Radical Reactions

Dithiocarbamate Group Transfer Cyclization Reactions of Carbamoyl Radicals under "Tin-Free" Conditions**

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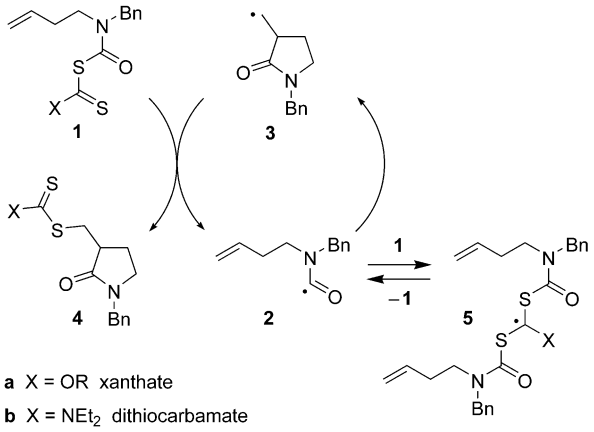
The use of radical reactions in modern organic synthesis is now well-established.[1] Despite the many well-documented advantages of free-radical chain reactions in organic chemistry, the majority of examples still rely on the use of tributyltin hydride in stoichiometric amounts, and a major area of current research is the development of processes which seek to either alleviate the problems associated with toxic tin residues, or remove the need for tin completely.[2] Among these methods, the group transfer chemistry of xanthates, extensively developed by Zard and co-workers, is one of the most powerful.[3] Xanthate precursors to acyl,[4] alkoxycarbonyl,[5] and a variety of other carbon-centered[6] and nitrogen-centered[7] radicals have been reported, and found numerous applications in synthesis.[5,8] However, group transfer of xanthates from carbamoyl radical precursors has not been described. Herein we describe the difficulties associated with using xanthates as carbamoyl radical precursors, and report a solution based on replacing the classical xanthate with a dithiocarbamate group.

Carbamoyl radicals, or aminoacyl radicals, offer a useful means to introduce an amide functional group into an organic molecule through a nonclassical disconnection. A number of elegant methods for the generation of carbamoyl radicals are known.[9] Faced with a problematic carbamoyl radical cyclization in the course of a recent synthetic endeavor, we considered that xanthate chemistry would offer a potential solution. The principle is outlined in Scheme 1: radical cyclization of carbamoyl radical **2** should lead to the alkyl radical **3**, which after addition to the carbon–sulfur double bond of a carbamoyl xanthate **1a** and fragmentation of the resulting carbon-centered radical gives the desired lactam **4a** along with the initial radical **2**, which can continue the chain process. An alternative reaction pathway available to carbamoyl radical **2** is addition to the radical precursor **1** to give the intermediate radical **5**. However, this process is fast and reversible as **5** will fragment back to **1** and **2**.[10] The continuous regeneration of carbamoyl radical **2** by this degenerate pathway means it should be capable of undergoing cyclizations which would not otherwise compete favorably with premature reduction of **2** under conditions used for tin hydride (or other hydrogen atom abstraction).[9d,g–l]



Scheme 1. Group transfer radical cyclization of carbamoyl radicals.

A survey of the literature showed that carbamoyl xanthates have been proposed as intermediates in the reaction between readily prepared carbamoyl chlorides and xanthate salts, which ultimately affords the corresponding S-substituted thiocarbamates upon loss of carbon oxysulfide.[11] Aware of this behavior, we investigated the possibility that the reaction could be stopped at the carbamoyl xanthate stage by choosing appropriate conditions. However, despite extensive variations of temperature, solvent, xanthate salt (R = ethyl, neopentyl), leaving group,[12] and stoichiometry we were unable to isolate the desired carbamoyl xanthate **1a** in anything other than small amounts (< 10% yield). All the conditions tried invariably gave a complex mixture of compounds (e.g. compounds **1a**, **6**–**9** in the reaction shown in Scheme 2);[13] formation of S-substituted thiocarbamates was not observed in our experiments. Incorporation of an electron-withdrawing group (phenylsulfonyl) on the nitrogen atom in place of the benzyl group also failed to alleviate this problem.[9g,14] Frustratingly, the desired cyclization of **1a** to the expected pyrrolidinone **4a** is readily achieved in 67% yield simply upon irradiation of a refluxing toluene solution of **1a** using a halogen or tungsten lamp, but the overall process remains untenable in the absence of an efficient method for the preparation of **1a**.

