Tetrahedron Letters 49 (2008) 6955–6958

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Novel light-fluorous TEMPO reagents and their application in oxidation reactions

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ARTICLE INFO

Article history:
Received 21 July 2008
Revised 11 September 2008
Accepted 15 September 2008
Available online 19 September 2008

Keywords:
Fluorous-TEMPO
Fluorous solid-phase extraction
Oxidation reaction

ABSTRACT

The synthesis of two light-fluorous TEMPO derivatives is reported, along with their application in oxidation reactions.

The 'fluorous' concept has rapidly expanded in recent years, with many novel fluorous-tagged reagents reported and many reactions being adapted for use in conjunction with the fluorous biphase concept. There are now many excellent reviews of this emerging area.[1–5]

One of the most widely used stable free radicals is 2,2,6,6-tetramethylpiperidine-1-oxyl or TEMPO **1**. In order to assist in the purification of reactions containing TEMPO, there have been several reports of tagged TEMPO-type reagents, including resin-bound[6] and polymer-supported[7–9] TEMPO-derivatives; an ionic liquid-based TEMPO system by Jiang and Ragauskas[10,11] and, concurrent with our own work, two reports of heavy fluorous-based TEMPO derivatives by Pozzi and co-workers[12,13] and Reiser and co-workers.[14]

Herein, we report the synthesis, characterisation, properties and reactions of two light fluorous-TEMPO reagents, **2** and **3** (Fig. 1). These were designed to be smaller and simpler than the alternative tagged-TEMPO reagents. The compounds were prepared starting from 4-oxo-TEMPO **5**, itself prepared from 2,2,6,6-tetramethyl-4-oxopiperidine **4** by oxidation with Oxone® (Scheme 1).[15] With the aim of attaching two simple fluorous ponytails by a reductive-type amination approach, we next prepared the fluorous-amine **6** from the commercially available fluorous alcohol **7**, via tosylation,[16,17] azidation[18] and reduction with lithium aluminium hydride[18] (56% over three steps). Reductive amination gave the mono-tagged TEMPO **8**. All attempts at alkylation of this secondary amine failed. However, formation of the fluorous amide proved to be more successful. Starting from the same fluorous alcohol **7**, oxidation using Jones' reagent gave the carboxylic acid,[19] which was converted into the acid chloride with thionyl chloride and triethylamine. Amide formation proceeded in good yield to give the fluorous-TEMPO reagent **2** [20] in 16% overall yield over the five steps

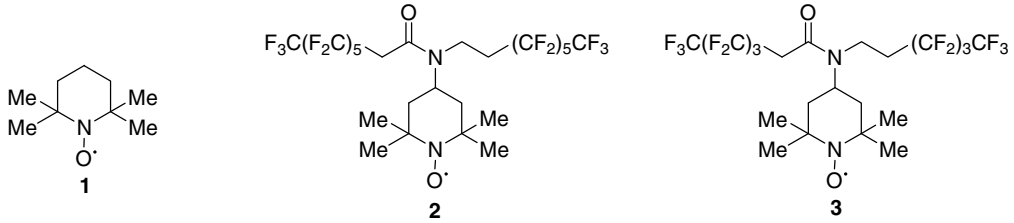

Figure 1.

