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Aryl radical cyclizations of *N*-(2-halobenzoyl)-cyclic ketene-N,S-acetals

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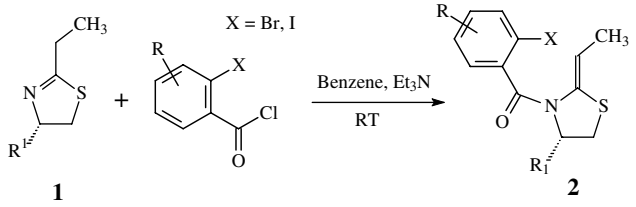
Abstract—2-Ethylthiazolines react with 2-halobenzoyl chlorides to form *N*-(2-halobenzoyl)-cyclic ketene-N,S-acetals, which undergo stereo-controlled radical cyclizations to afford (*R*,*S*,*S*)-3-alkyl-10-methyl-2,3,10,10a-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one and (*R*,*R*,*S*)-3-alkyl-10-methyl-2,3,10,10a-tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one.

In recent years, there has been considerable interest in the cyclization of radicals onto heterocyclic compounds.[1,2] Important synthetic routes to prepare various heterocycles and many new methodologies have been developed. Normally, radical cyclizations generate a mixture of five- and six-membered ring compounds.[3,4] The product ratio obtained depends on the structure of the initiator and reactants as well as the reaction conditions.[5–7]

Cyclic ketene-N,S-acetal chemistry has been actively investigated in our laboratory,[8] but radical cyclizations onto cyclic ketene-N,S-acetals as a route to heterocyclic structures remains unreported. Radical cyclizations onto electron-rich enamines are known.[9] Cyclic ketene-N,S-acetals are more electron-rich agents than enamines. They simultaneously combine both enamine and vinyl thioether functions, which enhance the π-electron density at the double bond and also provide two heteroatoms when converted to a cyclization product.[10] Many classes of ketene acetals are extremely reactive and difficult to handle, which probably accounts for their less frequent application in organic synthesis. While improved handling and storage methods have been developed,[8] the generation of cyclic ketene-N,S-acetals as intermediates and their subsequent use in nucleophilic cyclization reactions[10] suggests they may be more broadly applicable in synthesis.

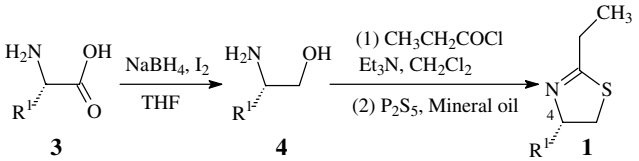


1 **2**

Scheme 1. Reaction of 2-ethylthiazolines **1** with 2-halobenzoyl chlorides

We now find that 2-ethylthiazolines **1** readily react with 2-halobenzoyl chlorides to afford *N*-(2-halobenzoyl)-cyclic ketene-N,S-acetals **2** in excellent yields (Scheme 1) in benzene at room temperature. Furthermore, these *N*-(2-halobenzoyl)-cyclic ketene-N,S-acetals serve as

Table 1. The synthesis of 2-ethyloxazolines



3 **4** **1**

Entry	R^1 in **3**	Product **1**	Yield[a] (%)
1	$-CH(CH_3)_2$	**1a**	60
2	$-CH_2CH(CH_3)_2$	**1b**	63

[a] All are isolated yields based on **3**.

Keywords: Radical cyclization; Cyclic ketene-N,S-acetals; 2-Alkylthiazolines; Stereoselective cyclization; Tetrahydrothiazolo[3,2-*b*]isoquinolin-5-one.
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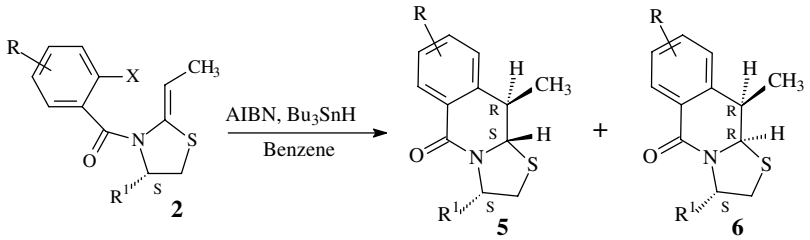
Table 2. Aryl radical cyclization of *N*-2-halobenzoyl cyclic ketene-N,S-acetals[a]



