

Efficient radical addition of tertiary amines to electron-deficient alkenes using semiconductors as photochemical sensitisers

Siniša Marinković and Norbert Hoffmann*

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

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Tertiary amines can be added to electron-deficient alkenes with yields up to 98% in a radical chain reaction initiated by a photochemical electron transfer using inorganic semiconductors like TiO₂ as sensitiser.

Radical reactions have become a valuable tool in preparative organic chemistry.¹ Among radicals having a nucleophilic character which can be considered for addition reactions with electron deficient alkenes, α -aminoalkyl radicals seem very attractive.² Recently, we described an efficient procedure involving a photochemical electron transfer to initiate the intermolecular radical addition of tertiary amines to electron deficient alkenes.³ Under the same conditions, radical tandem reactions could also be carried out efficiently.⁴

In principle, photochemical excited semiconductors like TiO₂ could initiate the radical addition of tertiary amines. Photochemical reactions with TiO₂ were studied, for instance, for detoxification of waste water,⁵ oxidations and reductions,⁶ solar energy harvesting⁷ or in the context of organic synthesis.⁸ Metal sulfides like ZnS and CdS have been used for the formation of dehydromers of olefins or enol/allyl ethers and for the addition of allyl radicals to imines or diazo compounds.⁹

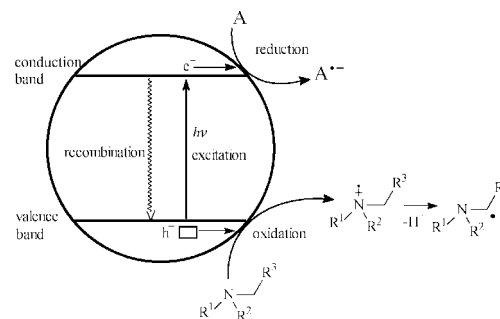
During photochemical excitation, an electron is transferred from the valence band into the conduction band.¹⁰ The resulting electron hole h^+ of the valence band can be filled by electron transfer from a reductive species such as a tertiary amine (Scheme 1) with the formation of a radical cation and of nucleophilic α -aminoalkyl radicals by deprotonation.

We started our investigations by irradiating a suspension of SiC, TiO₂ (anatase) or ZnS in a solution containing (5*R*)-menthyloxy-2[5*H*]furanone **1a** and *N*-methylpyrrolidine **2a** in acetonitrile (Table 1, entries 1–3). Low conversion rates were observed for TiO₂ and ZnS while no transformation could be detected for SiC. The yields based on conversion were rather

low. Much faster conversions was observed when the reaction was carried out in **2a** as solvent (Table 1, entries 4–7) and yields increased under these conditions. The concentration of **1a** was changed and it turned out that 5×10^{-2} mol L⁻¹ with a corresponding quantity of TiO₂ is the optimal concentration (Table 1, entries 4, 6 and 7). Under these reaction conditions, *N*-*tert*-butylpyrrolidine **2b** was added to **1a** with the same efficiency (entry 8). As mentioned previously, the addition of the amine took place exclusively from the less-hindered side of the furanone **1a**.³ Unfortunately, little selectivity was observed for the asymmetric carbon in the α -position of the nitrogen.

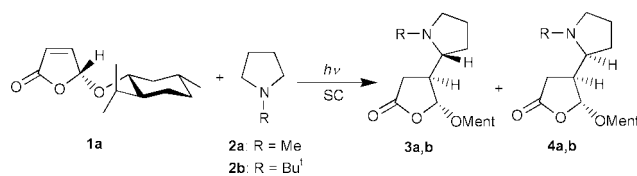
Under the optimised conditions,[†] the reaction of various α,β -unsaturated lactones with methylpyrrolidine **2a** was examined (Table 2). Generally, high conversion rates and high yields were observed. However, in the case of lactone **1e** possessing two substituents in the 4-position, the conversion rate was low. A low reactivity for β -disubstituted enones is also observed when homogeneous reaction conditions were applied.³

When TiO₂ was used as sensitiser for the addition of *N*-methylpiperidine **2c**, only a slow reaction was observed and



Scheme 1 Formation of α -aminoalkyl radicals by single electron transfer to an electronically excited semiconductor particle.

Table 1 Reaction of (5*R*)-menthyloxy-2[5*H*]furanone **1a** with *N*-methylpyrrolidine **2a** and *tert*-butylpyrrolidine **2b** under different reaction conditions; 0.1 equivalent of the semiconductor (SC) with respect to **1a** was added



Entry	Semiconductor	$c(\mathbf{1a})/\text{mol L}^{-1}$	$c(\mathbf{2a,b})/\text{mol L}^{-1}$	R	Irradiation time/h	Conversion (%)	Yield ^a (%)	Ratio $c(\mathbf{3})/c(\mathbf{4})$
1	SiC	10^{-2}	4×10^{-1}	Me	8	—	—	—
2	TiO ₂	10^{-2}	4×10^{-1}	Me	9	59	25	47/53
3	ZnS	10^{-2}	4×10^{-1}	Me	9	68	28	45/55
4	TiO ₂	10^{-2}	Solvent	Me	2.5	100	53	45/55
5	ZnS	10^{-2}	Solvent	Me	2.5	100	59	45/55
6	TiO ₂	5×10^{-2}	Solvent	Me	2.5	73	90	45/55
7	TiO ₂	10^{-1}	Solvent	Me	2.5	50	39	45/55
8	TiO ₂	5×10^{-2}	Solvent	Bu ^t	3.5	83	88	45/55

^a Based on conversion of **1a**.

