ORGANIC LETTERS

2010
Vol. 12, No. 4
752−754

Facile Preparation of 3-Substituted Benzisothiazoles from *o*-Mercaptoacylphenones

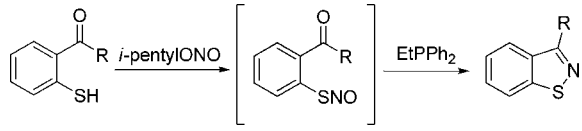
Nelmi O. Devarie-Baez and Ming Xian*

Department of Chemistry, Washington State University, Pullman, Washington 99164

mxian@wsu.edu

Received December 9, 2009

ABSTRACT

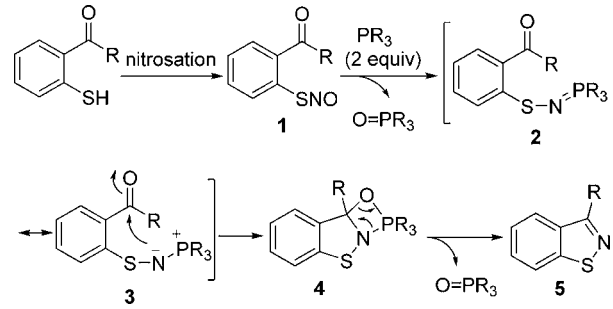


A synthesis of 3-substituted benzisothiazoles starting from readily available *o*-mercaptoacylphenones is presented. The key cyclization step features a mild *S*-nitrosation and its succeeding intramolecular aza-Wittig reaction leading to the construction of the title compounds.

Benzisothiazole is a unique heterocyclic structure that has been visualized as an important pharmacophore of some bioactive molecules. These molecules have been reported to possess many interesting biological activities such as antibacterial,[1] anti-HIV,[2] antiproliferative activities of B-lymphoblastic leukemia cells,[2] and others.[3] As an example, Ziprasidone, which contains a key benzisothiazole subunit, is an FDA-approved antipsychotic drug for the treatment of schizophrenia.[4] Due to the importance of this scaffold in drug discovery, the synthesis of benzisothiazoles has received considerable attention from organic chemists. Currently, most of the methods to access benzisothiazoles rely on multistep chemical manipulations.[5] Only a few single flask strategies have been developed and the range of the substrates is limited.[6]

In our recent efforts to develop chemical probes for the detection of protein *S*-nitrosation,[7] it was noticed that organophosphines reacted with *S*-nitrosothiols to form azaylide intermediates under very mild conditions. These reactive intermediates could undergo intramolecular reactions with different electrophiles attached on the phosphine substrates, leading to the formation of different final products. With this information in mind, we proposed a new synthesis of 3-substituted benzisothiazoles from readily available *o*-mercaptoacylphenones. As shown in Scheme 1, nitrosation of the *o*-mercaptoacylphenone starting material should provide the corresponding *S*-nitroso derivative **1**. It is well-known that *S*-nitroso compounds are unstable species and their purification/isolation is always problematic.[8] Therefore,

Scheme 1. Proposed Synthesis of Benzisothiazoles



(1) Zani, F.; Vicini, P. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 219.

(2) Vicini, P.; Geronikaki, M. I.; Bernadetta, B.; Poni, G.; Cabras, C. A.; La Colla, P. *Bioorg. Med. Chem.* **2003**, *11*, 4785.

(3) (a) Genokaki, A.; Eleftheuriou, P.; Vicini, P.; Alam, I.; Dixit, A.; Saxena, A. K. *J. Med. Chem.* **2008**, *51*, 5221. (b) Morini, G.; Poli, E.; Comini, M.; Menozzi, A.; Pozzoli, C. *Arch. Pharm. Res.* **2005**, *28*, 1317.