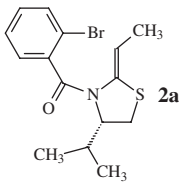
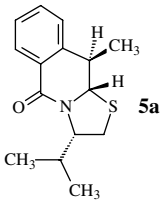
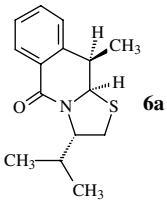
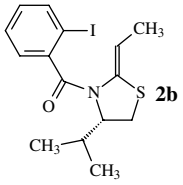
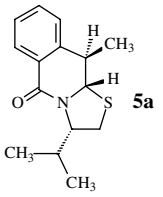
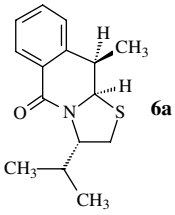
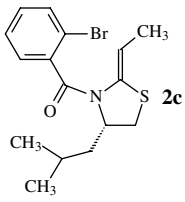
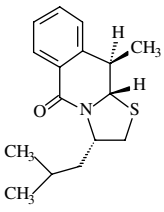
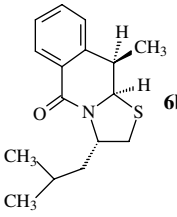
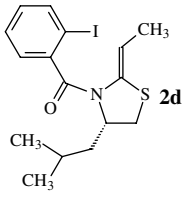
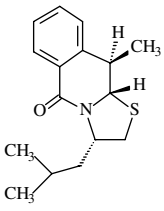
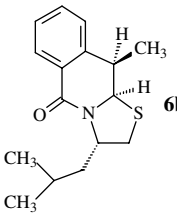
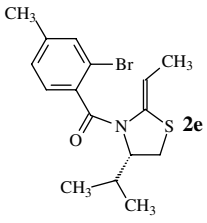
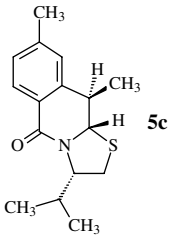
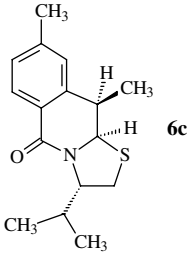
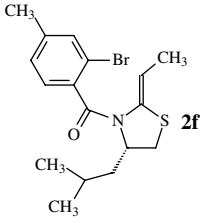
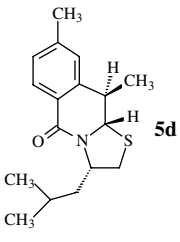
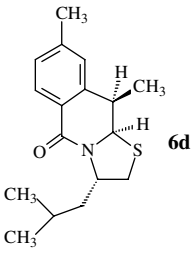
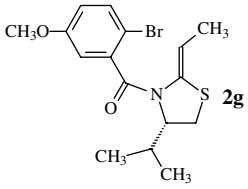
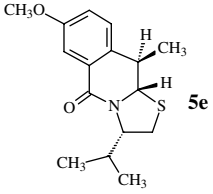
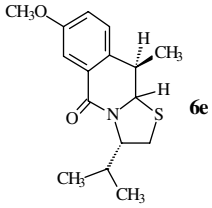
N-2-Halobenzoyl cyclic ketene-N,S-acetal **2**	Product 1	Product 2	Yield[b] (**5**+**6**) (%)
 **2a**	 **5a**	 **6a**	78 Ratio of **5a**/**6a** = 1.4/1
 **2b**	 **5a**	 **6a**	82 Ratio of **5a**/**6a** = 1.5/1
 **2c**	 **5b**	 **6b**	70 Ratio of **5b**/**6b** = 1.1/1
 **2d**	 **5b**	 **6b**	68 Ratio of **5b**/**6b** = 1.3/1
 **2e**	 **5c**	 **6c**	77 Ratio of **5c**/**6c** = 1.5/1
 **2f**	 **5d**	 **6d**	67 Ratio of **5d**/**6d** = 1.2/1

Table 2 (*continued*)

N-2-Halobenzoyl cyclic ketene-N,S-acetal **2**	Product 1	Product 2	Yield[b] (**5**+**6**) (%)
 **2g**	 **5e**	 **6e**	79 Ratio of **5e/6e** = 1.4/1

[a] The mole ratio of **2**/Bu_3SnH/AIBN used was 10/10/1. Reactions were refluxed in dry benzene under argon for 10 h.
[b] Isolated yields based on **1**.

