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Catalytic aerobic photooxidation of primary benzylic amines using hindered acridinium salts

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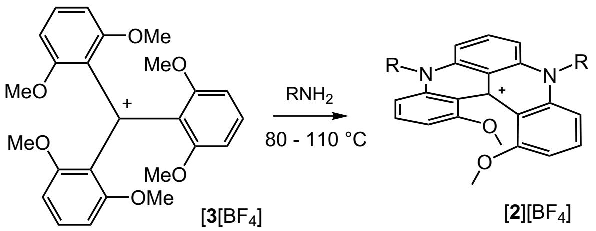
Abstract—Hindered acridinium cations, simply prepared by the addition of primary amines to the known methylium tris(2,6-dimethoxyphenyl) cation, catalyze the aerobic photooxidation of primary benzyl amines into benzylimines. A mechanistic rationale for the electron-transfer process is proposed.

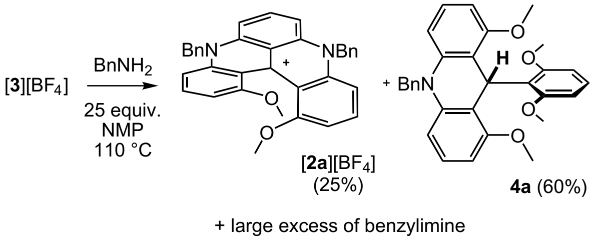
The functional group transformation of activated amines to imines has been strongly studied in synthetic organic chemistry.[1,2] Quite a few of the oxidative processes that have been developed are photochemical reactions that use molecular oxygen (O_2) as a stoichiometric oxidant and photoactive dyes as catalysts. Acridinium salts, which have been studied over the years as cellular stains with biological and diagnostic purposes as well as in various fluoroionophores,[3] have been particularly used in the above-mentioned context as these compounds possess a keen ability to promote photoinduced electron transfer and to be reduced under irradiation.[4] Herein, we confirm this trend and report the catalytic aerobic photooxidative behavior of hindered acridinium cations of type **1**, which are able to transform primary benzylic amines into imines.

Previously, 1,13-dimethoxyquinacridinium cations of type **2** have been reported.[5] These cationic moieties are prepared in one step and good yield by the reactions of primary alkyl amines with the readily available salts of cation **3** (Eq. 1); the synthesis occurring through sequential aromatic substitution (S_NAr) of four MeO substituents by nitrogen containing residues. The molecular framework of cations **2** contains four *ortho*-condensed aromatic rings. Due to the steric repulsions between the two remaining methoxy substituents, these derivatives adopt a twisted helical conformation. As such, compounds of type **2** may be regarded as [4]heterohelicenium derivatives with *P* or *M* configuration. Recently, these derivatives were shown to be highly configurationally stable, more than [6]helicene, and a general resolution protocol was reported.[6]



(1)

Recently, the synthesis of the cation **2a** derived from benzylamine was attempted (Eq. 2). To our surprise, only a moderate yield of 25% was obtained for salt [**2a**][BF_4] whereas yields in the range of 70–85% are routinely achieved with linear primary amines as nucleophiles (R = *n*-alkyl chains).[6] ^1H NMR analysis of the



(2)

Keywords: Amine; Imine; Photooxidation; Acridinium; Electron transfer.

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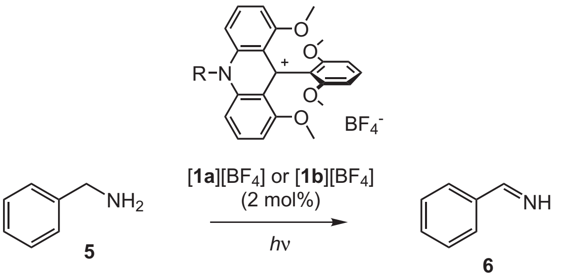
crude mixture revealed an essentially complete transformation of the benzylamine **5** in excess (25 equiv) into benzylimine **6**; benzyl-tetramethoxyphenyl-acridine **4a** being isolated from the crude mixture (60%).[7]

In view of the literature precedents on the aerobic photooxidation catalyzed by acridinium derivatives,[4] the in situ formation of compound [**1a**][BF_4][5b] was considered (Fig. 1). This species would catalyze the oxidation of **5** into **6**. Acridine **4a** would then be the result from the necessary reduction of cation **1a**.



