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The facile synthesis of benzothiazolylideneacetates and 1,4-benzothiazines through a highly controllable oxidation of benzothiazolylacetates

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ABSTRACT

The synthesis of benzothiazolylideneacetates and 1,4-benzothiazine was found to be highly controllable via simple exchange of corresponding oxidants. It turned out that the treatment of benzothiazolylacetates with *m*-CPBA gave 1,4-benzothiazines via oxidative ring expansion process, and with DDQ gave benzothiazolylideneacetates via dehydrogenation, in good yield, respectively. The structures of both skeletons were confirmed by their X-ray diffractions. A previously reported method for the synthesis of benzothiazolylideneacetates was thus proved to be incorrect.

Benzothiazolylideneacetates **1**, a newly designed skeleton, were recently synthesized from benzothiazolylacetates through *m*-CPBA-mediated dehydrogenation process by Takayama et al.[1] It can be converted to benzothiazolylidenehydroxamic acid derivatives **2** as novel class of peptide deformylase (PDF) inhibitors. With a view to the unique skeleton and its biological interest, we dedicated to synthesize a series of benzothiazolylidenehydroxamic acid derivatives as histone deacetylase inhibitors (HDACi) for the discovery of novel anticancer lead compounds.[2] By employing the reported method,[1] the treatment of methyl 3-ethyl-benzothiazol-2-ylacetate **4a** with *m*-CPBA afforded an orange solid, which is similar to the product derived from previous report[1] according to its ^{1}H NMR and mass spectra. However, the resulting orange solid was found not to be the benzothiazolylideneacetate as structurally assigned by Takayama,[1] but instead was confirmed by X-ray diffraction structurally as 1,4-benzothiazine **3a**.

It is notable that 1,4-benzothiazine is the pharmacophore of phenothiazines, which are well established anti-psychotic drugs,[3] and is also known as the basic unit for their utility as dyestuffs,[4] photographic developers,[5] ultraviolet light absorbers, and antioxidants.[6] In view of these multifarious useful applications, many efforts have been made to develop synthetic access to 1,4-benzothiazines. The most commonly used methods are three types including (1) the reaction of 2-aminobenzenethiols with α-haloketones or α-haloesters;[7] (2) the oxidative cyclocondensation of 2-aminobenzenethiols with 1,3-dicarbonyl compounds through key disulfides formation process using dimethylsulfoxide as oxidant,[8] aerial oxidation[9] in solvent-free system using hydrazine hydrate as catalyst, or using microwave[10] technique; (3) the oxidative ring expansion of N-substituted benzothiazolines in refluxing dimethylsulfoxide under nitrogen atmosphere,[11] in toluene or dichloromethane using sulfuryl chloride as oxidant,[12] or in toluene/*t*-BuOK using iodine as oxidant.[13]

Our finding belongs to the oxidative ring expansion category, which prompted us to further investigate the oxidative properties of benzothiazolylacetate in order to extend the utility of this *m*-CPBA-mediated method since none of the oxidative ring expansion methods has been reported to afford 3-unsubstituted 1,4-benzothiazine under such simple reaction systems. In addition, what i ntrigued us is how to find a synthetic access to benzothiazolylideneacetate since the previously reported protocol was found to be incorrect.[1] Herein, we would like to describe our preliminary results on the synthesis 1,4-benzothiazines **3**, and the newly developed synthetic access to benzothiazolylidene acetates **1** (Fig. 1).

The methyl 3-ethyl-benzothiazol-2-ylacetate **4a** prepared by a published method[14] was first subjected to the oxidative treatment with *m*-CPBA to produce an orange solid in good yield. The structure of the corresponding product was previously assigned as (*Z*)-benzothiazolylideneacetate **1a**.[1] The reason for this structural assignment was based on the clear NOE between methylene proton and olefinic proton. To our surprise, the X-ray diffraction of the above product reveals a 1,4-benzothiazine skeleton **3a** instead of benzothiazolylideneacetate **1a** (Fig. 2).

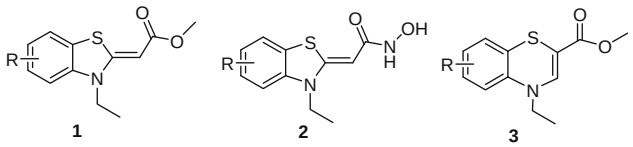

Figure 1.

