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Highly Efficient Photochemical Addition of Tertiary Amines to Electron Deficient Alkenes. Diastereoselective Addition to (5*R*)-5-Menthyloxy-2[5*H*]-furanone

Samuel Bertrand, Cédric Glapski, Norbert Hoffmann* and Jean-Pierre Pete

Laboratoire de Réactions Sélectives et Applications, UMR CNRS et
Université de Reims Champagne-Ardenne, UFR Sciences, B.P. 1039
F-51687 REIMS Cedex 2, France.

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Abstract: Tertiary amines derived from pyrrolidines can be added very efficiently (isolated yields up to 94%) to (5*R*)-5-mentyloxy-2[5*H*]-furanone. The addition, which follows a radical chain mechanism initiated by a photoinitiated electron transfer (PET) from the tertiary amine to the excited aromatic ketone, occurs with a complete facial selectivity on the furanone ring. The method can be generalized to the addition of tertiary amines and N-protected secondary amines to electron deficient alkenes.

Radical reactions have become an important tool in preparative organic chemistry,[1] but the control of selectivity still needs considerable efforts.[2] In this context, chiral auxiliaries possessing a rigid structure have been applied successfully. With (5*R*)-5-menthyloxy-2[5*H*]-furanone **1**, the reaction is highly diastereoselective when carried out in the ground state[3] while little selectivity is observed for the corresponding excited state.[4] Thus symmetric ketyl radicals produced photochemically from secondary alcohols can be added diastereospecifically to **1**.[5] The high reactivity of ketyl radicals in the addition to α,β-unsaturated carbonyl compounds can be attributed to their nucleophilic character.[1,6] α-Aminoalkyl radicals should show the same behaviour. They can be produced through a multi step process involving a photoinduced electron transfer (PET) to the excited sensitizer such as aromatic ketones.[7] Although ketyl radicals obtained by this method have been successfully used in organic synthesis[8], rather low chemical yields have been reported for the addition of α-aminoalkyl radicals to α,β-unsaturated esters and ketones[9] and very few reports include their use for the synthesis of complex molecules.[10] The formation of oligomers and degradation products are limiting factors of the addition of tertiary amines to α,β-unsaturated carbonyl compounds, either photochemically[11] or in the presence of peroxydes.[12] However, it was recognized that further efforts were required for a better efficiency as well as for higher regio- and stereoselectivity of these photochemical reactions.[13] As formation of by-products may be due to side reactions of the sensitizer or ketyl radicals, we anticipated that electron donating substituents on the aromatic ring of the phenyl ketones might suppress undesirable coupling reactions and allow an important increase in the chemical yield. In order to verify this hypothesis, we decided to study the photosensitized radical addition of tertiary amines to electrophilic alkenes. We now report that the addition of NC-H bonds of tertiary amines initiated by a PET process, can proceed with high chemical yield and even with complete facial selectivity on chiral furanones.

Our interest in chiral induction in radical reactions led us to first examine the influence of the type of sensitizer on the photoinduced addition of N-methylpyrrolidine to **1**. When a solution of N-methylpyrrolidine **2a** (10 mmol) and **1** (0.5 mmol) in acetonitrile (25 ml) was irradiated at 350 nm in the presence of acetophenone or benzophenone, the expected adducts **3**, **4** could only be obtained with moderate yields. In

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E-mail: norbert.hoffmann@univ-reims.fr Fax: + 33 3 26 05 31 66

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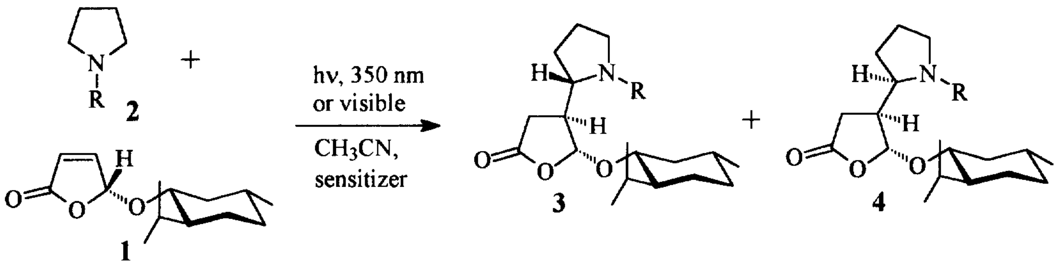
order to avoid mixed adducts and other by-products due to side reactions of these ketones[9], we considered *para*-substituted phenylketones as sensitizers. The results are summarized in Scheme 1 and Table 1.