(3)

To test this hypothesis and see whether a synthetically useful process could result from the observation, two different acridinium salts were prepared, compounds [**1a**][BF_4] and [**1b**][BF_4] (Fig. 1, R = Bn, *n*-Pr), by the room temperature reaction of [**3**][BF_4] with benzylamine and *n*-propylamine (83% and 81%, respectively).[5,8] Solutions of these derivatives (2 mol %) in benzylamine **5**, used both as reagent and as solvent, were prepared and subjected to photoirradiation (600 W lamp, Eq. 3).[9] An in situ formation of benzylimine **6** was observed, of which the yield was measured by ^{1}H NMR spectroscopy using an internal standard (mesitylene, 2 mol %).[10] Table 1 summarizes the results that were obtained in these and other experiments. Figure 2 represents the formation of benzylimine (yield, %) under irradiation as a function of time (hours).

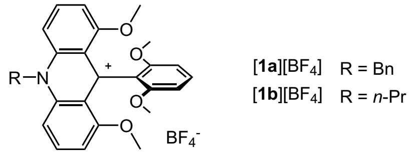


Figure 1. Hindered acridinium salts of type [**1**][BF_4].

Table 1. Catalytic photooxidation of benzylamine **5** in the presence of acridinium salts [**1a**][BF_4] and [**1b**][BF_4]

Entry	Catalyst[a]	Temperature (°C)	Irradiation	Time (h)	Yield (%)[b]
1	[**1a**][BF_4]	50	Yes	20	22
2	[**1b**][BF_4]	50	Yes	20	20
3	[**1a**][BF_4]	70	Yes	19	71
4	[**1b**][BF_4]	70	Yes	24	74
5	[**1a**][BF_4]	50	No	20	1
6	[**1b**][BF_4]	50	No	20	3
7	[**1a**][BF_4]	70	No	23	19
8	[**1b**][BF_4]	70	No	23	27

[a] 2 mol %.

[b] As measured by ^{1}H NMR spectroscopy using mesitylene as internal reference.

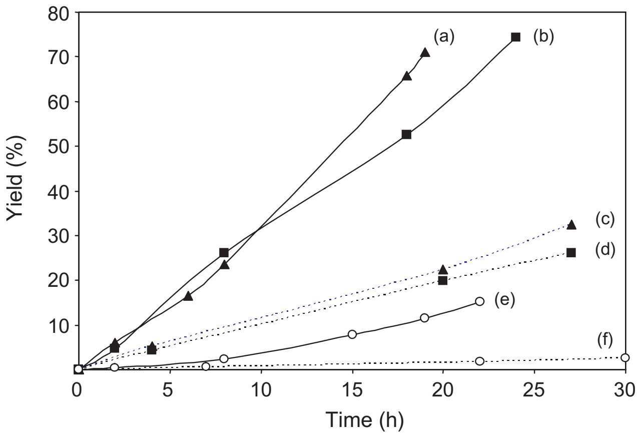


Figure 2. Synthesis of benzylimine **6** (yield, %) under irradiation as a function of time (h); reactions catalyzed with (a) [**1a**][BF_4], 70 °C; (b) [**1b**][BF_4], 70 °C; (c) [**1a**][BF_4], 50 °C; (d) [**1b**][BF_4], 50 °C; (e) [**2b**][BF_4], 70 °C; (f) [**2b**][BF_4], 50 °C.

Rather strong temperature dependence was observed as the rate of photooxidation is ~3.5 times faster at 70 °C than at 50 °C; little reaction being observed at room temperature. After about 20 h, yields of 22% and 71% were obtained for **6** at 50 and 70 °C, respectively, using salt [**1a**][BF_4] (Table 1, entries 1 and 3). Similar results were obtained for [**1b**][BF_4] (entries 2 and 4). As it could be expected, essentially no formation of **6** was observed when the reaction was performed without irradiation at 50 °C (entries 5 and 6). More surprisingly, a significant amount of **6** was afforded at 70 °C in the absence of light (entries 7 and 8). This result can be rationalized by the fact that some acridinium cations can undergo thermal electron transfer in the absence of light.[11]

