Stereoselective radical-tandem reaction of aniline derivatives with (5*R*)-5-menthyloxy-2,5-dihydrofuran-2-one initiated by photochemical induced electron transfer

Samuel Bertrand,[a] Norbert Hoffmann,*[a] Jean-Pierre Pete[a] and Véronique Bulach[b]

[a] *Laboratoire de 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*

[b] *UMR CNRS No. 7513, Université Louis Pasteur, Laboratoire de Cristallochimie et de Chimie Structurale, Institut Le Bel, 4 rue Blaise Pascal F-67070 Strasbourg, Cedex, France*

Received (in Liverpool, UK) 23rd July 1999, Accepted 5th October 1999

The radical tandem reaction of simple alkyl derivatives of aniline to a chiral furanone can be carried out stereoselectively in high yields; the furanone is also involved as oxidant in a rearomatisation process (formation of by-products) where it can be replaced efficiently by acetone.

Radical reactions have become a valuable tool in preparative organic chemistry,[1] even if control of the stereochemistry involved in these processes is still a challenge in organic synthesis.[2] Radical induced cyclisations and radical-tandem processes are particularly interesting due to the large variety of complex organic molecules available using these methods.[3]

Among radicals having a nucleophilic character which can be considered for addition reactions with electron deficient alkenes, α-aminoalkyl radicals[4] seem very attractive. When prepared directly from tertiary amines, these radicals were reported to add with moderate yields.[5] Similar results were described on the tandem addition of $PhNMe_2$.[6] These reactions become efficient only with functionalised amines especially with α-silylated tertiary amines.[4,7] However, we recently described a very efficient addition of tertiary amines to electron deficient alkenes, using 4,4′-dimethoxybenzophenone or Michler's ketone as sensitizers to produce α-aminoalkyl radicals *via* a photoinduced electron transfer process (PET).[8,9]

We envisaged that an easy and general access to 1,2,3,4-tetrahydroquinoline derivatives might include a multistep process induced by PET. We now report an efficient and stereoselective tandem reaction of *N*,*N*-dialkylanilines with (5*R*)-5-menthyloxy-2,5-dihydrofuran-2-one **1**[10] and the origin of the rearomatisation step involved during the reaction. Owing to their biological activity, these compounds are of great interest.[11]

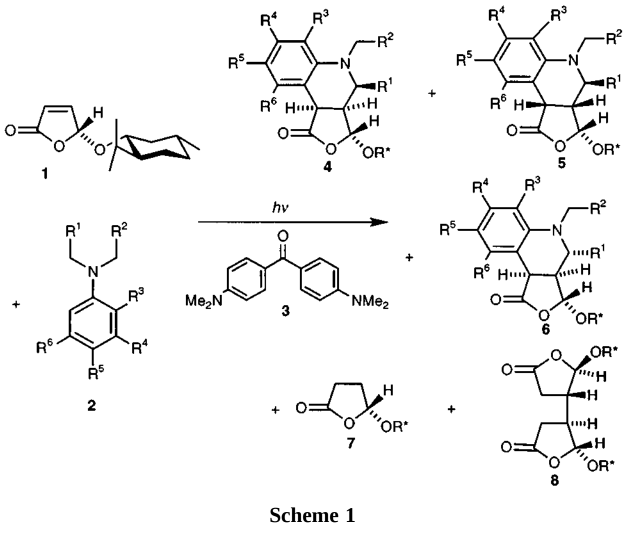
When a solution of **1** and *N*,*N*-dimethylaniline **2a** in MeCN was irradiated in the presence of 4,4′-bis(*N*,*N*-dimethylamino)-benzophenone **3**, four products were isolated from the reaction mixture (Scheme 1, Table 1, entry 1).† The diastereomers **4a** and **5a** were the expected products from a radical tandem addition of the tertiary aromatic amine to **1**. The configuration of the main product **4a** was also determined by X-ray analysis (Fig. 1).‡ From the structure of **4a**, it could be deduced that the attack of the α-aminoalkyl radical **A** on **1** proceeded mainly *anti* with respect to the menthyloxy substituent.