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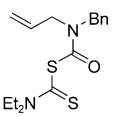
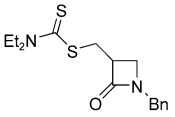
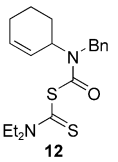
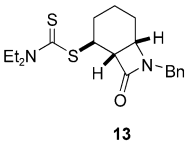
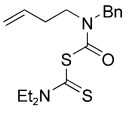
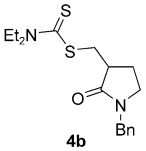
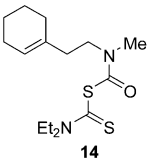
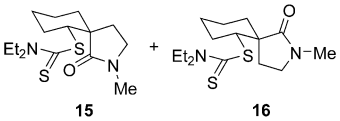
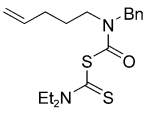
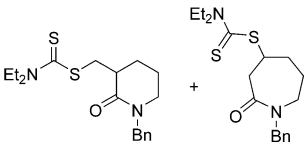
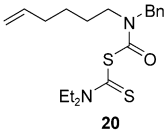
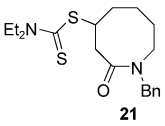
In a search for a "xanthate-like" radical precursor, our attention turned to the corresponding *N*,*N*-dialkyl dithiocarbamates. Apart from aromatic amines, such compounds were described in a patent as unstable to heat.[15] In fact, the desired dithiocarbamate **1b** can be prepared in high yield (>95%) from the corresponding carbamoyl chloride **6** by treatment with commercially available sodium diethyldithiocarbamate trihydrate, without any of the problems known from the corresponding xanthates (Scheme 2). More importantly, *N*,*N*-dialkyldithiocarbamates substitute for xanthates in group transfer radical cyclization reactions of carbamoyl radicals. Two methods can be used to initiate the radical process. The first simply involves irradiation with visible light using a 500-W halogen lamp. The second uses commercially available dilauroyl peroxide (DLP) as an initiator, added portionwise. The desired cyclization of **1b** to **4b** can be achieved in up to 96% yield (Table 1, entry 3).

The results of the cyclization of a selection of dithiocarbamates to the corresponding cyclic amides are shown in Table 1.[16] A range of ring sizes can be achieved with this chemistry. As has been previously demonstrated by others,[9d,e,i–l] carbamoyl radicals efficiently cyclize to form four-membered rings (Table 1, entries 1 and 2). In the case of β lactam **13**, a single diastereomeric adduct is formed, the configuration of which has been proven by X-ray crystallography. The stereochemical outcome is consistent with group transfer to the intermediate cyclohexyl radical occurring on the less hindered convex face of the [4.2.0]bicyclic ring system. Five-membered rings are also formed with complete regioselectivity and in good to excellent yields through the 5-*exo-trig* radical cyclization mode (Table 1, entries 3 and 4). The orientation of the resulting dithiocarbamate group in the spirobycyclic γ lactams **15** and **16** relative to the heterocycle has been tentatively assigned on the basis of NOESY experiments.[17]

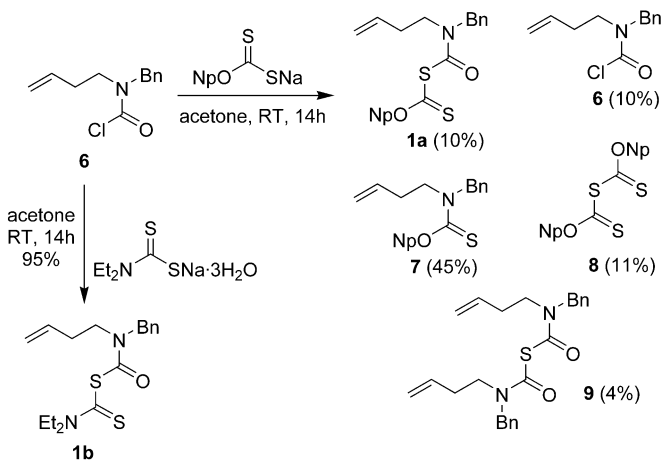
Table 1: Carbamoyl radical cyclization reactions through dithiocarbamate group transfer.[a]

Entry	Radical precursor	Lactam product(s)[b]	Method	Yield [%]
1	 **10**	 **11**	A	70
2	 **12**	 **13**	A	92
3	 **1b**	 **4b**	A B	96 80
4	 **14**	 **15** **16**	A	78 (**15**:**16** 1:5)
5	 **17**	 **18** **19**	A B	65 (**18**:**19** 8.4:1) 58 (**18**:**19** 5.6:1)
6	 **20**	 **21**	C	37

[a] Reaction conditions: A: *hν*, cyclohexane, reflux; B: DLP, cyclohexane, reflux; C: DLP, chlorobenzene, reflux. [b] Details on the synthesis of the lactams along with analytical data are given in the Supporting Information.

