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Catalyst-free photo-induced aerobic radical synthesis of lactams from *N*-alkenyl trichloroacetamides in 2-methyltetrahydrofuran as the radical initiator under violet light†

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The first violet light-mediated synthesis of γ- and δ-lactams from *N*-alkenyl trichloroacetamides is reported in tetrahydrofuran or 2-methyltetrahydrofuran alone. These catalyst and additive-free reactions are achieved with non-anhydrous solvents and under an air atmosphere where the solvent serves as the radical initiator.

Introduction

Alkyl radicals play a pivotal role as intermediates in the construction of carbon–carbon bonds[1–3] usually by addition to alkenes.[4] Traditionally, they are generated from alkyl halides through a homolytic cleavage of a C–X (X = I, Br, Cl) bond in the presence of toxic tributyltin hydride (TBTH) and azobisisobutyronitrile (AIBN) as the radical initiator. In this process, tributyltin hydride serves a dual purpose facilitating the generation of $Bu_3Sn^•$ radical species as the radical chain carrier and also operating as a hydrogen donor (Scheme 1a).[5,6] Alkyl radicals from alkyl halides were also generated under tin free conditions specifically in the presence of triethylborane and oxygen as the radical initiator (Scheme 1b).[7,8] Over the past decade, photoredox catalysis has also become a reliable tool for the formation of these radicals under mild conditions, usually in the presence of a photocatalyst, an amine and under light irradiation (Scheme 1c).[9] Finally, alkyl radicals generation could also be carried out under catalyst-free photochemical reactions *via* electron donor–acceptor (EDA) complexes.[10] Scheme 1d depicts an example of inter single-electron-transfer (SET) from transient enamines to alkyl bromides ending in the formation of an alkyl radical for the α-alkylation of aldehydes.[11]

Recently we reported the first air-tolerant photocatalyzed synthesis of γ- and δ-lactams from trichloroacetamides under blue LEDs irradiation and non-anhydrous conditions.[12] In this investigation the best results were achieved in the presence of 1 mol% of $Ir(ppy)_3$ as the photocatalyst, *N*,*N*-diisopropylethylmine (5 equiv.) in a mixture of THF and acetone as a solvent. The reaction carried out with 19 different substrates, were also undertaken in the absence of amines providing the corresponding lactams with acceptable yields despite the extended reaction time. As a continuation of this work we decided to start an investigation with the goal of exploring the same reaction under photocatalyst and base free conditions.

Herein we present our findings related to the green and sustainable synthesis of γ- and δ-lactams from *N*-alkenyl trichloroacetamides in the presence of tetrahydrofuran or 2-methyltetrahydrofuran alone as the radical initiators and the solvents under violet light irradiation.

Results and discussion

As mentioned earlier, reaction of *N*-alkenyl trichloroacetamides under photoredox conditions allowed us recently to access a wide range of lactams under mild conditions. The best results, under blue LEDs irradiation, were achieved in a mixture of THF/acetone (Table 1, entry 1) or in THF (entry 2). In acetone using the same conditions, the yield was lower (entry 3). During that stage of the investigation we decided to check the exact reaction time for the full conversion of **1a** to **2a**. Thus, we conducted a TLC analysis to track the reaction's progress in THF and found that it had reached completion within just 2 hours of irradiation providing lactam **2a** with a good yield (entry 4). The quantity of amine was reduced to 1 equiv. without affecting significantly the course of the reaction (entries 5 and 6). As part of our efforts to use economical green procedures, we decided to run the reaction in the presence of ammonia instead of DIPEA. Thereby, the reactions not only concluded in a shorter time but also provided better