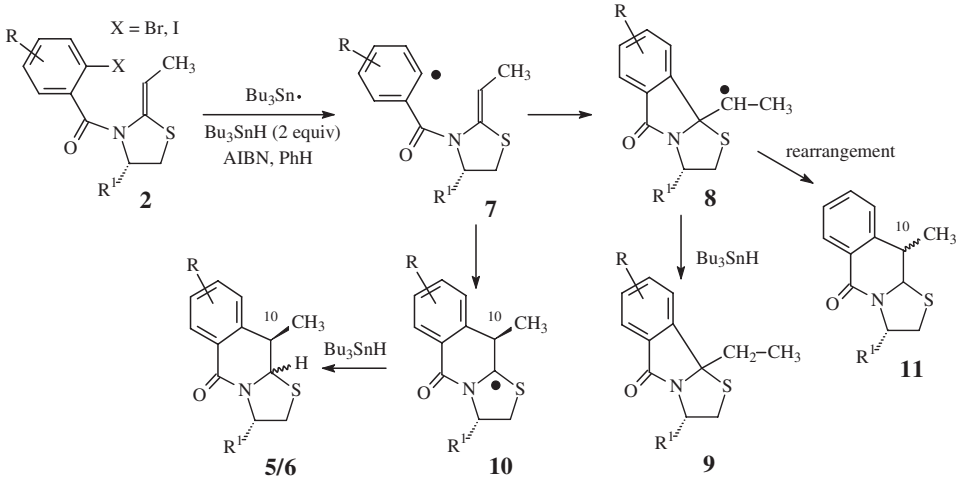
precursors for aryl radical cyclizations. The facile formation of cyclic ketene-N,S-acetal double bonds shown in Scheme 1, may be followed immediately by an aryl radical cyclization with no need for further purification of **2**. In addition, by initially building a stereogenic center at C-4 of these 2-ethylthiazolines **1**, the *N*-(2-halobenzoyl)-cyclic ketene-N,S-acetal formed by *N*-benzoylation can then undergo stereocontrolled radical cyclization.

The synthesis of 2-ethylthiazolines with a stereogenic center at C-4 proceeds as shown in Table 1. Amino acids **3** (*S*-configuration) were reduced by $NaBH_4$–I_2 in THF to give amino alcohols **4**.[11] These were treated with acid chlorides to afford the corresponding hydroxyamides, which were converted to 2-ethylthiazolines **1** with P_2S_5.[12]

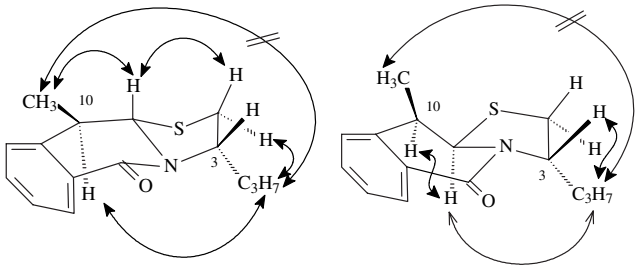
We recently reported that 2-alkylthiazolines react with acid chlorides to afford *N*-acyl cyclic ketene acetals.[13] *N*-(2-Halobenzoyl)-cyclic ketene-N,S-acetals were formed analogously in excellent yields using 2-halobenzoyl chlorides where the halogen is bromide or iodide (Scheme 1). After the removal of triethylamine and benzene from the product mixture by rotary evaporation, these crude *N*-(2-halobenzoyl)-cyclic ketene-N,S-acetals **2** were used without further workup in radical cyclizations. These cyclizations occurred in good yields in refluxing benzene (Table 2).