Care was taken not to increase the reaction temperature above 70 °C as to limit the formation of dimethoxyquinacridinium salts of type [**2**][BF_4], which arise at elevated temperature from the nucleophilic addition of primary amines onto [**1**][BF_4] salts.[6] Although unlikely at 50 or 70 °C, the presence of such cationic species **2** in minor amount was nevertheless feasible, thus rendering a test of their aerobic photooxidative behavior necessary. The oxidation reaction was thus tested in the presence of 2 mol % of [**2b**][BF_4]. Much lower yields of **6** were ob-

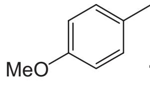
Table 2. Catalytic photooxidation of benzylamine **5** in the presence of acridinium salt [**2b**][BF_4]

Entry	Catalyst[a]	Temperature (°C)	Irradiation	Time (h)	Yield (%)[b]
1	[**2b**][BF_4]	50	Yes	30	3
2	[**2b**][BF_4]	70	Yes	22	15
3	[**2b**][BF_4]	50	No	30	0.2
4	[**2b**][BF_4]	70	No	23	1

[a] 2 mol %.

[b] As measured by ^{1}H NMR spectroscopy using mesitylene as internal reference.

Table 3. Catalytic aerobic photooxidation of substituted benzylamines **7**, **8**, and **9** in the presence of acridinium salt [**1a**][BF_4] (2 mol %) and light irradiation



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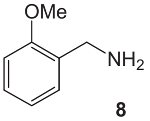

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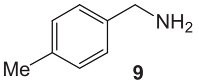

9

Entry	Amine[a]	Temperature (°C)	Time (h)	Yield (%)[b]
1	**7**	50	19	15
2	**8**	50	19	11
3	**9**	50	19	18
4	**7**	70	17	33
5	**8**	70	17	39
6	**9**	70	17	39

[a] 1 equiv.

[b] As measured by ^1H NMR spectroscopy using mesitylene as internal reference.

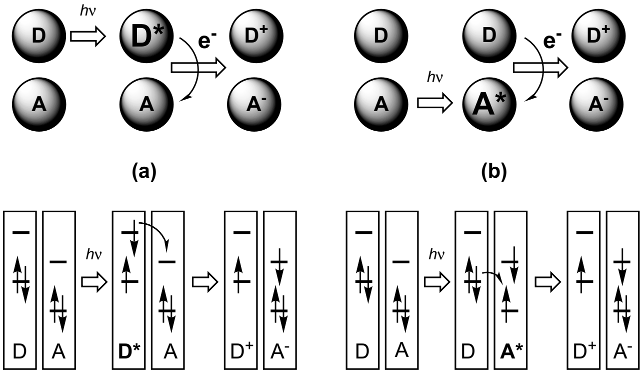

Figure 3. Pathways (a) and (b) for the photoinduced electron transfer from donor (D) to acceptor (A) molecules.

tained in conditions similar to those described previously (Table 2). This result was not unexpected due to the more electron-rich nature of cation **2** versus **1**. One can thus assume that most of benzylimine **6** is generated by the reaction of **5** with acridinium salts [**1**][BF_4] and not with by-products of type [**2**][BF_4].

A series of benzyl amines (**7**–**9**, Table 3) substituted with electron-donating groups on the aromatic nucleus (*p*-OMe, *o*-OMe, *p*-Me) was then tested using cation [**1a**][BF_4] as catalyst. The results of the aerobic photooxidative reactions at 50 and 70 °C are reported in Table 3. Altogether, the reactions of amines **7** to **9** have been less efficient than those of **5**. At 70 °C, yields in the range of 33–39% were obtained after 17 h whereas under essentially the same conditions **5** was afforded in 71% yield (Table 1, entry 3).

These latter results were surprising at the first sight as one generally expects electron-rich molecules to be more easily oxidized than electron-poor derivatives. However, it is known that electron-transfer processes can happen following two pathways (Fig. 3). One is the photoinduced promotion of one electron from the HOMO of a donor molecule into its LUMO ($D \rightarrow D^*$) and then an electron transfer to the LUMO of the acceptor compound A ($D^* \rightarrow A$ to give D^+ and A^-, Fig. 3, path a). The second, which seems to be favored by acridinium derivatives, is the reaction of an acceptor molecule in its excited state (A*) with a donor moiety ($D \rightarrow A^*$ to give D^+ and A^-, Fig. 3, path b).[12] In the latter case, one then expects that the presence of electron-rich substituents on the donor molecule, in our case the amine, raises the level of the HOMO orbital of the donor D and thus limit the efficiency of the electron transfer to the excited acceptor moiety A*. As this is observed for electron-rich amines, pathway b seems indeed to be favored.