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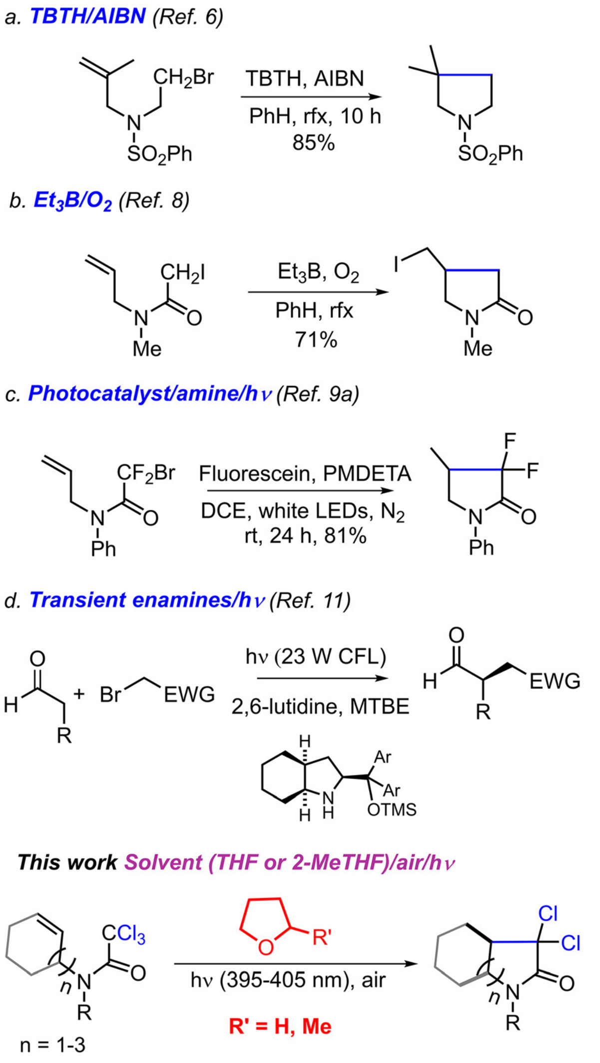


Scheme 1 Selected examples for the strategies used to generate alkyl radicals from alkyl halides.

yields (entries 7 and 8).[13] It is worth noting that when the reactions were carried out in the absence of amines, the cyclization process was extremely slow (entries 9–10). Some control reactions were also undertaken in the absence of the catalyst and despite the sluggishness of the reaction, lactam **2a** was isolated with very good yields (entries 11 and 12). Further control experiments established that, in the absence of the catalyst and the amine, light is necessary for reactivity (entries 13 and 14 in contrast with entries 15 and 16). The reactions achieved under photocatalyst and amine-free conditions suggest that another reaction mechanism is operating in the formation of lactam **2a** involving the solvent and trichloroacetamide **1a** under blue LEDs' irradiation.

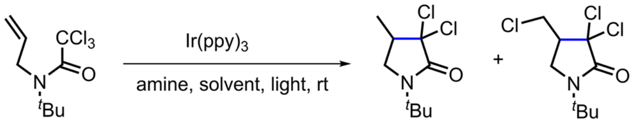
With these results in hand and knowing that **1a** absorbs at $\lambda < 400$ nm in almost all solvents used in organic synthesis (Fig. 1), we decided to examine the reaction under different light sources to ascertain if the cyclization process could be accelerated. The first reaction was carried out from **1a** (0.2 mmol) with available violet light (395–405 nm) and in a mixture of THF/acetone (1 : 1) as the solvent.

To our great surprise, the reaction reached completion after a mere 14 hours of irradiation providing the corresponding γ-lactam as a mixture of **2a** and **3a** in an 82% global yield (entry 17). In THF a similar yield was achieved (entry 18) with almost the exclusive formation of **2a**. Scaling up the reaction to 2 mmol had no impact on the reaction outcome (entry 19). In the presence of the photocatalyst (1 mol%) and the amine (1 equiv.) the reaction concluded in only 1 h providing **2a** with a very good yield (entry 20). Notably, the same reaction in toluene, DCM, AcOEt, ethanol, acetone, DMSO, MeCN, water, dioxane or diisopropylether did not take place, leaving trichloroacetamide **1a** unaltered (entry 21). Only in diethy ether, a slight conversion was observed (entry 22). Next, and in line with our commitment to upholding green chemistry protocols, we decided to carry out the reaction in 2-methyltetrahydrofuran as a sustainable green solvent.[14] Thus, when **1a** was irradiated with violet light in 2-methyltetrahydrofuran for 14 h, **2a** was isolated with an excellent yield (entries 23 and 24). Moreover, when the reaction was monitored by ^{1}H NMR spectroscopy, we discovered that it had concluded within just 4 hours (entry 25). As it was commented in our previous work,[12] here also the reactions were carried out under non-anhydrous conditions in an aerobic environment showing a full tolerance to air and moisture.

Beside the simplicity of setting up the reaction which consists in mixing trichloroacetamide **1a** and the non-anhydrous solvent followed by irradiation with violet light, the reactions achieved in THF or in 2-MeTHF, were simply concentrated by the end of the process to give lactam **2a** almost pure as a white solid (Fig. 2). As it is shown in the latter, the spectrum of the crude displays only the signals belonging to lactam **2a** alone. Thereafter, a simple crystallization in the scarce quantity of ether or a rapid filtration using a short chromatography column provided analytically pure **2a** as a white solid.

