Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 4249–4251

Tetrahedron Letters

Synthesis and catalytic activity of a fluorous-tagged TEMPO radical

Gianluca Pozzi,* Marco Cavazzini, Orsolya Holczknecht, Silvio Quici and Ian Shepperson

CNR-Istituto di Scienze e Tecnologie Molecolari (ISTM), via Golgi 19, 20133 Milano, Italy

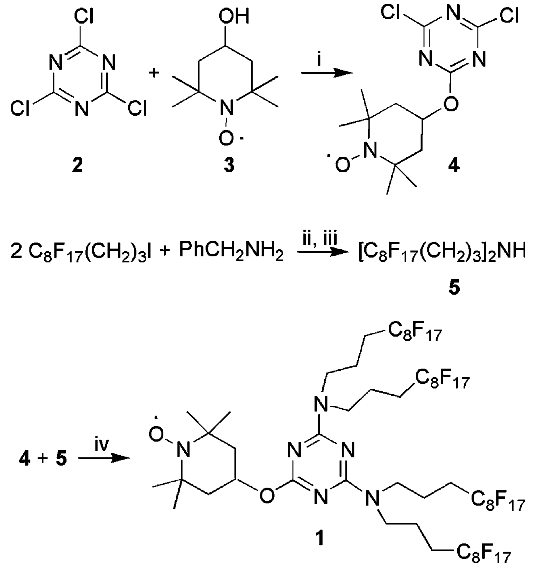
Received 25 March 2004; revised 5 April 2004; accepted 6 April 2004

Abstract—A fluorous-tagged TEMPO radical has been prepared and its catalytic activity in the chemoselective oxidation of alcohols to carbonyl compounds has been investigated. The new fluorous radical proved to be an efficient, selective and easily recoverable catalyst, which can be conveniently used in standard organic solvents and then isolated and recycled by fluorous liquid–liquid extraction.

© 2004 Elsevier Ltd. All rights reserved.

The original Fluorous Biphase System (FBS) concept[1] has expanded to include many other separation techniques based on the phase behaviour of molecules containing at least one highly fluorinated domain (fluorous molecules).[2] Fluorous catalytic oxidation reactions, where the substrates are converted to products of greater polarity, which are easily expelled from the fluorous phase, were one of the first targets of the FBS approach and still attract a lot of interest. Metal complexes of (among others) porphyrins,[3] β-diketonates,[4] polyazamacrocycles[5] and bipyridines,[6] have been thus immobilised in perfluorocarbons by modifying the ligand structure with long perfluoroalkyl chains. Their use as catalysts in several FBS oxidation processes, including alkene epoxidation, alkane hydroxylation, selective oxidation of organic sulfides to sulfoxides and oxidation of alcohols to carbonyl compounds, has been demonstrated.[7] These organometallic complexes can effectively operate in perfluorocarbons and then be easily recovered by simple phase separation from reaction products showing the usual affinity for organic solvents. In comparison, fluorous metal-free oxidation catalytic systems have received little attention, despite their obvious potential for environmentally friendly processes. Examples are limited to epoxidation reactions promoted by fluorous ketones in the presence of H_2O_2 or Oxone.[8–10] Here, we report the synthesis of **1** (Scheme 1), a fluorous derivative of the stable free radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), and its use as catalyst for the metal-free, chemoselective oxidation of primary and secondary alcohols to aldehydes and ketones, respectively.

1,3,5-Trichlorotriazine **2** was reacted with the commercially available 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical **3** in dry toluene at room temperature, in the presence of powdered KOH as a base (step i), to give



Scheme 1. Synthesis of **1**.

Keywords: Alcohols; Aldehydes; Ketones; Oxidation; Biphasic catalysis.

* Corresponding author. Tel.: +39-2-503-14159; fax: +39-2-503-141459; e-mail: gianluca.pozzi@istm.cnr.it

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.021

4 in 45% yield. The fluorous secondary amine **5** was conveniently prepared according to a modification of Rábai's method.[11] Selective dialkylation of benzylamine (step ii) followed by hydrogenolysis of the N-benzyl protective group (step iii) afforded **5** in 88% overall yield. A two-fold excess of fluorous amine **5** was then reacted with **4** in boiling THF (step iv). The ammonium salt **5**·HCl formed thereby was easily recovered by filtration of the cold reaction mixture, while **1** was recovered from the liquid phase in 65% yield after flash column chromatography on silica.[12]

The fluorous radical **1** is preferentially soluble in perfluorocarbons at room temperature, as indicated by partition coefficients (P) measurements between perfluoro-1,3-dimethylcyclohexane (PDMC) and standard organic solvents. For instance, $P_{\mathrm{PDMC/Toluene}}$ is equal to 40. Fortunately, **1** is also readily soluble in ethers such as *tert*-butyl methyl ether (MTBE) and, at low concentrations, in CH_2Cl_2. This residual affinity for organic solvents increases with the temperature and greatly simplified both the preparation of **1** and the search for convenient reaction conditions when it was tested as a catalyst in the oxidation of alcohols.

