Thiocarbonyl compounds as regulating reagent in the radical addition of tertiary amines with alkenes using photoelectron transfer conditions†

Dominique Harakat, Jens Pesch, Siniša Marinković and Norbert Hoffmann*

Received 9th January 2006, Accepted 1st February 2006
First published as an Advance Article on the web 14th February 2006
DOI: 10.1039/b600220j

The efficiency of the photoinduced radical addition of tertiary amines to olefinic double bonds is significantly enhanced and the stereoselectivity is influenced when thiocarbonyl compounds are added to the reaction mixture.

Radical reactions have become an important tool in organic chemistry.[1,2] Much research in this field presently concerns the investigation or the improvement of selectivity, especially stereoselectivity.[3]

Radical addition of simple tertiary amines to alkenes represents an interesting example. Despite the great variety of resulting products possessing biological activity, this reaction has rarely been applied to organic synthesis since the products are often isolated in low or moderate yields. Recently, we have developed an efficient method for performing such transformations.[4] A photochemically-induced electron transfer step using an electron donor-substituted aromatic ketone as a sensitizer in catalytic amounts was used to initiate the radical chain reaction. In this way, α-aminoalkyl radicals were generated and added to electron deficient alkenes. In contrast to using conventional sensitizers like benzophenone or acetophenone, high yields (up to 94%) were observed and the sensitizer could be recovered up to 80% after the reactions. Heterogeneous catalysis using an inorganic semiconductor as a sensitizer was also successfully applied with yields of up to 98%.[5] The reaction could be performed with a large variety of electron deficient alkenes. More complex transformations like radical tandem addition cyclization reactions have also been carried out.[6] For a recent application of this method in the field of catalytic enantioseletive reactions see ref. 7.

Although a large variety of nitrogen-containing heterocycles were accessible, only a restricted number of tertiary amines, mainly cyclic compounds, could be transformed. In order to enhance the scope of our method, we became particularly interested in extending the reaction to tertiary amines possessing only a weak reactivity under our standard conditions. In such cases, the primary photochemical processes should also take place. One possibility of optimization might be structure variation of the sensitizer in order to influence these primary processes. Therefore, we investigated various aromatic ketones in combination with different tertiary amines, reactive and unreactive ones.[8] However, all significant values like triplet quenching rates were of the same order of magnitude.

Therefore, we wondered whether we could influence the interplay between the different radical intermediates involved in the mechanism. In the field of radical polymerization, it is well known that regulating reagents like thiocarbonyl compounds can trap a terminal radical of a growing chain and thus start a new one.[9] Furthermore, it has been recently shown in the radical addition of xanthates to alkenes that the xanthate group can reversibly add to reactive radical intermediates in such a way as to stabilize these intermediates.[10] In contrast to the previously investigated reactions, none of the substrates of our reaction contained a thiocarbonyl function. We therefore decided to add simple thiocarbonyl compounds to the reaction mixture. Their influence on the reactivity and stereoselectivity are described in this paper.

We started our investigation with the addition of triethylamine **2** to furanone **1** (Scheme 1). The irradiation was carried out at $\lambda = 350$ nm and 4,4′-dimethoxybenzophenone was used as the sensitizer. Under standard reaction conditions as described in ref. 4 no significant reaction was observed. However, in the presence of the dithiocarbamate **3** (5 equiv. with respect to **1**), a fast reaction was observed and the diastereomeric adducts **4** were isolated in high yields.‡ The amine was added in excess [1 : 1 (v/v) mixture with acetonitrile as solvent]. Preliminary tests revealed the thiocarbonyl derivative **3** to be a particularly efficient regulator. In the case of dimethylisopropylamine **5**, two regioisomers **6** and **7** were isolated. It should be mentioned that the addition occurred preferentially at the isopropyl substituent which indicates that the thermodynamically more stable tertiary radical is more easily added. This observation is in contrast to previous ones where the formation of the α-aminoalkyl radicals occurred under kinetic conditions and the kinetic products (in our case **6**) were favored.[11] Therefore, not only the reactivity but also the regioselectivity is affected by the presence of the thiocarbonyl compound.

