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New Applications of Dithiocarbamates in Organic Synthesis

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ABSTRACT: *The application of dithiocarbamates in group transfer radical cyclization reactions is described. Carbamoyl diethyldithiocarbamates are synthesized in two high-yielding steps from secondary amines and act as sources of carbamoyl radicals through chemical or photochemical initiation. Group transfer radical cyclization reactions lead to dithiocarbamate-functionalized lactams.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:568–571, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20336

INTRODUCTION

The high radicophilicity of the thiocarbonyl group has resulted in a long association with synthetic free-radical chemistry. Radicals typically add reversibly at the sulfur of the thiocarbonyl group leading to a new carbon-centered radical, which can in turn undergo further free-radical processes. This reactivity forms the basis of a number of important functional group transformations, including the Barton–McCombie deoxygenation of alcohols [1], and the use of Barton esters for the decarboxylation of carboxylic acids [2]. More recently, the radicophilicity of the xanthate group has been exploited to great effect by Zard for the generation of a variety of radicals that have found application in a number of versatile and effective carbon–carbon bond-forming reactions [3].

Our own interest in the field of radical chemistry arose from a need to employ a carbamoyl radical cyclization as a key step in a natural product synthesis. The intramolecular addition of a carbamoyl radical **1** to a carbon–carbon double bond leads to the formation of a lactam **3** after H-atom transfer to the alkyl radical **2** (Fig. 1). This process represents an unusual synthesis of amides through a C—C bond-forming reaction, which complements the more usual C(O)—N bond-forming reaction between an amine and an activated carboxylic acid derivative.

Although a number of methods have been developed for the generation and cyclization of carbamoyl radicals [4–8], in all but one case they rely on a hydrogen transfer step to continue the radical chain process. This places a limit on the size and type of ring system that can be formed, since the rate of intermolecular hydrogen atom transfer to the initial carbamoyl radical to form **4** becomes comparable to, or can exceed, the rate of intramolecular cyclization, especially for more difficult, and hence slower, cyclizations. Indeed, highest yields are typically observed for the formation of γ-lactams through a 5-exo trig cyclization reaction, an extremely rapid reaction in free-radical chemistry, and extension to the formation of larger ring systems is problematic. However, four-membered ring formation can be effective in some cases, and the cobalt group transfer

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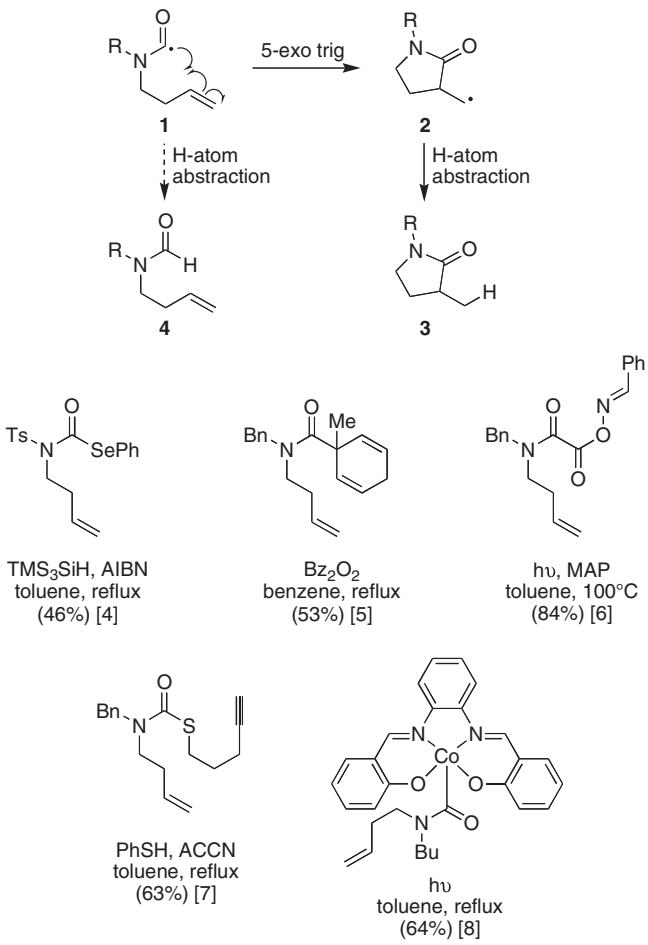

FIGURE 1 Carbamoyl radical cyclization precursors (yields in parentheses are for five-membered ring formation).