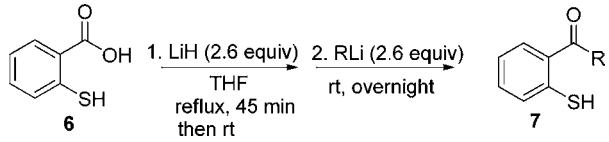
(4) (a) Seeger, T. F.; Seymour, P. A.; Schmidt, A. W.; Zorn, S. H.; Shulz, D. W.; Lebel, L. A.; McLean, S.; Guanowsky, V.; Howard, H. R.; Lowe, J. A., III; Heym, J. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 101. (b) Prakash, C. *Drug Metab. Dispos.* **1997**, *25*, 897. (c) Walinsky, S. W.; Fox, D. E.; Lambert, J. F.; Sinay, T. G. *Org. Proc. Res. Dev.* **1999**, *3*, 126.

10.1021/ol9028447
Published on Web 01/15/2010

the application of *S*-nitroso compounds in organic synthesis is very rare.[9] However, in our hypothesis, these *S*-nitroso intermediates were not necessary to isolate. We expected to treat them immediately with the phosphine substrates after their formation. As such, an azaylide intermediate **2** should be formed. Finally, an intramolecular aza-Wittig reaction should occur to furnish the desired benzisothiazole **5**.[7a,b]

The preparation of the *o*-mercaptoacylphenone starting material was straightforward (Scheme 2): deprotonation of

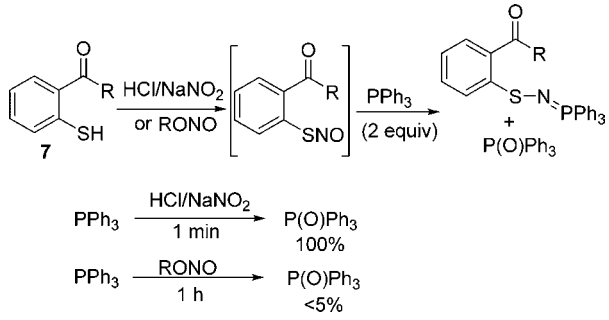
Scheme 2. Preparation of *o*-Mercaptoacylphenones



the thiosalysilic acid **6** in THF under refluxing conditions and subsequent treatment with a series of organolithiums at room temperature resulted in the corresponding *o*-mercaptoacylphenones **7** in good yields (see the Supporting Information for details).

Upon the production of **7**, the conditions of *S*-nitrosation were studied (Scheme 3). When **7** was treated with either

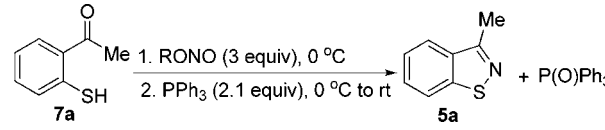
Scheme 3. Study of Nitrosation



$HCl/NaNO_2$ or alkyl nitrites, the two most commonly used nitrosation conditions, we observed immediate formation of *S*-nitroso compounds at both rt and 0 °C, by the characteristic deep red color. Attempts to isolate the *S*-nitroso compounds led to decomposition. To convert the unstable *S*-nitroso intermediates to azaylide intermediates, phosphine substrates such as PPh_3 were added directly into the reaction mixture. As expected, the $HCl/NaNO_2$ condition led to the oxidation of phosphine substrates completely, which suggests this is not suitable for this one-step strategy. We found that alkyl nitrites are quite safe for PPh_3. No significant oxidation of PPh_3 by alkyl nitrites was observed after 1 h at rt (monitored by TLC and ^{31}P NMR). Therefore, we next explored alkyl nitrite-mediated benzisothiazole formation using **7a** as the model substrate.

With use of THF as the reaction solvent, different commercially available alkyl nitrites including EtONO, *t*-BuONO, and *i*-pentylONO were evaluated (Table 1).

