ORGANIC LETTERS

2010
Vol. 12, No. 23
5526−5529

A Selective and Convenient Method for the Synthesis of 2-Phenylaminothiazolines

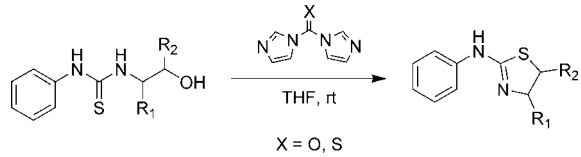
April L. Bernacki,* Lingyang Zhu, and D. David Hennings

Array BioPharma, 3200 Walnut Street, Boulder, Colorado 80301, United States

april.bernacki@arraybiopharma.com

Received October 7, 2010

ABSTRACT



A series of 2-phenylaminothiazolines have been prepared from the corresponding *N*-(2-hydroxyethyl)-*N*′-phenylthioureas under mild reaction conditions using either thio-CDI (1,1′-thiocarbonyldiimidazole) or CDI (1,1′-carbonyldiimidazole) to promote the cyclization. This protocol provides the desired cyclization products in good yield with excellent selectivity. The scope and selectivity of this methodology are also described.

The 2-aminothiazoline ring system is a moiety that can be found in biologically relevant compounds including neuronal nicotinic acetylcholine receptor modulators,[1] nitric oxide-synthase inhibitors,[2] antimicrobial agents,[3] and antimicotic agents.[4] Although there are several methods reported for the conversion of 2-hydroxyethyl-thioureas to the corresponding 2-aminothiazolines, most have significant liabilities. One common method is acid-promoted dehydrative cyclization[5] which employs harsh reaction conditions that are not compatible with acid-labile substrates or materials prone to acid-catalyzed racemization. Mitsunobu conditions[6] are milder but tend to give mixtures of N and S cyclization products (formation of 2-imidazolidinethiones and 2-aminothiazolines). The use of sulfonyl chlorides as activating agents preferentially forms the 2-aminooxazoline in most cases.[7] In the course of our research, we found that treatment of *N*-(2-hydroxyethyl)-*N*′-phenylthioureas with either thio-CDI (1,1′-thiocarbonyldiimidazole) or CDI (1,1′-carbonyldiimidazole) will form 2-aminothiazolines in good yield and with excellent selectivity.

During the preparation of thiourea **1** from 3-aminobenzonitrile, it was discovered that although the desired unsymmetrical thiourea was the major product a small

(1) Faghih, R.; Gfesser, G. A.; Lynch, C. L.; Gopalakrishnan, M.; Gopalakrishnan, S.; Malysz, J.; Gubbins, E. J.; El Kouhen, R.; Li, J.; Sarris, K. A.; Michmerhuizen, M. J.; Wang, Y. Thiazoline and oxazoline derivatives as nAChR modulators and their preparation and use in the treatment of diseases. WO 2008002956.

(2) Bigot; Carry, J.-C.; Mignani, S. 2 - aminothiazoline derivatives and their use as inhibitors of inducible NO-synthase. WO 2003040115.

(3) Bonde, C.; Gaikwad, G. *Bioorg. Med. Chem.* **2004**, *12*, 2151–2161.

(4) Baumann, R. J.; Mayer, G. D.; Fite, L. D.; Gill, L. M.; Harrison, B. L. *Chemotherapy* **1991**, *37*, 157–165.

(5) (a) Xu, X.; Qian, X.; Li, Z.; Song, G.; Chen, W. *J. Fluorine Chem.* **2005**, *126*, 297–300. (b) Klayman, D. L.; Woods, T. S. *J. Org. Chem.* **1975**, *40*, 2000–2002.

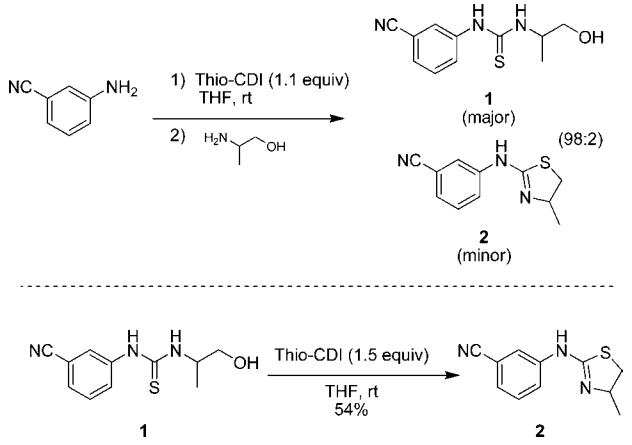
(6) (a) Kim, T. H.; Cha, M.-H. *Tetrahedron Lett.* **1999**, *40*, 3125–3128. (b) Long, K.; Boyce, M.; Lin, H.; Yuan, J.; Ma, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3849–3852.

