Tetrahedron 66 (2010) 2940–2943

Contents lists available at ScienceDirect

Tetrahedron

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

Baeyer–Villiger oxidation of ketones in ionic liquids using molecular oxygen in the presence of benzaldehyde

Anna Chrobok [*]

Silesian University of Technology, Department of Chemical Organic Technology and Petrochemistry, ul. Krzywoustego 4, Gliwice 44-100, Poland

ARTICLE INFO

Article history:
Received 9 November 2009
Received in revised form 3 February 2010
Accepted 22 February 2010
Available online 25 February 2010

Keywords:
Oxidation
Ionic liquids
Ketones
Lactones
Oxygen

ABSTRACT

A new and efficient method for the synthesis of lactones involving the application of an oxygen/benzaldehyde system as the oxidant and ionic liquids as solvents is reported. A significant rate enhancement was observed at 90 °C when the oxidation of ketones was carried out in the presence of a free radical initiator. The oxidation of model cyclic ketones, such as cyclopentanone, cyclohexanone, 2-methylcyclohexanone, 2-norbornone, 2-adamantanone and cycloheptanone gave lactones in high yields (84–90%) within relatively short periods of time, with the possibility of effective ionic liquids recycling. Additionally, discussion of the free radical mechanism of this reaction is proposed.

1. Introduction

The Baeyer–Villiger (BV) reaction is commonly used for the synthesis of lactones and esters by the oxidation of cyclic and linear ketones. This important reaction has been used in many different applications, including the synthesis of antibiotics, steroids, pheromones and monomers for polymerisation.[1] The most often used oxidants in this process are organic peroxyacids and hydrogen peroxide. However, Mukaiyama et al. found that in situ preparation of organic peroxyacids by the oxidation of an aldehyde with molecular oxygen can be also an effective oxidation system for the BV reaction.[2] This reaction is carried out using benzaldehyde, acetaldehyde or isobutyraldehyde as the aldehyde component. The most frequently used catalysts are Fe_2O_3, nickel or copper complexes, or Fe/MgAl hydrotalcites.[3] Dichloromethane, carbon tetrachloride, benzene and acetonitrile typically are employed as the reaction solvent. Although the BV reaction has been known for nearly a hundred years, a large variety of new reaction systems (e.g., oxidant, catalyst, and solvent) continue to be investigated.[4]

In recent years, ionic liquids have become very popular as environmentally benign solvents for many oxidation reactions.[5] Ionic liquids are useful reaction media because they possess desirable characteristics, such as thermal stability, low viscosity, a wide temperature range for liquid state, low vapour pressure and an excellent ability to dissolve organic compounds, salts and metals.[6]

There has been one promising report in the literature about using *m*-chloroperoxybenzoic acid as an oxidant and an ionic liquid as a solvent in the BV reaction.[7] The authors report almost three- to fourfold rate acceleration in $bmimBF_4$ compared to the same reaction carried out in acetonitrile or chloroform. Nevertheless, this method suffers from several disadvantages, in particular, the use of an organic peroxyacid as the oxidant is relatively expensive and hazardous, and limits the commercial application of this method.

In an effort to improve and simplify this procedure, a new and efficient approach to the synthesis of lactones that involves a O_2/benzaldehyde system as the oxidant and an ionic liquid as the solvent is presented. These studies focused mainly on the oxidation of cyclohexanone to ε-caprolactone. This process is of great importance in the chemical industry; currently, most ε-caprolactone is prepared by oxidation of cyclohexanone using either O_2/acetaldehyde (BASF) or peroxyacetic acid (Perstorp).

2. Results and discussion

2.1. Ionic liquids as solvents for the Baeyer–Villiger oxidation

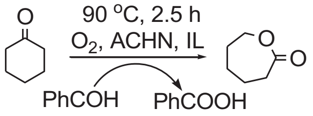
The room temperature ionic liquid 1-butyl-3-methyl imidazolium bis(trifluoromethanesulfonyl)imide $bmimNTF_2$ was selected as a model hydrophobic, water- and air- stable solvent for BV reaction. The effect of using different so-called sacrificial aldehydes has been well documented. Based on the literature data, benzaldehyde was

---

[*] Tel.: +48 32 237 2917; fax: +48 32 237 1032.
E-mail address: anna.chrobok@polsl.pl

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.02.082

employed, which has been reported to be particularly effective in BV reactions.[3] All experiments were carried out in a well-stirred round-bottom flask reactor with a blanket of oxygen at atmospheric pressure according to the general Scheme 1.



