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Oxidation of Trialkylamines by $BrCCl_3$ – Scope, Applications and Mechanistic Aspects

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Abstract: The catalyst free photochemical reaction of trialkylamines and $BrCCl_3$ induced by visible light was investigated. The course of the reaction was found to depend strongly on the nature of the amine substrates. While *N*-methyl-1,2,3,4-tetrahydroisoquinolines yielded 3,4-dihydroisoquinolinium salts, aliphatic trialkylamines produced hydrohalide salts and streptocyanines as the major products. The addition of KCN inhibits the streptocyanine formation and results in the clean formation of α-aminonitriles instead. The light-absorbing species and the underlying reaction mechanism were studied by DFT calculations and experimental observations.

Introduction

Doubtlessly, light is one of the most powerful agents for the transformation of matter existing in nature.[1] Consequently, chemists have successfully applied light to promote and generate new types of chemical reactions for centuries.[2] While the excitation of organic molecules by visible or ultraviolet light opens up opportunities for new reaction modes through excited singlet or triplet states, the number of publications involving photochemical transformations is still surprisingly low. The last decade has seen a resurgence of preparative photochemistry, mainly due to a renewed interest in photoredox catalysis.[3] The underlying general principle of photocatalysis allows the activation of organic molecules via single electron transfer (SET), photon induced hydrogen atom transfer (PHAT) or energy transfer.[4] Different types of photocatalysts such as transition metal complexes,[4a, 5] organic dyes,[6] and semiconductors[7] have been used to collect light and transfer the energy to the substrates, in order to induce a chemical reaction in the latter.

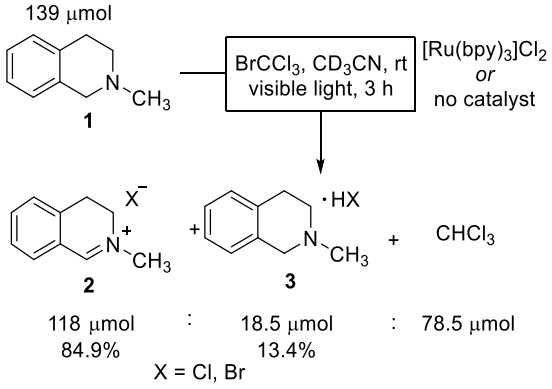
A representative photoredox-catalyzed process is the oxidative generation of iminium ions from tertiary amines. Various methodologies have been developed to this end which utilize different photocatalysts to effect this dehydrogenation.[6b, 6c, 8] Remarkably, *N*-aryl-1,2,3,4-tetrahydroisoquinolines were almost exclusively used as the substrates, limiting the applicability of the method for the synthesis of natural products. Due to their high HOMO energy and the conjugative stabilization of the dehydrogenation products, these substrates are highly reactive and spontaneously form 1-hydroperoxides when exposed to air.[9] Thus, we became interested in the development of a complementary method to generate iminium ions from the less readily oxidized amines lacking an N-aryl substituent and its subsequent application to natural product total synthesis.

Results and Discussion

Tetrahydroisoquinolines + $BrCCl_3$ – Oxidation and Protonation

N-Methyl-1,2,3,4-tetrahydroisoquinoline (**1**) was chosen as a test substrate since this heterobicyclic system is frequently found as a substructure in plant-derived natural products.

Stephenson *et al.*[8a, 8b] described the use of $[Ru(bpy)_3]Cl_2$, $BrCCl_3$, and visible light to generate *N*-aryl-3,4-dihydroisoquinolinium salts. The reported reaction conditions were applied to compound **1**, using deuterated acetonitrile as the solvent, an argon inert atmosphere, and a 24 W compact fluorescent lamp (CFL) as the source of visible light (Scheme 1). The reaction was complete within 3 h, producing the expected iminium salt **2** as well as an unexpected by-product identified as the protonated *N*-methyl tetrahydroisoquinoline (**3**) along with chloroform. (^{1}H NMR).



Scheme 1. Photogeneration of iminium ions. Amounts were quantified by ^{1}H NMR spectroscopy with an internal standard.

To prove the involvement of the photocatalyst in the transformation, a blank reaction without catalyst was conducted. Interestingly, after 3 h of irradiation the color of the reaction medium had changed from colorless to amber. ^{1}H NMR analysis revealed oxidation of the amine with the formation of the iminium salt and the protonated amine in the same absolute and relative amounts as in the presence of the photocatalyst.

Intrigued by these unexpected results, additional experiments were performed. Exclusion of UV light with a UV filter (0.5 M benzophenone in ethanol, 3 cm layer thickness) as well as the use of (UV-free) blue LEDs (λ_{max} = 462 nm) again yielded the iminium salt and amine hydrohalide without variation of the product ratio. On the other hand, no reaction was detected in the absence of light (excluding the possibility of a simple ionic mechanism) or in the absence of $BrCCl_3$.

During the course of this research, the Zeitler group published the same observation in a remarkable catalyst-free visible light oxidation of numerous *N*-aryl- and *N*-methyl-tetrahydroisoquinolines with polyhalomethanes.[10] While these results were in perfect agreement with our own observations in terms of the formation of the iminium salt, the formation of the side product **3** and the application of the catalyst-free photodehydrogenation to non-tetrahydroisoquinoline systems were not reported. The UV light induced reaction between tetrahalomethanes and amines to yield ammonium halides has already been described in the 1960's. This reaction has been proposed to proceed via charge transfer complexes (electron-donor-acceptor complexes, EDA) which were thought to absorb UV light to undergo decomposition to hydrohalides and haloform (the yield of the hydrohalides, as well as the proton source were not further investigated).[11] However, as reported by Zeitler *et al.*,[10] blue but not green light promoted the reaction even under rigorous exclusion of UV light through filters.