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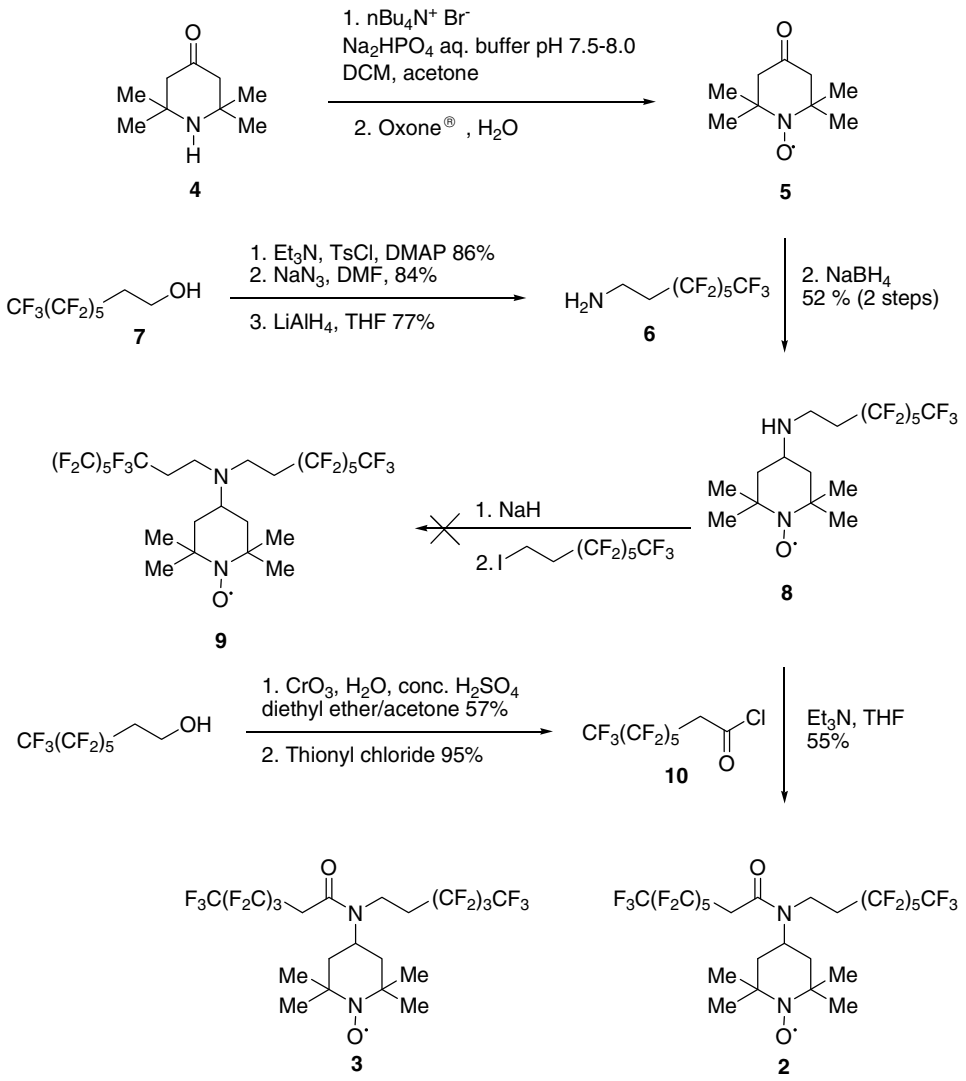
doi:10.1016/j.tetlet.2008.09.092



Scheme 1. Synthesis of light-fluorous TEMPO reagents.

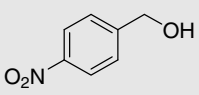
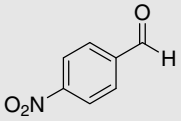
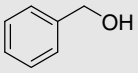
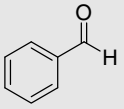
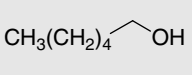
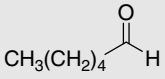
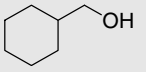
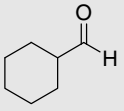
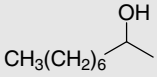
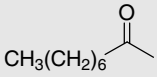
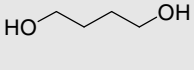
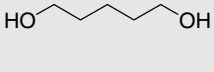
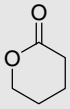
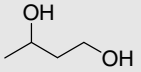
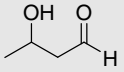
starting from **7**. Initially, the synthetic sequence was performed using two $CF_3(CF_2)_5$ fluorous ponytails; the sequence was later repeated with two shorter $CF_3(CF_2)_3$ ponytails to give **3**, which proved to be equally effective and in comparable yield.

The partition coefficients for the two fluorous-TEMPO reagents were determined by stirring 25 mg of the fluorous-TEMPO in a mixture of 1 ml of an organic solvent and 1 ml of a fluorous solvent thermostated at 25 °C for 24 h. The best ratio obtained for **2** was 39:61 for dichloromethane: FC-72; all other fluorous/organic solvent combinations for **2** and also for the lighter fluorous analogue **3** were less successful, suggesting that fluorous-organic liquid–liquid extraction would not be possible for reactions containing these reagents. Therefore, it was necessary to use fluorous solid-phase extraction employing fluorous-silica[21–23] to utilise, separate and recycle these light-fluorous-TEMPO reagents.