With the optimized conditions in hand, we then evaluated the scope of the reaction to assess its potential applications and limitations (Fig. 3). This involved mainly testing different substrates to access diverse structural lactam motifs. From trichloroacetamides **1b–1g**, as evidenced in our previous research, the substituent on the nitrogen has no influence on the course of the reaction since γ-lactams **2b–2g** were isolated with good yields. The reaction from **1h** and **1i** with a substituted allyl chain furnished lactams **2h** and **2i** with excellent to acceptable yields. From *N*-propargyl trichloroacetamide **1j**, **2j** was isolated with a modest yield probably due to side reactions on the lactam since a full conversion was observed. Operating from **1k** with a butenyl chain, the corresponding δ-lactams **2k** was isolated with a very good yield. From its analogue **1l**, a diastereoselective cyclization was observed furnishing **2l** with a modest yield. From *N*-pentenyl trichloroacetamide **1m**, although with a low yield, only the challenging 8-*endo* cyclization took place to give lactam **2m**. The methodology was successfully applied to achieve the bicyclic indol (**2n** and **2o**), isoquinoline (**2q**) and the challenging morphan (**2r** and **3s**) scaffolds respectively.

Table 1 Photo-promoted synthesis of **2a** from **1a**, reaction conditions screening[a]



1a **2a** **3a**

Entry	Ir(ppy)$_3$ (mol%)	Amine (equiv.)	Solvent	Light	Time (h)	**2a** yield (%)	**3a** yield (%)
1	1	DIPEA (5)	THF/acetone (1 : 1)	Blue LEDs	14	81[b]	—
2	1	DIPEA (5)	THF	Blue LEDs	14	86[b]	—
3	1	DIPEA (5)	Acetone	Blue LEDs	14	60[b]	—
4	1	DIPEA (5)	THF	Blue LEDs	2	78	—
5	1	DIPEA (1)	THF/acetone (1 : 1)	Blue LEDs	2	70	—
6	1	DIPEA (1)	THF	Blue LEDs	2	73	—
7	1	NH_3 (11)[c]	THF/acetone (1 : 1)	Blue LEDs	1	82	—
8	1	NH_3 (4)	THF	Blue LEDs	0.5	88	—
9	1	—	THF/acetone (1 : 1)	Blue LEDs	62	29	29
10	1	—	THF	Blue LEDs	62	54	12
11	—	DIPEA (5)	THF/acetone (1 : 1)	Blue LEDs	120	89	—
12	—	NH_3 (11)	THF/acetone (1 : 1)	Blue LEDs	180	96	—
13	—	—	THF/acetone (1 : 1)	Blue LEDs	216	54	—
14	—	—	THF	Blue LEDs	216	44[d]	11
15	—	—	THF/acetone (1 : 1)	—	160	—	—
16	—	DIPEA (5)	THF/acetone (1 : 1)	—	160	—	—
17	—	—	THF/acetone (1 : 1)	Violet LEDs	14	57	25
18	—	—	THF	Violet LEDs	14	82	2
19[e]	—	—	THF	Violet LEDs	14	94	2
20	1	DIPEA (1)	THF	Violet LEDs	1	93	—[f]
21	—	—	Solvent[g]	Violet LEDs	14	—	—
22	—	—	Diethyl ether[h]	Violet LEDs	14	8	8
23	—	—	**2-MeTHF**	Violet LEDs	14	**92**	—
24[e]	—	—	**2-MeTHF**	Violet LEDs	14	**90**	—
25	—	—	**2-MeTHF**	Violet LEDs	**4**	**85**	—[f]

[a] Reactions were performed with **1a** (0.2 mmol scale) in solvent (4 mL, 0.05 M) at rt and under air atmosphere, blue LEDs (435–445 nm), violet LEDs (395–405 nm). [b] See ref. 12. [c] For the results achieved from other substrates see the ESI.† [d] Conversion 57%. [e] Reaction achieved from 2 mmol of **1a** in 40 mL of solvent. [f] Traces. [g] In toluene, DCM, AcOEt, ethanol, acetone, DMSO, MeCN, water, dioxane or diisopropylether no reaction took place and **1a** was recovered. [h] Conversion 27%.

Finally, from tricloroacetamide **1p**, unlike what was previously reported under reductive conditions (in the presence of TBTH and AIBN in refluxing benzene),[15] β-lactam **4p** was isolated as the main compound. The latter results from a 4-*exotrig* cyclization followed by chlorine atom transfer from **1p** and then elimination. This unprecedented behaviour is probably due to conformational preferences since the reaction is performed at room temperature. It is worth mentioning that the reaction from *N*-allyl-2,2,2-trichloroacetamide or allyl 2,2,2-trichloroacetate did not proceed to give the corresponding γ-lactam or γ-lactone showing the importance of having a substituent on the nitrogen in the trichloroacarbamoyl alkenyl derivative for the cyclization process.[16]