Application – Synthesis of α-Aminonitriles

After the reaction conditions were established for the model amine **1**, their application in the synthesis of useful synthetic intermediates and natural products was attempted. α-Aminonitriles are important building blocks in organic synthesis and proved to be versatile starting materials for the preparation of a variety of N-heterocyclic natural products.[12] Consequently, the photogenerated iminium ion was intercepted by potassium cyanide to form the corresponding α-aminonitrile **4** (Scheme 2). Among the different solvents tested (see the Supporting Information), acetonitrile gave the best results. Based on the original reaction conditions, one-pot and stepwise procedures for the α-aminonitrile synthesis were evaluated. In all cases, the expected α-aminonitrile **4** was obtained in excellent yields. Alternatively, compound **4** can be obtained by replacing KCN for a non-toxic cyanide source such as potassium ferricyanide $K_3[Fe(CN)_6]$ (see the Supporting Information).[13]

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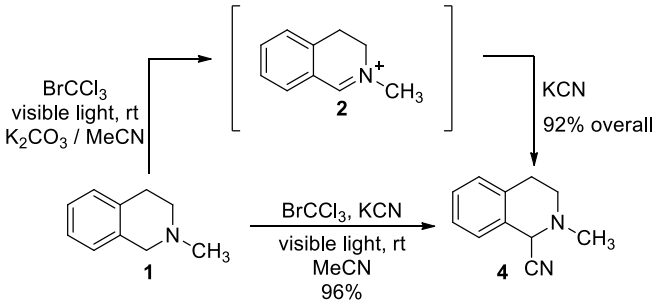
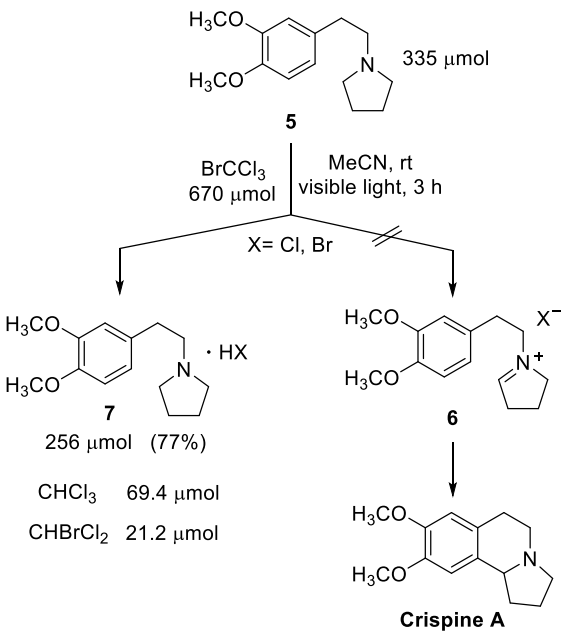


Scheme 2. Synthesis of α-aminonitrile **4**.

Crispine A Precursor + $BrCCl_3$ – Exclusive Protonation

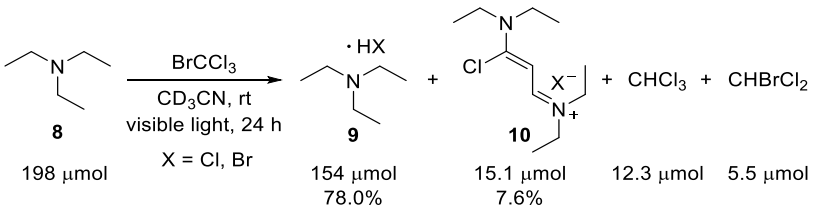
To evaluate the scope of the reaction, other aliphatic amines were tested as the reactants. Since the alkaloid crispine A could be obtained from iminium salt **6** (also available from the corresponding α-aminonitrile),[6a] pyrrolidine **5** was selected as a study case (Scheme 3). However, after subjecting pyrrolidine **5** to the reaction conditions established for the oxidation of **1**, no formation of iminium ion **6** was observed and a protonation of pyrrolidine **5** to its hydrohalide salt **7** occurred. The quantification of the product by ^{1}H NMR spectroscopy using an internal standard added after the photoreaction revealed that a fraction of the starting material had been consumed but apart from baseline clutter, no other defined product could be identified.



Scheme 3. Generation of pyrrolidine hydrohalide **7**. Amounts were quantified by ^{1}H NMR spectroscopy with an internal standard.

Trialkylamines + $BrCCl_3$ – Protonation and Streptocyanine Formation

To understand this reaction behavior, we applied the reaction protocol to triethylamine (**8**). The reaction mixture turned amber within minutes and once again, the amine was predominantly protonated to its hydrohalide salt **9**. (Scheme 4). Chloroform and bromodichloromethane were also produced as judged by ^{1}H, ^{13}C and HSQC-NMR spectroscopy. In search for an oxidized species which must be formed in order to maintain the overall redox balance of the process, the chlorinated *N,N*-diethylvinylamine derivative **10** was identified as a co-product and characterized spectroscopically.



Scheme 4. Formation of triethylamine hydrohalide **9** and chloro-streptocyanine **10**. Amounts were quantified by ^{1}H NMR spectroscopy with an internal standard.

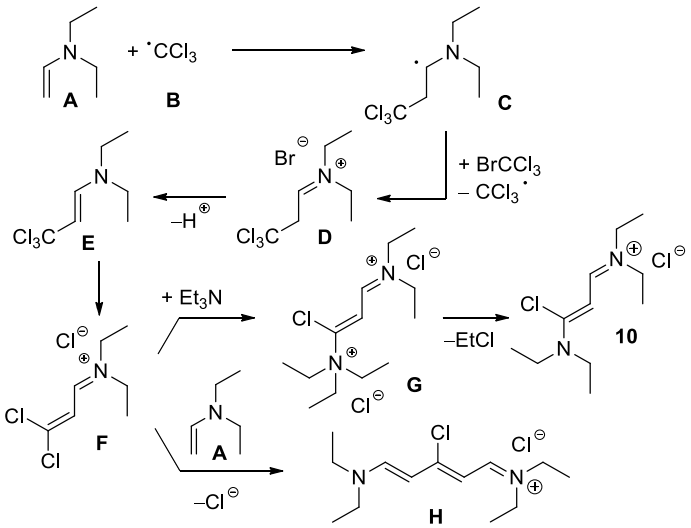
To exclude the formation of hydrogen halides through hydrolysis of polyhalomethanes to phosgene or ultimately to CO_2,[14] moisture was again rigorously excluded in a glovebox and an inert atmosphere. Nevertheless, the formation of the hydrohalide salts again proceeded smoothly. To rule out the involvement of the solvent as a potential hydrogen source, NMR experiments in different deuterated or chlorinated solvents were performed (see Supporting Information). The results revealed that the solvent did not actively participate in the reaction, so the only hydrogen source in question was the amine itself through an oxidative mechanism. The deprotonation of the initially formed iminium ion yields an enamine which should be more labile to oxidation than the parent amine itself due to conjugation of the lone pair on nitrogen with the olefinic double bond which increases the HOMO energy. A series of oxidations and deprotonations of a smaller quantity of the amine could then explain the protonation of the amine.

