OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Synthesis of *N*-Formyl-2-benzoyl Benzothiazolines, 2-Substituted Benzothiazoles, and Symmetrical Disulfides from *N*-Phenacylbenzothiazolium Bromides

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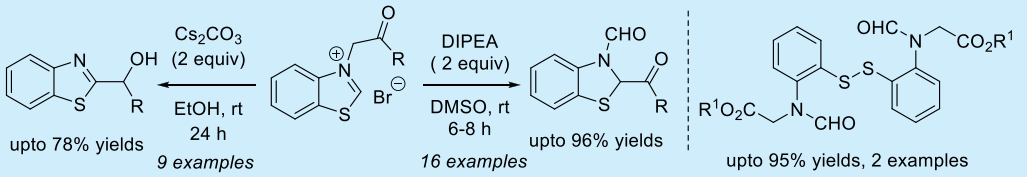
Supporting Information



- An unusual hydrolysis-cascade reaction
- Aerobic disulfide and imine intermediate formation
- First synthesis of *N*-formyl-C2-substituted benzothiazolidines
- Facile synthesis of 2-substituted benzothiazoles

ABSTRACT: An unusual aerobic hydrolysis-cascade reaction has been developed with *N*-phenacylbenzothiazolium bromides by treatment with organic and inorganic base. The corresponding *N*-formyl-2-benzoyl benzothiazoline and 2-substituted benzothiazole products were obtained in moderate to good yields under mild reaction conditions. Also, symmetrical disulfide was formed when keto group was replaced with ester. The scopes of the reactions are fairly broad tolerating aryl, heteroaryl, and alkyl groups.

Benzothiazolines are important classes of heterocycles, which display a wide range of biological and medicinal activities and are used as antiglutamates, antioxidants, anticonvulsants, and also as efficient reducing agents[1] (Figure 1). Thus, interest in the rapid construction of benzothiazolines

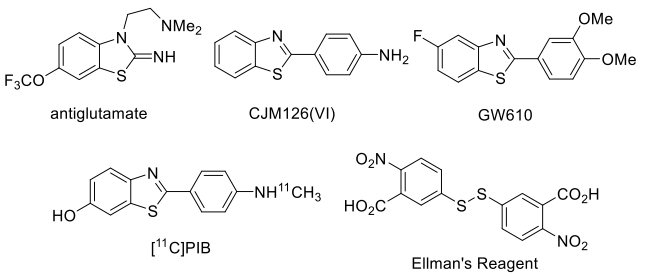


Figure 1. Representative bioactive benzothiazoline, benzothiazoles, and symmetrical disulfide.

has been observed over the years. Traditionally, benzothiazoline derivatives are obtained from the condensation of 2-aminothiophenols with carbonyl compounds, which requires harsh conditions.[2] Kwon and co-workers developed an alternate phosphine-triggered general base-catalyzed double-Michael reaction between 2-aminothiophenols and allenes for the preparation of C2-functionalized benzothiazolines.[3a] Nevertheless, diverse methods need to be developed for the preparation of differently substituted benzothiazolines.

Similarly, benzothiazole motifs are present in a myriad of natural products and biologically active compounds.[4] In particular, 2-substituted benzothiazoles are utilized as antiparasitics, antituberculotics, antitumor agents, and calcium channel antagonists (Figure 1).[5] Thus, a range of synthetic methodologies have been developed for the preparation of 2-substituted benzothiazole derivatives.[6] However, little attention was given for the C2-substituted benzothiazoles with benzylic hydroxyl group.[7] Also, one of the current challenges in synthetic organic chemistry is to develop efficient, selective, and metal-free oxidation of organic substrates that utilize dioxygen as the terminal oxidant.[8]

N-Phenacylbenzothiazolium bromides are useful heterocyclic ammonium salts, which can generate reactive azo-methine ylides[9] by deprotonation with bases. A range of cycloaddition reactions have been developed with them by engaging different olefinic dipolarophiles.[10] Also, hydrolysis reactions have been carried out with strong bases like sodium hydroxide to generate hemiketalic 1,4-benzothiazines.[11] However, to the best of our knowledge, substituted benzothiazolines have not been prepared from *N*-phenacylbenzothiazolium bromides. Herein, we report unexpected formations of *N*-formyl-2-benzoyl benzothiazolines, 2-substituted benzothiazoles, and disulfides from *N*-phenacylbenzothiazolium bromides.[9]