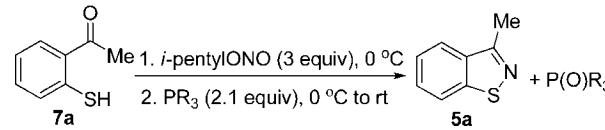
Table 1. Exploration of Alkyl Nitrites and Solvents



entry	RONO	solvent	yield of **5a** (%)
1	EtONO	THF	0
2	*t*-BuONO	THF	33
3	*i*-PentylONO	THF	70
4	*i*-PentylONO	dioxane	35
5	*i*-PentylONO	DMF	60
6	*i*-PentylONO	$CHCl_3$	58
7	*i*-PentylONO	CH_2Cl_2	65
8	*i*-PentylONO	benzene	56
9	*i*-PentylONO	toluene	48

Given the instability of *S*-nitroso compounds, the nitrosation step and subsequent azaylide formation with PPh_3 were carried out at 0 °C. Interestingly, EtONO did not lead to any detectable benzisothiazole formation, while *t*-BuONO provided the desired product **5a** in a moderate yield (33%). Isopentyl nitrite (*i*-pentylONO) proved to be the best reagent, which furnished **5a** in very good yield (70%). We carefully studied the effect of temperature on the process and found that 0 °C was the optimal condition.

Table 2. The Effects of Phosphine Substrates



entry	PR_3	yield of **5a** (%)
1	PBu_3	19
2	$P(OEt)_3$	47
3	PPh_3	70
4	2-PyP$(Ph)_2$	48
5	*n*-$BuPPh_2$	71
6	$EtPPh_2$	80

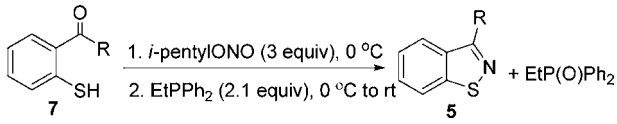
(5) (a) McKinnon, D. M.; Lee, K. R. *Can. J. Chem.* **1988**, *66*, 1405. (b) Pedras, M.; Soledade, C.; Suchy, M. *Bioorg. Med. Chem.* **2006**, *14*, 714. (c) Fink, D. M.; Scrupczewski, J. T. *Tetrahedron Lett.* **1993**, *34*, 6525.

(6) (a) Creed, T.; Leardini, R.; McNab, H.; Nanni, D.; Nicolson, I. S.; Reed, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1079. (b) Wirschun, W. G.; Hitzler, M. G.; Jochims, J. C.; Groth, U. *Helv. Chim. Acta* **2002**, *85*, 2627.

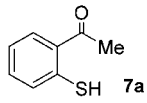
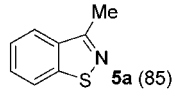
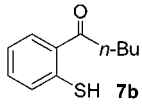
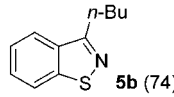
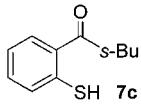
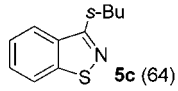
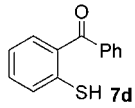
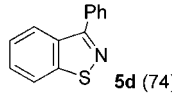
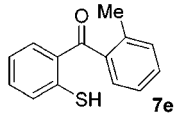
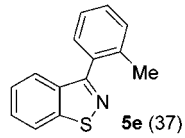
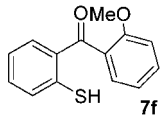
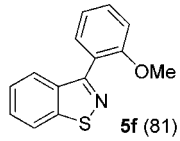
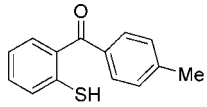
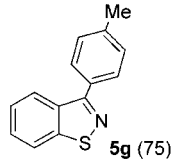
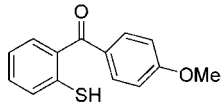
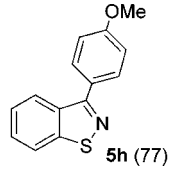
(7) (a) Wang, H.; Xian, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6598. (b) Zhang, J.; Wang, H.; Xian, M. *Org. Lett.* **2009**, *11*, 477. (c) Zhang, J.; Wang, H.; Xian, M. *J. Am. Chem. Soc.* **2009**, *131*, 3854. (d) Wang, H.; Zhang, J.; Xian, M. *J. Am. Chem. Soc.* **2009**, *131*, 13238.