(7) (a) It was originally reported by Kim et al. that treatment of *N*-(2-hydroxyethyl)-*N*′-phenylthioureas with TsCl and NaOH produced the corresponding 2-phenylaminothiazolines. Further analysis of the cyclization products, as described in their subsequent corrigendum, revealed that no sulfur was present and that the products were indeed the 2-phenylamino-2-oxazolines when N1 was not substituted. Kim, T. H.; Min, J. K.; Lee, G.-J. *Tetrahedron Lett.* **1999**, *40*, 8201−8204; *Tetrahedron Lett.* **2001**, *42*, 2413. (b) Lee, G.-J.; Kim, J. N.; Kim, T. H. *Bull. Korean Chem. Soc.* **2002**, *23* (1), 19–20. (c) Heinelt, U.; Schultheis, D.; Jager, S.; Lindenmaier, M.; Pollex, A.; Beckmann, H. S. g. *Tetrahedron* **2004**, *60*, 9883–9888.

10.1021/ol102428m
Published on Web 11/01/2010

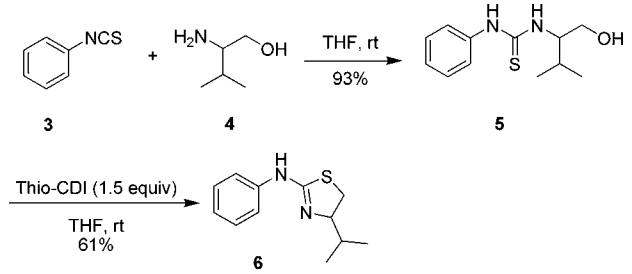
amount of the thiazoline cyclization product was observed (Scheme 1). To confirm that thio-CDI was indeed promoting cyclization, thiourea **1** was purified and resubjected to the reaction conditions with a full equivalent of thio-CDI. The reaction proceeded readily at room temperature, and phenylaminothiazoline **2** was isolated in 54% yield. This serendipitous result led us to further explore the scope and general utility of this novel transformation.

Scheme 1. Discovery of Thiazoline Formation under Novel Conditions



We chose *N*-phenylthioureas with simple alkyl-substituted amino alcohol side chains to study this transformation. These substrates can be easily prepared by reaction of phenylisothiocyanate (**3**) with the appropriate amino alcohol in THF at ambient temperature.[8] The model substrate used for optimization of the methodology (thiourea **5**, Scheme 2) was prepared in 93% yield from phenylisothiocyanate (**3**) and valinol (**4**). To confirm the result observed with compound **1**, thiourea **5** was treated with thio-CDI which gave the desired product, thiazoline **6,** in 61% isolated yield.

Scheme 2. Synthesis of a Model System Using Thio-CDI



With the initial proof of concept in hand, we looked at optimizing the reaction with the addition of an auxiliary base. Bases such as KOtBu, Cs_2CO_3, K_2CO_3, Et_3N, imidazole, and DBU were screened, all at 2 equiv in relation to the thiourea starting material (**5**). We found that, in general, the inorganic bases were detrimental to the reaction (low assay yields with the balance of the material being unidentified impurities as well as residual starting material), whereas the weaker amine bases had little to no effect on the yield. The performance of the reaction was also assessed using solvents other than THF. Acetone, toluene, CH_2Cl_2, and EtOAc perform comparably to THF, while more polar solvents (DMF, NMP, and acetonitrile) gave lower yields. On the basis of these results, it was determined that our preferred conditions for this transformation are to use THF at ambient temperature with no additional base.

Although the reaction conditions described above were successful in converting hydroxyethyl-thioureas to the corresponding thiazolines under mild conditions, the use of thio-CDI on a larger scale can be problematic. Thio-CDI is fairly expensive compared to other activating reagents and has limited availability in large batch sizes. It is a foul-smelling solid that is unstable to moisture, which leads to storage problems. For these reasons, we decided to investigate alternative reagents to promote the cyclization.