Scheme 1 Irradiation of (5*R*)-5-menthyloxy-2[5*H*]-furanone **1** with different pyrrolidine derivatives **2**.

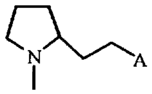
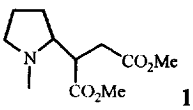
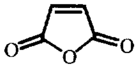
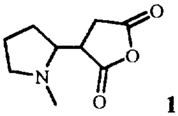
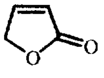
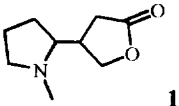
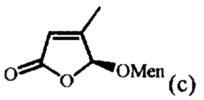
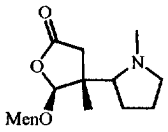
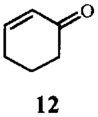
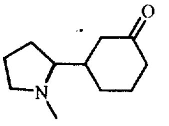
Table 1 Influence of the sensitizer and the N-substituent on the photoinduced addition of tertiary amines **2** to **1** (a).

Starting Amine	R	Sensitizer	Triplet E_T (kcal.mol^{-1})	Irradiation time (min)	Isolated yield (%) (b)
2a	Me	benzophenone	69.2 (c)	10	44
		acetophenone	74 (c)	10	41
		4-t-butylacetophenone	72.1 (d)	10	67
		4-methoxyacetophenone	70.1 (d)	7	78
		xanthone	74.1 (c)	10	80
		4,4'-dimethoxybenzophenone	69.4 (d)	5	85
		4,4'-dimethoxybenzophenone		5	94 (e)
		4,4'-dimethylaminobenzophenone	62 (c)	5	83 (f)
		4-dimethylaminobenzaldehyde	70 (c)	12	73
2b	Et	4,4'-dimethoxybenzophenone		5	81
2c	i-Pr	4,4'-dimethoxybenzophenone		5	82
2d	t-Bu	4,4'-dimethoxybenzophenone		5	81
2e	TMS	4,4'-dimethoxybenzophenone		5	45
2f	t-BuMe$_2$Si	4,4'-dimethoxybenzophenone		12	77
2g	Benzyl	4,4'-dimethoxybenzophenone		120	-

(a) A solution of **1** 120mg (0.5 mmol) in acetonitrile (25 ml) was irradiated in the presence of **2** (10 mmol) and the sensitizer (0.05 mmol). (b) Yields of purified products **3** and **4**. (c) Murov, S.L. *Handbook of Photochemistry*, Marcel Dekker Inc., 1973. (d) Wagner, P.J.; Truman, R.J.; Puchalski, A.E.; Wake, R. *J. Am. Chem. Soc.* **1986**, *108*, 7727-7738. (e) **1** (0.125 mmol), acetonitrile (25 ml), **2a** (50 mmol). (f) Irradiation with visible light (halogen lamp 500 W).

The yields increased and the best results were obtained with sensitizers possessing an alkoxy or dimethylamino substituent in the *para* position. With 4,4'-dimethoxybenzophenone, an efficient and clean reaction was observed with formation of the adducts. **3** and **4** were isolated as a mixture of diastereomers.[14] No reduction of **1** could be detected in the reaction mixture. In contrast to the complete facial selectivity at the furanone ring, the configuration of the second asymmetric centre (in the α-position of the amine function) could not be controlled during the process. Under optimized conditions, the corresponding adducts were isolated with a chemical yield of 94 %. A quantum yield of 4 was determined by using the transformation of butyrophenone into acetophenone (Φ=0.35) as an actinometer[15] which indicates that a radical chain process is involved in this reaction.