Scheme 1.

Figure 1 (curves A, B, C) shows the reaction profiles for the selective oxidation of cyclohexanone to ε-caprolactone at 40, 60 and 90 °C. A two-fold molar excess of benzaldehyde was employed. High yields of lactone formation in a relatively short time period (even at 40 °C) was observed. However, a significant rate enhancement was observed at 90 °C (Fig. 1, curve D) when the oxidation was carried out in the presence of a free radical initiator, either 1,1′-azobis(cyclohexanecarbonitrile) ACHN, (half-live at 90 °C 469 min[8]) or azoisobutyronitrile AIBN (half-live at 90 °C 26 min[8]). Nearly complete conversion of cyclohexanone was observed after 2.5 h, providing the desired lactone in 90% yield. The free radical nature of this process will be discussed later.

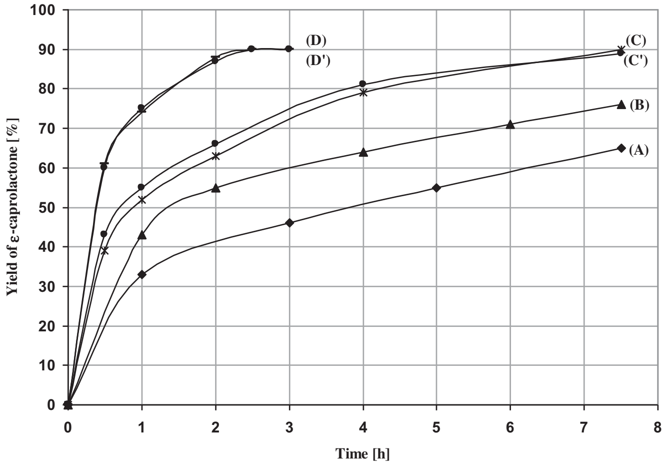


Figure 1. Oxidation of cyclohexanone (3 mmol) in the presence of benzaldehyde (6 mmol) with oxygen in bmimNTf$_2$ (2 mL) as a solvent. Curve (A) at 40 °C; (B) 60 °C; (C) 90 °C; (C′) in the presence of Fe_2O_3 (1 mol %) at 90 °C; (D) in the presence of ACHN (0.033 mol dm^{-3}) at 90 °C; (D) in the presence of ACHN (0.033 mol dm^{-3}) and Fe_2O_3 (1 mol %) at 90 °C. Yields determined by GC.

Additionally, the use of a metal catalyst in this process was investigated (Fig. 1, curves C′ and D′). Fe_2O_3 — a commonly used catalyst — does not influence the reaction course, regardless of whether ACHN is presented.

The highest reaction rates were observed in the first 0.5 h of the reaction. The influence of the concentration of benzaldehyde on the yield of ε-caprolactone was evaluated after 0.5 h and 2 h. As indicated in Table 1, the best yields were obtained when a 1:2 ratio cyclohexanone/benzaldehyde was used. Larger ratios do not influence the reaction yield any further. Additionally, the optimum concentration of ACHN was determined to be 0.033 mol dm^{-3} with a fixed amount of benzaldehyde (Table 2).

Table 1
The influence of benzaldehyde amount on the oxidation of cyclohexanone (3 mmol) with oxygen in bmimNTf$_2$ (2 mL) as a solvent, in the presence of ACHN additive (0.033 mol dm^{-3}) at 90 °C

Cyclohexanone/ benzaldehyde ratio [mol/mol]	Yield[a] of ε-caprolactone after 30 min [%]	Yield[a] of ε-caprolactone after 2.5 h [%]
1/1	39	68
1/1.5	47	75
1/2	61	90
1/3	62	87

[a] Yields determined by GC.

Table 2
The influence of ACHN additive on the oxidation of cyclohexanone (3 mmol) in the presence of benzaldehyde (6 mmol) with oxygen in bmimNTf$_2$ (2 mL) as a solvent at 90 °C

Concentration of ACHN [mol dm^{-3}]	Yield[a] of ε-caprolactone after 30 min [%]	Yield[a] of ε-caprolactone after 2.5 h [%]
—	43	71
0.016	55	80
0.033	61	90
0.066	60	87

[a] Yields determined by GC.