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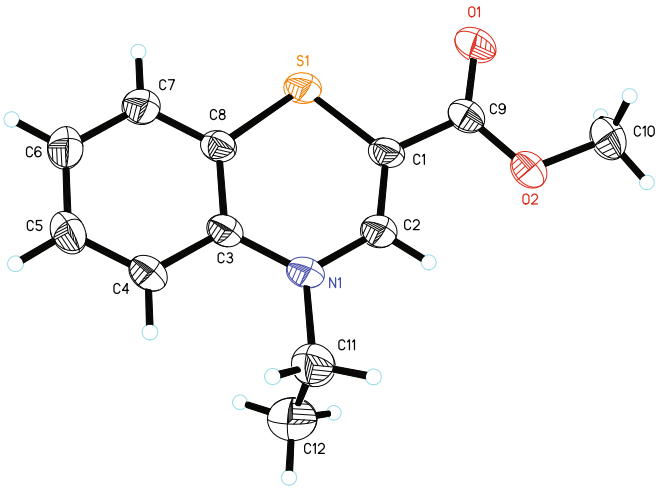


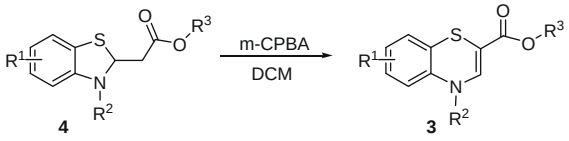
Figure 2. ORTEP view and atom numbering scheme for **3a**.

A literature survey shows that the 1,4-benzothiazine **3** was presumably formed through an oxidative ring expansion process. Notably, the previously reported oxidative ring expansion processes often suffer from the low yield, relative harsh and tedious conditions such as heat, additional acetic anhydride, and toluene/*t*-BuOK/I_2 system. The mild reaction condition combined with good yield in this *m*-CPBA-mediated protocol suggests that the reaction mechanism may differ from that of previous report.

The mechanism was therefore proposed as depicted in Scheme 1. The sulfenic acid intermediate **B** is proposed to form through the *m*-CPBA-mediated oxidative ring opening and deprotonation of methylene group via a concerted six-membered cyclic transition state **A**. Then, *m*-chlorobenzoic acid-assisted ring closure of intermediate **B** and subsequent deprotonation of **C** afford the 1,4-benzothiazine **3**. Based on this hypothetic reaction mechanism, we next extend the reaction to a series of substrates to examine the scope of this newly developed method, and the results are summarized in Table 1. It is clear that all substrates **4** gave corresponding 1,4-benzothiazines **3** in good yield (75–82%). The structure of these newly formed products was assigned mainly based on the consistency of olefinic proton chemical shift at around 7.08 ppm (ranging from 7.07 to 7.09 ppm) for all products with that of product **3a**.

On the other hand, apparently the oxidation of sulfur atom of benzothiazoline is the prerequisite for proceeding to the above ring expansion according to the proposed mechanism. As a consequence, we wondered that dehydrogenation oxidants such as DDQ, which is not able to provide oxygen, might be an optional reagent to convert benzothiazolylacetate to benzothiazolylideneacetate via dehydrogenation process. To our amazement, as shown in Table 2, the treatment of all substrates **4** with DDQ in dichloromethane at room temperature gave expected dehydrogenation benzothiazolylideneacetates **1** in good yield (56–80%). The structure of **1a** was confirmed by the X-ray diffraction of the corre-

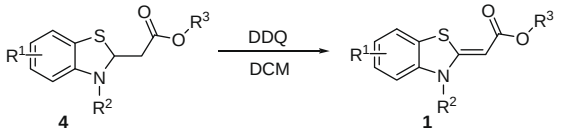
Table 1
m-CPBA-mediated oxidative ring expansion of **4** to **3**



Entry	R^1	R^2	R^3	Yield (%)[a,b]
1(**3a**)	H	Et	Me	80
2(**3b**)	H	Me	Me	76
3(**3c**)	H	Me	Et	75
4(**3d**)	H	Me	*i*-Pr	82
5(**3e**)	H	*n*-Pr	Me	78
6(**3f**)	H	*n*-Bu	Me	79
7(**3g**)	H	*n*-Pentyl	Me	77
8(**3h**)	F	Me	Me	75
9(**3i**)	OCH_3	Me	Me	82