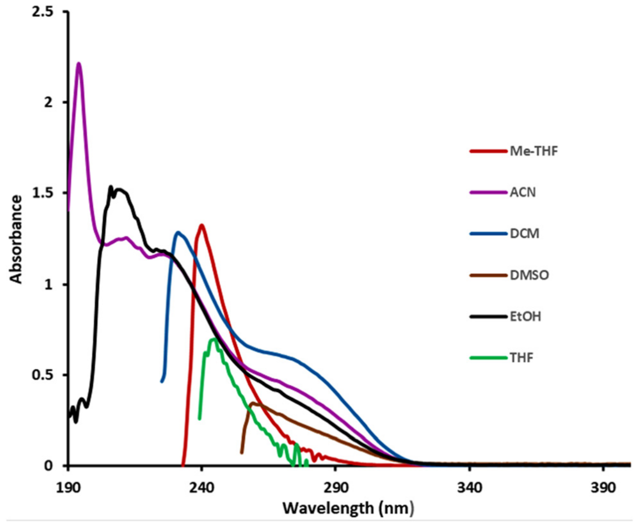


Fig. 1 UV absorption spectra of **1a** in different solvents.

Mechanistic studies

In this work, we have reported the first photo-induced intramolecular cyclization for the synthesis of β-, γ- and δ-lactams from *N*-alkenyl-trichloacetamides in THF or 2-MeTHF alone as solvents under violet LEDs irradiation. It should be highlighted that the presence of all three chloro atoms in trichloroacetamides **1** is crucial for the reaction to take place, as replacing one or two of these atoms with hydrogens resulted in no reaction even after 2 days of irradiation.

To gain a deeper understanding of the reaction mechanism, a series of control experiments was performed to capture the

