RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2016, **6**, 55360

Received 10th May 2016
Accepted 30th May 2016

DOI: 10.1039/c6ra12180b

www.rsc.org/advances

Synthesis of substituted γ- and δ-lactams based on titanocene(III)-catalysed radical cyclisations of trichloroacetamides†

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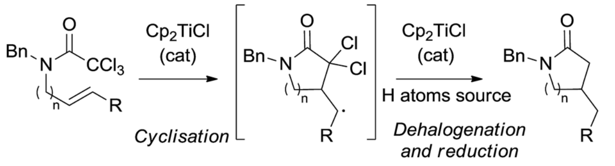
A new procedure for the synthesis of γ- and δ-lactams based on a Cp_2TiCl-catalysed cyclisation of trichloroacetamides under mild reaction conditions is reported. Theoretical studies supported the observed regioselectivity in the cyclisations and the mechanism involved in the dehalogenation process.

Since its characterization in 1972 by Green *et al.*,[1] biscyclopentadienyltitanium(III) chloride, Cp_2TiCl, has emerged as a useful tool in organic chemistry, being extensively applied in several synthetic processes. Seminal work by RajanBabu and Nugent, Gansäuer and others has shown that epoxides,[2–4a] allylic halides,[4b] and some carbonyl derivatives[3d,e,4c,5] are suitable starting materials for monoelectronic reduction to the corresponding carbon-centered radicals. These radicals are involved in interesting processes,[6] such as reduction reactions, addition to alkenes or alkynes, pinacol couplings, and Barbier-, Wurtz-, and Reformatsky-type reactions, which have also been applied in natural product synthesis.[7] Recently, other functionalities have been included in the arsenal of Cp_2TiCl chemistry. Thus, allylic and propargylic carboxylates,[8] ozonides,[9] nitriles,[10] imines,[11] chloroaminals,[12] and hemiaminals[13] are now used in relevant C–C bond-forming reactions. Within this context, the expansion of Cp_2TiCl-based protocols to new, easy to handle functionalities would be highly desirable.

Our attention was recently attracted to trichloroacetamides, which have been used as dichloromethylcarbamoyl radical precursors to synthesize nitrogen-containing heterocycles[14,15] and alkaloids,[16] using either atom transfer radical cyclisations (ATRC) mediated by Cu(I),[17] Ru(II),[18] Ni–AcOH,[19] and Fe(0)/$FeCl_3$,[20] or reductive methods based on Bu_3SnH,[21] and TTMSS.[22] However, the use of titanium reagents to generate radical species from trichloroacetamides has not been reported so far.

With these antecedents in mind, we thought that Cp_2TiCl would be able to generate the corresponding dichloromethylcarbamoyl radicals from trichloroacetamides under mild reaction conditions for their use in cyclisation reactions. Moreover, the final polyhalogenated compounds could be subsequently reduced by Cp_2TiCl and a hydrogen atom source, directly yielding non-halogenated final products. It is worth noting that this transformation could be carried out using substoichiometric amounts of Cp_2TiCl (Scheme 1).[6]

To check our hypothesis, we selected trichloroacetamide **1**, which has been previously used in related syntheses of polyhalogenated lactams.[14c,17c,d] Compound **1** reacted in the presence of 3 equiv. of Cp_2TiCl at room temperature to yield the corresponding γ-lactam **2**, albeit in low yield (24%) (Scheme 2a), and minor amounts of monohalogenated derivative **3** (16%) were also isolated, both products arising from a 5-*exo*-trig cyclisation. The reduction of the intermediate radicals in this process could derive from the presence of adventitious water in the solvent (THF), *via* Ti(III)-aquacomplexes.[23] This preliminary result indicated that our working hypothesis was correct. Nevertheless, three main drawbacks were observed: (i) the use of high amounts of Cp_2TiCl, (ii) a mixture of reaction products, and (iii) a low yield. To overcome these disadvantages, we decided to study the cyclisation process using different substoichiometric amounts of Cp_2TiCl and longer reaction times,



Scheme 1 Proposed Cp_2TiCl-catalysed radical cyclisation of trichloroacetamides.

