Synthesis of α-Chlorolactams by Cyanoborohydride-Mediated Radical Cyclization of Trichloroacetamides

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Abstract: A cyanoborohydride-promoted radical cyclization methodology has been developed to access α-chlorolactams in a simple and efficient way, using $NaBH_3CN$ and trichloroacetamides easily available from allylic and homoallylic secondary amines. This methodology allowed the synthesis of a library of α-chlorolactams (mono and bicyclic), which were tested for herbicidal activity, *trans*-3-chloro-4-methyl-1-(3-trifluoromethyl)phenyl-2-pyrrolidinone being the most active.

Introduction

Borohydrides are involved in two interesting applications in synthetic radical chemistry: a) they enable methodologies to be developed with a reduced amount of organotin reagent/hydride, generated *in situ* by reduction of a catalytic trialkyltin halide; b) they provide a tin-free procedure in which borohydrides play a conceptually different role, acting as radical precursors of boryl radicals and reducing carbon-centered radicals by hydrogen atom transfer.

As a source of hydride, borohydrides can be employed to reduce the amount of tin reagents in radical processes involving catalytic tin hydride reactions. Either sodium borohydride or cyanoborohydride can be used as the stoichiometric reducing agent of trialkyltin halides, allowing the tin hydride reagent to be generated *in situ.*[1] Furthermore, polymer-bound tin hydrides can also be used in catalytic quantities with a stoichiometric amount of a corresponding reducing reagent (e.g. a borohydride).[2] On the other hand, ten years ago Ryu envisioned the synthetic potential of radical methodologies based on cyanoborohydride, harnessing the latter's ability to form boryl radicals and react as a hydrogen donor.[3-5] Since then, cyanoborohydride reagents[6-8] have been used as radical mediators and iodoalkanes as proradicals (Scheme 1) in several studies.[9]

In this context, the expansion of borohydride–based protocols to new, easy to handle functionalities would be highly desirable. The current paper introduces the use of sodium cyanoborohydride and AIBN as the initiator to promote radical cyclizations from trichloroacetamides.[10] The synthetic procedure enables the preparation of valuable α-chlorolactams and also constitutes a new tool to generate dichloromethylcarbamoyl radicals, which allow nitrogen-containing heterocycles to be synthesized in intramolecular processes.[11]

Insert Scheme 1

Results and Discussion

Initial Studies. Our initial interest was in performing radical ring-closing reactions in a catalytic manner from trichloroacetamides using a supported tin hydride reagent, generated in situ by a reducing agent (*e.g.* $NaBH_4$). The few examples of reductive radical cyclization using grafted

polymers with organotin reagents feature bromides as proradical carbon-center species.[12] In order to apply this chemistry to the radical cyclization of trichloroacetamides, we decided to use a stannylated polynorbornene, which was reported[13] and recently employed by Albéniz for radical reductive bromoaryl reduction processes using polymethylhydrosiloxane (PMHS) as a reductor.[14]

Trichloroacetamide **1** was chosen as a model substrate for the initial studies and submitted to the reaction conditions depicted in Table 1 using a supported tin reagent provided by the Albéniz group. When the reagent was employed with $NaBH_4$ and AIBN, it led to the full decomposition of **1** in MeCN (entry 1) and to the formation of the formylated amine **3** in *t*-BuOH (entry 2). Avoiding the use of the tin-supported reagent (entry 3), $NaBH_4$ promotes a clean reduction process (**1** → **3**) when using *t*-BuOH as the solvent, *via* a hydride attack upon the trichloroacetamide carbonyl group with a concomitant release of the trichloromethyl anion as a leaving group. In fact this transformation constitutes a new procedure to obtain formamides from secondary amines via trichloroacetylation and treatment with sodium borohydride.[15] Studies on the scope of this process are underway.