Table 1 Reaction of different aniline derivatives **2a**–**f** with **1** in the presence of acetone except when indicated

								Yield(%)				
Entry	**2**	R¹	R²	R³	R⁴	R⁵	R⁶	**4**	**5**[b]	**6**	**7**	**8**
1[a]	**a**	H	H	H	H	H	H	38	2	—	18	7
2	**a**	H	H	H	H	H	H	74	3	—	—	—
3	**b**	H	H	Me	H	H	H	60	2	—	—	—
4[c]	**c**	H	H	H	Me,H	H	H,Me	21,49	1,3	—	—	—
5	**d**	H	H	H	H	Me	H	78	3	—	—	—
6	**e**	H	H	Me	Me	H	H	64	3	—	—	—
7	**f**	H	H	$-(CH_2)_2-$		H	H	53	3	—	—	—
8	**g**	Me	Me	H	H	H	H	36	—	29	—	—
9	**h**	$-(CH_2)_2-$		H	H	H	H	39	—	32	—	—
10	**i**	$-(CH_2)_3-$		H	H	H	H	48	—	26	—	—

[a] The reaction was been carried out in the absence of acetone. [b] **5** was isolated in the same fraction as **4**. [c] Two regioisomers were formed.

The large amount of byproducts **7** and **8** limited the transformation of **1** into the tricyclic adducts **4a** and **5a**. When the concentration of **1** was diminished (5×10^{-3} mol l^{-1}), the reduction product **7** could be isolated in higher yield (23%), while the formation of **8** could be suppressed. The observation that the reduction products **7** and **8** and products **4a** and **5a** were isolated with similar yields might indicate a coupling of the processes responsible of their formation. Further, formation of **4a** and **5a** needs an oxidation step for rearomatisation. Little information is available on this oxidising step in the absence of oxygen for similar reactions.[12] In order to decrease the amount of reduction products of **1** and to get more information on the formation of the byproducts **7** and **8**, we carried out the reaction with **2a** labeled by deuterium either at the 2, 4 or 6 position of the aromatic ring (**2a′**) or on the methyl groups (**2a″**). From **2a′**, we found that **7′** had incorporated deuterium exclusively in the α-position (degree of deuterium incorporation: 45%). From **2a″**, the deuterium was transferred to the β-position of **7″** (degree of deuterium incorporation: 55%). In both cases deuterium was found in one of the α-positions of **8**. Therefore, the mechanism of the reaction of **1** can be summarised as in Scheme 2. Formation of the α-aminoalkyl radical **A** involves a PET process induced by excited Michler's ketone **3**.[9,13] Addition of **A** to **1** leads to the oxoallyl radical **B** which yields **C** after an intramolecular addition process on the electron rich aromatic ring. The rearomatisation occurs by transfer of a hydrogen atom to **1**. This transfer proceeds in two steps