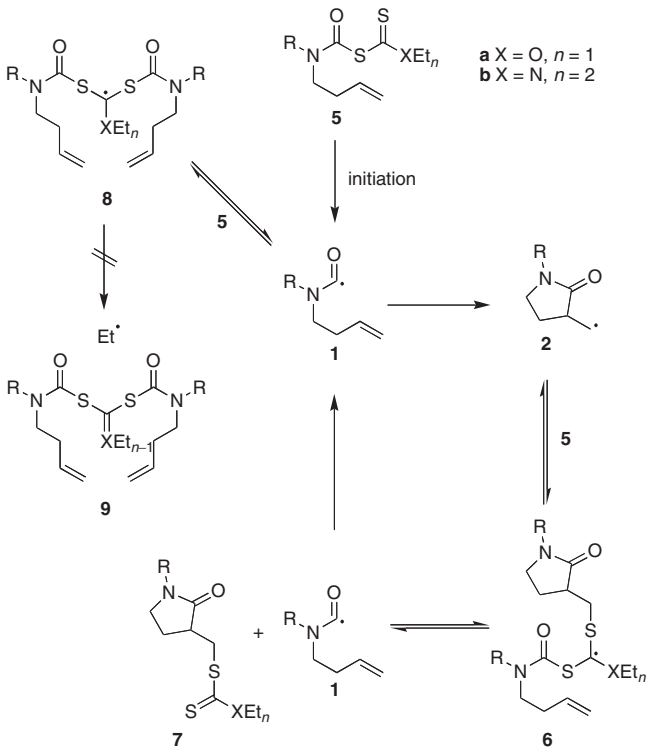

FIGURE 2 Group transfer cyclization of carbamoyl radicals.

methodology of Pattenden and coworkers has found notable application in a formal synthesis of the β-lactam antibiotic thienamycin [8,9].

RESULTS AND DISCUSSION

The inherent limitations of free-radical chain processes that rely on a H-atom abstraction step are overcome to a great extent by the xanthate group transfer chemistry developed by Zard [3]. The principle is shown in Fig. 2, in the context of our own interest in developing a method that is applicable to the synthesis of more challenging ring systems than a γ-lactam. A carbamoyl xanthate **5a** should act as a source of carbamoyl radical **1**, which can cyclize to form alkyl radical **2**. Xanthate group transfer via addition of **2** to the thiocarbonyl group of **5a** and subsequent fragmentation of **6a** leads to the desired product **7a** along with carbamoyl radical **1** to continue the chain process.

The competitive addition of carbamoyl radical **1** to the thiocarbonyl group of the starting xanthate **5a** represents a degenerate reaction process—the symmetrical radical **8a** will simply fragment back to **1** and a molecule of **5a**. The alternative fragmentation of **8a** (or indeed **6a**) to a primary ethyl radical is unlikely on energetic grounds. The degenerate reaction pathway and the absence of a H-atom transfer step means that carbamoyl radicals, such as **1**, generated from xanthate precursors **5a** should have sufficient lifetime to adopt conformations required for less facile cyclizations (than the simple 5-exo trig case).

Preparation of **5a** was attempted from the reaction of readily prepared carbamoyl chloride **10** with a xanthate salt (Fig. 3). The major product of the reaction was O-ethyl thiocarbamate **11**. Formation of **11** can be rationalized by attack of the xanthate salt on the initially formed **5a** at the thiocarbonyl carbon, followed by further ionic processes that also regenerate xanthate salt, resulting in further breakdown of **5a** [10]. Despite intensive investigation of the reaction conditions, we were unable to limit this reaction and prepare a carbamoyl xanthate such as **5a** in anything greater than 30% yield.

Reasoning that a carbamoyl dithiocarbamate **5b** should be less susceptible to nucleophilic attack

