Polyethylene glycol radical-initiated benzylic C–H bond oxygenation in compressed carbon dioxide†

Jin-Quan Wang and Liang-Nian He*

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The PEG radical originating from the thermal/oxidative degradation of PEG in dense CO_2 was successfully applied to the oxygenation of benzylic hydrocarbons under organic solvent-free conditions. In addition, in our study, dense CO_2 could improve the oxygenation reaction.

The selective catalytic oxygenation of hydrocarbons with O_2 as the terminal oxidant is a fundamental industrial technology, and its success largely depends on the use of metal catalysts to promote both the rate of reaction and selectivity to partial oxidation products.[1] The Wacker oxidation of alkenes to carbonyl compounds catalyzed by palladium salts,[2] the production of ethylene oxide from ethylene in the presence of silver salts,[3] and terephthalic acid from *p*-xylene catalyzed by manganese and cobalt salts[4] are representative commercial processes. Recently, Ishii, Recupero, Sheldon and others have developed an elegant and effective system for C–H bond oxygenation, even under mild conditions, by hydrogen abstraction from *N*-hydroxyphthalimide (NHPI).[5] However, in order to maintain the solubility of NHPI and activity of the catalytic system, the oxygenation reaction is generally carried out in CH_3COOH or toxic PhCN. Despite the usefulness of this method for the oxidation of C–H bonds, the development of new and environmentally more benign catalytic systems for oxidation is a sustained goal in organic synthesis.[6]

Polyethylene glycol (PEG) and its derivatives are commonly known to be inexpensive, thermally stable, have an almost negligible vapor pressure, and be toxicologically innocuous and environmentally benign media for chemical reactions and phase transfer catalysts.[7] We have also developed several methodologies for organic transformations using PEG as a solvent or support for a catalyst.[7d–g] On the other hand, the oxidative thermal degradation of PEG[8] was also encountered because PEG is susceptible to free radical oxidative attack in the presence of O_2 at elevated temperatures over 70 °C. In this respect, PEG and O_2 can react to form PEG peroxide in excess air through a so-called random chain scission process. Recently, we reported that the PEG radicals from oxidative degradation could be used to induce the oxidation of benzylic alcohols.[9] We would like to disclose here that the PEG radical originating from the thermal/oxidative degradation of PEG in dense CO_2 was also successfully applied to the oxygenation of benzylic hydrocarbons under organic solvent-free conditions.

We first chose the oxygenation of ethyl benzene to investigate this PEG radical chemistry, and carried out a reaction with 0.7 mmol PEG-1000 (molecular weight: 1000 Da) and 2.5 MPa O_2 at 100 °C for 12 h. Under these conditions, no oxidation product was detected (Table 1, entry 1). However, a catalytic amount of $Co(OAc)_2$, remarkably, could promote the reaction, and thus a 15% yield of acetophenone with excellent selectivity was achieved (Table 1, entry 2), concomitant with 1-phenylethanol (2%). The reaction was further improved by adding 7.5 MPa CO_2 (Table 1, entry 3), presumably due to the unusual "expanded effect" of PEG in dense CO_2, due to the lowered melting points, raised diffusion rates and lowered solvent viscosity.[7,10] Indeed, as judged by visual inspection through a window-equipped high-pressure reactor, we found that PEG and its derivatives are expandable with CO_2. In addition, a lower temperature led to a decrease in yield (Table 1, entry 5). Moreover, PEG and O_2 (Table 1, entries 4 and 6) were found to be indispensable for this transformation. These facts indicate that PEG oxidative/thermal degradation plays a critical role in the oxygenation of ethyl benzene to acetophenone, and that "PEG/O_2/CO_2" possibly serves as a radical initiator, oxidant and solvent, which makes this methodology efficient and more environmentally friendly.