Both fluorous-TEMPO reagents were used in a variety of oxidation reactions, initially with the heavier Rf-TEMPO **2** and later with the lighter Rf-TEMPO **3**. Two different methods were employed for the selective and high yielding oxidation of primary alcohols to aldehydes and both methods gave good results.[24] Both aromatic and aliphatic alcohols were oxidised in excellent yields to the aldehyde, with no overoxidation to the carboxylic acid observed in any case. The fluorous-TEMPO **3** recovered from the oxidation of *p*-nitrobenzyl alcohol (Table 1, entry 1, method A) was re-employed three additional times for the same reaction, also using Method A, with no deterioration of reaction yield and only small loss in % recovery of the fluorous-TEMPO on each occasion (ca. 10%). Double oxidation of diols (Table 1, entries 6 and 7) gave the cyclic lactones in very good yields. The reagent could also be employed for the oxidation of secondary alcohols to ketones, albeit in lower yields (Table 1, entry 5). Given their remoteness from the radical centre, it was not surprising that similar yields for the oxidation reactions were obtained for both the lighter and heavier Rf-TEMPO reagents. All reaction mixtures were easily purified by fluorous solid-phase extraction (SPE): the reaction mixture was extracted with water, dried and concentrated and immediately loaded on to the fluorous silica. This was eluted first with 10% water in methanol, to elute the organic product(s), followed by 100% methanol to elute the Rf-TEMPO. This ease of recycling offers a considerable advantage over the current alternative fluorous-based TEMPOs, which require lengthier purification processes.

In conclusion, we have prepared two light fluorous-TEMPO reagents and employed them as effective reagents for oxidation reactions. The rapid synthesis of these compounds, their comparatively low molecular weight and ease of recycling via fluorous solid-phase purification give these fluorous-TEMPO reagents, we believe, a considerable advantage over alternative fluorous and solid-supported TEMPO reagents.

Table 1
Oxidation reactions using fluorous-TEMPOs **2** and **3**

Entry	Starting material	Product	Method[a]	Lighter Rf-TEMPO **3**		Heavier Rf-TEMPO **2**	
				Yield[b] (%)	Recovered fluorous-TEMPO[c] (%)	Yield[b] (%)	Recovered fluorous-TEMPO[c] (%)
1			A B	76 65	91 89	86 (89, 82)[d] —	97 (94, 95)[d] —
2			A B	89 69	94 95	— —	— —
3			A B	87[d] 61	94 92	91	94
4			A B	89[d] 75	96 93	92	97
5			A B	62 0	87 94	74 —	95 —
6			A B	71 64	89 88	— —	— —
7			A	73 (1:1.3 mixture product:SM)	92	—	—
8			A B	0 0	96 97	0 0	98 89

[a] *Method A*: alcohol (1 equiv), fluorous-TEMPO (0.03 equiv), 0.5 M KBr (0.3 equiv), NaOCl and $NaHCO_3$ (aq Buffer). *Method B*: alcohol (1 equiv), fluorous-TEMPO (0.1 equiv), Bu_4NBr (0.4 equiv), Oxone® (2.2 equiv).
[b] Purified and isolated yields. All compounds gave satisfactory spectroscopic and analytical data.
[c] Each reaction mixture was purified using fluorous solid-phase extraction using fluorous-silica: the organic material was first eluted using 10% water in methanol, followed by elution with 100% methanol to remove the fluorous-TEMPO.
[d] Figures in parentheses are the yields and recovery for the second and third runs using the recycled Rf-TEMPO.

Acknowledgements

We wish to thank Pfizer (CASE award to MJP) and the EPSRC (DTA award to MJP) for funding of the project and Dr. Peter Jones and Dr. Peter Stephenson (both Pfizer) for helpful discussions. Further, we wish to thank Mr. Greg Coumbarides for fluorine NMR spectra. The EPSRC National Mass Spectrometry Service (Swansea, UK) is gratefully acknowledged for running all high resolution mass spectra.

