ORGANIC LETTERS

2006
Vol. 8, No. 21
4811−4813

Novel Alternative for the N–S Bond Formation and Its Application to the Synthesis of Benzisothiazol-3-ones

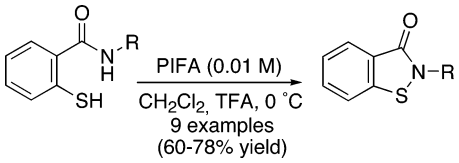
Arkaitz Correa, Imanol Tellitu,* Esther Domínguez,* and Raul SanMartin

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Euskal Herriko Unibertsitatea, P.O. Box 644, 48080 Bilbao, Spain

imanol.tellitu@ehu.es

Received July 28, 2006

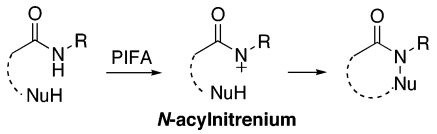
ABSTRACT



The synthesis of a series of benzisothiazolone derivatives starting from the readily available methyl thiosalicylate is presented. The key cyclization step features the formation of a *N*-acylnitrenium ion, generated by the hypervalent iodine reagent PIFA, and its succeeding intramolecular trapping by the thiole moiety leading to the construction of the title compounds by formation of a new N–S bond.

The continuous demand for highly efficient and environmentally benign synthesis of fine chemicals has encouraged the development of mild, safe, and highly chemoselective oxidizers. In this field, hypervalent iodine reagents constitute a paramount family of compounds which have received a great deal of attention due to their ready availability, low toxicity, easy handling, and reactivity similar to that of heavy metal reagents. Thus, their efficient use in metal-free transformations relies not only on the extremely mild reaction conditions required but also on their ability to oxidize chemoselectively a wide range of functionalities such as alcohols, amines, sulfides, and carbonyl compounds, among others.[1] In particular, our attention has been caught by the ability of the hypervalent iodine reagent [phenyliodine(III)-bis(trifluoroacetate)] (PIFA) to oxidize conveniently substituted amides to the corresponding *N*-acylnitrenium ions,[2] which are powerful electrophiles that easily undergo intramolecular heterocyclization reactions, as depicted in Scheme 1. Thus, by employing this simple strategy, a wide variety of appealing N-heterocycles via C−N bond formation have been achieved.[3]

Scheme 1. General PIFA-Mediated Amidation Process



***N*-acylnitrenium**

To expand the chemistry of nitrenium ions as useful synthetic intermediates in organic synthesis,[4] we have

(1) For recent reviews on the synthetic applications of polyvalent iodine reagents, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (c) Wirth, T. *Top. Curr. Chem.* **2003**, *224*, 1. (d) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111. (e) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (f) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656.

(2) This ability was first reported in 1990; see: Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581.

(3) See, for example: (a) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (b) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2003**, *44*, 3483. (c) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230. (d) Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *J. Org. Chem.* **2005**, *70*, 2256. (e) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Org. Lett.* **2005**, *7*, 3073.

(4) For some reviews on the chemistry of nitrenium ions, see: (a) Abramovitch, R. A.; Jeyaraman, R. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Eds.; Academic Press: Orlando, 1984; p 297. (b) Falvey, D. E. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Eds.; Wiley-Interscience: Hoboken, NJ, 2004; p 594. (c) Borodkin, G. I.; Shubin, V. G. *Russ. J. Org. Chem.* **2005**, *41*, 473.

10.1021/ol061867q CCC: $33.50
Published on Web 09/15/2006

recently reported the first successful intramolecular reaction of these electrophilic intermediates with amine functionalities (Nu = NR, Scheme 1) developing a novel versatile method for the construction of new N−N linkages.[5] Thus, in connection with this previous work and following with our research on the synthesis of highly valuable heterocycles through oxidative processes mediated by the environmentally friendly reagent PIFA, we report here a novel approach toward the synthesis of benzisothiazol-3-one derivatives of type **1**. This novel approach (see Scheme 2) features the

Scheme 2. Proposed Strategy for the Synthesis of Benzisothiazolones **1**

PIFA-mediated oxidation of properly substituted amides **2** and the subsequent trapping of the so-obtained N-centered electrophilic species by the thiole moiety to form a new N−S bond.