Using the same reaction conditions, the cyclic tertiary amines **8** and **9** were successfully transformed. In the absence of **3** these transformations were significantly slower and unselective so that no pure product could be isolated. The sensitizer, although used in catalytic amounts (0.1 equiv.) was recovered up to 90%. The regulating reagent **3** was recovered up to 70%. Compound **3** absorbed at $\lambda = 350$ nm, but this compound was not capable of sensitizing the reaction. In the presence of the thiocarbonyl compound and in the absence of the sensitizer, no significant transformation took place.

Using the same reaction conditions, the amines **2**, **8**, **9** and **10** were added to the acrylamide **11** (Scheme 2). Owing to the restricted Michael acceptor activity, this alkene possessed only low

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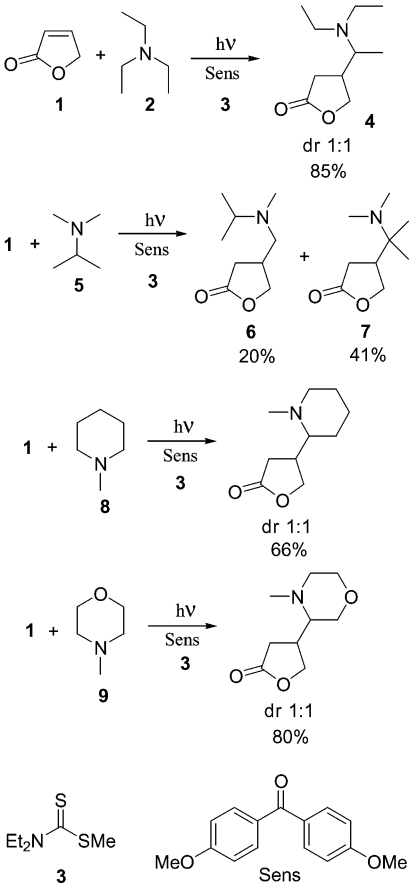
Laboratoire des Réactions Sélectives et Applications, UMR CNRS et Université de Reims Champagne-Ardenne, UFR Sciences, B.P. 1039, F-51687 Reims, cedex 02 France. E-mail: norbert.hoffmann@univ-reims.fr; Fax: +33 (0)3 26 91 31 66; Tel: +33 (0)3 26 91 31 96

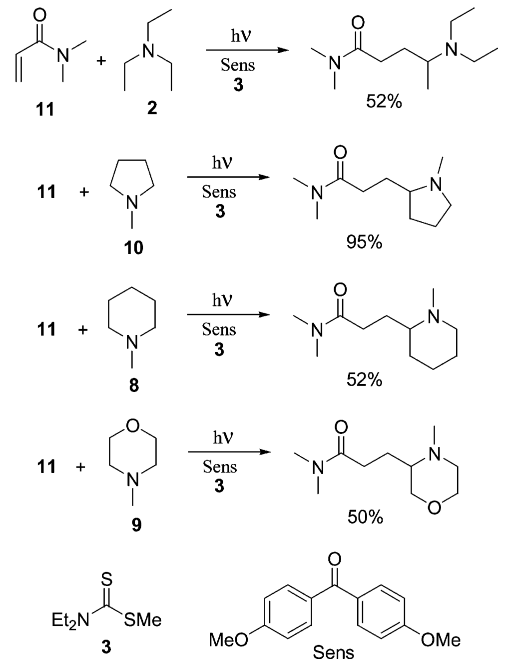
† Electronic supplementary information (ESI) available: NMR data of radical addition products of tertiary amines and mass spectra from **16** and **17**. See DOI: 10.1039/b600220j