The generation of triethylamine hydrohalide (**9**) from triethylamine (**8**), polyhalomethanes and UV-light has been described by Collins,[15] Foster[16] and Stevenson[11c] already in the early 1960's. However, the nature of co-product **10** was not established until today.[17] The formation of chloro-streptocyanine **10** is in accordance with a recent publication of the Bach group, in which similar but non-chlorinated cyanines were detected as the products of the reaction of CH_2Cl_2 and DIPEA. These conjugated chromophores resulting from N-dealkylation/condensation with the polyhalomethane and reaction of the resulting iminium salts with enamines (formed through oxidation/deprotonation) were shown to be responsible for the amber color in similar photo-induced reactions.[18]

Mechanism of Streptocyanine Formation

The mechanism for the formation of cyanine dye **10** and its higher homologue **H** might be as follows (Scheme 5): Enamine **A** is attacked by the electrophilic trichloromethyl radical **B** to furnish radical **C** which is brominated by $BrCCl_3$ to iminium salt **D**. Deprotonation yields enamine **E** which eliminates chloride to produce the reactive vinylogous Viehe salt **F**.[17] This in turn could then react with trimethylamine through addition/N-dealkylation to produce the

observed streptocyanine **10**. Alternatively, reaction with enamine **A** yields the pentamethinecyanine **H**.



Scheme 5. Suggested course of the formation of streptocyanine dye **10** and its higher homologue.

The UV/vis spectrum of the reaction mixture of the light-induced $BrCCl_3$ oxidation of **8** revealed two clear maxima at 310 nm and 414 nm (Figure 1) which are in good accordance with the values reported by Bach and coworkers for the CH_2Cl_2-derived, non-halogenated trimethine and pentamethine cyanine products of DIPEA. Another, broader maximum or shoulder can be found around 505 nm. In the systematics of the cyanine dyes with a 90–100 nm increase in λ_{max} per additional ethylene unit this would correspond to a heptamethinecyanine.

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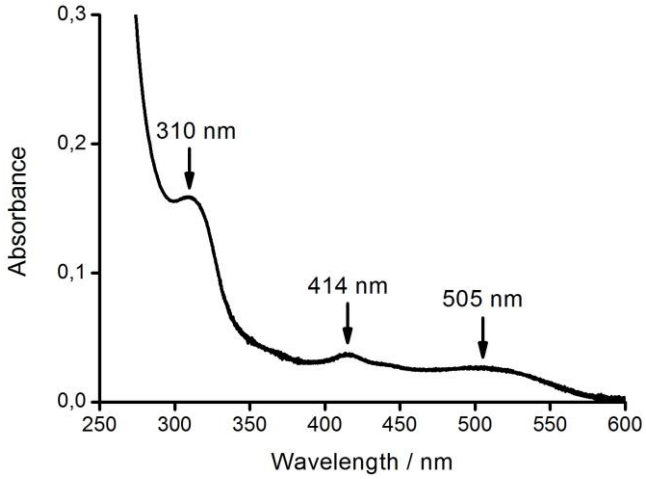

Figure 1. UV/vis spectrum of the reaction mixture of **8** and $BrCCl_3$ showing absorption maxima of polymethinecyanines.

Apart from the oxidation state of the C_1-unit, another major difference between $BrCCl_3$ and CH_2Cl_2 in their reaction with triethylamine lies in the respective kinetics. While the reaction mixture containing $BrCCl_3$ turns yellow quickly under ambient lighting and turns brown after 3 min exposure to light from a blue LED, the mixture containing CH_2Cl_2 remains colorless even after the same irradiation procedure.

Competition between Different Reaction Pathways

By addition of a base like potassium carbonate, the formation of the amine hydrohalide was reduced and chloro-streptocyanine **10** was accumulated (Figure 2) (A ratio 2:3 of protonated amine to streptocyanine was achieved). This represents a particularly simple way to synthesize 1,3-difunctionalized C_3 building blocks. In contrast, the addition of solid potassium cyanide to the reaction mixture exclusively resulted in the formation of 2-(diethylamino)propanenitrile (**11a**, Figure 2) and no significant color change was observed. NMR spectroscopy revealed that streptocyanine formation did not take place in the presence of cyanide. Since the formed α-aminonitrile **11a** is volatile, the protocol was applied to tributylamine and 2-(dibutylamino)-pentanenitrile **11b** was isolated in 95% yield. In this reaction, TMSCN is not able to compete with KCN in terms of reaction velocity and suppression of byproduct formation.

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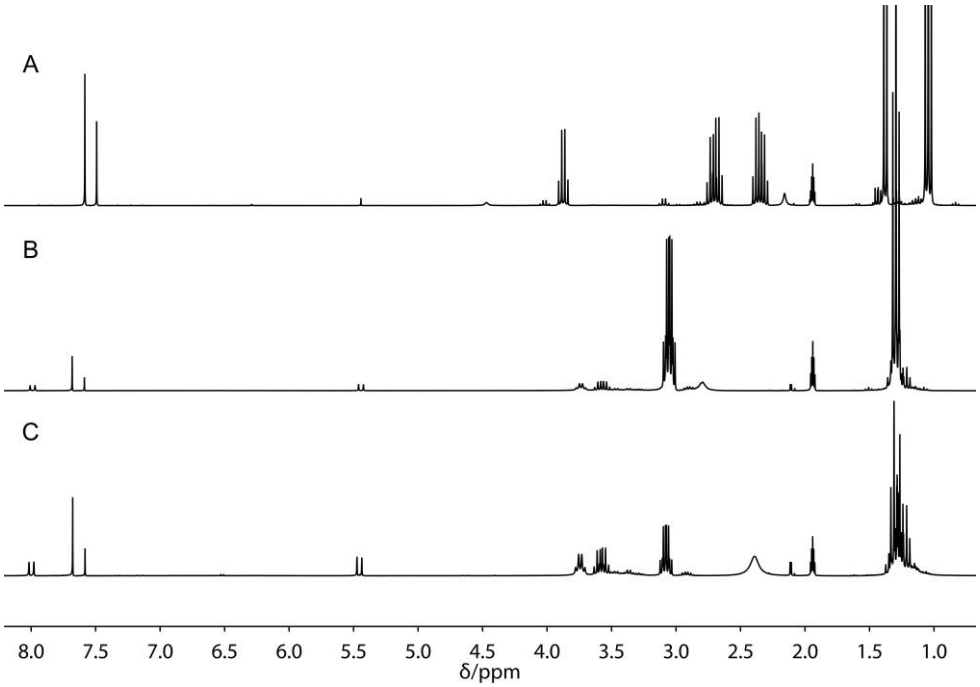
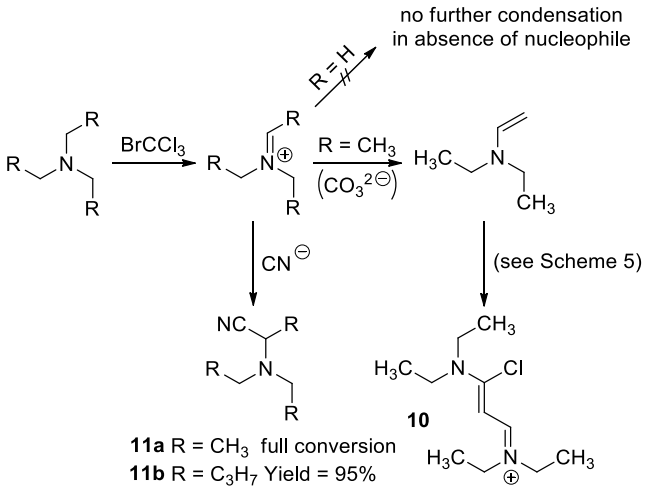


Figure 2. Crude ^{1}H NMR spectra (acentonitrile-d_3) of the triethylamine oxidation with different additives: (A) Potassium cyanide as an additive results in α-aminonitrile formation. (B) Without additive, the amine hydrohalide and the cyanine dye are formed. (C) Addition of potassium carbonate results in the accumulation of the cyanine dye.