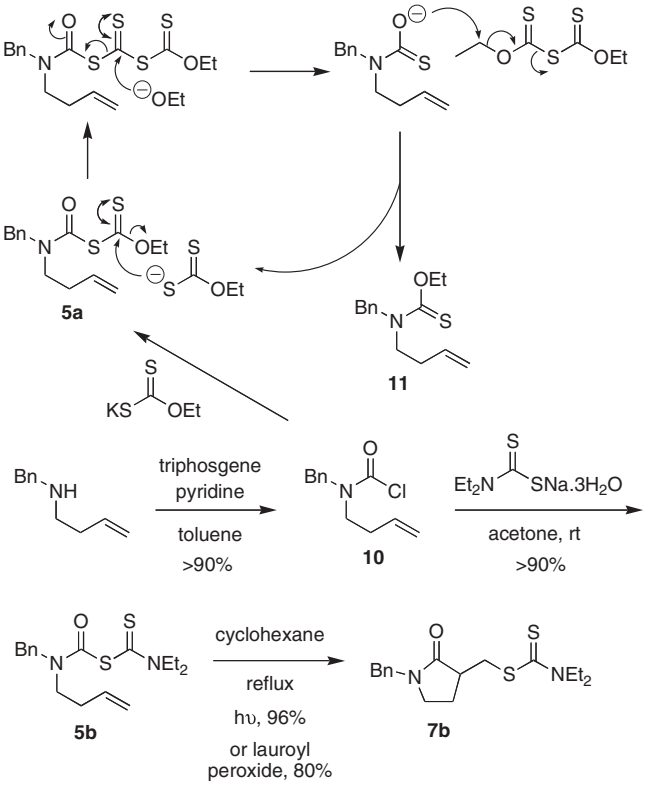

FIGURE 3 Preparation and cyclization of carbamoyl dithiocarbamates.

because of the increased electron density in the thiocarbonyl group compared with a xanthate, we investigated the reaction of carbamoyl chloride **10** with commercially available diethyldithiocarbamate sodium salt. In stark contrast to the xanthate case, we were delighted to find this resulted in a clean transformation to the carbamoyl dithiocarbamate **5b** in high yield. Furthermore, carbamoyl dithiocarbamates were found to undergo group transfer radical cyclization reactions in an analogous manner to that expected for the xanthate (Fig. 2). Initiation of a radical chain process, using either a peroxide or more conveniently by irradiation using a 500-W halogen lamp, gave the functionalized γ-lactam **7b** in high yield (Fig. 3) [11].

Dithiocarbamates, along with other thiocarbonyl-based functional groups, have been extensively investigated as mediators in living radical polymerizations by the reversible addition-fragmentation chain transfer (RAFT) mechanism [12]. However, despite the structural similarity of dithiocarbamates to xanthates, examples of their use in small-molecule free-radical reactions are rare [13–16]. The thiocarbonyl of a dithiocarbamate is expected to be more electron-rich than that in a xanthate because of the more pronounced electron-

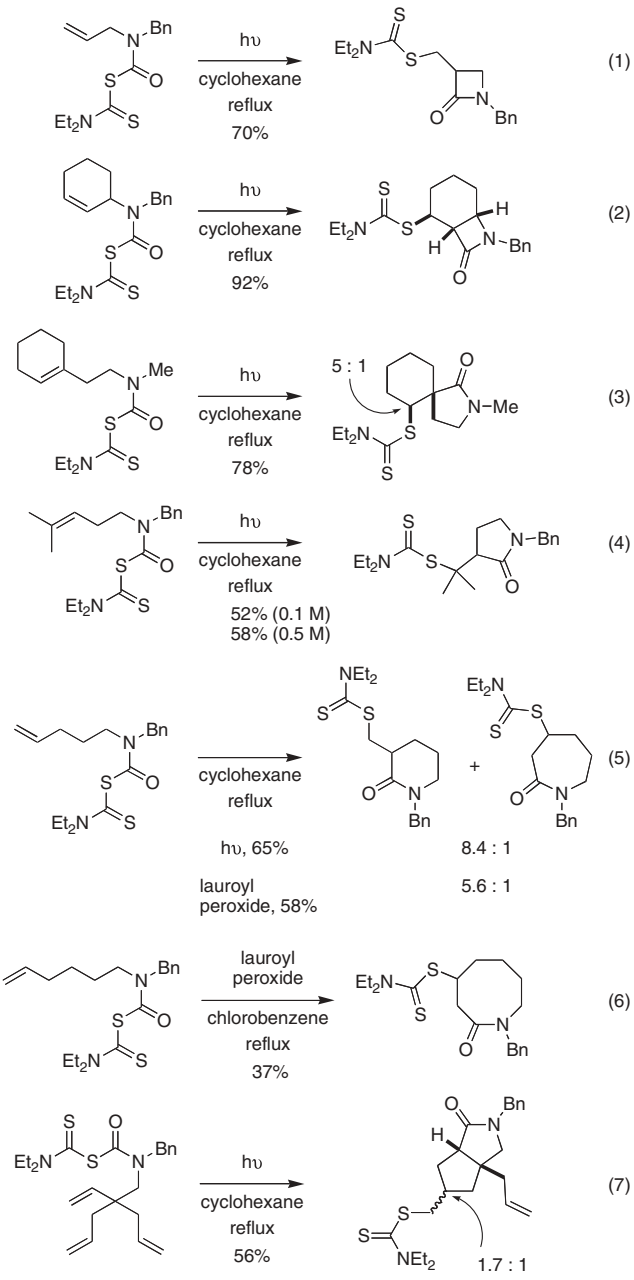

FIGURE 4 Synthesis of four to eight membered ring lactams.

