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Radical cyclizations in 1,4-dimethylpiperazine

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Abstract—*N*-Allylic or *N*-vinylic α,α,α-trichloroacetamides, upon heating in 1,4-dimethylpiperazine, undergo radical cyclization to give the corresponding γ-lactams.

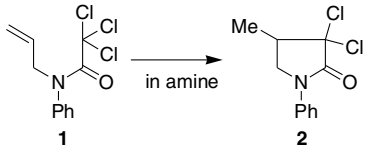
Much interest has been shown in radical cyclizations for the synthesis of a variety of carbo- and heterocyclic compounds, including natural products.[1] A combination of a radical initiator such as AIBN [azobis(isobutyronitrile)] and a hydrogen donor such as Bu_3SnH has frequently been used for radical reactions. There are, however, some disadvantages in using Bu_3SnH such as its toxicity and the difficulty of product purifications. Therefore, several substitutes for the use of Bu_3SnH have been studied in recent years.[2]

Herein we report that radical cyclization of *N*-allylic and *N*-vinylic α,α,α-trichloroacetamides can be performed by heating in 1,4-dimethylpiperazine (1,4-DMP) used as a solvent to give the corresponding γ-lactams in good yields.

Organic amines are known to work as electron donors in single electron transfer (SET) reactions, and they have been used for reductive dehalogenation of α-halo carbonyl compounds; that is, *N*,*N*-dimethylaniline,[3] 1,3-dimethyl-2-phenylbenzimidazoline (DMBI),[4] 1-benzyl-1,4-dihydropyridines,[5] morpholine[6] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[7] have been employed for dehalogenation via a radical mechanism. However, no example was reported for the formation of radical cyclization product even when appropriate radical acceptors were tethered to the molecules, except for the case of photoirradiation in the presence of triethylamine and alkyl bromides.[8]

As an initial study for the cyclization, *N*-allylic α,α,α-trichloroacetamide **1** was heated in boiling triethylamine for 30 min but gave no reaction product. A similar treatment in boiling tripropylamine, however, afforded **2** in 2% yield along with the starting material **1** (82%) (Scheme 1). On the other hand, when compound **1** was treated in boiling cumene, the boiling point of which (155 °C) is almost the same as that of tripropylamine (156 °C), no cyclization product was obtained after 90 min of heating. These results strongly suggested that the cyclization of **1** giving **2** would proceed by heating in amine having a high boiling point.

We next examined the cyclization of **1** in boiling amine in more detail (Table 1). When compound **1** was heated in a secondary amine such as dibutylamine (bp: 159 °C) for 30 min, the cyclization product **2** was obtained in 44% yield (entry 3). The use of a primary amine such as heptylamine (bp: 157 °C) gave a complex mixture of products (entry 4). A cyclic secondary amine such as piperidine gave an undesired compound **3** (34% yield)



1 **2**

Scheme 1. Cyclization of **1**.

Keywords: *N*-allylic α,α,α-trichloroacetamide; Anion radical; 1,4-Dimethylpiperazine; Radical cyclization; Single electron transfer.
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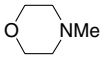
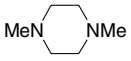
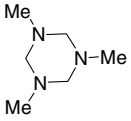
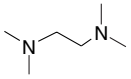
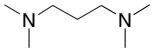
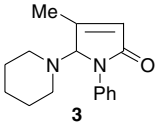
Table 1. Reaction of **1** in boiling amines

Entry	Amine	Bp	Time (min)	Yield of **2**[a] (%)
1	Et_3N	89	30	0 (97)
2	Pr_3N	156	30	2 (82)
3	Bu_2NH	159	30	44 (32)
4	$CH_3(CH_2)_6NH_2$	157	30	—
5		106	20	34[b] (0)
6		106	90	18 (77)
7		116	90	46 (33)
8		133	2	75 (0)
9		162	90	2 (0)
10		122	30	17 (32)
11		145	30	26 (58)

[a] Numbers in parentheses are % yields of the starting material.
[b] Yield of compound **3**.



3

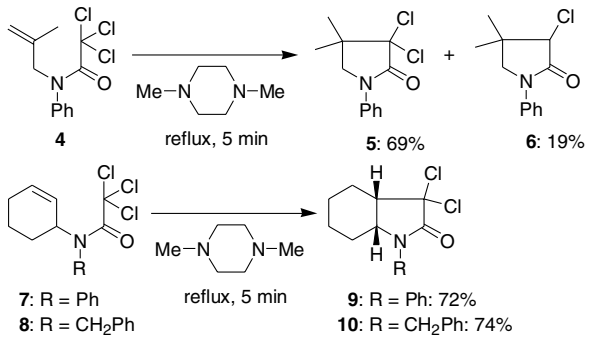
(entry 5), which might be formed from **2** since compound **3** was obtained in 79% yield by treating **2** in boiling piperidine for 30 min. Of the cyclic tertiary amines examined (entries 6–9), 1,4-dimethylpiperazine (1,4-DMP) (bp: 133 °C) was found to be best for the cyclization of **1** (entry 8). The reaction of **1** in boiling 1,4-DMP was completed within 2 min to give product **2** in 75% yield. Acyclic diamines such as tetramethylethylenediamine and tetramethylpropanediamine gave product **2** in poor yields (entries 10 and 11).