Benzisothiazol-3-ones are of widespread interest because of their effective antifungal, antibacterial, and antipsychotic properties.[6] Furthermore, it has been shown that certain benzisothiazolone compounds also possess anti-HIV activity.[7] As a result, a number of routes leading to the target compounds have been described in the literature, but although they have been proven to be useful protocols, some of them are of limited use because they require the employment of highly toxic and corrosive agents such as chlorine gas.[8] Therefore, the development of a chlorine-free synthetic protocol would be rather desirable, and in this context, we envisaged that the employment of PIFA would be of high practical value.[9]

Our synthetic study started by an effective preparation of the required 2-mercaptoamide derivatives **2a**−**j** following an $AlMe_3$−promoted aminolysis protocol[10] on commercially available methyl thiosalicylate (**3**), as outlined in Table 1. Next, on the basis of our previous experience and to optimize the experimental conditions for the proposed cyclization step, we selected *para*-methoxyphenylamide **2a** as a model system that could guarantee the stability of the corresponding *N*-acylnitrenium intermediate.[11] Thus, we briefly examined its behavior under the action of PIFA using different solvents (trifluoroethanol, CH_2Cl_2, acetonitrile, and toluene), temperatures (from 0 to 60 °C), and additives (TFA and $BF_3{\cdot}OEt_2$) to conclude that the optimal results were obtained when amide **2a** was treated with PIFA (0.01 M) in CH_2Cl_2 at 0 °C in the presence of TFA (3.0 equiv) thus leading to benzisothiazolone **1a** in 78% yield.

Having established an optimal protocol for the key cyclization step and with the aim to determine its scope with respect to the amide motif, we analyzed the influence of the nature of this functionality on the efficiency of the cyclization step. Thus, when amides **2a**−**j** were treated with the easy-to-handle reagent PIFA under the optimized reaction conditions, the effectiveness of the proposed cyclization proved to be suitable for *N*-arylamides **2a**−**g** yielding the corresponding benzisothiazolones **1a**−**g** in good yields (see Table 1). Consequently, these results suggest that activated (**2a**,**c**), nonactivated (**2b**,**d**), and moderately deactivated (**2e**,**f**) aryl rings, as well as the methoxypyridyl system (**2g**), are able to stabilize the *N*-acylnitrenium intermediate and, therefore, to accomplish successfully the scheduled cyclization. To our delight, alkylamides **2h** and **2j** also rendered successfully the corresponding benzisothiazolones **1h** and **1j**, respectively. Thus, although the previously reported oxidative process for the construction of N−N linkages by employing amine moieties as the nucleophilic counterpart of the reaction proved to be restricted to aromatic amides,[5] the presented process can be efficiently extended to certain alkyl amides.[12] Finally, we find no apparent explanation for the fact that although a wide range of experimental conditions were tested on amide **2i** they all failed to afford the desired heterocycle, leading, in all cases, to a complex mixture of products.

In summary, we have developed a new and efficient synthetic protocol for the preparation of benzisothiazol-3-one derivatives of type **1** based on an oxidative cyclization approach mediated by the hypervalent iodine reagent PIFA.

(5) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501. To the best of our knowledge, this is the only report in which a non-carbon species has been used as the nucleophilic counterpart of this amidation process.

(6) For some selected monographs, see: (a) Pain, D. L.; Peart, B. J.; Wooldridge, K. R. H. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 6, p 175. (b) Chapman, R. F.; Peart, B. J. *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, p 371.

(7) Rice, W. G.; Supko, J. G.; Malspeis, L.; Buckheit, R. W.; Clanton, D.; Bu, M.; Graham, L.; Schaffer, C. A.; Turpin, J. A.; Domagala, J.; Gogliotti, R.; Bader, J. P.; Halliday, S. M.; Coren, L.; Sowder, R. C.; Arthur, L. O.; Henderson, L. E. *Science* **1995**, *270*, 1194.

(8) (a) Davis, M. *Adv. Heterocycl. Chem.* **1972**, *14*, 58. (b) Baggaley, K. H.; English, P. D.; Jennings, L. J. A.; Morgan, B.; Nunn, B.; Tyrrell, A. W. R. *J. Med. Chem.* **1985**, *28*, 1661.

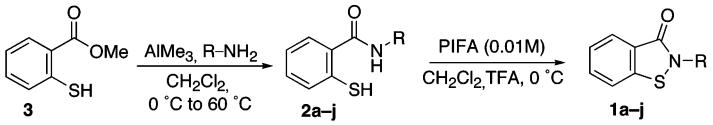
(9) Some selected examples of chlorine-free synthesis by employing (a) a PIFA-mediated Pummerer-type reaction of sulfides: Wang, H.-M.; Huang, H.-Y.; Kang, I.-J.; Chen, L.-C. *Heterocycles* **2001**, *55*, 1231. (b) An amidation−cyclization process of 2,2′-dithiobenzoates: Jin, C. K.; Moon, J.-K.; Lee, W. S.; Nam, K. S. *Synlett* **2003**, 1967. (c) A transamination of sulfenamides: Shimizu, M.; Takeda, A.; Fukazawa, H.; Abe, Y.; Shibuya, I. *Heterocycles* **2003**, *60*, 1855. (d) An amidation−cyclization process of 2,2′-dithiobenzamides: Sano, T.; Takagi, T.; Gama, Y.; Shibuya, I.; Shimizu, M. *Synthesis* **2004**, 1585.