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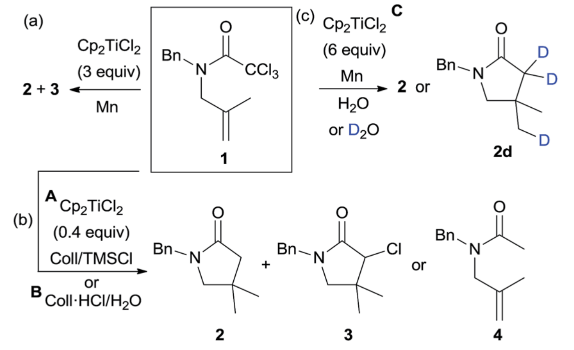
† Electronic supplementary information (ESI) available: Experimental data. Computational details. Copies of ^1H NMR and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c6ra12180b



Scheme 2 Cp_2TiCl-mediated/catalysed cyclisations of trichloroacetamide **1**.

Table 1 Study of the radical cyclisation of **1** promoted by Cp_2TiCl

Entry	Protocol[a]	Eq. of Cp_2TiCl_2	Yield (**2** or **2d** : **3** ratio)	Yield (**4**)
1	A[b]	0.2	58% (7 : 3)	—
2	A[c]	0.2	62% (8 : 2)	—
3	A	0.2	90% (8 : 2)	—
4	A	0.4	91% (1 : 0)	—
5	A	0.6	63% (1 : 0)	—
6	A	0.8	51% (1 : 0)	—
7	B	0.4	0%	79%
8	B	0.6	0%	81%
9	B	0.8	0%	88%
10	C	6	36% (1 : 0)	—
11	C[d]	6	30% (1 : 0)	—

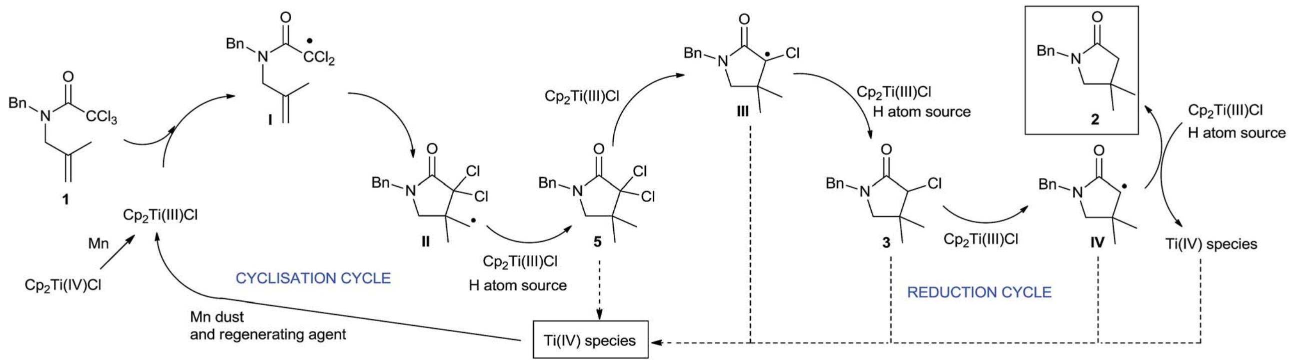
[a] Protocol A: 8 eq. of Mn dust, 6 eq. of 2,4,6-collidine, and 4 eq. of TMSCl, 72 h. Protocol B: 8 eq. of Mn dust, 4 eq. of 2,4,6-collidine hydrochloride, and 10 eq. of H_2O, 72 h. Protocol C: 12 eq. of Mn dust, and 10 eq. of H_2O, 72 h. [b] 24 h of reaction. [c] 48 h of reaction. [d] 10 eq. of D_2O were used.

in order to determine the influence of these factors on the yields of the final products. In these studies, we used the aprotic combination of Mn dust and Me_3SiCl/2,4,6-collidine (Coll) as a regenerating agent of titanocene(III) species (see Scheme 2b, protocol A).[4a,6] Additionally, it is worth noting that the reduction of the generated radicals required a hydrogen atom source. Thus, we also checked the cyclisation of **1** in the presence of an efficient hydrogen atom source such as H_2O, using substoichiometric amounts of Cp_2TiCl (Scheme 2b, protocol B). In this case, the regenerating agent of the titanocene(III) species was the mixture of Mn dust and 2,4,6-collidine hydrochloride (Coll·HCl).[3a–c] The results are depicted in Table 1.