(8) For selected reviews on *S*-nitrosothiols, see: (a) Williams, D. L. H. *Acc. Chem. Res.* **1999**, *32*, 869. (b) Al-Sadoni, H. H.; Ferro, A. *Curr. Med. Chem.* **2004**, *11*, 2679. (c) Wang, P.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev.* **2002**, *102*, 1091. (d) Oae, S.; Shinhama, K. *Org. Prep. Proc. Int.* **1983**, *15*, 165.

Table 3. One-Pot Synthesis of 3-Substituted Benzisothiazoles



7 5

entry	s.m.	benzisothiazole (yield%)
1	 **7a**	 **5a** (85)
2	 **7b**	 **5b** (74)
3	 **7c**	 **5c** (64)
4	 **7d**	 **5d** (74)
5	 **7e**	 **5e** (37)
6	 **7f**	 **5f** (81)
7	 **7g**	 **5g** (75)
8	 **7h**	 **5h** (77)

At lower temperature such as −20 °C, longer reaction times were needed for the nitrosation step, which resulted in a decrease of yield. At higher temperatures, like 20 °C, the decomposition of the *S*-nitroso intermediate seemed to dominate the second step and led to lower yield of the product. We also studied the solvent effects on this reaction. As shown in Table 1, most of the solvents, i.e., dioxane, DMF, CH_2Cl_2, benzene, etc., proved to be efficient for this transformation and furnished the desired product in good yields. However, THF seemed to be the most effective choice.

Although PPh_3 showed good reactivity in this synthesis, we wondered if a better phosphine substrate could be identified. Therefore, a series of phosphine reagents were examined (Table 2). Trialkylphosphine reagents such as PBu_3 (entry 1) turned out to be ineffective for this reaction while $P(OEt)_3$ resulted in the formation of **5a** in a moderate yield. Triphenylphosphine derivatives such as 2-$PyPPh_2$ and *n*-$BuPPh_2$ produced the product in moderate to good yields (entries 4 and 5). Interestingly, when $EtPPh_2$ was used, the highest yield of **5a** was obtained (entry 6).

With the optimized conditions/reagents in hand, the benzisothiazole synthesis was tested with a series of *o*-mercaptoacylphenones (**7a**−**h**, Table 3). In all cases, the desired products were obtained in good yields. A typical procedure is as follows: compound **7** was dissolved in THF at 0 °C and was treated with *i*-pentylONO (3 equiv). The reaction was continued for 5 min at 0 °C. Then, a solution of $EtPPh_2$ (2.1 equiv) in THF was added quickly to the reaction and the mixture was allowed to stir for 10 min at 0 °C and 50 min at rt. The desired product was obtained by flash column chromatography.

In conclusion, a facile synthesis of 3-substituted benzisothiazoles from *o*-mercaptoacylphenones has been developed. We demonstrated that *S*-nitrosothiols, albeit unstable, could be useful synthetic intermediates. Further expansion of the utility of *S*-nitrosothiols in organic synthesis is ongoing in our laboratory.

Acknowledgment. We thank NSF CAREER Award (CHE-0844931) for financial support. We also thank Prof. P. Garner and Prof. R. Ronald (Washington State University) for helpful discussions.

Supporting Information Available: Synthetic procedures, spectroscopic data, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9028447

(9) Examples are: (a) Carevo, M.; Motherwell, W. B.; Potier, P. *Tetrahedron Lett.* **2001**, *42*, 4377. (b) Carevo, M.; Motherwell, W. B.; Potier, P.; Weibel, J.-M. *Chem. Commun.* **2002**, 2394. (c) Shinhama, K.; Kim, Y. H.; Oae, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1771.