Table 2 Addition of **2a** to electron deficient alkenes (a).

alkene	Irradiation Time (min)	Product	Yield (%)
 **5** : A = CN **6** : A = CO_2Me	60	 **13** : A = CN **14** : A = CO_2Me	80 (b) 87 (b)
 7 cis **8** trans	10	 **15**	69 73
 **9**	7	 **16**	76
 **10**	5	 **17**	86
 **11**	120	 **18**	71 (d)
 **12**	180	 **19**	90

(a) For the irradiation conditions see table 1 and text. (b) The reaction was carried out in pure N-methylpyrrolidine. (c) Men: (1R)-(+)-menthyl, (d) Conversion = 55 %

Similar results were obtained with the N-alkylpyrrolidines **2b-2d**. In all cases, the approach of the α-aminoalkyl radical *anti* to the menthyloxy substituent was observed and the expected adducts were isolated in high yields as a mixture of diastereomers (55/45). The hydrogen abstraction always occurred from an endocyclic position whatever the primary, secondary or tertiary nature the α-H available on the side chain. To extend the scope of the reaction to secondary amines, we examined the addition of N-protected secondary pyrrolidines to **1**. When the benzyl group (**2g**) was used as protection group, a very slow degradation of **1** without any trace of the expected adducts was observed. When N-silyl substituents were used and especially with **2f**, carrying a t-butyldimethylsilyl group on the nitrogen, the corresponding adducts **3f** and **4f** were isolated with high yields.

The high reactivity and the high yields observed for the addition of tertiary amines to the furanone **1** led us to study the addition of **2a** as model of tertiary amines to other electron deficient alkenes, sensitized by 4,4'-dimethoxybenzophenone (Table 2). The reaction could be extended to a great variety of electron deficient alkenes with a similar efficiency. To avoid polymerization in the case of **5** and **6**, the irradiation of these compounds was carried out in **2a** as solvent. When the β-carbon of the alkene is doubly substituted, a considerable decrease of the reactivity was observed as shown by the reaction time of **1** or **10** and **11** respectively. The addition process can be extended to other cyclic enones like cyclohexenone **12**. In the latter case, 4,4'-dimethylaminobenzophenone was used as sensitizer and the irradiation was carried out with visible light (halogen lamp 500 W) in order to avoid the photodimerization of **12**.

In conclusion, we have shown that tertiary amines can be added to electron-poor alkenes with high chemical yield and high facial selectivity by a radical chain reaction initiated by a PET process from the amine to an external sensitizer. The stereoselective addition to **1** allows an easy access to polyfunctional molecules as starting material for asymmetric synthesis of natural products.[16]

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14. **3:** ^{1}H NMR ($CDCl_3$): $\delta = 0.78$ (d; 6.9; 3H) 0.87 (d; 7.6; 3H) 0.94 (d; 6.9; 3H) 0.74-1.09 (m; 3H) 1.11-1.58 (m; 4H) 1.62-1.89 (m; 4H) 2.01-2.34 (m; 2H) 2.31(s; 3H) 2.50-2.61 (m; 4H) 2.80 (dd; 17.6/10.5; 1H) 3.05 (m; 1H) 3.52 (td; 10.7/4.2; 1H) 5.60 (d; 1.9; 1H) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 15.5$, 20.7, 22.2, 22.4, 23.1, 25.3, 28.7, 28.7, 31.1, 34.3, 39.7, 40.7, 42.8, 47.7, 57.0, 65.2, 77.1, 102.3, 176.4 ppm; **4**: ^{1}H NMR ($CDCl_3$): $\delta = 0.79$ (d; 6.9; 3H) 0.89 (d; 7.6; 3H) 0.94 (d; 6.9 ; 3H) 0.74-1.02 (m; 3H) 1.13-1.49 (m; 4H) 1.60-1.84 (m; 4H) 2.03-2.72 (m; 7H) 2.29(s; 3H) 3.06 (m; 1H) 3.54 (td; 10.7/4.2; 1H) 5.40 (d; 1.5 ; 1H) ppm. ^{13}C NMR ($CDCl_3$): $\delta = 15.6$, 20.9, 22.2, 22.4 , 23.1, 25.4, 25.9, 28.8, 31.3, 34.3, 39.8, 40.5, 42.7, 47.7, 56.8, 65.4, 76.7, 103.0, 176.4 ppm. The configuration of the asymmetric center on the pyrrolidine ring has been established by chemical correlation.[16]
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