As shown in Table 1, the fluorous-tagged radical **1** proved to be an effective catalyst for the selective oxidation of the model substrate 1-octanol with various inexpensive, safe and easy to handle stoichiometric oxidants, such as trichloroisocyanuric acid (TCCA, entry 1),[13] bleach (entries 2 and 3),[14] and [bis(acetoxy)iodo]benzene (BAIB, entries 4–6).[15] It has been recently shown that alcohols are selectively oxidised with oxygen under FBS conditions in the presence of catalytic amounts of TEMPO and fluorous copper(I) complexes at 90 °C.[16,17] A single homogeneous phase is formed at such a temperature,[17] overcoming mass transfer limitations. The FBS oxidation of 1-octanol catalysed by **1** in the presence of BAIB (entry 4) proceeded slower than the analogous reaction carried out in CH_2Cl_2 (entry 5), because the present reaction system remains biphasic at room temperature. However, when the oxidation was carried out in pure CH_2Cl_2, fluorous liquid–liquid extraction of the homogeneous mixture allowed us to isolate **1** from the organic products in a few minutes. The recovered catalyst was then reused five times (entries 6–10), with a minor loss of catalytic activity observed in the fifth recycle.

We next examined the oxidation of a variety of alcohols with BAIB (Table 2, entries 1–8). In a typical reaction, a water-cooled jacketed vial fitted with a stirring bar was charged with a solution of 4-bromobenzyl alcohol (187 mg, 1 mmol) and *n*-decane (71 mg, 0.5 mmol, internal standard for GC) in CH_2Cl_2 (2 mL). To the stirred solution thermostatted at 20 °C, **1** (106 mg, 0.05 mmol) was added. After 5 min BAIB (354 mg, 1.1 mmol) was also added and the reaction mixture was vigorously stirred. After 2 h a portion (10 μL) of the solution was diluted with CH_2Cl_2 (0.1 mL) and analysed by GC. The remaining solution was extracted with perfluoro-1,3-dimethylcyclohexane (3 × 2 mL). The combined fluorous extracts containing **1** were evaporated to dryness under vacuum to recover the catalyst. 4-Bromobenzaldehyde was obtained in 97% yield after elution of the organic layer through a short silica pad (light petroleum ether/CH_2Cl_2, 1:1).

The amount of **1** (5 mol %) used in these experiments was lower than that generally used in BAIB-promoted oxidations catalysed by TEMPO (10 mol %).[15] Nevertheless, primary and benzylic alcohols were smoothly oxidised to the corresponding aldehydes under these conditions (entries 1–4). The oxidation of secondary alcohols (entries 5–8) was generally slower, reaction rates depending on the steric hindrance of the substrate analogously to what was found with TEMPO.[15] When quick oxidation of secondary alcohols is required, BAIB can be conveniently replaced with bleach (entries 9–11). In this case reactions are carried out with a catalyst loading of 1 mol %.

In summary, we have developed a fluorous-tagged TEMPO derivative, which is an efficient, selective cata-

Table 1. Oxidation of 1-octanol to octanal catalysed by **1**

Entry	Oxidant	Solvent	T (°C)	t (min)	Conv.[a] (%)	Sel.[a] (%)
1	TCCA[b]	CH_2Cl_2	0	15	>99	87
2	NaOCl[c]	MTBE	0	10	>99	94
3	NaOCl[d]	MTBE	0	30	95	96
4[e]	BAIB[f]	CH_2Cl_2/PDMC	20	120	56	>99
5	BAIB	CH_2Cl_2	20	120	93	>99
6[g]	BAIB	CH_2Cl_2	20	120	92	>99
7	BAIB	CH_2Cl_2	20	120	93	>99
8	BAIB	CH_2Cl_2	20	120	87	>99
9	BAIB	CH_2Cl_2	20	120	91	98
10	BAIB	CH_2Cl_2	20	120	85	98

[a] Determined by GC (internal standard method).

[b] TCCA = trichloroisocyanuric acid (1.05 mol equiv with respect to the substrate, catalyst loading = 1 mol %). Reaction conditions see Ref. 13.

[c] Aqueous NaOCl (1.25 mol equiv with respect to the substrate, catalyst loading = 1 mol %). Reaction conditions see Ref. 14. Co-catalyst = KBr.

[d] Aqueous NaOCl (1.25 mol equiv with respect to the substrate, catalyst loading = 1 mol %). Bromide-free conditions.