Six-membered rings are also readily obtained using this chemistry, with a small amount of the seven-membered ring lactam **19** formed in addition to the expected product **18** (Table 1, entry 5). Lactam **19** presumably arises through a 7-*endo-trig* pathway, although ring expansion of the alkyl radical arising from the 6-*exo-trig* pathway through 3-*exo-trig* cyclization onto the amide carbonyl group followed by cyclopropyloxy radical fragmentation prior to group transfer cannot be excluded.[9d]

We are not aware of any reports of the cyclization of carbamoyl radicals being used to form ring sizes larger than



Scheme 2. Reaction of carbamoyl chlorides with xanthate and dithiocarbamate salts. Np = neopentyl.

six. The formation of an eight-membered ring using this chemistry is therefore notable (Table 1, entry 6). Although the yield is only moderate, there are relatively few reports of direct formation of an eight-membered ring in the radical chemistry literature.[18] The use of a higher-boiling solvent was found to be beneficial in this case.

The replacement of a xanthate with an *N*,*N*-dialkyl dithiocarbamate in the above process is notable and has little precedent in the literature: work on controlled radical polymerization has shown that dithiocarbamates only undergo radical group transfer reactions if an electron-withdrawing group is placed on the nitrogen atom.[19,20] In the present case, even though the carbon–sulfur double bond in *N*,*N*-dialkyl dithiocarbamate **1b** is more electron rich than in xanthate **1a**, efficient group transfer to the nucleophilic alkyl radical **3** is still observed.

In conclusion, *N*,*N*-diethyldithiocarbamates are ideal substitutes for xanthates in a new method for generating carbamoyl radicals undergoing efficient group transfer to both primary and secondary alkyl radicals after cyclization. The overall process is simple to carry out, requires no special precautions, and has a number of advantages over existing radical methodologies: the lack of toxic tin hydrides, the mild and safe method for initiating the radical chain process, the functionalization of the final radical which can lead to further useful chemical transformations,[21] and the nonreliance on slow (syringe pump) addition and high-dilution techniques. We are currently extending this work to include other radical acceptors, asymmetric variants, and applications in target-directed synthesis.

Experimental Section

Representative procedure for the preparation of carbamoyl diethyldithiocarbamates from secondary amines:

Pyridine (10.1 mmol) was added dropwise to a solution of triphosgene (2.9 mmol) in toluene (70 mL); the resulting suspension was treated with a solution of the secondary amine (7.8 mmol) in toluene (10 mL). The reaction was stirred overnight at room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O. The organic layer was washed with 0.3 M HCl, water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude carbamoyl chloride which was used directly in the next step.

A solution of the crude carbamoyl chloride (ca. 6.6 mmol) in acetone (45 mL) was treated with sodium diethyldithiocarbamate trihydrate (26.2 mmol). The reaction was stirred overnight at room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O. The organic layer was washed with water and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude carbamoyl diethyldithiocarbamate, which in most cases was sufficiently pure to be used directly in the cyclization reactions.

Representative procedure for the photomediated cyclization (method A): Carbamoyl dithiocarbamate (0.8 mmol) was dissolved in cyclohexane (8 mL) and oxygen was removed from the resulting solution using a nitrogen stream for ca. 15 min. The solution was irradiated with a 500-W halogen or tungsten lamp that generated sufficient heat to bring the solvent to reflux. The reaction progress was monitored by thin-layer chromatography (TLC). After the reaction was complete (1–8 h) the solvent was removed under reduced pressure and the crude was purified by column chromatography.

Representative procedure for the DLP-induced cyclization (method B): Carbamoyl dithiocarbamate (0.4 mmol) was dissolved in cyclohexane (4 mL) and oxygen was removed from the resulting solution using a nitrogen stream for ca. 15 min. The solvent was heated to reflux and DLP (0.04 mmol) was added to the boiling solution. The reaction progress was monitored by TLC and fresh portions of initiator were added every 1.5–2 h. After the reaction was complete (2–10 h) the solvent was removed under reduced pressure and the crude was purified by column chromatography.

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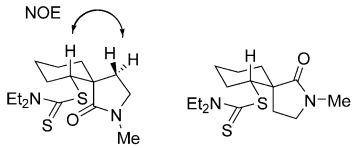
[16] All dithiocarbamate radical precursors were prepared in $>80\%$ yield from the corresponding secondary amine in a two-step procedure (see Experimental Section), with the exception of **14** which was prepared from the corresponding tertiary dimethylamine.

[17] The coupling constants for the proton on the carbon atom adjacent to the sulfur atom in both **15** and **16** are consistent with an equatorial arrangement of the dithiocarbamate group on the cyclohexane ring. This proton shows a NOE interaction to one of the pyrrolidinone ring hydrogen atoms in the case of **15**, whereas no NOE interaction is observed to either of these hydrogen atoms in the case of **16**.



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