Note that metal salts could promote this radical reaction. We next screened commercially available metals salts (Table 1, entries 7–13). The results show that Co and Mn salts, which could accelerate the generation of free radicals,[5a] generally improved the yield of acetophenone (Table 1, entries 7–9), while the other salts, such as of Cu, Ni and Pd, demonstrated no positive effect on the oxygenation reaction (Table 1, entries 10–13). Moreover, acetates showed generally higher activities than halides in this study (Table 1, entries 3, 7–9). In order to understand this process in more depth, parallel experiments were conducted with and without $Co(OAc)_2$ in the oxygenation of ethyl benzene, and the spent PEG was detected by ESI-MS techniques (Fig. S1 in the ESI†). The results hint that $Co(OAc)_2$ indeed accelerates the oxidative degradation of PEG, as previously reported,[12] and that it was also beneficial for the oxygenation reaction (Table 1, entries 1 and 2). Based on these results, $Co(OAc)_2$ in this study can be assumed to have acted as an initiator for generating PEG radicals and to have promoted the decomposition of intermediate hydroperoxides into the product, as similarly reported in radical reactions catalyzed by NHPI in the presence of $Co(OAc)_2$.[5] Moreover, when the reaction was carried out at an elevated

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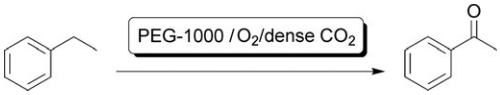
State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China. E-mail: heln@nankai.edu.cn; Fax: +86 22 23504216; Tel: +86 22 23504216

† Electronic supplementary information (ESI) available: General information, EPR spectrum, GC chart, ESI-MS spectrum and NMR charts. See DOI: 10.1039/b908993d

Table 1 Screening reaction conditions for the oxidation of ethyl benzene[a]



Entry	Metal salt	T/°C	Conversion (%)	Yield of acetophenone (%)[b]
1[c]	None	100	0	0
2[c]	$Co(OAc)_2$	100	17	15
3	$Co(OAc)_2$	100	24	22
4[d]	$Co(OAc)_2$	100	0	0
5	$Co(OAc)_2$	80	16	15
6[e]	$Co(OAc)_2$	100	0	0
7	$CoCl_2 \cdot 6H_2O$	100	12	11
8	$MnCl_2 \cdot 4H_2O$	100	12	11
9	$Mn(OAc)_2 \cdot 4H_2O$	100	14	13
10	CuCl	100	0	0
11	$CuCl_2 \cdot 2H_2O$	100	0	0
12	$PdCl_2$	100	0	0
13	$NiCl_2 \cdot 6H_2O$	100	5	5
14[f]	$Co(OAc)_2$	100	3	0
15	$Co(OAc)_2$	120	66	65

[a] Reaction conditions: 1.93 mmol ethyl benzene, 2% metal salts, 0.7 mmol PEG-1000, 2.5 MPa O_2, 7.5 MPa CO_2, 12 h. [b] Yield based on GC-MS, using biphenyl as an internal standard. [c] Without CO_2. [d] In the absence of O_2. [e] CH_3COOH was used in place of PEG, as in the principal industrial methods employing simple cobalt salts as homogeneous catalysts.[11] [f] In the presence of TEMPO (0.193 mmol).

temperature (120 °C), the yield of the desired product could be further improved up to 65% (Table 1, entry 15). However, in order to differentiate the activity of the substrates and to validate whether the oxidation could be performed under milder conditions, 100 °C was selected as the reaction temperature for further investigations. On the other hand, the oxygenation reaction was completely suppressed by TEMPO (2,2,6,6-tetramethyl-piperidine-1-oxyl), which supports the free radical process (Table 1, entry 14).

Since the oxygenation might be initiated by PEG radicals from the oxidative degradation of PEG, we next evaluated the effect of the molecular weight of PEG on the oxygenation of ethyl benzene (Table 2). Indeed, molecular weights from 300–6000 gave a similar yield under otherwise identical conditions. However, PEG-20 000 was inactive (Table 2, entry 5), presumably due to the increased mass transport limitation of gaseous O_2 in highly viscous long chain PEGs.[13] Notably, the effect[9] of the molecular weight of the PEG (Table 2) and the influence[9] of the quantity of PEG on the reaction support the notion that the degraded PEG accumulates and cannot interfere with the reaction.