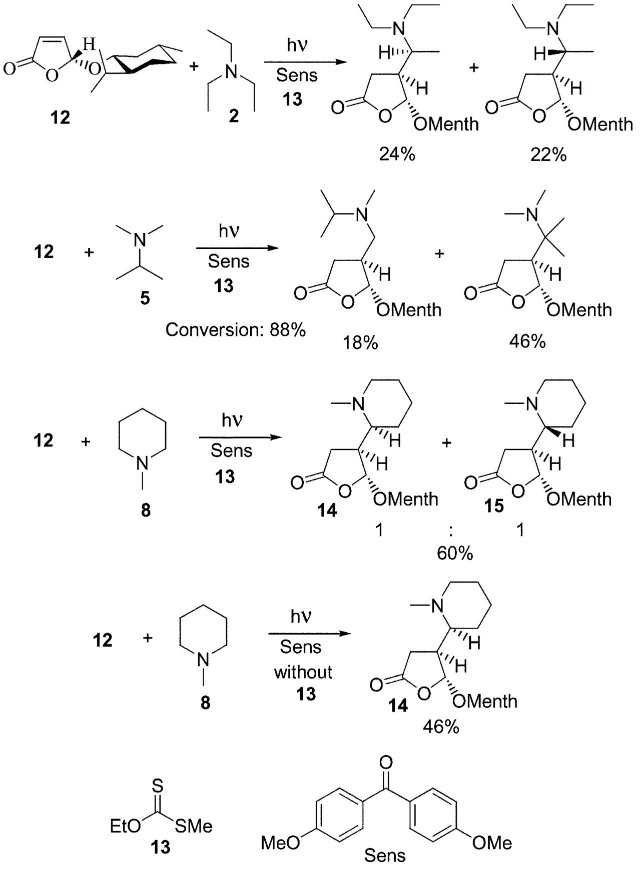
Scheme 1

reactivity with respect to the addition of nucleophilic α-aminoalkyl radicals. Consequently, no significant reactivity was observed in the absence of the dithiocarbamate **3**. However, in the presence of **3**, the adducts were obtained in good yields. Owing to its enhanced reactivity, the addition of *N*-methylpyrrolidine **10**[4,5] was particularly efficient. In these cases, the reaction was carried out in a 1 : 1 (v/v) mixture of acetonitrile and the corresponding amine.

Using the more sensitive menthyloxyfuranone **12** as the olefinic reaction partner and dithiocarbamate **3** as the regulator, the reaction was less efficient. Although a transformation took place, product isolation in the presence of **3**, even in small quantities, caused problems since the amine adducts partially decomposed during workup. In this case, the reaction could be efficiently performed using the xanthate **13** (11 equiv. with respect to **12**) (Scheme 3). In the presence of the thiocarbonyl compound and the absence of the sensitizer, no significant transformation took place. The radical addition occurred stereospecifically *anti* with respect to the menthyloxy substituent. As with furanone **1** (Scheme 1), the configuration of the chiral center in the α-position of the nitrogen was not controlled. The regioselectivity of the reaction of dimethylisopropylamine **5** was almost the same as for **1**. For the addition of *N*-methylpiperidine **8**, we have shown that the presence of a thiocarbonyl compound in the reaction mixture also affects the stereoselectivity of the reaction. In the absence of such a compound, only diastereoisomer **14** was formed, however, in lower yield.[4] The corresponding isomer **15** was not detected.