Insert Table 1

Most important was the use of less reactive hydride source, $NaBH_3CN$ instead of $NaBH_4$, in refluxing *t*-BuOH. Thus, a full conversion of trichloroacetamide **1** to monochloromorphans **2** was gratifyingly observed using $NaBH_3CN$ and the tin-supported reagent (entry 4). Moreover, when the reaction from **1** was performed without polymer (i.e. without a tin hydride source), it unexpectedly gave a clean conversion to monochloromorphan **2a** (entry 5). Initially, the reaction was performed over a period of 12 h, but we were pleased to observe that reducing the reaction time to 4 h did not affect the outcome (entry 6).

Interestingly, the process stopped at the level of a-chlorolactam and further reduction did not take place, since the cyanoborane radical anion ($BH_2CN^{\bullet -}$) failed to abstract the final chlorine atom. It is known that halogen substituents weaken the bond dissociation energy,[6] which allowed the homolytic cleavage of tri- and dichloroamides in the transformation of **1** to **2**, but not an additional reduction. Moreover, a potential reduction of α-chlorolactam **2**, via hydride transfer seems to be precluded since secondary alkyl halides are quite unreactive when sodium cyanoborohydride is used.[16]

We then decided to explore the effect of the number of chlorine atoms on the cyclization reaction. Monochloroacetamide **4a-1** was submitted to the previously described reaction conditions and a low conversion was observed, giving only traces of γ-lactam **5** together with small amounts of the reduced compound **4a-0** (Table 2, entry 1). As expected, the cyanoborane radical anion ($BH_2CN^{\bullet -}$) failed to fully abstract the single chlorine atom, while the dichloro- (**4a-2**) and trichloroacetamide **4a** underwent the most efficient conversions, the latter providing the highest amount of the cyclized product **5**, as an epimeric mixture, showing that the additional chlorine atoms facilitates the cyclization.[17]

Insert Table 2

Next examined was the effect of the counter cation in the cyclization of trichloroacetamide **4a**. $NaBH_3CN$ and Bu_4NBH_3CN led to the expected g-lactam **5** in similarly good yields (Scheme 2). Sodium cyanoborohydride led preferentially to the formation of the thermodynamically more stable product ***trans*-5**, while in the case of tetrabutylammonium cyanoborohydride, the steric hindrance generated by the counter cation Bu_4N^+ favored the formation of ***cis*-5**. The influence of the counter cation on the course of the reaction indicated that the reacting radical species was the cyanoborane radical anion ($BH_2CN^{\bullet -}$). As our research was then focused on the synthesis of trans β-alkyl-α-chlorolactams, the impact of the counter cation was not explored any further.

Insert Scheme 2

Under the same conditions, but using $NaBD_3CN$ instead of $NaBH_3CN$, the dideuterated products **5a-D_2** were obtained (Scheme 3), with the incorporation of 89-90% deuterium (determined by NMR), thus confirming that the origin of the hydrogen atoms was the borohydride species. No major changes in diastereoselectivity were observed.

Insert Scheme 3

Based on the above results, as well as the photo-induced radical cyclizations from aromatic halides with $NaBH_3CN$[18] and Ryu's research,[6] the following radical mechanism is proposed (Scheme 4): after the initiation phase (using AIBN), $BH_2CN^{\bullet -}$ abstracts a chlorine atom from the

trichloroacetamide (*e.g.* **4a**) to yield dichlorocarbamoylmethyl radical **I**, which undergoes cyclization in a 5-*exo* fashion to give radical **II**. The primary C-centered radical is then reduced by cyanoborohydride to afford dichlorolactam **III** along with a borane radical anion, which can sustain the radical chain by abstracting a chlorine atom from trichloroacetamide **4a**, returning the dichloromethyl radical **I** and the chlorinated borane ($NaBH_2ClCN$). Finally, a dehalogenation occurs through radical **IV** to afford a monochlorinated lactam (*e.g.* **5**).[16b]