To initiate the investigation, *N*-phenacylbenzothiazolium bromide **1a** was initially treated with 2 equiv of DABCO in

Received: June 10, 2019

DOI: 10.1021/acs.orglett.9b01990
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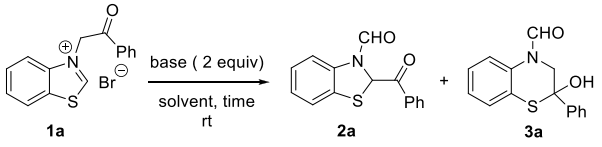
ethanol at room temperature (Table 1). Delightfully, after stirring for 1 day, (Table 1, entry 1), *N*-formyl-2-benzoyl

Table 1. Base Screening and Optimization of Reaction Conditions



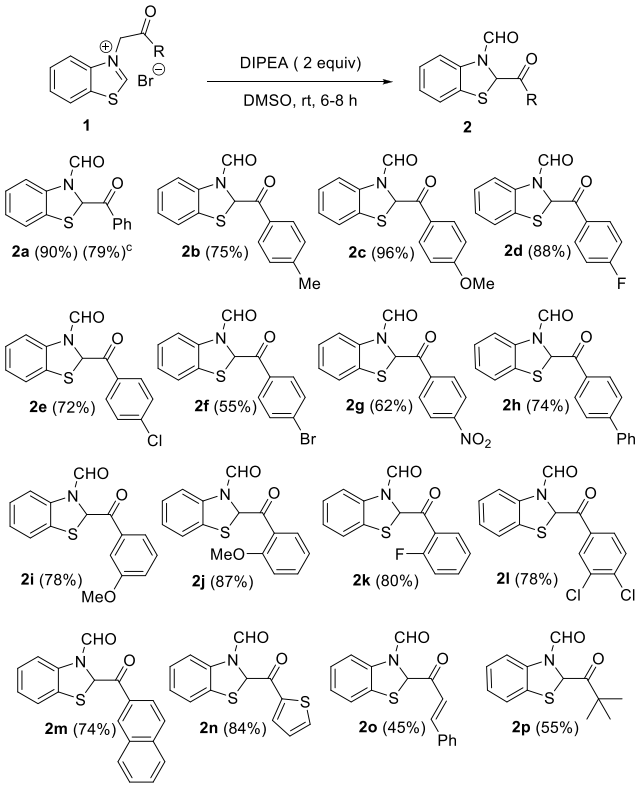
entry[a]	base	solvent	time (h)	yield[b] (2a)	yield[b] (3a)
1	DABCO	EtOH	24	25	10
2	pyridine	EtOH	24	18	72
3	piperidine	EtOH	24	42	48
4	DBU	EtOH	24	68	15
5	Na_2CO_3	EtOH	36	57	0
6	DIPEA	EtOH	6	80	5
7	DIPEA	CH_3CN	6	80	15
8	DIPEA	DMF	6	82	10
9	DIPEA	$CHCl_3$	6	62	10
10	DIPEA	DMSO	6	90	5

[a]Reaction condition: 0.1 mmol of **1a** in 1 mL solvent using 2 equiv of base. [b]Isolated yield after silica gel column chromatography.

benzothiazoline **2a** was formed in 25% yield along with hemiketalic 1,4-benzothiazine **3a** (10%). The structure of **2a** was conformed by X-ray crystallography.[12] To improve the yield, different bases were screened. The yield of **2a** decreased with pyridine, but a significant 78% yield was attained for **3a**. Thus, it was expected that **3a** was an intermediate for the formation of **2a**. Piperidine provided almost equal amounts of **2a** and **3a**. Interestingly, the yield of **2a** was improved with DBU. The reaction also worked with inorganic base such as sodium carbonate, though moderate yield was detected. Finally, DIPEA was found to be the best base to provide 80% yield of **2a** in 6 h. To further enhance the yield, different solvents were checked. Similar yields were observed in CH_3CN and DMF, though the yield decreased in $CHCl_3$. Finally, DMSO turned out to be the best solvent to deliver product **2a** in 90% yield.