Table 2 The oxidation of ethyl benzene in different molecular weight PEGs[a]

Entry	PEG	Conversion (%)	Yield (%)[b]
1	300	23	21
2	600	23	21
3	1 000	24	22
4	6 000	25	23
5	20 000	0	0

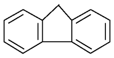
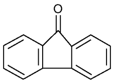
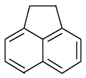
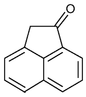
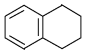
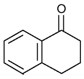
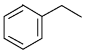
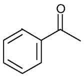
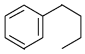
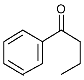
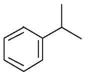
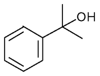
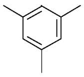
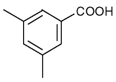
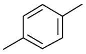
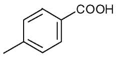
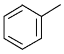
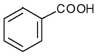
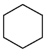
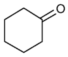
[a] Reaction conditions: 1.93 mmol ethyl benzene, 2% mmol $Co(OAc)_2$, 0.7 mmol PEG-1000, 2.5 MPa O_2, 7.5 MPa CO_2, 100 °C, 12 h. [b] Yields were determined by GC-MS with respect to an internal standard (biphenyl).

The generality of this methodology was evaluated under typical reaction conditions, as shown in Table 3. A variety of benzylic C–H bonds could be oxygenized into their corresponding oxygenated products (Table 3). Substrates favorable for forming relatively stable radicals showed a high reactivity, and selectively gave carbonyl compounds as major products.

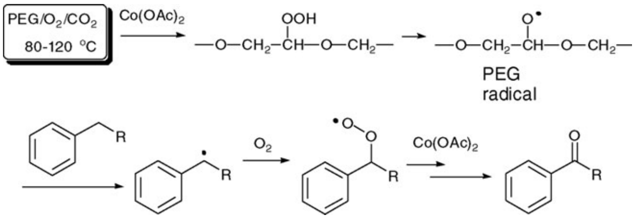
In particular, fluorene, 1,2,3,4-tetrahydronaphthalene and acenaphthene furnished moderate to high yields (Table 3, entries 1–3), possibly due to their relatively active C–H bonds being affected by ring strain and more stable radicals being formed *in situ*. Ethyl benzene, cumene and butyl benzene could also be oxidized with a high selectivity, although with a low reactivity so far (Table 3, entries 4–6). Even toluene and its derivatives successfully underwent benzylic C–H oxidations to generate the corresponding carboxylic acids in reasonable yields, alongside aldehydes as major by-products (Table 3, entries 7–9). We were pleased to find that this method was applicable even to cycloalkanes; for example, cyclohexane gave an 8% conversion to afford 4% cyclohexanone and 3% cyclohexanol (Table 3, entry 10). Nevertheless, the current industrial process shows just 3–7% conversion of cyclohexane at 160 °C.[14]

Based on aforementioned findings, a plausible mechanism for this protocol may be considered to involve a PEG radical formed *in situ* during the thermal degradation of PEG.[8b] A mechanistic scheme is therefore proposed, as delineated in Scheme 1. The reaction of PEG with O_2 is prone to generate PEG radicals, which induce the C–H bond oxygenation. The radical process could also be promoted by $Co(OAc)_2$. The proposed radical mechanism is supported by evidence, including the production of trace amounts of formylated products of the degraded PEG (Fig. S1), a broadening PEG molecule weight distribution (Fig. S2 in the ESI†), the generating of a peroxide intermediate, as detected by a KI/starch test, detected radical

Table 3 The generality of PEG radical-initiated benzylic C–H bond oxygenation[a]

Entry	Substrate	Product	Conversion (%)	Yield (%)[b]
1			100	83
2			65	58
3			86	73
4			24	20
5			14	13
6			14	12[d]
7			35	25[d]
8			38	28[d]
9[c]			24	20[d]
10			8	4[d]

[a] Reaction conditions: 1.93 mmol substrate, 2% mmol $Co(OAc)_2$, 0.7 mmol PEG-1000, 2.5 MPa O_2, 7.5 MPa CO_2, 100 °C, 12 h. [b] Isolated yield based on substrate. [c] 3 MPa O_2, 4 h. [d] Determined by GC-MS.



Scheme 1 The proposed mechanism.

species from electron paramagnetic resonance experiments (Fig. S3 in the ESI†), and the suppressing effect of TEMPO on the reactions (Table 1, entry 14).