The efficiency of the cyclization ending with a primary alkyl radical in these reaction conditions (**II** → **III**) is notable, since Ryu showed by theoretical calculations that the hydrogen transfer between alkyl radicals and $NaBH_3CN$ was slower than that observed with radicals bearing an electron-withdrawing group, which are formed in cyanoborohydride-mediated Giese-type reactions.[9a] Additionally, it cannot be ruled out that the mechanism of the chlorine atom transfer may be an electron transfer process between BH_2CN^{*-} (expected to be a strong reducing agent) and trichloroacetamide.[18]

Insert Scheme 4

Synthesis of α-chlorolactams. In order to further explore these results, we extended the methodology to the synthesis of a series of α-chlorolactams in collaboration with the Bayer Crop Science Division (Frankfurt am Main, Germany), due to their importance as herbicides in the agrochemical sector.[19] For example, flurochloridone (Figure 1) is a commercial herbicide (a racemic trans-cis mixture in a 3:1 ratio) that inhibits phytoene desaturase, an enzyme involved in carotenoid biosynthesis.[20] Commercial chloroacetamide herbicides, as exemplified by acetochlor (Figure 1), metazachlor, metolachlor and thenylchlor, are structurally related to chlorolactams but work by inhibiting the biosynthesis of very long chain fatty acids.[20] These acyclic chloroacetamides all contain a 2,6-dialkylphenyl moiety and it has been proposed that incorporating this structural element into a chlorolactam might lead to new herbicidal lead structures that block very long chain fatty acid biosynthesis instead of phytoene desaturase. Chlorolactams are also useful intermediates for the pharmaceutical and agrochemical industries[21] and can be found in natural products such as chloromatrine[22] (Figure 1).

Insert Figure 1

Several methods for α-chlorolactam preparation have been reported (Scheme 5): (i) lactamization of α-chloro-γ-amino acids;[23] (ii) radical cyclization using atom transfer radical cyclizations,[24] or promoted by Ni,[25] Bu_3SnH,[20c,26] or TTMSS;[27] (iii) α-monochlorination of lactams using NCS[28] or by enolate quenching with tosyl chloride;[29] (iv) mono reduction of dichlorolactams;[30] (v) chlorination followed by decarboxylation;[20b] (vi) substitution of the diazo moiety using anhydrous HCl;[31] and (vii) hydroxyl substitution using thionyl chloride.[32] However, most of these methods are inconvenient because they require noxious reagents, strong bases, or explosive diazocompounds and in many cases are low yielding.

Insert Scheme 5

In order to establish the substrate scope of the reaction and synthesize a small library of compounds, a series of trichloroacetamides (Figure 2) was submitted to the standard conditions (Table 1, entry 6).

Insert Figure 2

Most of the examined substrates afforded the corresponding γ-lactam in moderate to high yield, allowing direct access to the desired α-chloro-γ-lactams (Table 3). Compounds **5**-**16** (Table 3.A) were obtained as a mixture of diastereoisomers, with a majority of trans-g-lactams. In some cases, non-negligible amounts of α,α-dichloro γ-lactams (e.g. **6**-**8**) were obtained, clearly due to an early quenching of the radical chain reaction. In the case of substrate **4h**, no reduction of the chlorine on the phenyl ring was observed (Table 3, compounds **12**). Unexpectedly, trichloroacetamide **4r** did not cyclize and instead decomposed during the course of the reaction, even though **4r** has been previously reported[33] to cyclize under ATRC conditions. This failure could be due to a non-chemoselective process caused by a competitive reduction of the styrene moiety.[34] Electron-poor alkene **4s** cyclized in good yield, without any reduction of the ester moiety.

