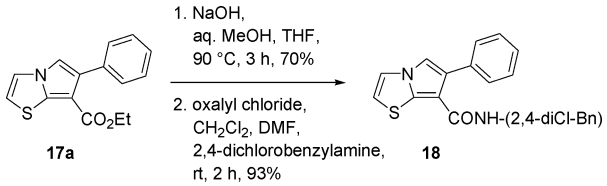


entry[a]	R =	product	yield[b] (%)
1	phenyl	**17a**	69
2	4-Cl-phenyl	**17b**	72
3	4-OMe-phenyl	**17c**	58
4	4-SO_2Me-phenyl	**17d**	62
5	3-pyridinyl	**17e**	53

[a] For reaction conditions, see the Supporting Information. [b] Isolated yields over two steps.

Finally, the arylated cycloadduct **17a** was saponified to provide the crystalline free acid, which upon treatment with oxalyl chloride and 2,4-dichlorobenzylamine in the presence of catalytic DMF, provided the expected amide **18** in very good overall yields for two steps (Scheme 2).[17]

Scheme 2. Preparation of Pyrrolo[2,1-*b*]thiazole-7-carboxamide



In conclusion, we have shown that thiazolium azomethine ylides equipped with a C-2 methanethiol leaving group readily participate in 1,3-dipolar cycloadditions when paired with appropriate dipolarophiles. It was also shown that elimination of methanethiol was indeed a suitable replacement for the known oxidation of the initial cycloadduct to form the fully aromatic pyrrolo[2,1-*b*]thiazole and in gram quantities. There are very limited examples of the pyrrolo[2,1-*b*]thiazole scaffold in the literature.[4] Our successful synthesis of this aromatic 5−5 system and the subsequent substitution chemistry has given us a scaffold from which novel, diverse, and druglike compound libraries can be prepared.

Acknowledgment. We thank William Jones (J&JPRD) for assistance with HRMS data acquistion and George Elgar (J&JPRD) for ^{1}H NMR assistance.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071229N

(17) Procedure from: Doherty, E. M.; Fotsch, C.; Bo, Y.; Chakrabarti, P. P.; Chen, N.; Gavva, N.; Han, N.; Kelly, M. G.; Kincaid, J.; Klionsky, L.; Liu, Q.; Ognyanov, V. I.; Tamir, R.; Wang, X.; Zhu, J.; Norman, M. H.; Treanor, J. J. S. *J. Med. Chem.* **2005**, *48*, 71−90.