The suggested cyclization mechanism (Scheme 2) illustrates two pathways that appear possible. Initially formed radical **7** would lead to either radical intermediate **8** or **10**. Radical **8** would generate five-membered ring compound **9** by hydrogen abstraction from Bu_3SnH, while radical **10** would produce six-membered ring compound **5/6**. Radical **7** was found to cyclize only to the more stable tertiary radical **10** rather than the less stable secondary radical **8**. Therefore, this afforded the less strained 6/5 ring products **5** and **6** upon hydrogen abstraction from Bu_3SnH. The more strained 5/5 ring fusion product **9** could not be detected. Cyclization to **8** followed by rearrangement to **10** seems highly unlikely, because this would lead to the generation of both *R*- and *S*-configurations of C-10 in product **5** and **6**. Only the *R*-configuration was formed.

^1H, ^{13}CNMR, GC–MS, $DEPT_{135}$, HETCOR, and NOESY verified the structures of **5/6**. This cyclization reaction could have given a mixture of four different diastereomers. The aryl radical could possibly have attacked the exocyclic double bond in **2** either *cis* or *trans* to the C-4 isopropyl group. Then, hydrogen abstraction by radical **10** could have occurred either



Scheme 2. Possible aryl radical cyclizations of *N*-2-halobenzoyl cyclic ketene-N,S-acetals.



Scheme 3. Selected NOESY correlations for compounds **5a** and **6a**.

cis or *trans* to the C-4 isopropyl function. HPLC and NMR data demonstrated that only two cyclization products **5** and **6** were formed, and these were the major products. These are given in Table 2. NOESY experiments definitively determined the stereochemistry of **5** and **6**. The methyl group on the central ring was *trans* to the isopropyl group of the oxazolidine ring in each case, confirming that aryl radical attack occurred *trans* to the isopropyl group as **2** was converted to **10**. Radical **10** abstracted hydrogen from Bu_3SnH both *trans* and *cis* to the isopropyl group to generate **5/6a–e** (Scheme 3).

The selectivity of the hydrogen abstraction step by radical **10** is reduced by presence of the methyl group at the 10-position. The 3-isopropyl group hinders *cis* hydrogen abstraction from Bu_3SnH by **10**. However, the 10-methyl group hinders *trans* hydrogen abstraction, but it still remains the dominant abstraction path. Studies of the selectivity in the hydrogen abstraction step are underway with (4*S*)-4-isopropyl-2-methylthiazoline, which will generate an intermediate radical analogous to **10** without the 10-methyl group. Furthermore, we have extended analogous aryl radical cyclizations to cyclic ketene-N,S-acetals generated from 2-alkylthiazines and cyclic ketene-N,O-acetals formed from 2-alkyloxazolines.[14]

In conclusion, this is the first report where the electron-rich double bond of a cyclic ketene-N,S-acetal was used for radical cyclization. This very nucleophilic double bond was produced by reacting 2-halobenzoyl chlorides with 2-ethylthiazolines in presence of Et_3N, and used in the next cyclization step without isolation or purification of the resulting ketene-N,S-acetal. The reactive (*N*-2-halobenzoyl)-cyclic ketene-N,S-acetals are readily prepared by the direct reaction of the corresponding benzoyl chlorides and 2-ethylthiazolines. The stereogenic centers in the starting materials control diastereoselectivity of cyclization products. Studies of the selectivity in the hydrogen abstraction step are underway with (4*S*)-4-isopropyl-2-methylthiazoline. The broad synthetic potential is evident from the ability to use both six- and five-membered ring cyclic ketene-N,X-acetals (X = S, O)[14] and in analogy with stereoselective radical-mediated cyclizations of norphedrine-derived α-iodoamides to generate enantiopure pyrrolidines.[15] A general experimental procedure is provided.[16]

Acknowledgements

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Supplementary data

The detailed synthetic and isolation procedures and the full spectral identification of all compounds are provided in Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.205.