Cp_2TiCl-catalysed cyclisations of compound **1** yielded the corresponding γ-lactam **2** as the main product. In absence of water, the best result was obtained when 0.4 equiv. of Cp_2TiCl was used after 72 h of reaction, which gave **2** in high yield (91%, see Table 1, entry 4). A mixture of **2** and **3** was obtained in a similar yield when less Cp_2TiCl was employed (Table 1, entry 3). When the amount of catalyst was increased (see Table 1, entries 5 and 6), compound **2** was isolated in worse yields. This fact could be justified considering that with low amounts of catalyst (0.2 equiv., entries 1–3) the dehalogenation process is slow, resulting in a lower yield of **2** and substantial amounts of **3**. Nevertheless, with more Cp_2TiCl (0.6 or 0.8 equiv., entries 5–6), side reactions can take place. Additionally, the highly oxophilic Cp_2TiCl complex could trap the dichloromethylcarbamoyl radical intermediate, yielding an inert enolate unable to continue the cyclisation reaction.[7d]

Taking into account that the use of TMSCl in these reaction conditions completely excludes the presence of adventitious water in the media, there must be an alternative source of hydrogen atoms. Newcomb[24] and Cuerva[23d] have previously proposed that THF, when used as a solvent, is also able to act as a hydrogen-atom donor in Ti(III)-mediated processes.[25] On the other hand, when the combination of Cp_2TiCl and water was used as the hydrogen atom source, acyclic product **4** was detected (Scheme 2b, and Table 1, entries 7–9). This fact shows that under these reaction conditions, the reduction of the generated radicals is faster than the 5-*exo*-cyclisation. Increasing the amounts of Cp_2TiCl to 6 equiv., we obtained product **2** (36%) (Table 1, entry 10). Under the same conditions, but using deuterium oxide instead of water, a trideuterated product **2d** was obtained (Table 1, entry 11), with 46% deuterium incorporation,[26] thus confirming that in this case the origin of the hydrogen atoms was *via* the titanocene(III) aqua-complex.[23]

Based on these results, the outcome of the reaction could be explained by the following mechanism (Scheme 3). The reaction begins with the dehalogenation between trichloroacetamide **1**



Scheme 3 Proposed mechanism for titanocene(III)-catalysed radical cyclisation of trichloroacetamides.

and Cp_2TiCl (generated from the reduction of Cp_2TiCl_2 with Mn dust) to yield radical **I**. Subsequently, this radical carries out a 5-*exo*-trig cyclisation, yielding cyclic intermediate **II**. The primary radical generated in this step is reduced by a hydrogen atom source, such as Ti(III)-aquacomplex or the solvent (THF), present in the reaction media, yielding lactam **5**. Then, consecutive dehalogenation processes yield α-carbonyl radicals **III** and **IV**, which are also reduced, thus leading to the final lactam **2**. The different titanocene(IV) species generated during the process are reintroduced in the catalytic cycle by the action of the regenerating agent and Mn dust, closing the catalytic cycle.

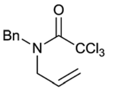
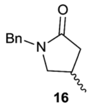
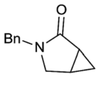
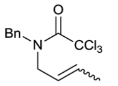
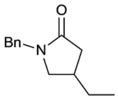
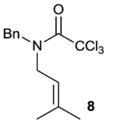
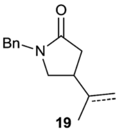
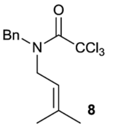
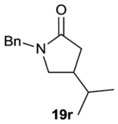
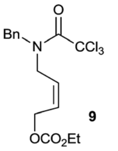
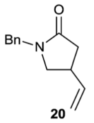
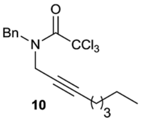
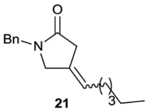
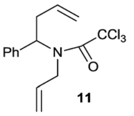
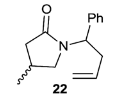
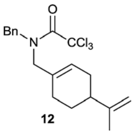
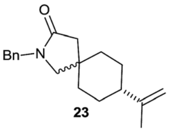
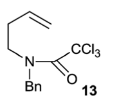
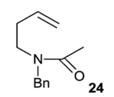
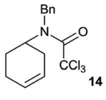
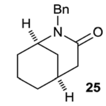
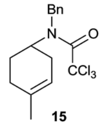
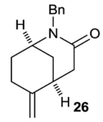
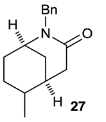
With these results in hand, we decided to extend the optimized reaction conditions to other substrates, including acyclic and cyclic compounds (Table 2).