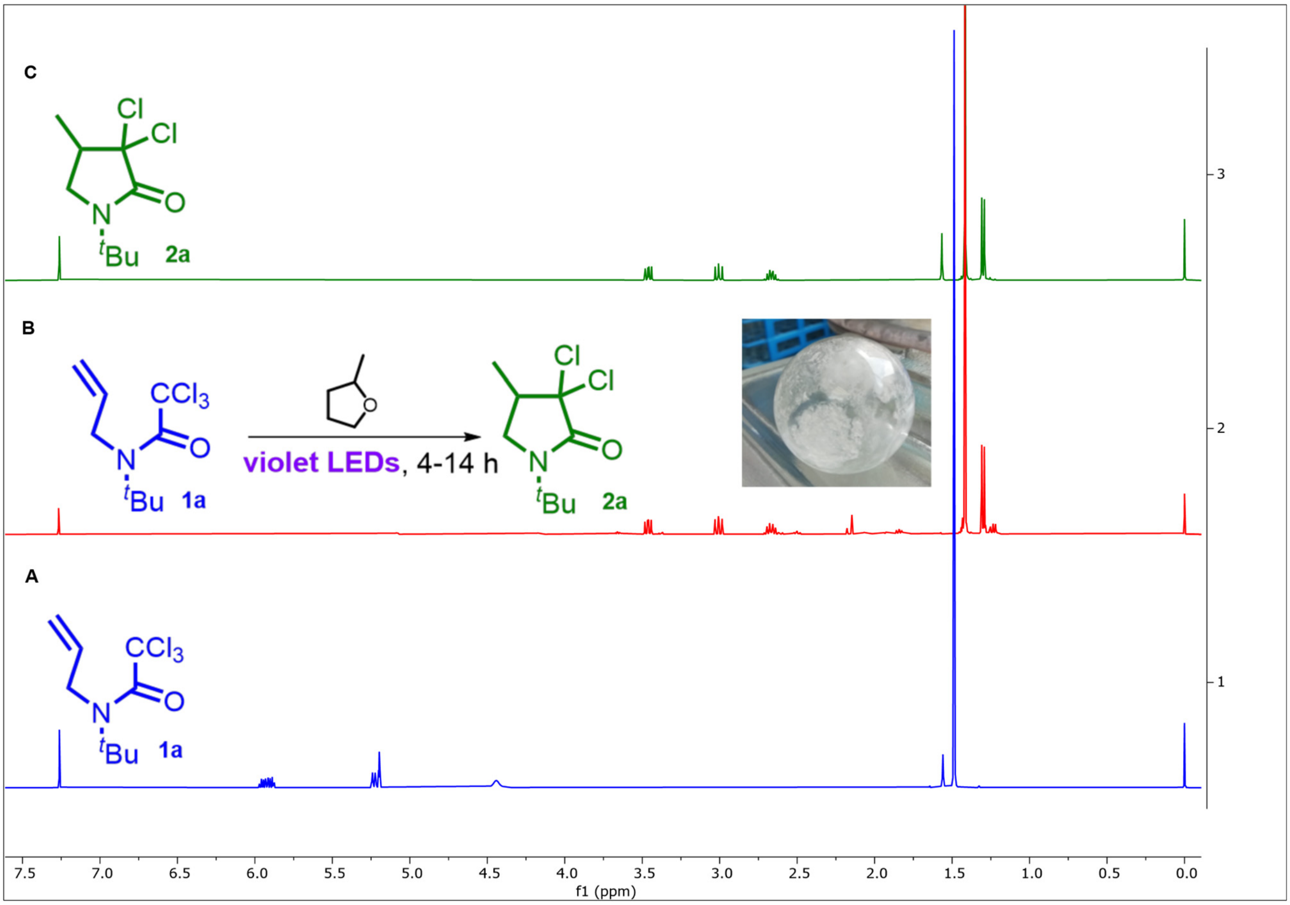


Fig. 2 Spectra of **1a** (A), the reaction after 4 or 14 h with the reaction flask after concentration (B) and pure **2a** (C).

possible intermediates. First, to unmistakably establish that radicals are involved in the cyclization process, (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) was used as a radical inhibitor. In the presence of TEMPO, the reaction did not take place and only few amounts of the radical-TEMPO adduct **6a** identified by ^{1}H NMR was isolated (Fig. 6).[17] Additionally, when the reaction was carried out from **1a** in THF-D$_8$, in contrast to the reaction in THF the deuterated analog of **2a** was not detected and trichloroatemide **1a** was recovered. This result can be explained by the strong isotope effect concerning the rate of a hydrogen abstraction from THF by carbon-centred radicals which is found to be approximately 8 times faster than a deuterium abstraction from THF-D$_8$.[18] To further establish the dependence of the reaction on light exposure, an on–off experiment was performed. Hence, the reaction flask was irradiated alternately with 1 hour of exposure to violet light and 1 h of darkness.

The conversion ratio, analysed by ^{1}H NMR spectroscopy, indicates that no product formation was observed in the dark phase, and thus establishes the light-dependent nature of the reaction eliminating the possibility of a light-induced chain mechanism (Fig. 4).

Additionally, cyclic voltammetry studies in acetonitrile, the more common solvent used for these measurements or THF the solvent of our reaction, detailed in Fig. 5a showed an irreversible behaviour for **1a** in a tetra-*n*-butylammonium hexafluorophosphate solution. This is probably due to the high reactivity of the dichloromethylcarbamoyl radical species **I** (see Fig. 6) which adds rapidly to the alkene to generate primary radical **II** even more reactive that the first one.

Moreover, the higher potentials necessary for the single electron transfer in **1a** analogues where one of both chlorine atoms were replaced by hydrogens could explain the inertia of these substrates when submitted to the cyclization optimized conditions (Fig. 5b).

In this work we have reported the first catalyst- and amine-free photocyclization[19] of trichloroacetamides demonstrating that formation of lactams **2** and **3** involves radical species. Given that the reaction effectively occurs solely in THF or 2-MeTHF under violet light irradiation, we concluded that the mechanism involved herein may suggest oxygen promoted generation of radicals or peroxides from the solvent to initiate the radical process in the synthesis of lactams.

Indeed, in the literature oxidation of tetrahydrofuran and 2-methyltetrahydrofuran with oxygen, in the presence of UV light was reported to give the corresponding hydroperoxides.[20]