The structural elucidation of epimeric lactams **5**-**16** was based on their NMR data, considering the steric and electric field effects in chlorine substituent chemical shifts.[35] Taking into account the coupling constants in the ^1H NMR spectra, both cis- and trans-compounds seem to have the same conformation, with the methyl substituent at a pseudo-equatorial disposition. The most

noteworthy diagnostic in the ^{13}C NMR spectra are signals of the methyl groups upfielded in the cis series (δ ~13.3) with respect to those of trans compounds (δ ~16.8), as well as the chemical shift for C-4 (δ 33.4 vs δ 38.2 in cis and trans series, respectively). In ^{1}H NMR data the signal due to the CHCl at C-3 is always more deshielded in cis compounds compared with the trans epimer by an average of + 0.35 ppm (e.g. δ 4.39 for cis-5 and δ 4.04 for trans-5, see Table in SI).

N-homoallyclic trichloroacetamides **4q** and **4s** cyclized in a 6-exo fashion to afford α-chloro-δ-lactams **24** and **25** in moderate yields (Table 3.D). In addition, the over-reduction products, **24b** and **25b**, were obtained in non-negligible amounts.[36] The diastereoisomeric ratio in favor of the trans isomer in **25** was the highest observed, as in the five-membered-ring lactam **23**. Thus, the ester group embedded in both compounds must have interacted with the cyanoborohydride in the last chlorine atom reduction that controls the diastereoselectivity of the process.

Under the standard conditions, *N*-cyclohex-2-enyl tricloroacetamides **4v-x** cyclized in a 5-*exo* fashion to afford α-chloro-*cis*-octahydroindoles **26-28** in moderate to good yield, as mixtures of diastereoisomers, with a majority of the *endo*-bicyclic lactam epimers (Table 3.E).

Insert Table 3

Finally, trichloroenamide **4y** was submitted to the standard conditions, affording 5-*endo* cyclization products in moderate overall yield, with ***endo*-26** as the major isomer (Scheme 6). The formation of *trans*-octahydroindole ***trans*-26** could be explained by the *in situ* generation of an acyl iminium species, which was reduced in a non-selective manner by the excess of $NaBH_3CN$. The formation of acyliminium ions from α-amino radicals has been previously reported, either by atom transfer followed by elimination or an electron transfer mechanism[37] or by oxidation.[37b]

Insert Scheme 6

The α-chlorolactams **5-28** were all tested for herbicidal activity at the Bayer Crop Science Division research site in Frankfurt. The most active compound was the *m*-CF_3-substituted *trans*-**15** derivative, which showed good broad-spectrum pre-emergence activity at 1.3 kg/ha and reasonable activity at 320 g/ha in the glasshouse. The *m*-CF_3-substituted phenyl ring and

herbicide symptomology (chlorosis, bleaching) observed for *trans*-**15** are typical of herbicidal inhibitors of phytoene desaturase, which is very likely the mode of action of this compound. Interestingly, *m*-CF_3 *cis*-**15** was herbicidally inactive and unfortunately, the 2,6-dimethyl derivatives **16**, which we had hoped might inhibit very long chain fatty acid biosynthesis, were also inactive. Although *trans*-**15** is itself a novel compound, the activity is not significantly better than flurochloridone (Figure 1) and the structure falls under the general patent claim from ICI.[19b] Consequently, it was decided not to follow up on this biological activity.

Conclusions

In conclusion, we have shown that α-chlorolactams can be easily prepared in good to high yields, employing cheap reagents, starting from easily accessible trichloroacetamides and using a simple procedure, which is easily performed on gram-scale. The generation of carbamoyldichloromethyl radicals from trichloroacetamides using $NaBH_3CN$/AIBN is described for the first time. Under these reaction conditions the carbocyclization upon alkenes (electronically rich, neutral or poor) provides an efficient synthetic entry to several classes of α-chlorolactams (pyrrolidinones, piperidones, octahydroindolones, and morphans). The standard conditions favored the diastereoselectivity toward the formation of thermodynamic *trans* β-substituted α-chlorolactam products.

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization data and copies of spectra of all compounds.

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Conflict of interest

The authors declare no competing financial interest.

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Scheme and Figure Legends

Scheme 1. Radical processes using sodium cyanoborohydride as a radical promoter to abstract an halogen atom and as a reducing agent via a hydrogen atom transfer in the last step of the radical chain process. (a) Ryu´s previous work (reference 6); (b) The current study.