Scheme 1

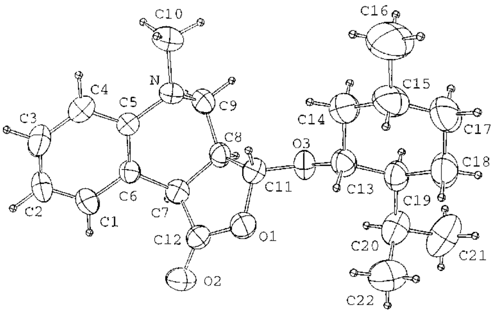


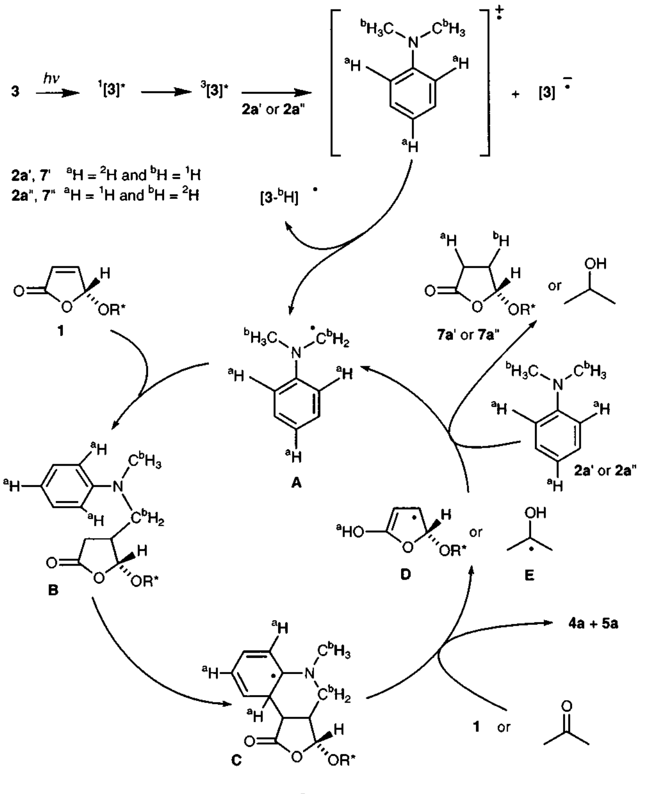
Fig. 1 ORTEP plot of **4a**. Ellipsoids are scaled to enclose 50% of the electronic density. Hydrogen atoms have arbitrary radii.

(Scheme 3). First an electron transfer from **C** to **1** takes place to yield the cationic species **F**. In the second step, a proton is transferred to the radical anion.

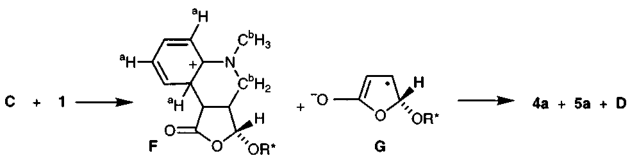
When starting from **2a′** deuterated on the aromatic ring, deuterium was transferred to the carbonyl function of **1**. The resulting radical **D** can produce **7′** deuterated at the α-position by tautomerisation and preferred abstraction of hydrogen from an *N*-methyl group of **2a′**.[4] Alternatively, **D** can add to **1** which leads to **8** after hydrogen abstraction from **2a′**. This mechanism also explains the deuteration in the β-position of **7″** and the α-position of **8** when started with **2a″**.

In order to avoid the hydrogen transfer to the substrate **1**, we added a mild oxidant to the reaction mixture (Scheme 2). By addition of acetone in excess, the formation of byproducts **5** and **6** could be completely suppressed and the yield of **4a** and **5a** was doubled (Table 1, entry 2).

Under these optimised reaction conditions, a variety of *N*,*N*-dialkylamino benzenes **2** similarly yielded the corresponding 1,2,3,4-tetrahydroquinolines **4**, **5** and **6** (Scheme 1, Table 1). In the case of the *N*,*N*-dimethylaminobenzenes **2a**–**f**, the facial diastereoselectivity was about 90% (Table 1, entries 1–7). In the reaction of **1** with **2g**–**i**, a total facial selectivity with *anti* approach *vs*. the menthyloxy substituent was observed. However, the configuration of the second chiral center, in the position α to the nitrogen atom, was not efficiently controlled and the products **6g**–**i** were isolated in similar yields (Table 1, entries 8–10).



Scheme 2



Scheme 3

In conclusion, we have described an efficient and stereoselective addition of tertiary aromatic amines to (5*R*)-(−)-5-menthyloxy-2,5-dihydrofuran-2-one **1** through a radical-tandem process. The reaction, leading to 1,2,3,4-tetrahydroquinoline derivatives **4** involves an oxidative addition on the aromatic ring. When carried out in the presence of acetone, the competitive reduction of **1** was suppressed.

Notes and references

† A Rayonet Photochemical Chamber Reactor equipped with lamps emitting at λ = 350 nm was used as light source. Solutions were degassed with argon prior to the irradiation.

Irradiation of derivatives **2** under optimised conditions (Table 1): A solution of **1** (240 mg, 1 mmol), **2** (20 mmol), **3** (30 mg, 0.1 mmol) and 1 ml acetone in 15 ml MeCN was irradiated for 6 to 7 h. The solvent was evaporated and the residue was subjected to flash chromatography.