References and notes

1. *Handbook of Fluorous Chemistry*; Wiley-VCH, 2004.
2. Dobbs, A. P.; Kimberley, M. R. *J. Fluorine Chem.* **2002**, *118*, 3–17.
3. Zhang, W. *Chem. Rev.* **2004**, *104*, 2531–2556.
4. Dandapani, S. *Qsar Comb. Sci.* **2006**, *25*, 681–688.
5. Gladysz, J. A.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3823–3825.
6. Kashiwagi, Y.; Ikezoe, H.; Ono, T. *Synlett* **2006**, 69–72.
7. Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795–1796.
8. Dijksman, A. E.; Arends, I.; Sheldon, R. A. *Chem. Commun.* **2000**, 271–272.
9. Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell'Anna, G. *Org. Lett.* **2004**, *6*, 441–443.
10. Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2005**, *46*, 3323–3326.
11. Jiang, N.; Ragauskas, A. J. *Org. Lett.* **2005**, *7*, 3689–3692.
12. Holczknecht, O.; Pozzi, G.; Quici, S. *Qsar Comb. Sci.* **2006**, *25*, 736–741.
13. Holczknecht, O.; Cavazzini, M.; Quici, S.; Shepperson, I.; Pozzi, G. *Adv. Synth. Catal.* **2005**, *347*, 677–688.
14. Gheorghe, A.; Cuevas-Yanez, E.; Horn, J.; Bannwarth, W.; Narsaiah, B.; Reiser, O. *Synlett* **2006**, 2767–2770.
15. Brik, M. E. *Tetrahedron Lett.* **1995**, *36*, 5519–5522.
16. Elshani, S.; Kobzar, E.; Bartsch, R. A. *Tetrahedron* **2000**, *56*, 3291–3301.
17. Briza, T.; Kvicala, J.; Paleta, O.; Cermak, J. *Tetrahedron* **2002**, *58*, 3841–3846.
18. Porcherie, O.; Guari, Y.; Reye, C. *New J. Chem.* **2005**, *29*, 538–543.
19. Achilefu, S.; Mansuy, L.; Selve, C.; Thiebaut, S. *J. Fluorine Chem.* **1995**, *70*, 19–26.
20. 3′,3′,4′,4′,5′,5′,6′,6′,7′,7′,8′,8′-Tridecafluorooctanoic acid (1-hydroxyl-2,2,6,6-tetramethylpiperidin-4-yl)-(3″,3″,4″,4″,5″,5″,6″,6″,7″,7″,8″,8″,8″-tridecafluoro-octyl)-amide **2**: Orange/red solid; R_f 0.42 (4:1 [DCM/ether] 1% TEA); mp 48–49 °C (petrol) ; ν_{MAX}/cm^{-1} (KBr disc) 2979 w, 2899 w, 1702 m, 1639 s (amide), 1436 m, 1365 m, 1294 m (CF_3), 1236 s (CF_3), 1221-1159 br s ($8 \times CF_2$), 1144 s (CF_2) and 1114 s (CF_2); δ_H could not be obtained; δ_C (100 MHz: $CDCl_3$) 161.9 (CH_2CON), 57.7 (*C*HN), 34.1 (CH_2CO), 33.9 (CH_2CH_2N), 30.5 (CH_2CHN), 30.3 (CH_2CHN), 28.2 (CH_2CH_2N), 21.8 (CH_3), 19.6 (CH_3), 11.9 (CH_3) and 11.8 (CH_3); δ_F (282.4 MHz; $CDCl_3$) −81.1 (*C*F_3), −112.7 (*C*F_2), −118.6 (*C*F_2), −121.5 (*C*F_2), −124.3 (*C*F_2) and −126.5 (*C*F_2); *m/z* (EI) 877 ($M+H^+$, 100%) and 857

(M+H$^+$, $-F$, 58%). Found: C, 33.37; H, 2.22; N, 2.15; F, 56.28; $C_{25}H_{23}F_{26}N_2O_2$ requires C, 34.22; H, 2.64; F, 56.30; N, 3.19; O, 3.65.
21. Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837–11865.
22. Matsugi, M.; Curran, D. P. *Org. Lett.* **2004**, *6*, 2717–2720.
23. Curran, D. P. *Synlett* **2001**, 1488–1496.
24. *Typical experimental procedures for oxidation reaction*:
Method A: General procedure for the mild oxidation of alcohols using fluorous TEMPO and NaOCl: A solution of the alcohol (1 equiv) in CH_2Cl_2 was cooled to 0 °C and treated with a solution of fluorous TEMPO (0.03 equiv) in CH_2Cl_2. The reaction mixture was stirred at 0 °C for 5 min before being treated with a 0.5 M solution of KBr (0.3 equiv) and NaOCl solution buffered with $NaHCO_3$. The reaction mixture was stirred at 0 °C for 1 h before being allowed to warm to room temperature over 20 min. The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 ml). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by fluorous silica column chromatography, eluting first with 10% water in methanol to give the organic product(s), followed by elution with 100% methanol to give, after removal of the methanol in vacuo, the recovered fluorous TEMPO, which could be re-used without further purification.
Method B: General procedure for the mild oxidation of alcohols using fluorous TEMPO and Oxone®: A solution of the alcohol (1.0 equiv) and Bu_4NBr (0.4 equiv) in dry toluene was treated with a 0.1 M solution of fluorous TEMPO (0.1 equiv) in dry toluene and Oxone® (2.2 equiv) and stirred at room temperature for 8–48 h. After TLC showed complete conversion, the solvent was removed in vacuo and the residue was suspended between CH_2Cl_2 and water (10 ml, 1:1). The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 ml). The organic phases were combined, washed with water (15 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by fluorous silica column chromatography, eluting first with 10% water in methanol to give the organic product(s), followed by elution with 100% methanol to give, after removal of the methanol in vacuo, the recovered fluorous TEMPO, which could be re-used without further purification.