The reaction also can be carried out using other ionic liquids as solvents (Table 3). The use of three hydrophobic ionic liquids based on NTf$_2$ anions and other hydrophilic ones was explored. In all cases, relatively high conversions and yields of ε-caprolactone were observed. The best results were obtained for liquids with NTf$_2$ anions. Most likely, these highly hydrophobic liquids create an anhydrous reaction environment, so that hydrolysis of the lactone to the corresponding hydroxyacid is less competitive. This phenomenon was also observed in our previous study.[9]

Table 3
The influence of ionic liquid structure on oxidation of cyclohexanone (3 mmol) in the presence of benzaldehyde (6 mmol) with oxygen and ACHN additive (0.033 mol dm^{-3}) at 90 °C over 2.5 h

Ionic liquid	Conversion[a] [%]	Yield[a] of ε-caprolactone [%]
1-Butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide bmimNTf$_2$	96	90 (84)
Butylmethylpyrrolidinium bis(trifluoromethanesulfonyl)imide bmpNTf$_2$	95	89 (82)
trimethylbutylammonium bis(trifluoromethanesulfonyl)imide tmbaNTf$_2$	95	88 (79)
1-Butyl-3-methylimidazolium tetrafluoroborate, bmimBF$_4$	90	85 (76)
1-Ethyl-3-methylimidazolium methylsulfate, emimOSO$_3$Me	85	76 (65)
1-Butyl-3-methylimidazolium trifluoroacetate, bmimCF$_3$COO	80	72(65)
1-Butyl-3-methylimidazolium trifluoromethanesulfonate, bmimOTf	62	55 (46)

[a] Determined by GC; in parenthesis isolated yields.

The nature of the ionic liquid is quite important for the product isolation step. For hydrophobic ionic liquids, the post-reaction mixture was first washed with a saturated aqueous solution $NaHCO_3$ to remove benzoic acid and then the product was extracted with diethyl ether. At the end of the study, the ionic liquids were

Table 4
Recycling of bmimNTf$_2$ (8 mL) in the oxidation of cyclohexanone (12 mmol) in the presence of benzaldehyde (24 mmol) with oxygen and ACHN additive (0.033 mol dm^{-3}) at 90 °C over 2.5 h

Recycle of IL	Yield[a] of ε-caprolactone [%]	bmimNTf$_2$ Recovered [%]
Fresh, non-recycled IL	90	91
First	88	92
Second	88	90
Third	87	89

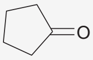
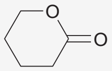
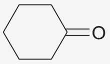
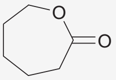
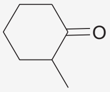
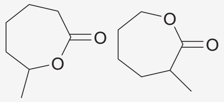
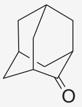
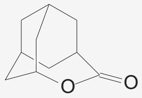
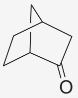
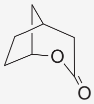
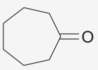
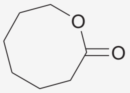
[a] Determined by GC.

recovered and reused in additional reactions, which gave nearly identical results. Table 4 shows the results of reactions using three recycles of bmimNTf$_2$ in the oxidation of cyclohexanone. Alternatively, it is possible to distil the product from the crude reaction mixture.

When hydrophilic ionic liquids were used as reaction solvents, the product was first extracted with diethyl ether. Next, the organic extract was washed with a saturated aqueous solution NaHCO$_3$, dried and concentrated.

Other cyclic ketones, such as cyclopentanone, 2-methylcyclohexanone, 2-norbornone, 2-adamantanone and cycloheptanone, can be oxidised using O$_2$/benzaldehyde as the oxidising agent, bmimNTF$_2$ as the solvent, and ACHN as the free radical initiator. These reactions proceeded efficiently without any additional catalysts, and the corresponding lactones were obtained in high yields (77–90%) within short times (Table 5). Only the oxidation of cycloheptanone afforded the corresponding lactone in insufficient yield (40%) what was also observed by other researchers.[2]