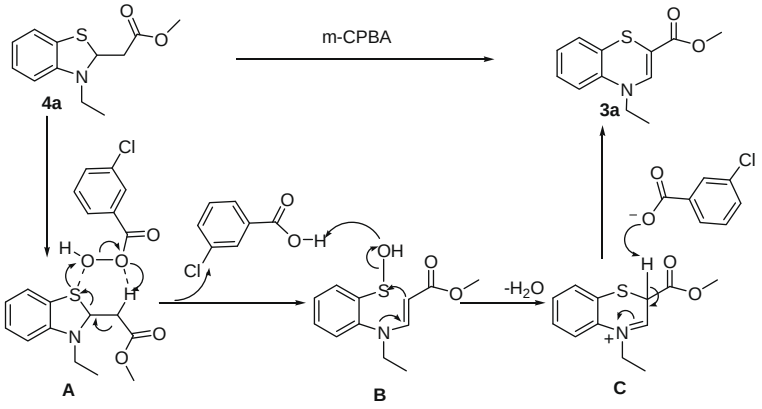
[a] Benzothiazolylacetates (1 mmol)were used for the oxidative ring expansion in DCM (4 mL) using 1.2 equiv of *m*-CPBA.
[b] Isolated yields.

Table 2
DDQ-mediated dehydrogenation of **4**



Entry	R^1	R^2	R^3	Yield[a,b] (%)
1(**1a**)	H	Et	Me	77
2(**1b**)	H	Me	Me	73
3(**1c**)	H	Me	Et	74
4(**1d**)	H	Me	*i*-Pr	76
5(**1e**)	H	*n*-Pr	Me	71
6(**1f**)	H	*n*-Bu	Me	70
7(**1g**)	H	*n*-Pentyl	Me	73
8(**1h**)	F	Me	Me	56
9(**1i**)	OCH_3	Me	Me	80

[a] Benzothiazolylacetates (1 mmol) were used for the oxidative ring expansion in DCM (4 mL) using 1.2 equiv of DDQ.
[b] Isolated yields.



Scheme 1. Proposed mechanism for the *m*-CPBA-mediated oxidative ring expansion of **4a** to **3a**.

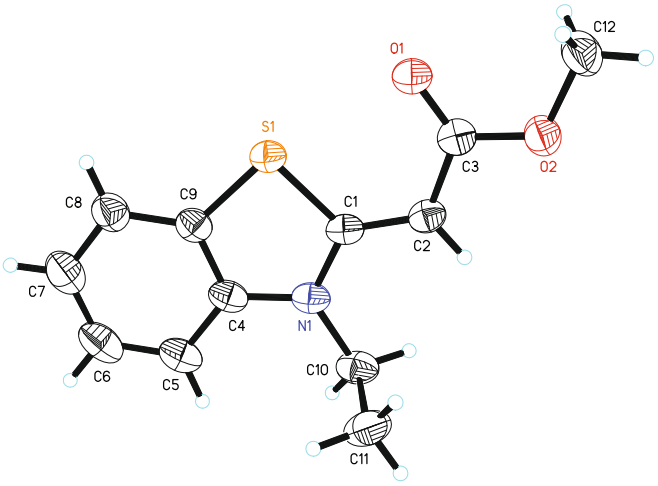


Figure 3. ORTEP view and atom numbering scheme for **1a**.

sponding single crystal as shown in Figure 3. It is also clear that the olefinic proton chemical shift of all products is near 5.20 ppm (ranging from 5.16 to 5.25 ppm), which establish all products structurally identical to product **1a**.