These results provide additional mechanistic information. The successful trapping with cyanide to form the α-aminonitrile proves the intermediacy of the iminium ion. If no nucleophiles are present, the iminium ion or the enamine formed by deprotonation can undergo further reactions and finally form the streptocyanine. We applied the protocol to trimethylamine which should yield the iminium salt almost equally well but cannot produce an enamine. A slow conversion to the hydrohalide and the concomitant formation of another compound was observed which could be identified as *N,N*-dimethylmethyleneiminium halide based on NMR experiments and comparison with literature values.[19] The need of an enamine intermediate for streptocyanine formation explains the different behavior of trimethyl- versus triethylamine which is further supported by a lacking color change in the case of trimethylamine.



Scheme 6. Reaction pathway of oxidized aliphatic amines with additives

Oxidation Mechanism – DFT Calculations

To understand the nature of the initial oxidation step, we used computational methods to identify the light-absorbing species and the underlying reaction mechanism.

Trimethylamine was chosen as the simplest possible computational model substrate to investigate the amine oxidation by bromotrichloromethane under irradiation with visible light at the UM062X/6-311++G(3df,2pd)/SMD(MeCN)//UM062X/6-311+G(2d,p)/SMD(MeCN) level of theory. Three obvious possible candidates for the initial photoexcitation would be either pure $BrCCl_3$, the amine–$BrCCl_3$ complex, or an *N*-bromoammonium ion produced in a nucleophilic substitution on $BrCCl_3$ (Scheme 7).

$$(CH_3)_3N + BrCCl_3 \underset{[\pm 0.0]}{\longrightarrow} (CH_3)_3N{-}BrCCl_3 \underset{[+4.9]}{\longrightarrow} (CH_3)_3NBr^+ + CCl_3^- \quad [+47.9]$$

Scheme 7. Candidates for photoexcitation, relative free energies in kcal/mol (level of theory: see text).

The absorption maxima of all three candidates were calculated although the *N*-bromoammonium ion is energetically too high-lying to be considered as a reasonably abundant species. None of them revealed an absorption band of sufficiently low energy according to TD-DFT calculations employing hybrid, long-range corrected hybrid, and double-hybrid density functionals, even if relativistic corrections were considered (Table 2,

see the Supporting Information for details). These results could be supported by ab initio calculations (see the Supporting Information for details).

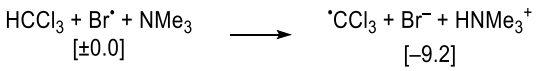
Table 2. Absorption maxima of trimethylamine (λ_{max}/nm) for the $S_1 \leftarrow S_0$ transitions calculated by TD-DFT.

	TD-B3LYP/ 6-311++G(3df,2pd)/ SMD(MeCN)	TD-LC-ωPBE/ 6-311++G(3df,2pd)/ SMD(MeCN)	TD-B2GP-PLYP/ def2-QZVPP(-g,-f)/ SMD(MeCN)/ZORA
$BrCCl_3$ (lit.: 251 nm)	253	226	234
$Me_3N{-}BrCCl_3$	297	207	215
Me_3NBr^+	281	272	270
$Me_3N{-}Br_2$	348	308	306
Br_2 (lit.: 415 nm)	456	416	410

Thus, pure $BrCCl_3$ is unlikely to be the photoinitiator since its absorption maxima (calc.: 253/226/234 nm, lit.: 251 nm) are far from the visible range. The reported molar extinction coefficient even at 365.5 nm is very low (0.02 $M^{-1}cm^{-1}$).[20] The absorption maximum of the charge-transfer complex of the amine with $BrCCl_3$ also lies in the ultraviolet range. However, it is well known that absorptivities of EDA complexes of tertiary amines and $BrCCl_3$ in the UV-A region are significant (e.g. 3 $M^{-1}cm^{-1}$ at 350 nm) most probably due to a broad absorption band.[11c] Therefore, it could be possible that a certain extent of light absorption through the EDA complex also occurs in the visible range. According to our calculations, the only species that shows an absorption maximum in the visible range was molecular bromine (calc.: 456/416/410 nm, lit.: 415 nm).[21] Nevertheless, we tried to exclude bromine as a potential impurity of the polyhalomethane reactant by using freshly distilled $BrCCl_3$ as already mentioned by the Zeitler group. Condensed compounds with an extended conjugation

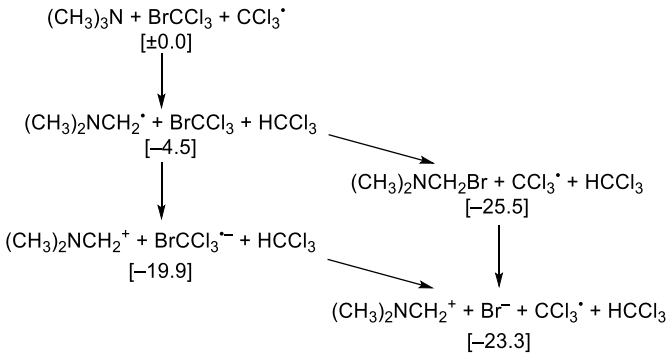
formed through oxidative decomposition in the starting amine can also be ruled out since freshly distilled amines (under argon atmosphere and light exclusion) behaved similarly.

Thus, an efficient photoexcitation of $BrCCl_3$ (or the corresponding amine complex), leading to electron-transfer (PET) or hydrogen-abstraction processes with the amine substrate appears less likely. A reasonable alternative would be a radical chain reaction via bromine radicals. However, in the presence of free amine as a base, such a process would end up producing trichloromethyl radicals as a thermodynamic minimum (Scheme 8).