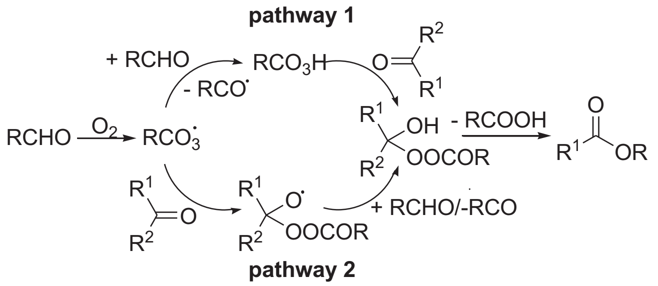
Table 5
Oxidation of ketone (3 mmol) in the presence of benzaldehyde (6 mmol) with oxygen and ACHN additive (0.033 mol dm^{-3}) in bmimNTf$_2$ (2 mL) as a solvent at 90 °C

Ketone	Lactone	Reaction time [h]	Conversion[a] [%]	Yield of lactone[a] [%]
		2	99	85 (77)
		2.5	96	90 (84)
		2	99	95 (90)
		4	100	96 (89)
		4	100	94 (86)
		10	49	(40)

[a] Determined by GC; in parenthesis isolated yields.

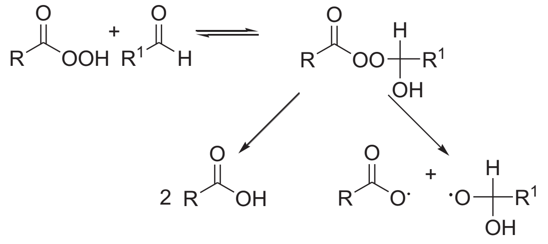
2.2. Discussion of the reaction mechanism

In the literature, two possible reaction pathways (Scheme 2) are postulated for the BV reaction using O$_2$/benzaldehyde system in classical organic solvents (e.g., dichloromethane, chloroform, acetonitrile).[3] The first step — oxidation of aldehyde — is undoubtedly a free radical process. The newly formed acylperoxy radical abstracts a hydrogen atom from the aldehyde to give a peroxyacid. The second step is thought to proceed via attack of the peroxyacid on the ketone (pathway 1), but the possibility of acylperoxy radical participation in the formation of the lactone cannot be excluded (pathway 2).[3] It is difficult to confirm, which species attacks the ketone: a peroxyacid or an acylperoxy radical. Recently Takehira et al. performed a BV reaction in acetonitrile using O$_2$/benzaldehyde system and Fe/MgAl hydrotalcite as the catalyst. They suggest that the active oxygen species must be peroxyacid, which is activated on the Fe^{3+} clusters as the active Lewis acid site.[3]



Scheme 2. Mechanism of BV reaction with O$_2$/benzaldehyde system.

The oxidation of benzaldehyde with molecular oxygen is strongly solvent dependent.[10] Peroxybenzoic acid (PBA) was isolated even in high yields (90%) as the primary product of benzaldehyde oxidation with oxygen in classical organic solvents. However, depending on the reaction conditions, the peroxyacid, that is, formed can react with another molecule of benzaldehyde to give benzoic acid as the main product (Scheme 3).[11]



Scheme 3. Possible reaction pathway of peroxybenzoic acid during the oxidation of benzaldehyde with molecular oxygen.[11]

When ionic liquids are used as the reaction medium, the situation is different. Only one literature report describes the oxidation of benzaldehyde with oxygen using an ionic liquid and a Ni catalyst (bmimPF$_6$/Ni(acac)$_2$).[12] Howarth observed the formation of benzoic acid as the main product (66% yield) at 60 °C after 24 h.

However, we know from our previous study that it is possible to carry out free radical oxidation processes in ionic liquids.[13] For this reason, additional experiments were performed. A variety of other ionic liquids (bmimNTf$_2$, tmbaNTf$_2$, bmpNTf$_2$, bmimBF$_4$, bmimOTf, bmimOSO$_3$Oc, bmimOSO$_3$Me, bmimCF$_3$COO) and catalysts Fe$_2$O$_3$, CoCl$_2$, MnCl$_2$, CuCl$_2$, NiCl$_2$, Ni(acac)$_2$ in the oxidation of benzaldehyde were explored. These systems were homogenous or partially homogenous. The oxidations were carried out at 20–60 °C for 2–24 h, with or without a metal catalyst, and with or without the free radical initiator AIBN (half-live at 60 °C 1219 min[8]). In all cases we observed high conversions of benzaldehyde and the formation of benzoic acid as a main product (40–70%); only traces of PBA were found (0.5–4%). For comparison, the yield of PBA after 1 h of benzaldehyde oxidation in bmimNTf$_2$ is only 1% while in CCl$_4$ is 26%. The data presented above clearly illustrate that it is not possible to obtain peroxybenzoic acid in ionic liquids under the reaction conditions that we used for the BV reaction. The stability of this relatively unstable peroxy compound was also checked. As shown in Table 6, PBA is relatively stable in bmimNTf$_2$ solution at 20 °C but after stirring it at 90 °C for 3 h 75% decomposed. This result may be caused by the influence of temperature — thermal