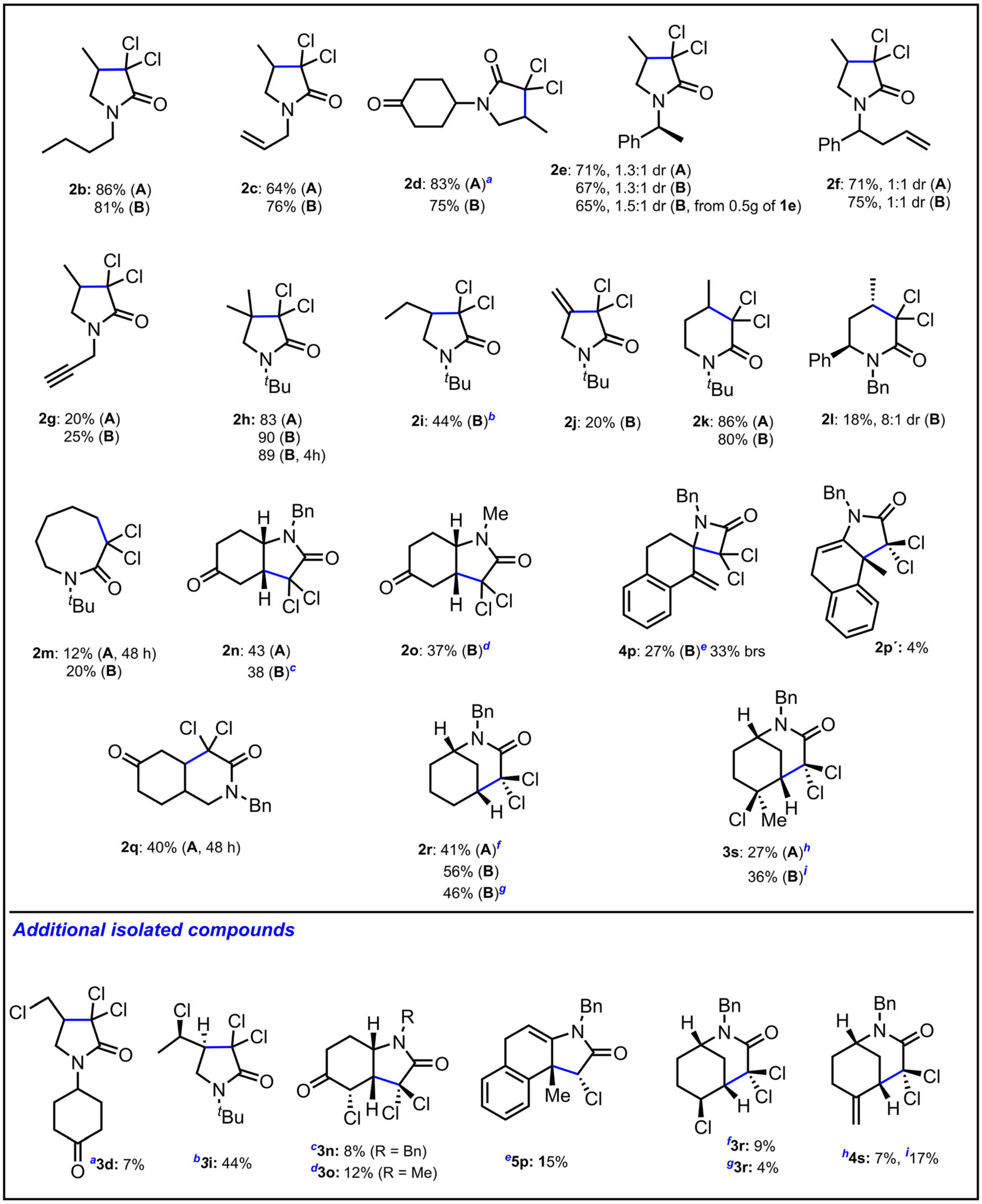


Fig. 3 Substrate scope in the synthesis of β-, γ- and δ-lactams from *N*-alkenyl-trichloroacetamides **1b–1s**. Unless otherwise stated all reactions were performed with trichloroacetamides **1b–1s** (0.2–0.4 mmol scale) in THF (A) or 2-MeTHF (B) (4–8 mL, 0.05 M) at rt and under violet LEDs (395–405 nm) irradiation for 14 h.

In another investigation, direct oxidative hydroperoxidation of α-ethereal C–H bond of aliphatic ethers *e.g.* THF was achieved *via* direct C–H bond insertion using singlet O_2. The reaction was carried out in the presence of a photosensitizer (typically *meso*-TPP or rose bengal) and Lewis acid (γ-Al_2O_3) under irradiation using a 100 W Hg lamp or a blue-LEDs array at room temperature under a 1 atm oxygen pressure.[21] Additionally, aerobic generation of THF radical **A** (Fig. 6) was established in the functionalisation of ethereal-based saturated heterocycles at 80 °C.[22] On the basis of the above-mentioned experiments and our own control experiments we decided to investigate the behaviour of THF and 2-MeTHF alone under violet light. Thus, when both solvents were irradiated separately overnight, after concentration, the residue contained mainly peroxides **B** which NMR data were identical to those reported previously.[21]

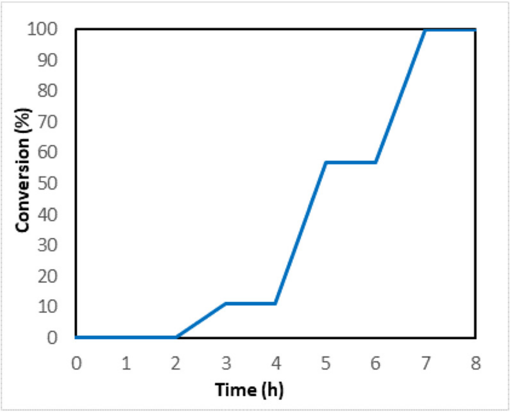


Fig. 4 Light on/off intermittent experiment for the synthesis of **2a** followed by ^{1}H NMR.