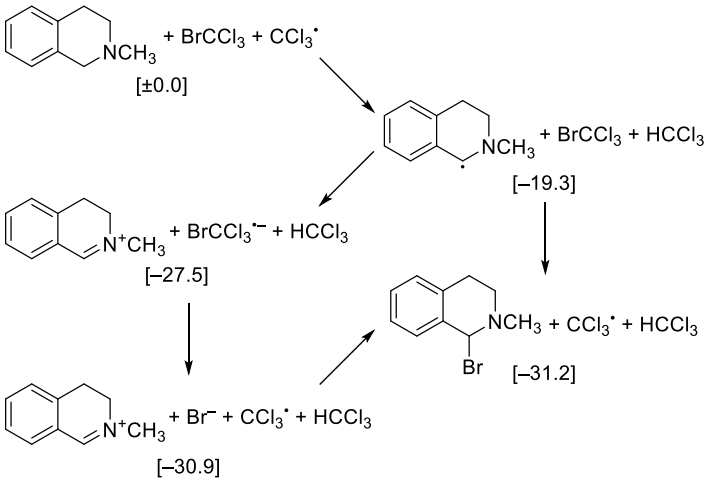


Scheme 8. Generation of trichloromethyl radicals, relative free energies in kcal/mol (same level of theory as in Scheme 6).

Accordingly, we propose a free-radical reaction propagated by trichloromethyl radicals in which the respective steps can proceed in an all-exergonic manner. The pathways were calculated for the simple model substrate (Scheme 9) as well as for the *N*-methyltetrahydroisoquinoline reactant (Scheme 10). The reaction would be initiated by a hydrogen abstraction and would then proceed via bromine transfer or via a sequential electron transfer/dissociation/recombination pathway.[22]



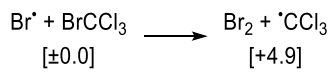
Scheme 9. Radical chain reaction via trichloromethyl radicals with trimethylamine as substrate, relative free energies in kcal/mol (same level of theory as in Scheme 6, the "$(CH_3)_2NCH_2Br$" should be regarded as a contact ion pair).



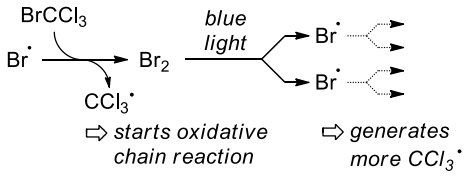
Scheme 10. Radical chain reaction via trichloromethyl radicals with *N*-methyl tetrahydroisoquinoline as substrate, relative free energies in kcal/mol (same level of theory as in Scheme 7).

As expected, the initial hydrogen abstraction is more exergonic in the latter case since a stabilized benzylic radical is being generated. The calculated thermochemical data and infeasible alternative pathways indeed suggest the reaction to take place through a radical mechanism involving trichloromethyl radicals. However, the pathway for the initial radical generation and the exact role of light in the process are still unknown.

The generation of molecular bromine and a trichloromethyl radical from the reaction of a bromine radical with bromotrichloromethane is only slightly endergonic (Scheme 11). A single bromine radical could therefore form a trichloromethyl radical, which starts the above-mentioned radical chain oxidation process. Furthermore, molecular bromine is produced, which, after irradtion with visible light, yields two bromine radicals, which in turn produces two trichloromethyl radicals and two molecules of Br_2 (Scheme 12).



Scheme 11. Alternative generation of trichloromethyl radicals, relative free energies in kcal/mol (same level of theory as in Scheme 6).



Scheme 12. Light-induced multiplication of radicals during the reaction.

It is however worth noting that the reaction of *N*-methyltetrahydroisoquinoline and $BrCCl_3$ also takes place under ultrasonication[23] and thermal conditions (exclusion of light in both cases). Nevertheless, the reaction rates and yields of the sonochemical and thermal reaction were lower compared to the photochemical process (yields: 38% sonochemically, 15% thermally (T = 70 °C) versus 62% photochemically, each after 3 h). The lability of bromotrichloromethane towards sonication has already been reported[23] and the resulting bond homolysis could be a trigger for the proposed free radical chain mechanism. Nevertheless, the significant accelerating effect of irradiation with blue light as suggested in Scheme 12 requires further investigation.

Conclusion

The reaction between trialkylamines and $BrCCl_3$ induced by visible light, heat or ultrasound was applied to various substrates. *N*-methyl-1,2,3,4-tetrahydroisoquinolines tend to yield iminium ions as the main products while aliphatic trialkylamines carrying β-hydrogen are being protonated instead. Since the solvent or traces of water were not involved in this process, the amine itself must be the sacrificial reductant to form hydrogen halide in its oxidative transformation through the reactive enamine into products such as chlorocyanine **10**. When additives are present, the reaction outcome can change. The addition of a base accumulates the cyanine dye whereas cyanide as an exemplified nucleophile exclusively produces the α-aminonitrile. DFT calculations for the iminium formation suggested a free-radical reaction propagated by trichloromethyl radicals in which the respective steps can proceed in an all-exergonic manner. Unfortunately, the initiation mechanism still remains unclear since neither pure $BrCCl_3$ nor the amine-$BrCCl_3$ complex or a *N*-bromoammonium ion show an appreciable absorbance in the visible range. A small steady state concentration

of molecular bromine could however be formed through Br-abstraction from $BrCCl_3$ by Br radicals and through continuous photolysis according to the proposed mechanism, constantly producing trichloromethyl radicals at a rate proportional to the flux of blue-light photons.

Some applications of the oxidation chemistry to the synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile, (±)-carnegine, 2-(dibutylamino)-pentanenitrile, and cryptostylines analogs were demonstrated to show the applicability of the photo-generated iminium salts (see the Supporting Information). The involvement of cyanine dyes as in situ-generated photocatalysts can be excluded as two of the variants of the amine oxidation by $BrCCl_3$ are not associated with any appreciable cyanine formation.