Table 6
Stability of peroxybenzoic acid (1.5 mmol) in bmimNTf$_2$ (2 mL) after 3 h of stirring at various temperatures

Temp [°C]	20	40	60	90
Decomposition of PBA [%][a]	1	6	13	75

[a] Determined by iodometric titration.

decomposition. PBA is moderately stable at room temperature but when is heated to 80–100 °C, it decomposes smoothly into benzoic acid and gases containing oxygen.[11] Therefore, even if peroxybenzoic acid forms during the oxidation of benzaldehyde in bmimNTf$_2$, it is thermally unstable or immediately reacts with another benzaldehyde molecule to form benzoic acid.

Additionally, the Baeyer–Villiger oxidation of ketones with O$_2$/benzaldehyde system in ionic liquids is accelerated by the addition of a free radical initiator (Fig. 1).

Based on these data, the mechanism of the BV reaction in ionic liquids occurs mainly via free radical pathways, which is in contrast to the reaction using typical organic solvents. An acylperoxy radical is generated in the first step by the oxidation of benzaldehyde; this radical is a key intermediate that then undergoes facile reaction with the ketone to give the corresponding lactone in high yield (Scheme 2, pathway 2).

3. Conclusion

In summary, an efficient method for the synthesis of lactones that utilises O$_2$/benzaldehyde system as the oxidant and ionic liquids as solvents was reported. This method avoids the use of very often expensive catalysts. The influences of reaction conditions (temperature, initiator concentration, structure of ionic liquid and the amount of benzaldehyde) were described. The use of hydrophobic ionic liquids based on NTf$_2$ anions at 90 °C with ACHN as the free radical initiator gave ε-caprolactone in 84% yield after 2.5 h. This new method is attractive also for the oxidation of other cyclic ketones, since it gives lactones in high yields. The ionic liquid solvent can be efficiently recycled. Additionally, the mechanism of this reaction in ionic liquids was discussed and the free radical nature of this reaction was postulated.

4. Experimental

4.1. Materials

Ionic liquids: bmpNTf$_2$, bmimOTf, bmimOSO$_3$Oc, emimOSO$_3$Me, bmimCF$_3$COO (Merck) and ketones (Acros Organics), oxygen (BOC, purity 99.99%) were commercial materials; bmimBF$_4$, bmimNTf$_2$ tmbaNTf$_2$,[14] peroxybenzoic acid[15] were prepared according to the known procedures. Benzaldehyde (Acros Organics), was purified by extraction with 10% aqueous solution Na$_2$CO$_3$ and distillation (bp=79–80 °C/25 mmHg).

4.2. Typical procedure for BV oxidation

A mixture of benzaldehyde (6.0 mmol), ketone (3.0 mmol), ionic liquid (2 mL) and ACHN (0.033 mol dm^{-3}) was placed into the 25 mL round bottom flask equipped with condenser and balloon with oxygen. The reaction mixture was stirred with magnetic stirrer at 90 °C for 2.5 h. The progress of the reaction was monitored by GC. After this time, post-reaction mixture was washed with a saturated aqueous NaHCO$_3$. Next, the ionic liquid layer was extracted with diethyl ether (6×5 mL). The organic phase was dried over anhydrous MgSO$_4$, filtered and concentrated in a vacuum. The yields of lactones after the purification by column chromatography with hexane/ethyl acetate (4:1) as an eluent were 46–90%.

4.3. Recycling of bmimNTf$_2$

After BV reaction, bmimNTf$_2$ was purified for recycling tests by extractions of post-reaction mixture: first with a saturated aqueous NaHCO$_3$ solution, and then with diethyl ether (6×5 mL). Next, bmimNTf$_2$ was concentrated and dried in a vacuum (60 °C, 8 h).