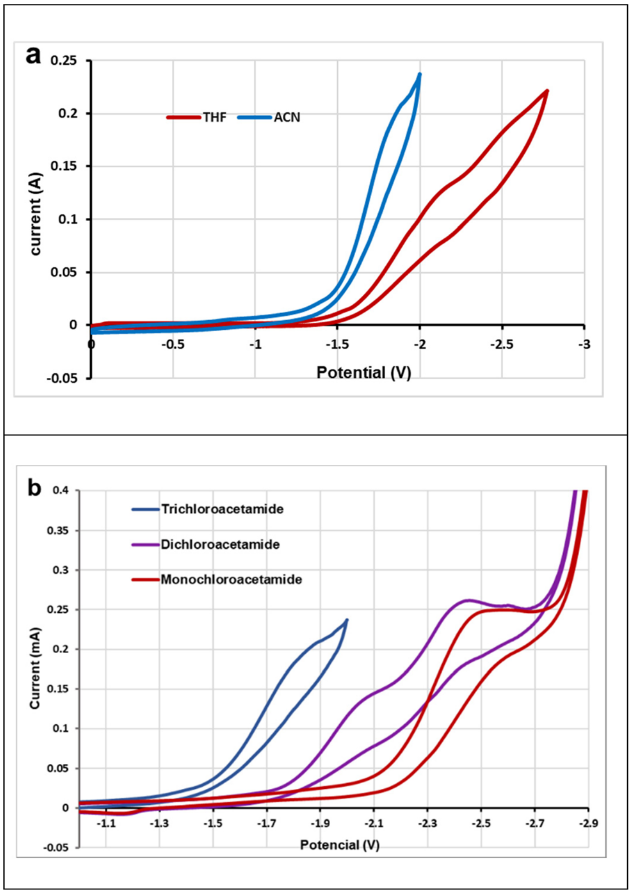


Fig. 5 (a) Cyclovoltameric study of **1a** in THF and in acetonitrile. (b) Cyclovoltammetric study of trichloroacetamide **1a** and its analogues α,α-dichloro and α-chloro acetamides in acetonitrile.

In view of these results, we propose the mechanism shown in Fig. 6 for the formation of lactams **2** and **3**. First, as it was reported in the literature (see ref. 22), oxygen under violet light irradiation interact with THF or 2-MeTHF to generate radical species **A** that acts as radical initiators[23] generating (carbamoyl)dichloromethyl radical **I** which evolves into radical **II** through cyclization.

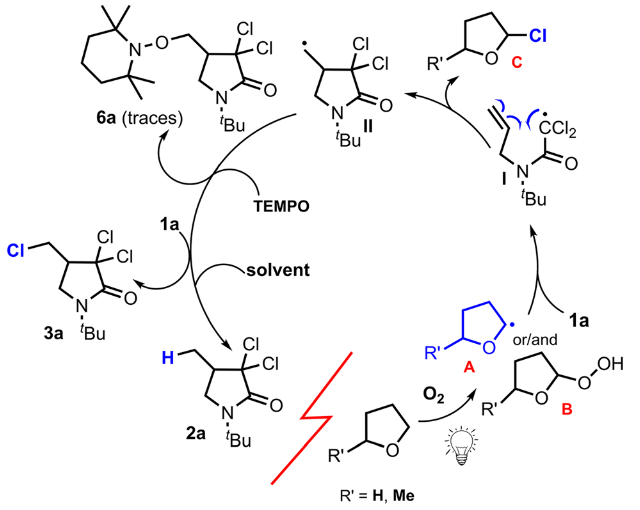


Fig. 6 Proposed mechanism for the formation of lactams **2** and **3**.

Indeed, analysis of the reaction mixture before concentration by ^{1}H NMR spectroscopy unequivocally revealed the presence of the signals corresponding to chloro derivative **C** (R′ = H).[24] Finally, intermediate **II** abstracts a hydrogen from the solvent to form lactam **2** or a chlorine atom from trichloroacetamide **1** to produce **3** through an atom transfer process. The probability of the latter to take place increases with the stability of radical **II**. Indeed, with trichloroacetamide **1s**, where a tertiary radical is formed, only **3s** was isolated (Fig. 3). **3s** evolves to **4s** through elimination.