‡ *Crystal data* for **4a**: $C_{22}H_{31}NO_3$, M = 357.50, orthorhombic, space group $P2_12_12_1$, a = 8.4839(3), b = 13.709(1), c = 17.887(1) Å, V = 2080.5(4) Å3, Z = 4, ρ_{calc} = 1.14 g cm^{-3}, μ(Mo-Kα) = 0.075 mm^{-1}. Data were collected on a Nonius CAD4-MACH3 diffractometer using Mo-Kα graphite monochromated radiation (λ = 0.71073 Å) at room temperature. Colorless crystal, 0.30 × 0.30 × 0.20 mm^3, 2428 reflections collected, 2.5 < θ < 26.3°. 1459 reflections having $I > 3\sigma(I)$ were used for structure determination and refinement. The structure was solved using direct methods and refined against |F|. Hydrogen atoms were introduced as fixed contributors. Absorption corrections from the psi curves of 7 reflections, transmission factors: 0.92/1.00. For all computations the Nonius OpenMoleN package (OpenMoleN, Interactive Structure Solution, Nonius B.V., Delft, The Netherlands 1997) was used. The known configuration of the menthol fragment was therefore used to assign the correct configuration. Final results: $R(F)$ = 0.039, $Rw(F)$ = 0.051, GOF = 1.046, maximum residual electronic density = 0.15 e Å^{-3}. CCDC 182/1432. See http://www.rsc.org/suppdata/cc/1999/2291/ for crystallographic data in .cif format.

1 J. Fossey, D. Lefort and J. Sorba, *Free Radicals in Organic Chemistry*, Wiley, Chichester, 1995.
2 D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1996.
3 K.-D. Warzecha, X. Xing, M. Demuth, R. Goddard, M. Kessler and C. Krüger, *Helv. Chim. Acta*, 1995, **78**, 2065; S. Bogen, L. Fensterbank and M. Malacria, *J. Org. Chem.*, 1999, **64**, 819 and references cited therein.
4 P. Renaud and L. Giraud, *Synthesis*, 1996, 913.
5 W.H. Urry and O. O. Juveland, *J. Am. Chem. Soc.*, 1958, **80**, 3322; R. C. Cookson, S. M. de B. Costa and J. Hudec, *Chem. Commun.*, 1969, 753; E. Farrant and J. Mann, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1083.
6 (*a*) R. B. Roy and G. A. Swan, *J. Chem. Soc.*, 1969, 1886; S. Murata, K. Teramoto, M. Miura and M. Nomura, *Heterocycles*, 1993, **36**, 2147; S. Araneo, F. Fontana, F. Minisci, F. Recupero and A. Serri, *Tetrahedron Lett.*, 1995, **36**, 4307.
7 Z. Su, P. S. Mariano, D. E. Falvey, U. C. Yoon and S. W. Oh, *J. Am. Chem. Soc.*, 1998, **120**, 10 676.
8 S. Bertrand, C. Glapski, N. Hoffmann and J. P. Pete, *Tetrahedron Lett.*, 1999, **40**, 3169; S. Bertrand, N. Hoffmann and J. P. Pete, *Tetrahedron Lett.*, 1999, **40**, 3173.
9 For photoinduced electron transfer see: J. Mattay, *Synthesis*, 1989, 233; G. J. Kavarnos, *Fundamentals of Photoinduced Electron Transfer*, VCH, New York, 1993.
10 For the synthesis of **1** and its application in organic synthesis see: J. Martel, J. Tessier and J. P. Demoute (Roussel Uclaf), *Eur. Pat Appl.*, 23454, 1981 (*Chem. Abstr.*, 1981, **95**, 24788a); B. L. Feringa, B. de Lange, J. F. G. A. Jansen, J. C. de Jong, M. Lubben, W. Faber and E. P. Schudde, *Pure Appl. Chem.*, 1992, **64**, 1865.
11 A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031.
12 X. M. Zhang and P. S. Mariano, *J. Org. Chem.*, 1991, **56**, 1655.

Communication 9/06051K