Experimental Section

General information

Solvents and reagents were purchased from commercial suppliers (Sigma Aldrich, Alfa Aesar, TCI chemicals, ABCR, Acros Organics and Fischer Scientific) and used as received unless noted otherwise. *N*-Methyl-1,2,3,4-tetrahydroisoquinoline,[24] 6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline,[25] and 1-(3,4-dimethoxyphenethyl)pyrrolidine[6a] were synthesized according to known literature procedures. Anhydrous dichloromethane and acetonitrile were distilled under argon atmosphere from CaH_2 or P_4O_{10} and collected over molecular sieves 4 Å (10 to 18 mesh, ACROS Organics). $BrCCl_3$ was distilled under argon atmosphere, collected over molecular sieves 4 Å (10 to 18 mesh, ACROS Organics) and keep it away from the light with an aluminum foil cover. Flash column chromatography was performed using silica gel (35–70 µm silica gel, Acros Organics). Thin-layer chromatography (TLC) was carried out on Merck silica gel plates (60 F_{254}) using defined solvent mixtures and visualized under UV light irradiation and/or TLC staining reagents. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were measured with a Tensor 27 with a diamond ATR unit from Bruker and are reported in terms of frequency of absorption (ν, cm^{-1}). A 300 MHz (300 MHz ^1H and 75.4 MHz ^{13}C), a 400 MHz (400 MHz ^1H and 100.6 MHz ^{13}C) spectrometer from Bruker were used to record the corresponding NMR

spectra with deuterated solvents ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; CD_3CN: δ_H = 1.94 ppm, δ_C = 1.32, 118.3 ppm; C_6D_6: δ_H = 7.16 ppm, δ_C = 128.06 ppm) as internal reference.[26] NMR yield was determined by using 99% CH_2Br_2 (2H at 4.92 ppm in $CDCl_3$ or 5.45 ppm in CD_3CN) as internal standard: addition of weighted amount of CH_2Br_2 was made after irradiation to avoid undesired chemical reactions of the NMR standard. ESI-HRMS spectra were recorded on a Q-TOF instrument with a dual source and a suitable external calibrant. Irradiation was performed using a 24 W CFL lamp "white light" or a blue LED (100 W, λ_{max} = 462 nm).

Computational chemistry

The hybrid DFT and TD-DFT calculations were performed using Gaussian 09 (Rev. D.01).[27] Double hybrid TD-DFT and ab initio calculations were performed using Orca 3.0.3.[28] DFT geometry optimizations with a spin-unrestricted formalism employed the M062X functional,[29] the 6-311+G(2d,p) basis set,[30] and SMD solvation for acetonitrile.[31] An ultrafine grid, a quadratically convergent SCF procedure (only in case the first-order SCF did not converge) and tight SCF as well as geometry optimization convergence criteria were used. The stationary points were identified as minima by calculation of the full exact hessian (yielding no imaginary frequencies). Single-point energies were calculated using the 6-311++G(3df,2pd) basis set in an otherwise identical way.[30] The final Gibbs free enthalpies were obtained by addition of the 6-311++G(3df,2pd) electronic energy and the 6-311+G(2d,p) Gibbs free enthalpy energy corrections. The excited-state calculations were performed using the previously obtained UM062X/6-311+G(2d,p)/SMD(MeCN) geometries. Hybrid TD-DFT calculations (40 transitions) employed the B3LYP,[32] PBE1PBE,[33] M062X,[29] CAM-B3LYP,[34] LC-ωPBE,[35] and ωB97XD[36] functionals together with the 6-311++G(3df,2pd) basis set[30] and SMD solvation for acetonitrile.[31] Tight SCF convergence criteria were used. Double-hybrid TD-DFT calculations (1 transition with a 20 state Davidson expansion space) were performed with the (RI-)B2GP-PLYP functional,[37] the def2-TZVPP as well as def2-QZVPP(-g,-f) basis sets in conjunction with the corresponding /J and /C fitting basis sets,[38] and SMD solvation for acetonitrile.[31] The RIJCOSX approximation,[39] tight

SCF convergence criteria, and enhanced grid settings (Grid5 FinalGrid6 GridX4) were used. The ZORA model was included to study relativistic effects.[40] Ab initio calculations at the CIS(D)[41] (1 transition with a 20 state Davidson expansion space) and EOM-CCSD[42] (1 transition) levels were performed with the aug-cc-pVDZ as well as aug-cc-pVTZ basis sets[43] together with SMD solvation for acetonitrile.[31] Tight SCF convergence criteria were used.

General procedure I: Oxidation of N-methyltetrahydroisoquinolines by bromotrichloromethane

In a pre-dried Schlenk tube and under argon atmosphere, *N*-methyl-1,2,3,4-tetrahydroisoquinoline (1.0 equiv, freshly distilled, degassed and dryed over molecular sieves 3 Å) and $BrCCl_3$ (3.0 equiv, freshly distilled, degassed and dryed over molecular sieves 3 Å) were dissolved in acetonitrile (degassed and dryed over molecular sieves 3 Å). After this, the reaction mixture was degassed with argon by three freeze-vacuum-thaw cycles. The mixture was then stirred and irradiated (24 W CFL lamp) for the indicated time span at room temperature. Once the reaction was complete (TLC monitoring), the product was either isolated and identified, or used in a continuous stepwise procedure.

***N*-Methyl-3,4-dihydroisoquinolin-2-ium halide (2) and *N*-methyl-1,2,3,4-tetrahydroisoquinoline hydrohalide (3)**

In a Young NMR tube and according to the general procedure I, *N*-methyl-1,2,3,4-tetrahydroisoquinoline **1** (20.4 mg, 0.139 mmol) and $BrCCl_3$ (27.3 μL, 0.277 mmol) were dissolved in 0.7 mL dry degassed CD_3CN. The reaction mixture was irradiated under visible light at room temperature for 3 h. In order to determine the yield of the reaction by NMR, 1,4-bis(trimethylsilyl)benzene (1.852 mg) was added as internal standard. An mixture of iminium ion **2** and hydrohalide **3** inseparable by column chromatography was observed.

R_f = 0.13 ($CHCl_3$/MeOH, 10 : 1)

Iminium salt 2: 57% NMR yield

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 9.26 (s, 1H, H-1), 7.84 (dd, *J* = 7.6, 1.3 Hz, 1H, H-8), 7.78 (td, *J* = 7.6, 1.3 Hz, 1H, H-6), 7.56–7.49 (m, 1H, H-7), 7.45 (d, *J* = 7.6 Hz, 1H, H-5), 3.99 (t, *J* = 8.1 Hz, 2H, H-3), 3.76 (s, 3H, NC**H**$_3$), 3.25 (t, *J* = 8.1 Hz, 2H, H-4) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, CD_3CN) δ = 167.8 (C-1), 138.8 (C-7), 137.2 (C-4a), 134.4 (C-8), 129.7 (C-5), 129.4 (C-6), 125.6 (C-8a), 51.0 (C-3), 28.9 (N**C**H$_3$), 25.5 (C-4) ppm. ESI-MS (*m/z*): 146.1 (100) $[C_{10}H_{12}N]^+$.