[e] FBS conditions. PDMC = perfluoro-1,3-dimethylcyclohexane.

[f] BAIB = [bis(acetoxy)iodo]benzene (1.1 mol equiv with respect to the substrate, catalyst loading = 5 mol %). Reaction conditions see Ref. 15.

[g] Entries 6–10: Catalyst recycling. Each reaction was carried out with the catalyst recovered from the previous run.

Table 2. Oxidation of alcohols to carbonyl compounds catalysed by **1**

Entry	Oxidant[a]	Substrate	*t* (h)	Conv.[b,c] (%)	Sel.[b] (%)
1	BAIB	1-Undecanol	2	>99 (80)	>99
2[d]	BAIB	4-Bromobenzyl alcohol	2	>99 (97)	>99
3	BAIB	Benzyl alcohol	2	>99	>99
4	BAIB	Cinnamyl alcohol	2	>99	76
5	BAIB	2-Octanol	24	92	>99
6[d]	BAIB	Cyclooctanol	14	91 (78)	>99
7[d]	BAIB	2-Undecanol	24	83	>99
8[d]	BAIB	1-Phenylethanol	6	93 (88)	>99
9	NaOCl	2-Octanol	0.25	92	>99
10	NaOCl	Cyclooctanol	0.25	99	>99
11	NaOCl	2-Undecanol	0.5	95	>99

[a] Reaction conditions: BAIB (catalyst loading = 5 mol%) see text; aqueous NaOCl (catalyst loading = 1 mol%, co-catalyst = KBr, $T = 20\,°C$) see Ref. 14.

[b] Determined by GC (internal standard method).

[c] Isolated yields in parentheses.

[d] Using catalyst **1** recovered from the reaction summarised in the previous entry.

lyst for the oxidation of alcohols under mild, homogeneous reaction conditions. The new fluorous catalyst offers the additional advantages of simplified workup procedure and easy recovery and recycling, which are usually associated with the use of heterogenised TEMPO.[18]

Acknowledgements

We gratefully acknowledge the European Union (Contract no HPRN-CT-2000-00002, Development of Fluorous Phase Technology for Oxidation Processes) for financial support.

References and notes

1. Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72–75.
2. Gladysz, J. A.; Curran D. P. (Eds.) *Tetrahedron* **2002**, *58*, Special Issue 'Fluorous Chemistry'.
3. Pozzi, G.; Montanari, F.; Quici, S. *Chem. Commun.* **1997**, 69–70.
4. Klement, I.; Lütjens, H.; Knochel, P. *Angew. Chem., Int. Ed.* **1997**, *36*, 1454–1456.
5. Vincent, J.-M.; Rabion, A.; Yachandra, V. K.; Fish, R. H. *Angew. Chem., Int. Ed.* **1997**, *36*, 2346–2349.
6. Quici, S.; Cavazzini, M.; Ceragioli, S.; Montanari, F.; Pozzi, G. *Tetrahedron Lett.* **1999**, *40*, 3647–3650.
7. For a recent review on fluorous technologies see: Dobbs, A. P.; Kimberley, M. R. *J. Fluorine Chem.* **2002**, *118*, 3–17.
8. Van Vliet, M. C. A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 263–264.
9. Legros, J.; Crousse, B.; Bourdon, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2001**, *42*, 4463–4466.
10. Legros, J.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron* **2002**, *58*, 3993–3998.
11. Szlávik, Z.; Tárkányi, G.; Gömöry, A.; Tarczay, G.; Rábai, J. *J. Fluorine Chem.* **2001**, *108*, 7–14.
12. Analytical data for **1**. Mp 73–77 °C. IR (KBr, selected data): 1573, 1525 (C=N), 1366 (N–O) cm^{-1}. Calcd C 31.70, H 1.95, N 3.96, found C 32.12, H 1.99, N 3.98. HRSM (ESI): *m/z* found 2144.20114 ($[M+Na]^+$), calcd for $[(C_{56}H_{41}F_{68}N_6O_2)Na]^+$ 2144.21027.
13. Jenny, C.-J.; Lohri, B., Schlageter, M. U.S. Patent 5 821 374, 1998; *Chem. Abstr.* **1997**, *127*, P65794x.
14. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.
15. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.
16. Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343–4346.
17. Contel, M.; Izuel, C.; Laguna, M.; Villuendas, P. R.; Alonso, P. J.; Fish, R. H. *Chem. Eur. J.* **2003**, *9*, 4168–4178.
18. Ciriminna, R.; Bolm, C.; Fey, T.; Pagliaro, M. *Adv. Synth. Catal.* **2002**, *344*, 159–163, and references cited therein.