The cyclisation of trichloroacetamides **6–15** occurred efficiently,[27] with moderate to high yields, providing straightforward access to a diversity of completely dehalogenated compounds. The cyclisation products mainly present a 5-membered ring (entries 1–8), although in some cases 6-membered rings were also obtained (entries 10–11). When both 5-*exo*-trig or 6-*endo*-trig cyclisations were possible in the same substrate (entry 7), we only obtained γ-lactam **22**, derived from a 5-*exo*-trig process. This selectivity could be explained by the different rates of these cyclisations in radical processes.[28] Moreover, the relative slowness of 6-*endo*-trig cyclisations compared with 5-*exo*-trig processes favours an early trapping of the intermediate radicals by titanocene species, avoiding and/or hindering the cyclisation processes. In fact, when trichloroacetamide **13** was submitted to our reaction conditions, we only recovered the corresponding dehalogenated acyclic compound **24** in good yield. On the other hand, these results also show that this reaction could be used as a mild and efficient procedure for complete dehalogenation of α-carbonyl polyhalogenated compounds.[29]

It is noteworthy that in the cyclisation of compound **6**, **17** was also obtained (65 : 35 ratio with respect to **16**). This bicyclic compound has been previously obtained as the main product in the Ru-catalysed radical cyclisation of a dichloro-derivative of **6**.[30] In our case, the formation of **17** implies the coexistence of two C-centred radicals, derived from dehalogenation and cyclisation steps. Cyclisation of **8** yielded a mixture of compounds **19** and **19r**, which derive from two different oxidative and reductive ending processes, as we have previously described.[23c] The reduced **19r** was prepared selectively, using a combination of 2 equiv. of Cp_2TiCl and 10 equiv. of H_2O. Cyclisation of compound **9** led to product **20** (entry 5), and subsequent removal of the carbonate group yielded an alkene. This termination step has been previously reported in several studies as being due to a Cp_2TiCl-mediated radical fragmentation of β-carboxy radicals.[6,7b,31] Our process also worked with alkynes as radical acceptors[32] (entry 6), yielding the corresponding γ-lactam **21**. The 6-*exo*-trig radical cyclisation of compounds **14–15** (entries 10–11) yielded morphans **25–27**, thus constituting a new procedure to achieve this bridged azabicyclic scaffold[33] through a titanocene(III)-based methodology.

To obtain deeper insight into the observed reactivity and selectivity of compounds **1** and **14**, and the absence of

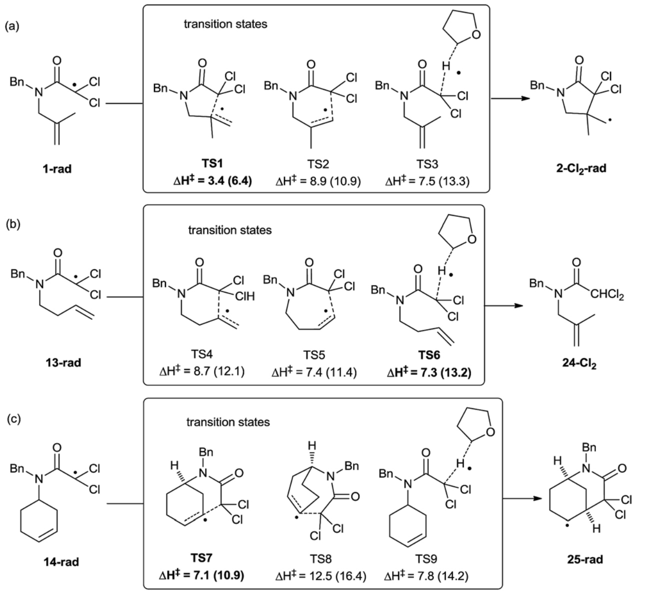
Table 2 Cp_2TiCl-catalysed cyclisation of trichloroacetamides **6–15**[a]

Entry	Acetamide	Product	Yield
1	 **6**	 **16** +  **17**	81%[b]
2	 **7**	 **18**	75%
3	 **8**	 **19**	70%[c]
4	 **8**	 **19r**	71%[d]
5	 **9**	 **20**	44%
6	 **10**	 **21**	58%[e]
7	 **11**	 **22**	61%[f]
8	 **12**	 **23**	65%[g]
9	 **13**	 **24**	85%
10	 **14**	 **25**	81%[h]
11	 **15**	 **26** +  **27**	48%[i]

[a] 0.4 equiv. of Cp_2TiCl, 8 equiv. of Mn dust, 6 equiv. of 2,4,6-collidine, and 4 equiv. of TMSCl, 72 h. [b] 65 : 35 products ratio. [c] 1 : 1 mixture of alkene and reduction products. [d] 2 equiv. of Cp_2TiCl, and 10 equiv. of H_2O were used. [e] 9 : 1 isomer ratio. [f] 7 : 3 isomer ratio. [g] 2 : 1 isomer ratio. [h] 19% of monohalogenated derivative was also obtained. [i] 1 : 1 isomer ratio.