After *N*-formyl-2-benzoyl benzothiazoline **2a** was obtained in decent yield, the scope and generality of the methodology were studied under the optimized conditions. At the beginning, the aryl group of ketone motif in **1** was varied (Scheme 1). It turned out that a range of substitutions at the *ortho*-, *meta*-, and *para*-positions of the aryl group were tolerated. Initially, different *para*-substitutions were checked, and good results were attained. For example, acceptable yield was achieved with benzothiazolium bromide **1b** having *para*-tolyl group. Gratifyingly, an excellent result was achieved with 4-anisyl group containing salt **1c**, and the corresponding product **2c** was isolated in 96% yield. Then different 4-halo substitutions were investigated, and the products **2d**−**2f** were obtained in varied yields. Though the yield for product **2d** having 4-fluoroaryl group was high, moderate yield was achieved for product **2f** having 4-bromophenyl group. Benzothiazolium bromide **1g** having electron poor nitro group also participated in the reaction, and moderate yield was detected. Then biphenyl group containing salt **1h** was employed in the reaction, and product **2h** was isolated in 74% yield. The reaction was also smooth with *m*-methoxy substituted aryl group containing salt **1i**, and gratifyingly the outcome was good (Scheme 1). Then *ortho*-substituted aryl group containing salts **1j** and **1k** was screened, and the desired products **2j**−**2k** were

Scheme 1. Scope of 1 with Varied Keto Groups[a,b]

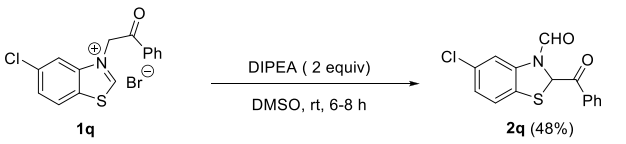


[a]Reactions were carried out with 0.2 mmol of **1** in 2 mL DMSO using 2 equiv of DIPEA at rt for 6−8 h. [b]Yields were determined after isolation from silica gel column chromatography. [c]Reaction was carried out with 1 mmol of **1a**.

obtained in high yields. A 3,4-disubstitution was also tolerated to deliver product **2l** in 78% yield. Benzothiazolium bromide **1m** having 2-naphthyl group also took part in the reaction, and 74% yield for **2m** was detected. Then a reaction was carried out with 2-thienyl substituted salt **1n**, and gratifyingly product **2n** was obtained in 84% yield. Moreover, our methodology is also suitable for cinnamyl and ^{t}butyl substituted benzothiazolium bromides **1o** and **1p**, though slightly lower yields were observed for the corresponding products **2o** and **2p**. When the reaction was carried out in 1 mmol scale, the yield slightly dropped for **2a**.

Then we decided to vary the aryl part of **1**, and thus, 5-cholosubstituted *N*-phenacylbenzothiazolium bromide **1q** was prepared (Scheme 2). Gratifyingly, the reaction progressed well to provide **2q** in moderate yield.

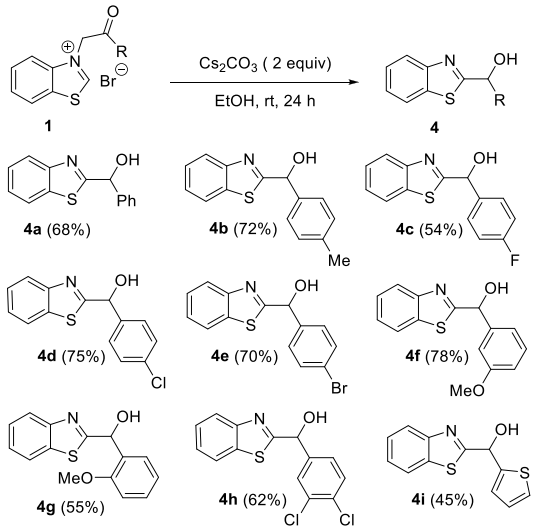
Scheme 2. Employment of 5-Chlorosubstiuted Salt 1b