The spectroscopic data are in accordance with those reported in the literature.[10, 44]

Hydrohalide 3: 41% NMR yield

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 12.39 (s, 1H, NH), 7.32–7.20 (m, 3H, H-6, H-7, H-8), 7.14 (d, *J* = 6.8 Hz, 1H, H-5), 4.38 (dd, *J* = 15.6, 3.4 Hz, 1H, H-1a), 4.38 (dd, *J* = 15.6, 8.3 Hz, 1H, H-1b), 3.60–3.52 (m, 1H, H-3a), 3.51–3.49 (m, 1H, H-4a), 3.32–3.18 (m, 1H, H-3b), 3.04–2.96 (m, 1H, H-4b), 2.83 (d, *J* = 4.9 Hz, 3H, NC**H**$_3$) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 132.2 (C-4a), 129.3, 127.8 (C-6 & C-7), 129.1 (C-8a), 128.9 (C-8), 127.5 (C-5), 54.5 (C-1), 51.4 (C-3), 42.9 (N**C**H$_3$), 26.0 (C-4) ppm. ESI-MS (*m/z*): 148.1 (100) $[C_{10}H_{14}N]^+$.

The spectroscopic data are in accordance with those reported in the literature.[45]

***N*-Methyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (4, Cyanide source KCN)**

In a reaction vial was equipped with *N*-methyl-1,2,3,4-tetrahydroisoquinoline **1** (70.0 mg, 0.478 mmol, 1.0 eq.), potassium carbonate (100 mg, 0.724 mmol, 1.5 eq.) and acetonitrile (6.0 mL) and degassed by argon bubbling in a ultrasonic bath for 5 min. Degassed $BrCCl_3$ (140 μL, 2.390 mmol, 5.0 eq) was added and the reaction mixture was irradiated with a blue LED at room temperature for 3 h. KCN (40 mg, 0.621 mmol, 1.3 eq.) was added and the solution was stirred in the dark for 2 h. The reaction mixture was poured into sat. $NaHCO_3$ solution (25 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were combined, dried over sodium sulfate and concentrated in vacuo. The crude product

was purified by flash column chromatography (cyclohexane/ethyl acetate/Et_3N: 1:2:0.1) to yield the title compound as a colorless oil (75.8 mg, 0.440 mmol, 92%).

R_f = 0.60 (cyclohexane/ethyl acetate/Et_3N: 1:3:0.1). IR (ATR) ν = 2976, 2854, 2806, 2220, 1496, 1454, 1144, 1100, 1066, 939, 850, 771, 744 cm^{-1}. ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.30–7.14 (m, 4-H, H-Ar), 4.73 (s, 1-H, H-1), 3.12–2.98 (m, 1H, H-4a), 2.94–2.74 (m, 3H, H-3, H-4b), 2.60 (s, 3-H, N–CH3) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 133.9 (C-8a), 129.6 (C-4a), 129.4, 128.5, 127.1, 126.5 (C-5, C-6, C-7, C-8), 116.5 (CN), 56.9 (C-1), 48.4 (C-3), 43.7 (N–CH3), 28.4 ppm. ESI-MS (*m/z*): 146.1 (100) $[C_{10}H_{12}N]^+$.

The spectroscopic data are in accordance with those reported in the literature.[46]

General procedure III: photochemical reaction of aliphatic trialkylamines and bromotrichloromethane

In a pre-dried Schlenk tube and under argon atmosphere, trialkylamine (1.0 equiv) and $BrCCl_3$ (3.0 equiv) were dissolved in dry acetonitrile. After this, the reaction mixture was degassed with argon by three freeze-vacuum-thaw cycles. The mixture was then stirred and irradiated (24 W household CFL bulb) for the indicated time span at room temperature.

1-(3,4-Dimethoxyphenethyl)pyrrolidine hydrohalide (7)

In a valved Young NMR tube and according to the general procedure III, 1-(3,4-dimethoxyphenethyl)pyrrolidine **10** (78.8 mg, 0.335 μmol) and $BrCCl_3$ (66.0 μL, 0.670 mmol) were dissolved in 0.7 mL dry degassed CD_3CN. The reaction mixture was irradiated under visible light at room temperature for 3 h. In order to determine the yield of the reaction by NMR, 1,4-bis(trimethylsilyl)benzene (2.572 mg) was added as an internal standard. Compound **12** was obtained in 77% yield.

IR (ATR) υ = 2955, 2688, 2596, 1515, 1260, 1236, 1141, 1023 cm^{-1}. ^1H NMR, COSY (400 MHz, CD_3CN) δ = 11.28 (s, 1H, N**H**), 6.88 (d, *J* = 2.0 Hz, 1H, Ph-2), 6.85 (d, *J* = 8.2 Hz, 1H, Ph-5), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6), 3.79 (s, 3H, OC**H**$_3$–Ph-3), 3.76 (s, 3H, OC**H**$_3$–Ph-4), 3.63–3.54 (m, 2H, H-2a, H-5a), 3.31–3.23 (m, 2H, H-1'), 3.10–3.03 (m, 2H, H-1'),

2.98–2.86 (m, 2H, H-2b, H-5b), 2.09–1.97 (m, 4H, 2H-3, 2H-4) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, CD_3CN) δ = 150.2 (Ph-3), 149.1 (Ph-4), 130.5 (Ph-1), 121.7 (Ph-6), 113.4 (Ph-2), 112.8 (Ph-5), 56.8 (C-1'), 56.3 (2xO**C**H_3), 54.3 (C-2, C-5), 32.0 (C-2'), 24.1(C-3, C-4) ppm. ESI-MS (*m/z*): 236.2 (100) $[C_{14}H_{22}NO_2]^+$; ESI-HRMS (*m/z*): calcd for $[C_{14}H_{22}NO_2]^+$ 236.1661, found 236.1648.

Triethylamine hydrohalide (9) and chloro-streptocyanine 10

In a Young NMR tube and according to the general procedure III, triethylamine **13** (10.0 mg, 98.8 μmol) and $BrCCl_3$ (29.2 μL, 0.296 mmol) were dissolved in 0.5 mL of deuterated acetonitrile. The reaction mixture was irradiated with a 24 W CFL lamp at room temperature for 24 h. After monitoring the reaction by ^{1}H NMR, triethylamine **13** was predominantly converted in triethylamine hydrohalide and chloro-streptocyanine dye **15** in 89 : 11 ratio, respectively.

Hydrohalide 9

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 11.17 (s, 1H, N**H**), 3.05 (qd, *J* = 7.3, 4.9 Hz, 6H, NC**H**$_2$), 1.30 (t, *J* = 7.3 Hz, 9H, NCH_2C**H**$_3$) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 46.6 (N**C**H_2), 8.9 (NCH_2**C**H_3) ppm. ESI-MS (*m/z*): 102.6 (100) $[C_6H_{16}N]^+$.