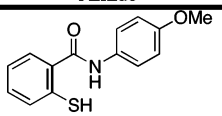
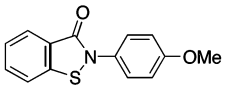
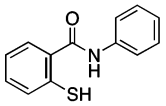
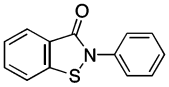
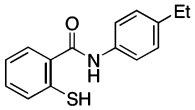
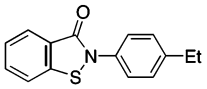
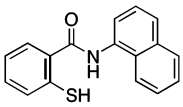
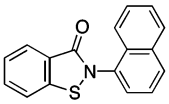
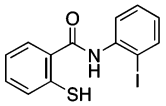
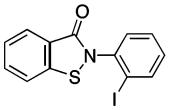
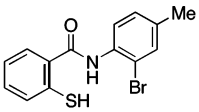
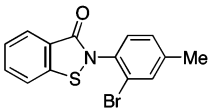
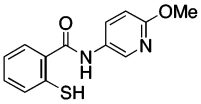
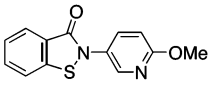
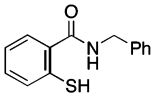
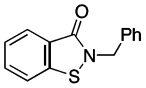
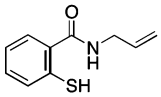
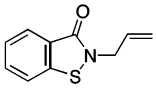
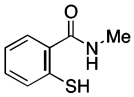
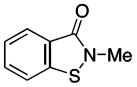
(10) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (b) Novak, A.; Humphreys, L. D.; Walker, M. D.; Woodward, S. *Tetrahedron Lett.* **2006**, *47*, 5767−5769.

(11) When nitrenium ions are stabilized by the electron-donating effect of a proper neighboring group (such as aryl, alkoxy, or nitrogen groups), they exhibit a sufficiently long life to undergo further organic reactions: (a) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577. (b) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazama, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739. (c) Falvey, D. E.; Kung, A. C. *J. Org. Chem.* **2005**, *70*, 3127.

(12) Computational calculations on alkylnitrenium ions show that there is substantial hyperconjugation from the vicinal σ bonds of the *N*-alkyl substituent. (a) Glover, S. A.; Scott, A. P. *Tetrahedron* **1989**, *45*, 1763. (b) Cramer, C. J.; Dulles, F. J.; Falvey, D. E. *J. Am. Chem. Soc.* **1994**, *116*, 9787. Apart from these theoretical studies, no other synthetic application of alkylnitrenium intermediates can be found in the literature, as far as we know. However, because of the low stabilization of deficient nitrogen species that a methyl group would produce, an alternative formation of an intermediate of type $ArCON(Me)-IPh(OCOCF_3)$ that reacts intramolecularly with the thiole group followed by reductive elimination of iodobenzene cannot be ruled out.

Table 1. Synthesis of Benzisothiazolones **1a**−**j** from Amides **2a**−**j**



entry	Amide	2 (%)[a]	Benzisothiazolone	1 (%)[b]
1		**2a** (92)		**1a** (78)
2		**2b** (95)		**1b** (71)
3		**2c** (95)		**1c** (66)
4		**2d** (95)		**1d** (62)
5		**2e** (95)		**1e** (64)
6		**2f** (91)		**1f** (67)
7		**2g** (61)		**1g** (70)
8		**2h** (60)		**1h** (60)
9		**2i** (63)[b]		**1i** (0)
10		**2j** (76)		**1j** (60)

[a] Isolated yields after purification by crystallization from Et_2O. [b] Isolated yields after purification by column chromatography.

The benefits from the use of such an innocuous oxidizer are clear in terms of lack of toxicity, safety, cost, and availability, properties that make this iodine reagent a rather useful tool in organic synthesis. In addition, our approach features the first successful intramolecular trapping of *N*-acylnitrenium ions by a thiole functionality developing a novel and easy method for the construction of N−S linkages.

Acknowledgment. Financial support from the University of the Basque Country (9/UPV 41.310-13656/2001) and the Spanish Ministry of Science and Technology (CTQ 2004-03706/BQU) is gratefully acknowledged. A.C. thanks the Basque Government for a predoctoral scholarship.

Supporting Information Available: Experimental details for compounds **2a**−**j** and **1a**−**j** and ^{1}H NMR and ^{13}C NMR spectra of all new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061867Q