In conclusion, the PEG radical, from the oxidative degradation of PEG, has been successfully used to oxygenate benzylic hydrocarbons in a mild and environmentally-friendly manner; dense CO_2 further improved the oxidation reaction. These findings provide a useful example to further develop free radical chemistry starting from PEG thermal oxidative degradation. Further broadening of this protocol to other organic reactions that require radical chemistry and the possibility of PEG recycling are currently being investigated. Given further time for in-depth investigations, the free radical chemistry of PEG thermal degradation will become an even more powerful tool for organic synthesis.

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Experimental

Safety warning

Experiments using large amounts of compressed gas, especially molecular O_2 and supercritical fluids, are potentially hazardous and must only be carried out using the appropriate equipment under rigorous safety precautions. In particular, CO_2 is introduced into the substrate-loaded reactor before O_2 is added. In other words, the following order should be used: O_2 after CO_2 after substrate to avoid an explosive regime; in addition, there could be peroxides in the present reaction system. The exact level of risk associated with the handling of oxidized PEG is currently unknown.

Experimental procedure

All experiments were carried out with substrate (1.93 mmol), PEG-1000 (0.7 g, 0.7 mmol) and $Co(OAc)_2$ (10 mg, 3%) in a 25 mL autoclave equipped with an inner glass tube. 3 MPa CO_2 and 2.5 MPa O_2 were introduced into the autoclave and heated to the reaction temperature. The final pressure was then adjusted to the desired pressure at the reaction temperature by introducing an amount of CO_2. The mixture was stirred continuously for the designed reaction time. Then, the reactor was placed into ice water, and CO_2 was released slowly by passing it through a cold trap containing diethyl ether to absorb the trace amount of reactant and product entrained by the CO_2. After depressurization, diethyl ether was added into the reactor. The products were then extracted by diethyl ether and analyzed by a gas chromatograph (Shimadzu-2014) equipped with a capillary column (HP-5 30 m × 0.25 μm) using a flame ionization detector. The structure and purity of the products were further identified using NMR (Bruker-300 MHz, Varian-400 MHz), GC-MS (HP G1800A), HPLC-MS (LCQ Advantage) and GC-HPLC by comparing retention times and fragmentation patterns with those of authentic samples. The EPR experiments were performed on a Bruker EMX-6 instrument.

References

1 (*a*) E. N. Jacobson, *Adv. Synth. Catal.*, 2004, **346**, 109; (*b*) T. Punniyamurthy, S. Velusumy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329.
2 (*a*) J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger and H. Kojer, *Angew. Chem.*, 1959, **71**, 176; (*b*) J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier and A. Sabel, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 80.
3 (*a*) T. E. Lefort, *Fr. Pat.*, 729 952, 1931; (*b*) T. E. Lefort, *U.S. Pat.* 1 998 878, 1935.
4 T. Yoshioka, *Petrotech (Tokyo, Jpn)*, 1978, **1**, 932.
5 For reviews and an article, see: (*a*) Y. Ishii, S. Sakaguchi and T. Iwahama, *Adv. Synth. Catal.*, 2001, **343**, 395; (*b*) F. Recupero and C. Punta, *Chem. Rev.*, 2007, **107**, 3800; (*c*) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal.*, 2004, **346**, 1051;

(*d*) G. Yang, Y. Ma and J. Xu, *J. Am. Chem. Soc.*, 2004, **126**, 10542.

6 (*a*) J. M. Thomas and R. Raja, *Catal. Today*, 2006, **117**, 22; (*b*) S. Stahl, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400; (*c*) J. Wöltinger, J. E. Bäckvall and Á. Zsigmond, *Chem.–Eur. J.*, 1999, **5**, 1460; (*d*) J. Zhu, A. Robertson and S. C. Tsang, *Chem. Commun.*, 2002, 2044; (*e*) R. Neumann, A. M. Khenkin and I. Vigdergauz, *Chem.–Eur. J.*, 2000, **6**, 875; (*f*) F. Loeker and W. Leitner, *Chem.–Eur. J.*, 2000, **6**, 2011; (*g*) R. Bal, M. Tada, T. Sadaki and Y. Iwasawa, *Angew. Chem., Int. Ed.*, 2006, **45**, 448; (*h*) F. Wang, J. Xu, X. Q. Li, J. Gao, L. P. Zhou and R. Ohnishi, *Adv. Synth. Catal.*, 2005, **347**, 1987; (*i*) M. Christmann, *Angew. Chem., Int. Ed.*, 2008, **47**, 2740; (*j*) X. B. Li and E. Iglesia, *Angew. Chem., Int. Ed.*, 2007, **46**, 8649; (*k*) C. Limberg, *Angew. Chem., Int. Ed.*, 2005, **44**, 6102.