Several common activating agents were screened using compound **5** as a test substrate to evaluate their reactivity and selectivity compared to the results using thio-CDI. Several cyclization products (**6**−**9**) as well as a substitution product (**10**) were observed as detailed in Table 1.[9] The use of diethylazodicarboxylate (Mitsunobu conditions, entry 1) gave a mixture of S and N cyclization products, with imidazolidinethione **9** being favored 3:1 over thiazoline **6**. Activation of the thiourea using MeI or tosyl chloride exclusively gave cyclization to oxazoline **7**, and although mesyl chloride was also selective for oxazoline **7**, 10% of thiazoline **6** was observed (entries 2−4). The results in entries 1−4 all corroborate the chemoselectivities reported in the literature for similar substrates.[6,7,10] Other activating agents that are novel to this type of transformation were also examined with mixed results. Both triphosgene and thiophosgene produced multiple cyclization products; however, the major product with these reagents was alkyl chloride **10**.

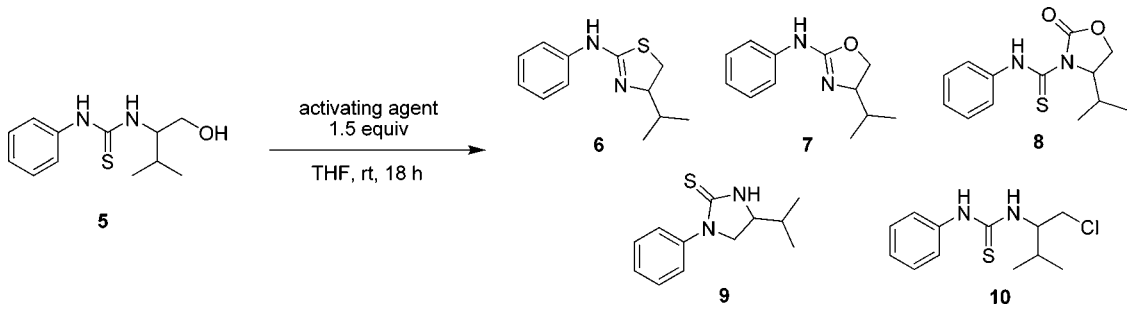
Performing the reaction using Vilsmeier reagent gave 60% of thiazoline **6** with the remaining 40% being comprised of multiple unidentified impurities. As expected, thio-CDI gave thiazoline **6** as the major product with only 3% of oxazoline **7**, but we were pleased to see that CDI gave exclusively thiazoline **6**. As the reaction profile for CDI is equal to or superior to thio-CDI, and CDI is not hampered by the limitations previously listed for thio-CDI, this reagent was chosen for further examination.

(8) (a) Kruse, L. I.; Kaiser, C.; DeWolf, W. E., Jr.; Frazee, J. S.; Garvey, E.; Hilbert, E. L.; Faulkner, W. A.; Flaim, K. E.; Sawyer, J. L.; Berkowitz, B. A. *J. Med. Chem.* **1986**, *29*, 2465–2472. (b) Lattanzi, A. *Synlett* **2007**, *13*, 2106–2110.

(9) The products were characterized using ^{1}H NMR and LC−MS analysis, and the product ratios were generated from the ^{1}H NMR integrations of the crude reaction mixtures.

(10) (a) Perez, E. M.; Oliva, A. I.; Hernandez, J. V.; Simon, L.; Moran, J. R.; Sanz, F. *Tetrahedron Lett.* **2001**, *42*, 5853–5856. (b) Hetenyi, A.; Szakonyi, Z.; Klika, K.; Pihlaja, K.; Fulop, F. *J. Org. Chem.* **2003**, *68*, 2175.

Table 1. Evaluation of Activating Agents for Thiazoline Formation[a]

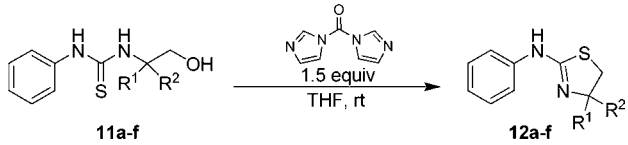


entry	activating agent	% **6**	% **7**	% **8**	% **9**	% **10**
1	Mitsunobu (DEAD)[b]	20	-	-	60	-
2	MeI	-	>99	-	-	-
3	MsCl[c]	10	85	-	-	-
4	TsCl	-	>99	-	-	-
5	thiophosgene	10	20	-	-	70
6	triphosgene	20	-	25	-	55
7	Vilsmeier−Haack[c]	60	-	-	-	-
8	Thio-CDI	97	3	-	-	-
9	CDI	>99	<1	-	-	-

[a] Product ratios were determined by ^{1}H NMR. [b] 20% of compound **5** observed. [c] Unknown impurities comprise the balance of the material.