References and notes

1. (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986; (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715; (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: London, 1992; (d) Giese, B. et al. *Org. React.* **1996**, *48*, 301.
2. (a) Leffler, J. E. *An Introduction to Free Radicals*; Wiley-Interscience: New York, 1995; (b) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: New York, 1995; (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1998.
3. (a) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525; (b) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529; (c) Crich, D.; Hwang, J. T.; Liu, H. *Tetrahedron Lett.* **1996**, *37*, 3105; (d) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *110*, 1272.
4. (a) Navarro-Vazquez, A.; Garcia, A.; Domingguez, D. *J. Org. Chem.* **2002**, *67*, 3213, 1272; (b) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951; (c) Allan, G. M.; Parsons, A. F.; Pons, J. F. *Synlett* **2002**, 1431.
5. (a) Basak, A.; Bag, S. S.; Rudra, K. R. *Chem. Lett.* **2002**, 710; (b) Tamura, O.; Matssukida, H.; Toyao, A. *J. Org. Chem.* **2002**, *67*, 5537.
6. (a) Nugent, B. M.; Williams, A. L.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877; (b) Wang, Q.; Padwa, A. *Org. Lett.* **2004**, *6*, 2189.
7. (a) Abeywickrema, A. N.; Beckwith, A. L. J. *J. Org. Chem.* **1987**, *52*, 4072; (b) Snieckus, V.; Cuevas, J. C.; Sloan, C. P. *J. Am. Chem. Soc.* **1990**, *112*, 896.
8. (a) Wu, Z.; Cao, L.; Pittman, C. U., Jr. *Recent Res. Devel. Polym. Sci.* **1998**, *2*, 467; (b) Zhu, P. C.; Pittman, C. U., Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 169; (c) Liu, Y.; Pittman, C. U., Jr. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 3655; (d) Zhu, P. C.; Lin, J.; Pittman, C. U., Jr. *J. Org. Chem.* **1995**, *60*, 5729; (e) Wu, Z.; Stanley, R. R.; Pittman, C. U., Jr. *J. Org. Chem.* **1999**, *64*, 8386; (f) Cao, L. Ph.D. Dissertation, Mississippi State University, 1999; (g) Li, H. MS, Thesis, Mississippi State University, 2005.
9. (a) Zhang, W.; Pugh, G. *Tetrahedron* **2003**, *59*, 3009; (b) Jabin, I.; Netchitailo, P. *Tetrahedron Lett.* **2001**, *42*, 7823.
10. Zhou, A. H.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2005**, *46*, 2045.

11. Mckennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3569.
12. Richard, H. G.; Atkinson, E. R.; Granchelli, F. E.; Bruni, R. J. *J. Med. Chem.* **1965**, *8*, 762.
13. Zhou, A. H.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2004**, *45*, 8899.
14. (a) Zhou, A. H.; Njogu, M.; Pittman, C.U., Jr., unpublished work; (b) Njogu, M. MS Thesis, Mississippi State University, 2005.
15. (a) Belvisi, L.; Gennari, C.; Poli, G. *Tetrahedron* **1992**, *48*, 3945; (b) Belvisi, L.; Gennari, C.; Poli, G. *Tetrahedron: Asymmetry* **1993**, *4*, 273.
16. General procedure of radical cyclization of cyclic ketene-N,S-acetals: Bromobenzoyl chloride (220 mg, 1.00 mmol) was added dropwise to a stirred solution of 2-ethylthiazolines **1a** (157 mg, 1 mmol) and triethylamine (130 mg, 1.20 mmol) in benzene 40 mL at room temperature. Then this solution was stirred for 3 h. The product mixture was filtered and the solvent was removed by rotary evaporation. Dry benzene (60 mL) was added to the crude residue. Then Bu_3SnH (0.36 mL, 1 mmol) and AIBN (17 mg, 0.1 mmol) were also added. The mixture was refluxed for 10 h and then the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography on silica gel. 3-Isopropyl-10-methyl-2,3,10,10a-tetrahydrooxazolo[3,2-*b*]isoquinolin-5-one was obtained (191 mg, 78% (**5**+**6**)). The same procedure for other aryl radical cyclization reactions.