In conclusion, hindered acridinium cations of type **1** are catalysts for the aerobic photooxidation of primary benzylamines into benzylimines making them interesting NAD^+ analogues.

Acknowledgements

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References and notes

1. Lines, R. In *Organic Electrochemistry*; Baizer, M. M., Ed.; M. Dekker: New York, 1983, p 463; Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990; Murahashi, S.-I.; Komiya, N. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley-Interscience, 2002; Vol. 2, pp 2881–2894.
2. For selected references on metal catalyzed aerobic oxidation of amines to imines, see: Bailey, A. J.; James, B. R. *Chem. Commun.* **1996**, 2343–2344; Yamaguchi, K.; Mizuno, N. *Chem. Eur. J.* **2003**, *9*, 4353–4361; Samec, J. S. M.; Éll, A. H.; Bäckvall, J. E. *Chem. Commun.* **2004**, 2748–2749; Samec, J. S. M.; Éll, A. H.; Bäckvall, J. E. *Chem. Eur. J.* **2005**, *11*, 2327–2334.
3. Jonker, S. A.; Van Dijk, S. I.; Goubitz, K.; Reiss, C. A.; Schuddeboom, W.; Verhoeven, J. W. *Mol. Cryst. Liq. Cryst.* **1990**, *183*, 273–282; Adamus, J.; Gebicki, J.; Ciebiada, I.; Korczak, E.; Denys, A. *J. Med. Chem.* **1998**, *41*, 2932–2933; Adamczyk, M.; Mattingly, P. G.; Moore, J. A.; Pan, Y. *Org. Lett.* **1999**, *1*, 779–781; Cooper, W. J.; Moegling, J. K.; Kieber, R. J.; Kiddle, J. J. *Mar. Chem.* **2000**, *70*, 191–200; Adamczyk, M.; Mattingly, P. G.; Moore, J. A.; Pan, Y.; Shreder, K.; Yu, Z. *Bioconjugate Chem.* **2001**, *12*, 329–331; Adamczyk, M.; Moore, J. A.; Shreder, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 395–398; Wroblewska, A.; Huta, O. M.; Patsay, I. O.; Petryshyn, R. S.; Blazejowski, J. *Anal. Chim. Acta* **2004**, *507*, 229–236.
4. Castellano, A.; Catteau, J. P.; Lablache-Combier, A. *J. Phys. Chem.* **1976**, *80*, 2614–2619; Shinkai, S.; Hamada, H.; Kuroda, H.; Manabe, O. *J. Org. Chem.* **1981**, *46*, 2333–2338; Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *Inorg. Chem.* **1990**, *29*, 653–659; Bockman, T. M.; Kochi, J. K. *J. Phys. Org. Chem.* **1997**, *10*, 542–562; Fukuzumi, S.; Suenobu, T.; Kawamura, S.; Ishida, A.; Mikami, K. *Chem. Commun.* **1997**, 291–292; Jones, G.; Yan, D. X.; Greenfield, S. R.; Gosztola, D. J.; Wasielewski, M. R. *J. Phys. Chem. A* **1997**, *101*, 4939–4942; Horng, M. L.; Dahl, K.; Jones, G.; Maroncelli, M. *Chem. Phys. Lett.* **1999**, *315*,

363–370; Ohkubo, K.; Fukuzumi, S. *Org. Lett.* **2000**, *2*, 3647–3650; Lee, I.-S. H.; Jeoung, E. H.; Kreevoy, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 7492–7496; Marcinek, A.; Zielonka, J.; Adamus, J.; Gebicki, J.; Platz, M. S. *J. Phys. Chem. A* **2001**, *105*, 875–879; Pedzinski, T.; Marciniak, B.; Hug, G. L. *J. Photochem. Photobiol., A* **2002**, *150*, 21–30; Nishimine, M.; Ohkubo, K.; Komori, T.; Fukuzumi, S. *Chem. Commun.* **2003**, 1886–1887; Ohkubo, K.; Suga, K.; Morikawa, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003**, *125*, 12850–12859; Fukuzumi, S.; Kotani, H.; Ohkubo, K.; Ogo, S.; Tkachenko, N. V.; Lemmetyinen, H. *J. Am. Chem. Soc.* **2004**, *126*, 1600–1601; Ito, N.; Arzhantsev, S.; Maroncelli, M. *Chem. Phys. Lett.* **2004**, *396*, 83–91; Joseph, J.; Kuruvilla, E.; Achuthan, A. T.; Ramaiah, D.; Schuster, G. B. *Bioconjugate Chem.* **2004**, *15*, 1230–1235; Bohne, C.; Faulhaber, K.; Giese, B.; Hafner, A.; Hofmann, A.; Ihmels, H.; Kohler, A. K.; Pera, S.; Schneider, F.; Sheepwash, M. A. L. *J. Am. Chem. Soc.* **2005**, *127*, 76–85.