Scheme 2. Effects of the counter cations.

Scheme 3. $NaBD_3CN$-mediated radical cyclization.

Scheme 4. Possible mechanism of the $NaBH_3CN$-mediated radical cyclization.

Scheme 5. Known methods for the synthesis of α-chlorolactams.

Scheme 6. Cyclization of trichloroenamide **4y**.

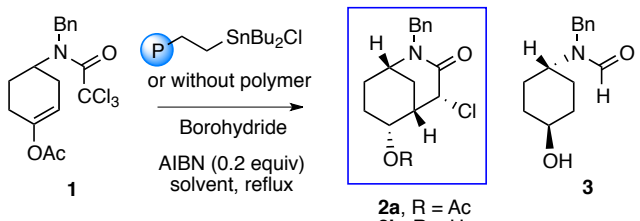
Figure 1. α-Chlorolactams/amides of biological interest.

Figure 2. Trichloroacetamides used in the $NaBH_3CN$/AIBN-promoted radical cyclizations.

TABLES

Table 1

Table 1. Initial studies to optimize reaction conditions.

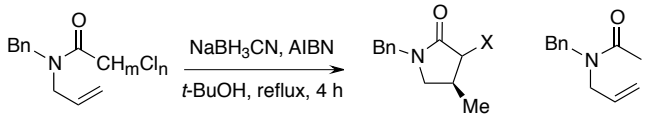


Entry	Polymer [a]	Borohydride [b]	Solvent	T (h)	Compd [c]
1	20%	$NaBH_4$	MeCN	12	--- [d]
2	20%	$NaBH_4$	*t*-BuOH	12	3 n.d. [e,f]
3	none	$NaBH_4$	*t*-BuOH	12	3 (77%)
4	20%	$NaBH_3CN$	*t*-BuOH	12	2a (30%) 2b (32%)
5	none	$NaBH_3CN$	*t*-BuOH	12	2a (85%)
6	none	$NaBH_3CN$	*t*-BuOH	4	2a (83%)

[a] P refers to the aliphatic scaffold VA-PNB (vinylic addition polynorbornene), see reference 13 and cited therein. [b] A 4:1 molar ratio was used. [c] Isolated yield. [d] Full decomposition. [e] n.d.: not determined. [f] Traces of **2** were observed in the NMR of the crude reaction mixture.

Table 2

Table 2. Effects of the number of chlorine atoms.



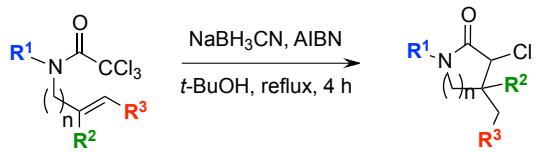
4 **5** (X = Cl or H) **4a-0**

Compd	m	n	Conversion [a]	5	4a-0
4a-1	2	1	32%	X = H; traces	31%
4a-2	1	2	90%	X = Cl; 70%	20%
4a	0	3	100%	X = Cl; 100% (73%) [b]	---

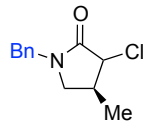
[a] Determined by NMR. [b] Isolated yield.

Table 3

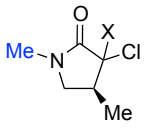
Table 3. Substrate scope of $NaBH_3CN$-mediated synthesis of α-chlorolactams



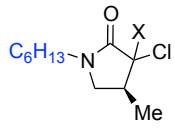
A. Scope of the *N*-substituent **R**^{1}



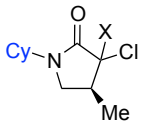
5 (73%)
d.r. 33:67 (cis:trans)
82% gram-scale



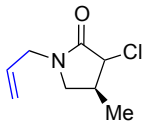
6 (59%)
d.r. 36:64 (cis:trans)
6a (5%)