Table 2 Reaction of different α,β -unsaturated lactones with methylpyrrolidine **2a** under different reaction conditions; 0.1 equivalent of the semiconductor with respect to **1a** was added

1	Irradiation time/h	Conversion (%)	Yield ^a (%)	Ratio c(3)/c(4)	
	1b	2	90	64	45/55
	1c	2	100	98	43/57
	1d^b	3.5	100	90	44/56
	1e	13	20	76	44/56

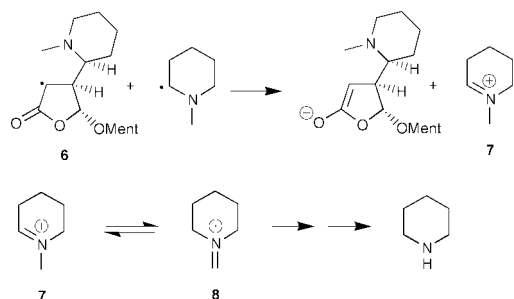
^a Based on conversion of **1**. ^b The starting concentration was 10^{-2} mol L⁻¹.

Table 3 Reaction of (*5R*)-menthyloxy-2-[5*H*]furanone **1a** with *N*-methylpiperidine **2c** under different reaction conditions; 0.1 equivalent of the semiconductor (SC) with respect to **1a** was added

Entry	Semiconductor	c(1a)/mol L ⁻¹	Conversion (%)	Yield ^a	
				4g	5
1	TiO ₂	5×10^{-2}	72	—	74
2	TiO ₂ ^b	5×10^{-2}	15	Trace	90
3	TiO ₂	10^{-2}	34	28	62
4	ZnS	10^{-2}	94	23	Trace

^a Based on conversion of **1a**. ^b The amine was distilled over CaH₂ under argon and the semiconductor was kept at 100 °C for 48 h.

product **5** resulting from a Michael addition of piperidine to **1a** was isolated (Table 3, entry 1). Due to their lower reactivity of α -aminoalkyl radicals derived from *N*-methylpiperidine, the oxidation of these radicals became competitive and demethylation occurred.¹¹ Even under strictly anhydrous conditions, this side reaction took place (entry 2). However, when the concentration of compound **1a** was reduced, the radical addition could be observed and product **4g** was isolated with moderate yield (entry 3). This result indicates that **1** or, more likely, the oxoallyl radical **6** might participate in the demethylation process via an electron transfer from the radical cation to **7** (Scheme 2). It should be noted that the radical addition always takes place on



Scheme 2 Possible mechanism of the oxidation of an α -aminoalkyl radical by an oxoallyl radical introducing the demethylation of **2c**.

the ring of **2a,c** and never at the methyl group. Therefore, we propose a tautomeric equilibrium of the iminium ions **7** and **8**.¹¹ As described previously, only one diastereomer was isolated.³ Such a bimolecular reaction between two reactive intermediates appears more realistic if the overall reaction takes place near the surface of the semiconductor.

Oxidation of an α -aminoalkyl radical by excited TiO₂ is also possible. Therefore, we searched to diminish the two-electron oxidation by changing the semiconductor (Table 3, entry 4). When ZnS was used as sensitizer, only product **4g** could be isolated. Despite the more rapid conversion, the yield of the desired product **4g** remained low. Probably, this semiconductor is less oxidative due to the higher energy level of its valence band edge¹² and its surface properties.

The most apparent difference between the reaction conditions of the homogeneous and the heterogeneous catalysis is the concentration of the tertiary amine. In the case of homogeneous catalysis, acetonitrile must be used as solvent to obtain the best results³ and the reaction is slower and less chemoselective when the tertiary amine is used as solvent. These results might be explained by the higher polarity of acetonitrile solutions which stabilise the radical ion pairs formed by electron transfer and decrease the rate of the back electron transfer. In the case of heterogeneous catalysis, the electron transfer from the amine to the sensitizer takes place at the surface of the semiconductor. Molecules at interfaces are less mobile than the same molecules in solution. Therefore, the back electron transfer can be slowed down only by enhancement of the subsequent deprotonation step. This acid–base reaction is facilitated by the presence of a large excess of tertiary amine. A higher concentration of the tertiary amine favours also the hydrogen abstraction of the oxoallyl radical **6** in the chain propagation.

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Notes and references

[†] *Experimental*: a Rayonet photochemical chamber reactor equipped with lamps emitting at $\lambda = 350$ nm was used as the light source.

A suspension of the substrate (7.5 mmol) and the semiconductor (0.15 mmol) in 150 ml of the tertiary amine was irradiated in Pyrex-tubes (outside diameter: 4 cm) under vigorous stirring with a magnetic stir bar. The mixture was filtered through Celite and the solvent was recycled by distillation under reduced pressure. The residue was purified by flash chromatography (silica gel, eluent: light petroleum–ethyl acetate: 2:1)

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