5. (a) Laursen, B. W.; Krebs, F. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 3432–3434; (b) Laursen, B. W.; Krebs, F. C. *Chem. Eur. J.* **2001**, *7*, 1773–1783.
6. Herse, C.; Bas, D.; Krebs, F. C.; Bürgi, T.; Weber, J.; Wesolowski, T.; Laursen, B. W.; Lacour, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3162–3166; Laleu, B.; Mobian, P.; Herse, C.; Laursen, B. W.; Hopfgartner, G.; Bernardinelli, G.; Lacour, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1879–1883.
7. Experimental characterization of compound **4a**: mp 245 °C; IR (film): v = 2996, 2931, 2829, 1616, 1587, 1496, 1470, 1452, 1434, 1387, 1360, 1322, 1286, 1240, 1253, 1227, 1162, 1104, 1082, 1056, 1018, 943, 905, 885, 852, 812, 786, 769, 760, 737, 721, 697 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.56 (s, 6H, OMe), 3.65 (br s, 6H, OMe), 5.13 (s, 2H, CH$_2$N), 6.19 (d, 2H, ^3J = 8.3), 6.23 (s, 1H), 6.24 (d, 2H, ^3J = 7.8), 6.41 (d, 2H, ^3J = 8.3), 6.84 (t, 2H, ^3J = 8.1), 6.96 (t, 1H, ^3J = 8.3), 7.19–7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 27.0 (CH), 53.4 (CH$_2$), 55.8 (OCH$_3$), 56.3 (OCH$_3$), 103.2 (CH), 104.8 (CH), 106.0 (CH), 114.2 (C), 124.2 (C), 126.2 (CH), 126.5 (CH), 126.9 (CH), 128.9 (CH), 138.6 (C), 143.5 (C), 157.9 (C), 159.2 (C).
8. Krebs, F. C. *Tetrahedron Lett.* **2003**, *44*, 17–21; Laleu, B.; Herse, C.; Laursen, B. W.; Bernardinelli, G.; Lacour, J. *J. Org. Chem.* **2003**, *68*, 6304–6308.
9. Oxidation conditions: benzylamine (50 equiv), salts [**1**][BF$_4$] or [**2b**][BF$_4$] (1 equiv), mesitylene (reference) (1 equiv), with or without irradiation, and in aerobic conditions.
10. The yield was established by integration of the (singlet) signals of the imine proton (e.g., δ 8.41 ppm for **6**) and the methyl protons of mesitylene (reference, 9H, 2 mol %), respectively.
11. Fukuzumi, S.; Ohkubo, K.; Tokuda, Y.; Suenobu, T. *J. Am. Chem. Soc.* **2000**, *122*, 4286–4294; Fukuzumi, S.; Yukimoto, K.; Ohkubo, K. *J. Am. Chem. Soc.* **2004**, *126*, 12794–12795.
12. van Willigen, H.; Jones, G.; Farahat, M. S. *J. Phys. Chem.* **1996**, *100*, 3312–3316; Fukuzumi, S.; Ohkubo, K.; Suenobu, T.; Kato, K.; Fujitsuka, M.; Ito, O. *J. Am. Chem. Soc.* **2001**, *123*, 8459–8467; Fukuzumi, S.; Fujita, M.; Noura, S.; Ohkubo, K.; Suenobu, T.; Araki, Y.; Ito, O. *J. Phys. Chem. A* **2001**, *105*, 1857–1868; Fukuzumi, S.; Fujita, S.; Suenobu, T.; Imahori, H.; Araki, Y.; Ito, O. *J. Phys. Chem. A* **2002**, *106*, 1465–1472.