cyclisation from compound **13**, we performed DFT calculations on those structures,[34] locating the transition states for all possible cyclisations and for the alternative hydrogen-atom transfer (HAT) process from THF (Scheme 4). The comparison of an intramolecular process (cyclisation) with an intermolecular one (HAT) is not straightforward, and should be done in terms of Gibbs free energy, but the large amount of THF available in the medium also allowed the utilization of enthalpies as representative values of the relative strength of the breaking and forming bonds. Our calculations confirm that γ-lactam derivatives are selectively formed through 5-*exo* processes, and also that in compounds containing one more carbon atom in the chain (**13**), the HAT process from THF becomes a competitive process. Initially, three transition structures were located from intermediate **1-rad**, the radical species derived from compound **1**. The structure lowest in energy corresponds to the 5-*exo*-trig cyclisation process (**TS1**, 3.4 kcal mol^{-1} at M06-2X level, Scheme 4a), favouring the formation of 5-membered rings, and the difference with the regioisomeric 6-*endo*-process (**TS2**, 8.9 kcal mol^{-1}) is large enough to ensure the complete selectivity of the reaction. The HAT process between **1-rad** and THF is also predicted to be higher in energy than **TS1** (**TS3**, 7.5 kcal mol^{-1}). The calculations at B3LYP level show higher absolute energy values, but similar trends. These results explain the favoured cyclisation and complete *exo*-selectivity shown in Table 2, entries 1–8.

When the homologous substrate **13-rad** was computed, the energy values varied substantially from the previous case (Scheme 4b), and the *endo* approach (**TS5**, $\Delta H^{\ddagger} = 7.4$ kcal mol^{-1}) became favoured over *exo* (**TS4**, $\Delta H^{\ddagger} = 8.7$ kcal mol^{-1}) at both computational levels (M06-2X and B3LYP) by *ca.* 1 kcal mol^{-1}. Even more interestingly, the hydrogen-atom abstraction from THF becomes competitive, presenting the lowest activation energy at M06-2X (**TS6**, 7.3 kcal mol^{-1}). Obviously, the HAT process shows similar activation barriers for substrates **1** and **13** (compare the energies of **TS3** *vs.* **TS6**), but notably, 5-*exo* cyclisation in **1** would be much faster than the 6-*exo* process in **13**. These values would explain the absence of cyclisation for compounds **13** and its conversion into **24** (Table 2, entry 9). The last two substrates in Table 2 (**14** and **15**) yield bicyclic adducts, through 6-*exo* cyclisations. In agreement with the experimental findings, **TS7** presents the lowest activation values with the two functionals ($\Delta H^{\ddagger} = 7.1$–$10.9$ kcal mol^{-1}, Scheme 4c), and its preference with respect to the HAT process increases slightly when compared with the previous substrate (**13**). Two opposite effects can explain the reactivity differences of Schemes 4b and c. Compound **14** is more prone to undergo cyclisation than **13** (**TS7** is *ca.* 1.0–1.5 kcal mol^{-1} lower in energy than **TS4**) due to its lower flexibility and higher preorganization, and the HAT process from THF is *ca.* 1 kcal mol^{-1} less favoured (**TS9** *vs.* **TS6**) due to a higher steric hindrance in **14**. Moreover, we also compared the transition state to form the bicyclo[3.2.2] compound (**TS8**), which is not energetically competitive ($\Delta H^{\ddagger} = 12.5$ kcal mol^{-1}).



Scheme 4 Enthalpy values computed for the transition states arising from **1-rad**, **13-rad**, and **14-rad** at M06-2X/6-311+G(d,p) level of theory. Values in parenthesis correspond to B3LYP/6-311+G(d,p).

Conclusions

In summary, in this work we report trichloroacetamides as new suitable starting materials for titanocene(III)-catalysed reactions. We have applied this reactivity for the cyclisation of a variety of unsaturated trichloroacetamides to yield the corresponding γ-lactams, using simple and mild reaction conditions. This method also allowed the preparation of δ-lactams, but only when a favourable conformation was present in the starting materials. The procedure additionally allows the complete dehalogenation of trichloroacetamides, providing a mild and efficient alternative for the complete reduction of a variety of α-carbonyl polyhalogenated compounds.

Acknowledgements

We thank the Regional Government of Andalucía (project P12-FQM-790), and MINECO (projects CTQ2014-53598, and CTQ2013-41338-P) for financial support.

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