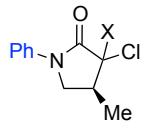
7 (46%)
d.r. 45:55 (cis:trans)
7a (11%)



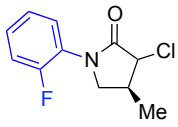
8 (46%)
d.r. 36:64 (cis:trans)
8a (44%)



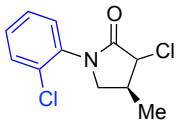
9 (61%)
d.r. 40:60 (cis:trans)



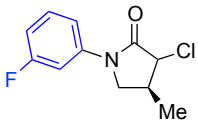
10 (46%)
d.r. 45:55 (cis:trans)
10a (5%)



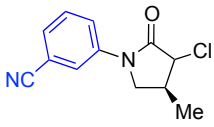
11 (43%)
d.r. 40:60 (cis:trans)
11b (17%)



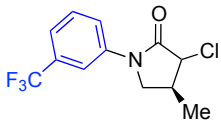
12 (49%)
d.r. 42:58 (cis:trans)
12b (11%)



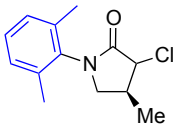
13 (49%)
d.r. 41:59 (cis:trans)
13b (9%)



14 (32%)
d.r. 26:74 (cis:trans)
14b (11%)

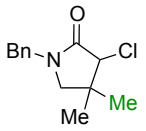


15 (29%)
d.r. 31:69 (cis:trans)
15b (8%)

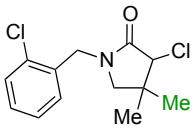


16 (47%)
d.r. 38:62 (cis:trans)

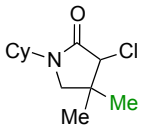
B. Scope of alkenes substituted in **R**^{2}



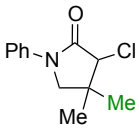
17 (65%)



18 (66%)

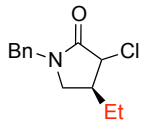


19 (57%)

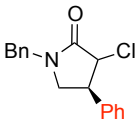


20 (69%)

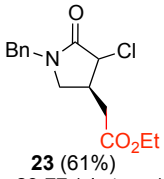
C. Scope of alkenes substituted in **R**^{3}



21 (58%)
d.r. 29:71 (cis:trans)

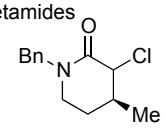


22 (---)

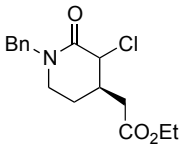


23 (61%)
d.r. 23:77 (cis:trans)

D. Scope of homoallylic trichloroacetamides

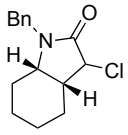


24 (49%)
d.r. 45:55 (cis:trans)
24b (8%)

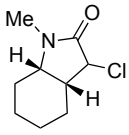


25 (31%)
d.r. 15:85 (cis:trans)
25b (30%)

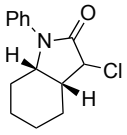
E. Scope of cyclic alkenes



26 (76%)
d.r. 24:76 (exo:endo)



27 (61%)
d.r. 18:82 (exo:endo)



28 (59%)
d.r. 24:76 (exo:endo)

[a] All yields refer to isolated yields following silica gel chromatography. Epimeric ratio determined by NMR. [b] In the compound numbering, **a** indicates a dichloroderivative (X = Cl) and **b** indicates an over-reduced dechlorinated compound.

Text for the Table of Contents

The generation of carbamoyldichloromethyl radicals from trichloroacetamides using $NaBH_3CN$/AIBN is described for the first time. Under these reaction conditions the carbocyclization upon alkenes (electronically rich, neutral or poor) provides an efficient synthetic entry to several classes of α-chlorolactams (pyrrolidinones, piperidones, octahydroindolones, and morphans).

Keywords: borohydrides • herbicides • lactams • radical cyclizations • synthetic methods