Then we found a facile formation of 2-substituted benzothiazole **4a** after treatment of *N*-phenacylbenzothiazolium bromide **1a** with cesium carbonate in ethanol (Scheme 3). Encouraged by this result, different keto groups containing benzothiazolium bromides **1** were screened in this condition. Initially, *p*-substituted aryl groups containing salts **1** were

DOI: 10.1021/acs.orglett.9b01990
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of 2-Substituted Benzothiazoles[a,b]



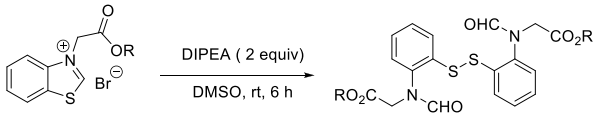
[a]Reactions were carried out with 0.2 mmol of **1** in 2 mL EtOH using 2 equiv of cesium carbonate at rt for 24 h. [b]Yields were determined after isolation from silica gel column chromatography.

employed in the reaction, and gratifyingly good results were observed (Scheme 3).

For example, product **4b** having tolyl group was isolated in 72% yield. Different 4-halo substitutions were also tolerated, and the corresponding products **4c**–**4e** were obtained in acceptable yields. The reaction also took place with *meta*-anisyl containing salt **1i**, and the desired product **4f** was attained in 78% yield. *ortho*-Anisyl group containing salt **1j** also participated in the reaction to deliver **4g** in moderate yield. Then 3,4-dicholosubstiuted salt **1l** was screened, and a good result was observed for product **4h**. Moreover, heteroaromatic thienyl keto group can also be incorporated in **1**, and the product **4i** was isolated in moderate yield. Interestingly, when ^{t}butyl keto group containing salt **1p** was employed, only formation of benzothiazoline **2p** was observed.

Then we observed formation of symmetrical disulfide **5a** after stirring methylester containing salt **1r** with DIPEA in dimethyl sulfoxide (Scheme 4). Organic disulfides are important

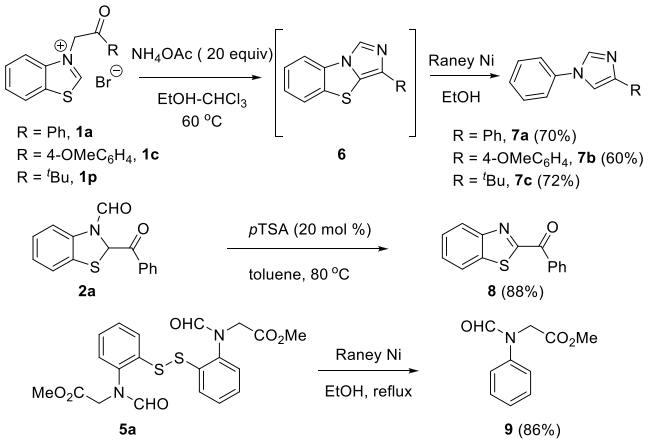
Scheme 4. Synthesis of Symmetrical Disulfides



structural moieties found in various marine natural products,[13] pharmaceuticals,[14] materials,[15] and polymers.[16] The reaction was also checked with ^{t}butyl ester containing salt **1s**, and product **5b** was formed in 95% yield.[17]

The synthetic utility of our method was demonstrated by performing few useful transformations (Scheme 5). Initially, a one-pot tandem reaction of **1a** was carried out with ammonium acetate to deliver **6a**, which was further treated with Raney Ni to deliver 4-substituted *N*-phenylimidazole **7a** in good overall yield. Similar yield was also observed when **2a** was treated under similar reaction conditions. Inspired by this outcome, other