To probe the generality of this methodology, a series of thioureas with substitution α to the amine of the amino alcohol was treated with CDI in THF (**11a**−**f**, Table 2).

Table 2. Scope of Synthesis of 4-Substituted Thiazolines



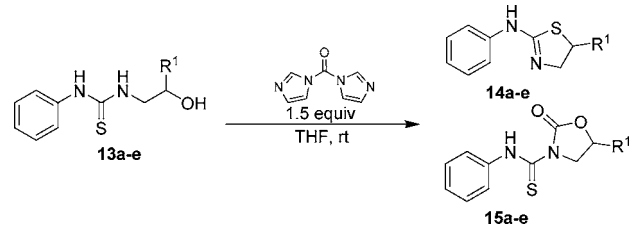
entry	starting material	R^1	R^2	yield[a]
1	**11a**	H	H	71%
2	**11b**	Me	H	74%
3	**11c**	Me	Me	75%
4	**11d**	Et	H	78%
5	**11e**	*i*Pr	H	82%
6	**11f**	(*R*)Ph	H	88%

[a] Yields determined after isolation by column chromatography.

In each case, the substrate was cleanly converted to the desired thiazoline product with isolated yields ranging from 71 to 88% (**12a**−**f**).

Continuing to evaluate the scope of this reaction, a series of thioureas with substitution α to the hydroxyl group of the amino alcohol (**13a**−**e**) were prepared and subjected to CDI in THF (Table 3). In this series of substrates, an interesting difference in chemoselectivity was observed. When R_1 is alkyl (ethyl and trifluoromethyl), the only isolable product was the corresponding oxazolidinone (**15a**,**b**), which is the result of intramolecular acylation (path b, Scheme 3). In these two examples, formation of the thiazoline product may have been disfavored due to increased steric hindrance around the electrophilic site (path a, Scheme 3). An electronic effect was also observed within the substrates examined. The more electron-rich *p*-methoxy analog (**13c**) highly favored formation of the desired thiazoline (**14c**), whereas the simple phenyl and *p*-CF_3 analogs gave both cyclization products in ∼2:1 ratio favoring the thiazoline. Presumably, the chemoselectivity observed with the phenyl substituents is a result of benzylic stabilization of the electrophilic site favoring path a (Scheme 3).

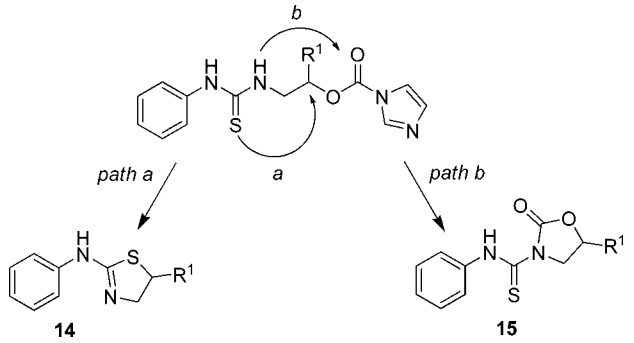
Table 3. Synthesis of 5-Substituted Thiazolines



entry	starting material	R^1	yield of **14**[a]	yield of **15**[a]
1	**13a**	Et	nd[b]	99%
2	**13b**	CF_3	nd[b]	88%
3	**13c**	4-OMe-Ph	81%	4%
4	**13d**	Ph	67%	29%
5	**13e**	4-CF_3-Ph	62%	27%

[a] Isolated yield after column chromatography. [b] nd = not detected.

Scheme 3. Proposed Reaction Pathways



In summary, we have demonstrated that CDI can be used to promote a selective dehydrative cyclization of *N*-(2-hydroxyethyl)-*N*′-phenylthioureas to form 2-aminothiazolines under very mild conditions. The cyclization tolerates substitutions of the ethyl group α to N1 or on the carbon bearing the hydroxyl group provided the substituent is an aryl moiety. Furthermore, the use of CDI, which is a stable, inexpensive, and easily handled activating agent, makes this methodology preparatively useful.

Acknowledgment. The authors wish to thank Phil Anderson, Cale Bibb, and Carman Bryant from Array BioPharma, Inc. for providing HRMS and IR data.

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

OL102428M