4.4. Oxidation of benzaldehyde in ionic liquids

A mixture of benzaldehyde (6.0 mmol) and ionic liquid (2 mL) was placed into the round bottom flask equipped with condenser and balloon with oxygen. The reaction mixture was stirred with magnetic stirrer at 20–60 °C in time periods 2–24 h with or without a metal catalyst (0.5–1 mol %), with or without a free radical initiator AIBN (0.033 mol dm^{-3}). Reaction products were extracted with diethyl ether (6×5 mL), concentrated and analysed by the aim of GC and iodometric titration.

4.5. Stability of PBA in bmimNTf$_2$

A mixture of PBA (1.5 mmol) and bmimNTf$_2$ (2 mL) was stirred at 20, 40, 60, 90 °C for 3 h. After this time the content of PBA was determined by iodometric titration.

4.6. Analysis

All products were characterised by comparison of their NMR spectra with authentic samples.[16] ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz in CDCl$_3$ (Varian Unity Inova plus, internal TMS). GC analysis was performed using Perkin–Elmer chromatograph and decane as the external standard.

Acknowledgements

This work was financially supported by the Ministry of Science and Higher Education (Grant no N N209 149236).

References and notes

1. (a) Krow, G. *Org. React.* **1993**, *43*, 251–798; (b) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737–750.
2. Yamada, T.; Takahashi, K.; Kato, K.; Takai, T.; Inoki, S.; Mukaiyama, T. *Chem. Lett.* **1991**, 641–644.
3. (a) Kawabata, T.; Fujisaki, N.; Shishida, T.; Nomura, K.; Sano, T.; Takehira, K. *J. Mol. Catal. A: Chem.* **2006**, *253*, 279–289; (b) Chisem, I. C.; Chisem, J.; Clark, J. H. *New J. Chem.* **1998**, *22*, 81–82; (c) Wang, X.; Li, F.; Zhang, H.; Wang, C.; Song, G. *Synth. Commun.* **1996**, *26*, 1613–1616; (d) Kaneda, K.; Ueno, S.; Imanaka, T.; Shimotsuma, E.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 2915–2917; (e) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* **1993**, *34*, 3405–3408; (f) Murahashi, S.-I.; Oda, Y.; Naota, T. *Tetrahedron Lett.* **1992**, *33*, 7557–7560.
4. Brink, G.; Arends, I.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105–4123.
5. Muzart, J. *Adv. Synth. Catal.* **2006**, *348*, 275–295.
6. (a) Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, 2007; (b) Binnemans, K. *Chem. Rev.* **2005**, *105*, 4148–4204; (c) Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615–2665.
7. Yadav, J. S.; Redy, B. V. S.; Basak, A. K.; Narasiah, A. V. *Chem. Lett.* **2004**, *33*, 248–249.
8. (a) Overberger, C. G.; Biletch, H.; Finestone, A. B.; Lilker, J.; Herbert, J. *J. Am. Chem. Soc.* **1953**, *75*, 2078–2082; (b) Van Hook, J. P.; Tobolsky, A. V. *J. Am. Chem. Soc.* **1958**, *80*, 779–782.
9. Baj, S.; Chrobok, A.; Słupska, R. *Green Chem.* **2009**, *11*, 279–282.
10. Dick, C. R.; Hanna, R. F. *J. Org. Chem.* **1964**, *29*, 1218–1220.
11. Denisov, E. T.; Afanas'ev, I. B.; Denisova, T. T.; Trepalin, S. V.; Drozdova, T. I. In *Oxidation and Antioxidants in Organic Chemistry and Biology*; Denisov, E. T., Afanas'ev, I. B., Eds.; Taylor&Francis Group: Boca Raton, 2005; pp 299–329.
12. Howarth, J. *Tetrahedron Lett.* **2000**, *41*, 6627–6628.
13. Baj, S.; Chrobok, A. *Int. J. Chem. Kinet.* **2008**, *40*, 287–293.
14. (a) Bonhote, P.; Dias, A.; Papageorgiou, N.; Kalyanasundaram, K.; Armand, M.; Graetzel, M. *Inorg. Chem.* **1996**, *35*, 1168–1178; (b) Shang, H.; Wu, J.; Zhou, Q.; Wang, L. *J. Chem. Eng. Data* **2006**, *51*, 1286–1288.
15. Moyer, J. R.; Manley, N. C. *J. Org. Chem.* **1964**, *29*, 2099–2100.
16. Gonzalez-Nunez, M. E.; Mello, R.; Olmos, A.; Asensio, G. *J. Org. Chem.* **2006**, *71*, 6432–6436.