The effects of reaction temperature in 1,4-DMP on the cyclization of **1** were next examined in more detail. When the cyclization of **1** was carried out at 100 °C instead of at reflux (at 133 °C for 2 min, entry 8 in Table 1), compound **2** was obtained in 77% yield after 15 min of heating. Treatment of **1** at 65 °C also gave **2** in 81% yield after 120 min of heating.[9] These results strongly indicate that product **2** was labile at a high temperature and that the cyclization of **1** took place at a relatively low temperature when 1,4-DMP was used as a solvent. Unfortunately, at a lower temperature such as room temperature, no cyclization of compound **1** occurred.

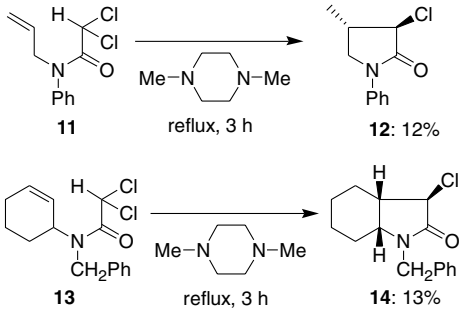
However, surprisingly, the cyclization of **1** occurred at room temperature by using dimethyl sulfoxide (DMSO) as a co-solvent. When compound **1** was treated in a 1:1 mixture of 1,4-DMP and DMSO at room temperature for 6 h, compound **2** and the dechlorinated product **11** were obtained in 50% and 17% yields, respectively, along with the starting material **1** (13%).

Nitromethane, acetonitrile, or dimethyl formamide could also be used as a co-solvent to give almost the same result as that obtained when DMSO was used. However, no reaction occurred when dichloromethane or benzene was used as a co-solvent. These results suggest that the cyclization of **1** at room temperature can occur only when a co-solvent having a high dielectric constant is used.[10]

The cyclization of *N*-allylic acetamide **4** also proceeded smoothly for 5 min in 1,4-DMP at reflux to give compound **5** and the partially dechlorinated compound **6** in 69% and 19% yields, respectively (Scheme 2). *N*-(Cyclohex-2-eny-1-yl)acetamides **7** and **8** gave the corresponding cyclization products **9** and **10** in 72% and 74% yields, respectively.



Scheme 2. Reactions of **4**, **7** and **8**.

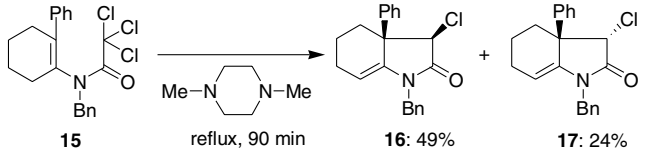


Scheme 3. Reactions of **11** and **13**.

N-Allylic α,α-dichloroacetamides were also found to give the desired products, but the cyclization was sluggish. Compound **11** in 1,4-DMP gave **12**[11] in 12% yield along with a considerable amount of the starting material (80%) after 3 h of heating (Scheme 3). Under similar conditions, compound **13** gave **14** in 13% yield along with the starting material (69%). The ^{1}H NMR spectra of compound **14** showed it to be a single stereoisomer. The orientation of its chlorine atom and the hydrogen atom at C-3a was tentatively assigned to be *cis* in the same manner as **12**.

Finally, when *N*-vinylic acetamide **15** was heated in 1,4-DMP for 90 min, 5-*endo-trig* radical cyclization products **16**[12] and **17**[12] were obtained in 49% and 24% yields, respectively (Scheme 4).

In conclusion, radical cyclization of *N*-allylic or vinylic trichloroacetamides proceeded smoothly in 1,4-DMP. Neither heavy metals (Sn, Ni,[13] Mn,[14] etc.) nor photochemical conditions were required in the present radical reactions. Furthermore, easy purification of cyclized products was realized by the use of volatile 1,4-DMP. Elucidation of mechanistic problems for the radical cyclizations, and application of this method to the synthesis of a variety of cyclic compounds are under intense investigation.



Scheme 4. Reaction of **15**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.146.

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