donating effect of nitrogen versus oxygen [17]. This will have an effect on the rate of addition of radicals toward the thiocarbonyl group. Nucleophilic radicals, such as simple alkyl radicals **2**, are expected to add more slowly to the thiocarbonyl group of a dithiocarbamate, and as with any radical process, a slow individual step can lead to unproductive radical reactions and a termination of the radical chain process. However, in the present case, the rate is clearly sufficient to maintain a chain process, when the two equilibria that lead to dithiocarbamate

group transfer are driven in the desired direction (Fig. 2). The intermediate **6b** in the group transfer process will fragment to carbamoyl radical **1** and lactam **7b**, the major driving force being the relative stability of **1** compared with the primary alkyl radical **2**.

The dithiocarbamate group transfer cyclization of carbamoyl radicals has proven to be a relatively general approach to functionalized lactams of various ring sizes (Fig. 4) [11]. After cyclization, dithiocarbamate group transfer to secondary (Eqs. (2), (3), (5), and (6)) and tertiary (Eq. (4)) radicals can also be achieved; although in the latter case yields are lower, presumably due to a slower addition step from the more hindered tertiary radical and less favorable equilibria during dithiocarbamate group transfer. Running the reaction at a higher concentration led to a slightly higher yield in this case. Formation of a bicyclic ring system through two consecutive 5-exo trig cyclizations and dithiocarbamate group transfer is also possible (Eq. (7)).

In conclusion, the dithiocarbamate group has been shown to be an efficient mediator of carbamoyl radical cyclization reactions, complementing the radical chemistry of xanthates. The procedure is experimentally simple, requiring neither high dilution nor syringe pump techniques, and avoids the use of toxic tin reagents characteristic of a large number of free-radical processes. The products of these reactions themselves contain a dithiocarbamate, which can be used for further functional group manipulation. It is hoped this methodology will find application in the synthesis of new heterocyclic ring systems of biological interest, including natural products.

REFERENCES

[1] Zard, S. Z. In Radicals in Organic Synthesis; Renaud, P.; Sibi, S. (Eds.); Wiley-VCH: Weinheim, 2001; Vol. 1, Ch. 1.6.

[2] Motherwell, W. A.; Imboden, C. In Radicals in Organic Synthesis; Renaud, P.; Sibi, S. (Eds.); Wiley-VCH: Weinheim, 2001; Vol. 1, Ch. 1.7.

[3] Zard, S. Z.; Quiclet-Sire, B. Chem Eur J 2006, 12, 6002–6016.

[4] Rigby, J. H.; Danca, D. M.; Horner, J. H. Tetrahedron Lett 1998, 39, 8413–8416.

[5] Bella, A. F.; Jackson, L. V.; Walton, J. C. Org Biomol Chem 2004, 2, 421.

[6] Scanlan, E. M.; Slawin, A. M. Z.; Walton, J. C. Org Biomol Chem 2004, 2, 716–724.

[7] Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. J Org Chem 2006, 71, 3192–3197.

[8] Gill, G. B.; Pattenden, G.; Reynolds, S. J. J Chem Soc, Perkin Trans 1 1994, 369–378.

[9] Reynolds, S. J.; Pattenden, G. J Chem Soc, Perkin Trans 1 1994, 379–385.

[10] Zard, S. Z. Angew Chem, Int Ed 1997, 36, 672–685.

[11] Grainger, R. S.; Innocenti, P. Angew Chem, Int Ed 2004, 43, 3445–3448.

[12] Moad, G.; Rizzardo, E.; Thang, S. H. Aust J Chem 2005, 58, 379–410.

[13] Yanagawa, M.; Moriya, O.; Watanabe, Y.; Ueno, Y.; Endo, T. Bull Chem Soc Jpn 1988, 61, 2203–2204.

[14] Bouhadir, G.; Legrand, N.; Quiclet-Zire, B.; Zard, S. Z. Tetrahedron Lett 1999, 40, 277–280.

[15] Thang, S. H.; Chong, Y. K.; Mayadunne, R. T. A.; Moad, G.; Rizzardo, E. Tetrahedron Lett 1999, 40, 2435–2438.

[16] Harakat, D.; Pesch, J.; Marinkovic, S.; Hoffmann, N. Org Biomol Chem 2006, 4, 1202–1205.

[17] Chiefari, J.; Mayadunne, R. T. A.; Moad, C. L.; Moad, G.; Rizzardo, E.; Postma, A.; Skidmore, M. A.; Thang, S. H. Macromolecules 2003, 36, 2273–2283.