7 (*a*) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64; (*b*) D. J. Heldebrant and P. G. Jessop, *J. Am. Chem. Soc.*, 2003, **125**, 5600; (*c*) Z. S. Hou, N. Theyssen, A. Brindmann and W. Leitner, *Angew. Chem., Int. Ed.*, 2005, **44**, 1346; (*d*) Y. Du, Y. Wu, A.-H. Liu and L.-N. He, *J. Org. Chem.*, 2008, **73**, 4709; (*e*) J.-Q. Wang, F. Cai, E. Wang and L.-N. He, *Green Chem.*, 2007, **9**, 882; (*f*) Y. Du, J.-Q. Wang, J.-Y. Chen, F. Cai, J.-S. Tian, D. L. Kong and L. N. He, *Tetrahedron Lett.*, 2006, **47**, 1271; (*g*) X.-Y. Dou, J.-Q. Wang, Y. Du, E. Wang and L.-N. He, *Synlett*, 2007, 3058.

8 For typical examples, see: (*a*) E. Bortel, S. Hodorowicz and R. Lamot, *Makromol. Chem.*, 1979, **180**, 2491; (*b*) S. Han, C. Kim and D. Kwon, *Polymer*, 1997, **38**, 317; (*c*) A. Riecke, *Angew. Chem.*, 1958, **709**, 251; (*d*) J. Glastrup, *Polym. Degrad. Stab.*, 1996, **52**, 217; (*e*) J. R. Conder, N. A. Fruitwala and M. K. Shingari, *J. Chromatogr.*, 1983, **269**, 171; (*f*) E. A. Altwicker, *Chem. Rev.*, 1967, **67**, 475.

9 J.-Q. Wang, L.-N. He and C.-X. Miao, *Green Chem.*, 2009, **11**, 1013.

10 For reviews and representative examples, see: (*a*) *Chemical Synthesis Using Supercritical Fluids*, ed. P. G. Jessop and W. Leitner, Wiley-VCH, Weinheim, 1999; (*b*) E. J. Beckman, *J. Supercrit. Fluids*, 2004, **28**, 121; (*c*) A. Baiker, *Chem. Rev.*, 1999, **99**, 453; (*d*) G. Musie, M. Wei, B. Subramaniam and D. H. Busch, *Coord. Chem. Rev.*, 2001, **219–221**, 789; (*e*) T. Sakakura, J. Choi and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365; (*f*) P. G. Jessop and B. Subramaniam, *Chem. Rev.*, 2007, **107**, 2666.

11 For examples, see: (*a*) M. P. Suresh and G. K. Bub, *Ind. Eng. Chem. Prod. Res. Dev.*, 1981, **20**, 481; (*b*) W. Partenheimer, *Chem. Ind.*, 1990, **40**, 321.

12 For representative examples, see: (*a*) A. Damińska, H. Kaczmarek and J. Kowalonek, *Polymer*, 1999, **40**, 5781; (*b*) A. M. Sakharov, L. I. Mazaletskaya and I. P. Skibida, *Kinet. Katal.*, 2001, **42**, 730; (*c*) B. Q. Chen, J. R. Evans and S. Holding, *J. Appl. Polym. Sci.*, 2004, **94**, 548.

13 T. Seki, J.-D. Grunwaldt and A. Baiker, *Chem. Commun.*, 2007, 3562.

14 U. Schuchardt, D. Cardoso, R. Sercheli, R. Pereira, R. S. da Cruz, M. C. Guerreiro, D. Mandelli, E. V. Spinacé and E. L. Pires, *Appl. Catal., A*, 2001, **211**, 1.