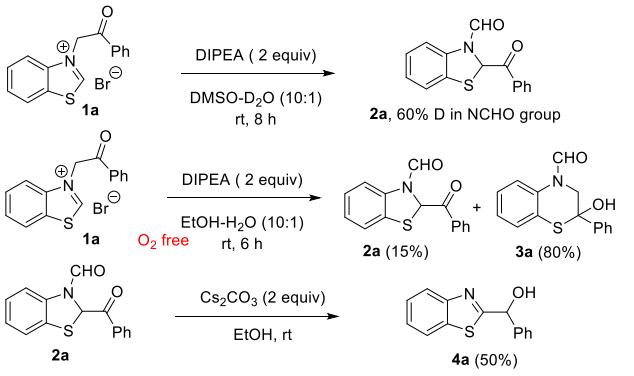
Scheme 5. Synthetic Transformations



derivatives **7b** and **7c** were also prepared. Then acid treatment of **2a** resulted in the formation of 2-benzoyl benzothiazole **8** in high yield. Finally, disulfide **5a** was refluxed in ethanol with Raney Ni. Gratifyingly, the desired methyl *N*-formyl-*N*-phenylglycinate (**9**) was formed in 86% yield.

To understand the mechanism of the reaction, few reactions were carried out (Scheme 6). After treatment of **1a** with DIPEA

Scheme 6. Control Experiments



in DMSO–D_2O mixture (10:1), product **2a** was formed with 60% D in the formamide functionality. Thus, it dictates that formamide motif could be generated from hydrolysis of **1a** with the moisture present in the solvent. Also, oxygen/air free reaction was performed in ethanol–water mixture solvent. Here the major product was **3a**. Thus, it is clear that oxygen is helping for an iminium ion formation, which led to formation of **2a**. Also, reaction of **2a** with cesium carbonate delivered **4a** in 50% yield. Thus, it was expected that **4a** was formed from **2a**.

A plausible mechanism has been shown in Scheme 7 for the formations of **2a**–**5a**. It is expected that **10** will first form by hydrolysis, which under basic condition generates **11**. Then an unusual imine (**12**) formation takes place under air.[18] Finally, cyclization of **12** delivers **2a**. Also, **11** is in equilibrium with **3a**, and interestingly, in our condition, **11** predominates. On cesium carbonate treatment, **2a** is hydrolyzed to form **13**. Then 1,2-hydride shift along with aromatization takes place, and benzothiazole **4a** is formed. Similarly, **1r** is converted to **14**, which under basic medium forms disulfide **5a**.

In summary, this report delineates an unusual aerobic hydrolysis-cascade reaction for the first synthesis of *N*-formyl-2-benzoyl benzothiazolines and green approaches for 2-

DOI: 10.1021/acs.orglett.9b01990
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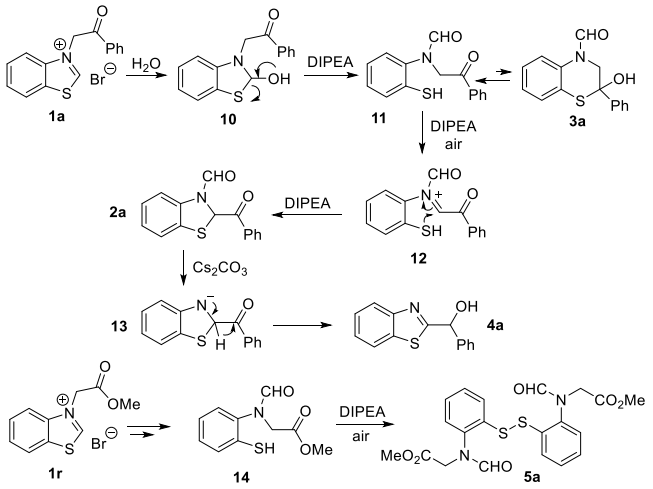
Scheme 7. Plausible Mechanism



substituted benzothiazoles and disulfides. The aerobic formation of iminium ion intermediates as well as disulfides and 1,2-hydride shift for aromatization is rare and will lead further investigations. Also, synthetic applications such as cascade formation of *N*-substituted imidazoles have been demonstrated. Given the high pharmaceutical importance of benzothiazoline and benzothiazoles, the newly synthesized products will be useful for the development of new drugs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01990.

Experimental procedures and characterization data of all products (PDF)

Accession Codes

CCDC 1921604 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank DST SERB, CSIR for the funding. We also thank CIF, Indian Institute of Technology Guwahati for the instrumental facility.

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