Conclusions

In summary, we have reported herein an unprecedented catalyst- and amine-free one-step radical cyclization for the effective synthesis of γ- and δ-lactams from *N*-alkenyl trichloroacetamides. The reactions are achieved under mild conditions in THF Or 2-MeTHF alone as solvents under air atmosphere and violet light irradiation. In this investigation we have reported a sustainable green strategy to access a wide range of lactams including indoles, isoquinoline and morphan scaffolds. We have also demonstrated that the solvent (THF or 2-MeTHF) acts as the radical initiator in the presence of oxygen allowing the radical cyclization to take place using the simplest reaction setup. Further work is underway to explore the potentiel of this reaction for the synthesis of advanced intermediates towards the synthesis of natural compounds.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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References

1 *Radicals in organic synthesis*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, Germany, 2001.

2 S. Z. Zard, *Radical Reactions in Organic Synthesis*, Oxford University Press, 2003.

3 K. J. Romero, M. S. Galliher, D. A. Pratt and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2018, **47**, 7851–7866 and the references therein.

4 B. Giese, J. A. González-Gómez and T. Witzel, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 69–70.

5 (*a*) W. P. Neumann, *Synthesis*, 1987, 665–683; (*b*) A. G. Davies, *J. Chem. Res.*, 2006, 141–148.

6 A. Padwa, H. Nimmesgern and G. S. K. Wong, *J. Org. Chem.*, 1985, **50**, 5620–5627.

7 (*a*) Y. Yamamoto, Triethylborane, in *Encycl. Reagents Org. Synth*, 2007, DOI: 10.1002/047084289X.rt219; (*b*) V. Darmency and P. Renaud, *Top. Curr. Chem.*, 2006, **263**, 71–106.

8 M. Ikeda, H. Teranishi, N. Iwamura and H. Ishibachi, *Heterocycles*, 1997, **45**, 863–866.

9 For alkyl radicals generation from alkyl halides using photoredox catalysis, see *inter alia*: (*a*) X. Zhuang, X. Shi, R. Zhu, B. Sun, W. Su and C. Jin, *Org. Chem. Front.*, 2021, **8**, 736–742; (*b*) Q. S. Zhao, G. Q. Xu, J. T. Xu, Z. Y. Wang and P. F. Xu, *Chem. Commun.*, 2020, **56**, 2206–2209; (*c*) X. Ju, Y. Liang, P. Jia, W. Li and W. Yu, *Org. Biomol. Chem.*, 2012, **10**, 498–501.

10 For reviews see: (*a*) Y. Q. Yuan, S. Majumder, M. H. Yang and S. R. Guo, *Tetrahedron Lett.*, 2020, **61**, 1–15; (*b*) G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461–5476.

11 E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchiorre, *Nat. Chem.*, 2013, **5**, 750–756.

12 G. Trenchs and F. Diaba, *Org. Biomol. Chem.*, 2022, **20**, 3118–3123.

13 For additional results achieved from other substrates in the presence of ammonia see the ESI.†

14 (*a*) C. J. Clarke, W. C. Tu, O. Levers, A. Bröhl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747–800; (*b*) F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. R. McElroy and J. Sherwood, *Sustainable Chem. Processes*, 2016, **4**, 7.

15 S. Jansana, F. Diaba and J. Bonjoch, *Org. Lett.*, 2019, **21**, 5757–5761.

16 E. W. Della and A. M. Knill, *Aust. J. Chem.*, 1995, **48**, 2047–2051.

17 For the characterization of **6a** see ref. 12.

18 L. Zhang, J. Cradlebaugh, G. Litwinienko, B. E. Smart, K. U. Ingold and J. W. R. Dolbier, *Org. Biomol. Chem.*, 2004, **2**, 689–694.

19 For reviews, see: (*a*) W. Liu and C. J. Li, *Synlett*, 2017, **28**, 2714–2754; (*b*) M. L. Deb, B. S. Saikia, P. J. Borpatra and P. K. Baruah, *Asian J. Org. Chem.*, 2022, **11**, e202100706.

20 G. I. Nikishin, V. G. Glukhovtsev, M. A. Peikova and A. V. Ignatenko, *Russ. Chem. Bull.*, 1971, **20**, 2202–2204.

21 A. Sagadevan, K. C. Hwang and M. D. Su, *Nat. Commun.*, 2017, **8**, 1–8.

22 N. Ahmed, R. J. Spears, T. D. Sheppard and V. Chudasama, *Chem. Sci.*, 2022, **13**, 8626–8633.

23 M. Newcomb, R. M. Sanchez and J. Kaplan, *J. Am. Chem. Soc.*, 1987, **109**, 1195–1199.

24 S. Lee, P. S. J. Kaib and B. List, *J. Am. Chem. Soc.*, 2017, **139**, 2156–2159.