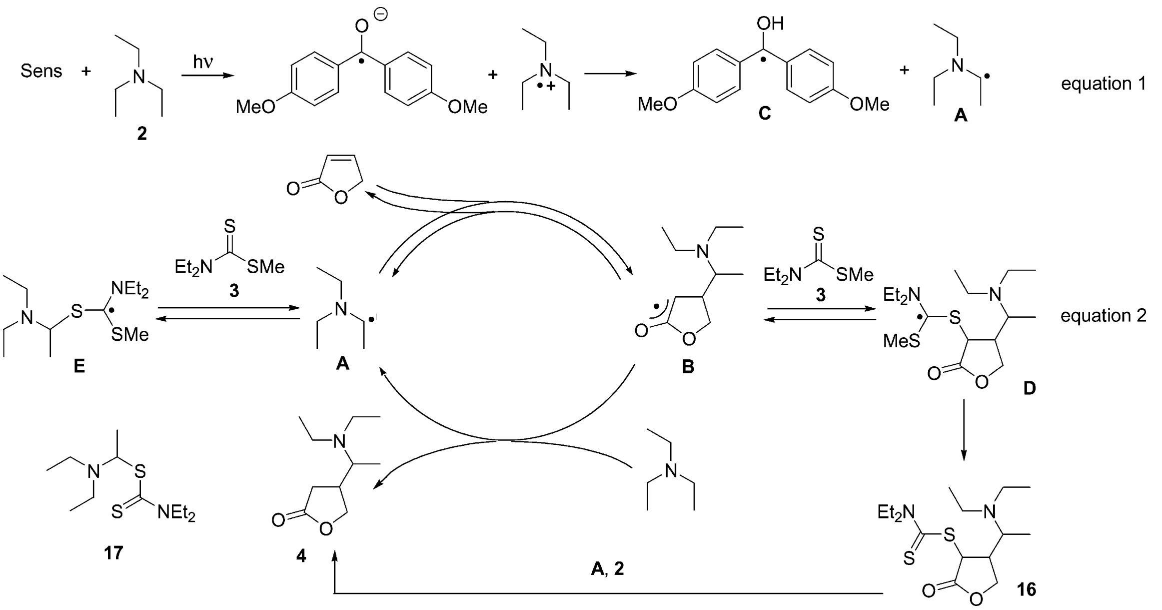


Scheme 2



Scheme 3

At this stage, we can only present a restricted mechanistic interpretation of all of these observations. Using 4,4′-dimethoxybenzophenone as an efficient sensitizer, nucleophilic α-aminoalkyl radicals **A** are first generated by photoinduced electron



Scheme 4 Possible reversible trapping of radical intermediates by thiocarbonyl compounds.

transfer (equation 1, Scheme 4). They add easily to the alkene, and electrophilic oxoallyl radicals **B** are generated (equation 2, Scheme 4) (see refs. 4 and 5 and refs. cited therein). After hydrogen abstraction from the tertiary amine, the final product is obtained and α-aminoalkyl radicals **A** are generated. Frequently, radical intermediates are unstable and their formation is reversible. For these reasons, the radical chain process is not always efficient for the radical addition of tertiary amines. Only low quantum yields have been measured.[4] Thiocarbonyl compounds like **3** or **13** are able to reversibly trap such intermediates and stabilize them (**D**, **E**). Such an effect is well established as 'persistent radicals'.[9,10,12] In this way, equilibria of the radical chain are shifted. After demethylation, the thiocarbonyl derivative **16** can be formed. Indeed, using electropray mass spectrometry, we were able to detect this product in the reaction mixture containing triethylamine at a concentration of 6×10^{-2} mol L^{-1}. Using the MS/MS technique, we were able to record the fragmentation and the high resolution spectra were also obtained. Both were in accordance with the proposed molecular structure. We observed that the signal intensity in the mass spectrum of the intermediate **16** decreased considerably when the concentration of triethylamine **2** was increased to 23.5×10^{-2} mol L^{-1} and the signal intensity increased when the amine concentration was diminished to 1.3×10^{-2} mol L^{-1}. The reductive elimination of the xanthate function in the presence of hydroxyalkyl radicals has been previously described.[10] An increased concentration of **2** and the corresponding α-aminoalkyl radicals should act in the same way to generate the final product **4** from **16**. The thiocarbamade derivative **17** was also detected by electrospray mass spectrometry which proves that α-aminoalkyl radicals **A** can add to thiocarbonyl compounds like **3** or **16**. An interaction of the thicarbonyl compounds with the radical ion pair or ketyl radicals **C** of the starting reaction is also possible and could affect the efficiency of this reaction step. Further mechanistic investigations will be carried out in order to explain the influence on reactivity, regio- and stereo-selectivity. It will be checked whether or not the addition of thiocarbonyl compounds more generally affects radical reactions, in particular those initiated by other means (BEt$_3$, AIBN, . . .).

In summary, the photoinduced radical addition of tertiary amines with olefins is significantly accelerated by the presence of thiocarbonyl compounds like dithiocarbamates or xanthates. Regio- and stereo-selectivity are also affected. Otherwise unreactive amines have also been efficiently added. Very likely, persistent radical effects are involved in the mechanism.

S. M. thanks the Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche for a doctoral fellowship. This work was funded by the CNRS and the Deutsche Forschungsgemeinschaft in the context of a bilateral French German research project.

Notes and references

‡ *Typical procedure*: 84 mg (1.00 mmol, 1.0 equiv.) of 2,4-dihydrofuran-2-one **1**, 24 mg (0.10 mmol, 0.1 equiv.) of 4,4′-dimethoxybenzophenone, 817 mg (5.00 mmol, 5.0 equiv.) of **3** and 50 mL of the appropriate amine are dissolved in 50.0 mL of absolute acetonitrile. The solution is evenly distributed to four Pyrex tubes (Ø = 2 cm) and degassed with argon for 20 min. After irradiation under UV-light (Rayonet, $\lambda = 350$ nm) for 15–30 min, the solvent and the excess amine are removed *in vacuo*. The pure products are obtained after flash chromatography on silica gel or neutral alumina.

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