In summary, we have developed a facile synthesis of 3-unsubstituted 1,4-benzothiazines **3**[15] from the corresponding benzothiazolylacetates **4** in 75–82% yield through the *m*-CPBA-mediated oxidative ring expansion pathway, thus a previously reported method for the synthesis of benzothiazolylideneacetate **2** was proved to give incorrect structure assignment. Further investigation led to a successful and efficient dehydrogenation process by using DDQ as dehydrogenation agent affording the desired benzothiazolylideneacetates **1**[15] in good yield (56–80%). Taking account of the mild condition and good yield of the above two highly chemoselective reactions, we believe that the newly developed methods are of great help to synthesize the 1,4-benzothiazines **3**, benzothiazolylideneacetate derivatives **1,** and its hydroxamic acid analogs **2**. Further work is currently in progress in our laboratory to extend the application of these new synthetic methods.

Acknowledgments

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References and notes

1. (a) Takayama, W.; Shirasaki, Y.; Sakai, Y.; Nakajima, E.; Fujita, S.; Sakamoto-Mizutani, K.; Inoue, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3273; b Takayama, W.; Shirasaki, Y.; Inoue, J. **2004**, JP 2004250412A.
2. (a) Rasheed, W. K.; Johnstone, R. W.; Prince, H. M. *Exp. Opin. Invest. Drugs* **2007**, *16*, 659; (b) Liu, T.; Kapustin, G.; Etzkorn, F. A. *J. Med. Chem.* **2007**, *50*, 2003.
3. Barker, J. C.; Miller, M. *Br. J. Psychiatry* **1969**, *115*, 169.
4. Tanaka, R.; Teramura, K.; Yokoyama, S. *Chem. Abstr.* **1966**, *65*, 9062.
5. Strain, W. H.; Dickey, J. B. *Chem. Abstr.* **1946**, *40*, 1889.
6. Rasmussen, C. R. *Chem. Abstr.* **1974**, *80*, 95987.
7. *Phenothiazines and 1,4-Benzothiazines: Chemical and Biomedical Aspects*; Gupta, R. R., Ed.; Elsevier: Amsterdam, 1988.
8. Dzvinchuk, I. B.; Vypirailenko, A. V.; Lozinskii, M. O. *Chem. Heterocycl. Compd.* **2004**, *40*, 1199.
9. Munde, S. B.; Bondge, S. P.; Bhingolikar, V. E.; Mane, R. A. *Green Chem.* **2003**, *5*, 278.
10. Dandia, A.; Sarawgi, P.; Hursthouse, M. B.; Bingham, A. L.; Light, M. E.; Drake, J. E.; Ratnani, R. *J. Chem. Res.* **2006**, 445.
11. Liso, G.; Trapani, G.; Latrofa, A.; Marchini, P. *J. Heterocycl. Chem.* **1981**, *18*, 279.
12. Chioccara, F.; Prota, G. *Synthesis* **1977**, 876.
13. Liso, G.; Trapani, G.; R eho, A.; Latrofa, A.; Marchini, P. *Synthesis* **1983**, 755.
14. Chikashita, H.; Takegami, N.; Yanase, Y.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3389.
15. *General procedure for the DDQ-mediated dehydrogenation of benzothiazolylacetates*: A solution of benzothiazolylacetates (1 mmol) and DDQ (1.2 equiv) in 4 mL of dichloromethane was stirred overnight. After completion of the reaction as monitored by TLC, and concentrated on rotary vacuum evaporator, the resulting crude product was purified by column chromatography on silica gel to give the corresponding benzothiazolylideneacetates **1** in high yield. All products give satisfied analytical data. The data for selected compound **1a**: White solid, mp 91–92 °C; IR (KBr, cm^{-1}): 2981, 2950, 1659, 1592, 1539, 1471, 1330; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.7 Hz, 1H), 7.31–7.27 (m, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 5.25 (s, 1H), 3.94 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 160.4, 140.2, 126.8, 126.1, 122.0, 121.9, 109.1, 77.7, 50.8, 40.2, 11.2; MS (EI): *m*/*z* (%): 235.1 ([M]$^+$, 100). The data for selected compound **3a**: Orange solid, mp 64–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.88 (t, J = 7.0 Hz, 1H), 6.76–6.69 (m, 2H), 6.49 (d, J = 8.1 Hz, 1H), 3.66 (s, 3H), 3.41 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 143.3, 139.2, 127.4, 127.2, 124.6, 121.3, 113.0, 93.4, 51.5, 46.1, 12.8; MS (EI): *m*/*z* (%): 235.1 ([M]$^+$, 100).