(*Z*)-*N*-(3-Chloro-3-(diethylamino)allylidene)-*N*-ethylethanaminium halide 10

A reaction vial was equipped with acetonitrile (1 mL) and potassium carbonate (1.35 g, 9.77 mmol, 1.0 eq.) and degassed by bubbling argon through it for 2 min. Under argon atmosphere triethylamine (27.4 μL, 20.0 mg, 0.198 mmol, 1.0 eq.) and bromotrichloromethane (40 μL, 80.5 mg, 0.406 mmol, 2.1 eq.) were added added. The flask was placed in front of a blue LED and irradiated at room temperature for 18 h. The reaction mixture was concentrated in vacuo and dissolved in acetonitrile (2 mL). The solid was removed by centrifugation (4700 rpm, 15 min, –5 °C) and concentrated in vacuo to yield a brown solid (23 mg), containing the streptocyanin and triethylamine hydrohalide (3:2).

^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 7.98 (d, *J* = 11.3 Hz, 1H, H-1), 5.44 (d, *J* = 11.3 Hz, 1H, H-2), 3.80–3.67 (m, 4H, NC**H**$_2$), 3.59 (q, *J* = 7.3 Hz, 2H, $^{\oplus}$NC**H**$_2$), 3.54 (q, *J* = 7.2 Hz, 2H, $^{\oplus}$NC**H**$_2$), 1.30–1.24 (m, 9H, 3xC**H**$_3$), 1.21 (t, *J* = 73 Hz., 3H, CH_3). ^{13}C NMR, HMBC, HSQC (100.6 MHz, CD_3CN) δ = 160.9 (C-1), 158.7 (C-3), 88.4 (C-2), 53.4, 45.4 ($^{\oplus}$N(**C**H$_2$)$_2$), 50.5, 49.0 (N(**C**H$_2$)$_2$), 14.5, 13.5, 12.3, 12.1(4x**C**H$_3$) ppm. ESI-MS (*m/z*): 217.3 (100) $[C_{11}H_{22}{}^{35}ClN_2]^+$, 219.0 (35) $[C_{11}H_{22}{}^{37}ClN_2]^+$. ESI-HRMS (*m/z*): calcd for $[C_{11}H_{22}{}^{35}ClN_2]^+$ 217.1471, found: 217.1459; calcd for $[C_{11}H_{22}{}^{37}ClN_2]^+$ 219.1442, found: 219.1437.

In the ^{13}C NMR spectrum, the signals at 50.5, 49.0, 13.5 and 12.1 ppm appear as very broad singlets, possibly due to hindered rotation. The NMR data match those reported for (*Z*)-*N*-(3-Chloro-3-(dimethylamino)allylidene)-*N*-methylmethanaminium perchlorate.[17]

2-(Dibutylamino)pentanenitrile 11b

In a reaction vial acetonitrile (5.0 mL) with potassium cyanide (83 mg, 1.275 mmol, 1.3 eq.) was degassed by bubbling argon through the solution for 20 s. Under argon, tributylamine (235 μL, 183.2 mg, 0.988 mmol, 1.0 eq.) and bromotrichloromethane (200 μL, 402.5 mg, 2.03 mmol, 2.1 eq.) was added. The vial was closed and irradiated for 16 h with a blue LED at 20 C. The solids filtered of and the organic layer concentrated in vacuo. The residue was filtered through a short plug of basic alumina with dichloromethane. The filtrate was

concentrated in vauco to yield the product (197.5 mg, 0.939 mmol, 95%) as a slightly yellow oil.

IR (ATR) υ = 2959, 2933, 2873, 2222, 1466, 1379, 1170, 1117, 1091, 1044, 938, 902, 878, 739 cm^{-1}. ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ = 3.54 (t, *J* = 7.7 Hz, 1H, H-1), 2.59–2.47 (m, 2H, H-1'), 2.36–2.24 (m, 2H, H-1''), 1.72–1.61 (m, 2H, H-2), 1.49–1.21 (m, 10H, H-2', H-2'', H-3, H-3', H-3''), 0.95–0.84 (m, 9H, H-4, H-4', H-4''). ^{13}C NMR, HMBC, HSQC (75.5 MHz, $CDCl_3$) δ = 118.5 (CN), 54.3 (C1), 51.4 (C1', C1''), 33.9 (C2), 30.2 (C2', C2''), 20.4 (C3',C3''), 19.3 (C3), 14.0 (C4', C4''), 13.5 (C4) ppm. ESI-MS (*m/z*): 211.3 (100) $[C_{13}H_{27}N_2]^+$, 184.3 (17) $[C_{12}H_{26}N]^+$.

2-(Dibutylamino)propanenitrile 11a

In a reaction vial deuterated acetonitrile (1.0 mL) with potassium cyanide (16.7 mg, 0.256 mmol, 1.3 eq.) was degassed by bubbling argon through the solution for 10 s. Under argon, triethylamine (27.4 μm, 20.0 mg, 0.198 mmol, 1.0 eq.) and bromotrichloromethane (40 μL, 80.5 mg, 0.406 mmol, 2.1 eq.) were added. The vial was closed and irradiated for 16 h with a blue LED at 20 C. The solids were removed by centrifuging (4700 rpm) for 10 min and the organic layer was analyzed.

IR (ATR) υ = 3628, 3545, 3024, 2980, 2943, 2267, 1634, 1474, 1457, 1387, 1209, 1189, 1105, 778, 761, 726 cm^{-1}. ^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 3.88 (q, *J* = 7.2 Hz, 1H, H-1), 2.70 (dq, *J* = 13.0, 7.3 Hz, 2H, H-1'), 2.35 (dq, *J* = 13.0, 6.9 Hz, 2H, H-1''), 1.38 (d, *J* = 7.2 Hz, 3H, H-2), 1.04 (t, *J* = 7.2 Hz, 6H, H-2', H-2'') ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, CD_3CN) δ = 118.2 (CN), 49.4 (C-1), 45.8 (C-1', C-1''), 18.4 (C-2), 13.4 (C-2', C-2'') ppm. ESI-MS (*m/z*): 127.4 $[C_7H_{15}N_2]^+$.

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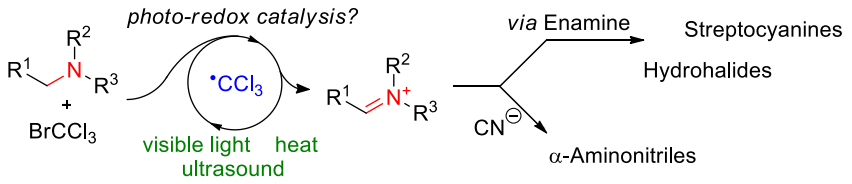

In the absence of any photocatalyst, $BrCCl_3$ engages in the visible light mediated photo-oxidation of trialkylamines by $BrCCl_3$. Depending on the amine, the additive, and the reaction conditions α-aminonitriles, streptocyanines or hydrohalide salts are formed. An investigation of the nature of the reaction as well as a mechanistic study based on DFT calculations and experimental observations is presented.

Amine Photo-oxidation*

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