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The Rearrangement of *tert*-Butylperoxides for the Construction of Polysubstituted Furans

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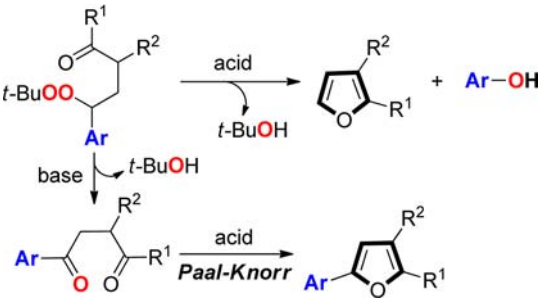
ABSTRACT



The Brønsted acid catalyzed rearrangement of *tert*-butyl peroxides provides a new strategy to construct 2,3-disubstituted furans via 1,2-aryl migration. In addition, *tert*-butyl peroxides could also be transformed into 2,3,5-trisubstituted or 2,5-disubstituted furans through a sequence of base-catalyzed Kornblum–DelaMare rearrangements and acid-promoted Paal–Knorr reactions.

1,2-Alkyl or aryl migrations to oxygen have been extensively studied in connection with the Criegee solvolysis of peresters[1] and the Baeyer–Villiger oxidation of ketones.[2] The acid-catalyzed decomposition of cumene hydroperoxide first reported by Hock and Lang[3] is the basis of the industrial synthesis of phenol and acetone (Scheme 1a). Hock cleavage of allylic hydroperoxides has also attracted much attention from both biochemistry,[4] which relates to the oxidative degradation of organic molecules especially lipids, and synthetic chemistry.[5] In 1951, Kornblum and DelaMare[6] found that dialkyl peroxides having a hydrogen on the carbon attached to the peroxide linkage will undergo decomposition in the presence of base, forming ketones and alcohols (Scheme 1b). The base-catalyzed Kornblum–DelaMare rearrangement has been also successfully employed as one of the key steps in the total synthesis of natural products.[7]

Furan as an important class of five-membered heterocycles can be found in many natural compounds, pharmaceuticals, and biochemicals. Polysubstituted furans play an important role in organic chemistry due to not only their wide occurrence as key structural units in many natural

(1) (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1948**, *560*, 127. (b) Hedaya, E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1861. (c) Hawkins, E. G. E. *Organic Peroxides*; Van Nostrand: New York, NY, 1961. (d) Davies, A. G. *Organic Peroxides*; Butterworths: London, 1961. (e) Lee, J. B.; Uff, B. C. *Quart. Rev., Chem. Soc.* **1967**, *21*, 449.

(2) (a) Leffler, J. *Chem. Rev.* **1949**, *46*, 385. (b) Bartlett, P. D. *Rec. Chem. Progr.* **1950**, *11*, 47. (c) Hassall, C. H. *Org. React.* **1957**, *9*, 74. (d) Anderson, G. H.; Smith, J. G. *Can. J. Chem.* **1968**, *46*, 1553. (e) Hawthorne, M. F.; Emmons, W. D.; McCallum, K. S. *J. Am. Chem. Soc.* **1958**, *80*, 6393.

(3) Hock, H.; Lang, S. *Ber.* **1944**, *77*, 257.

(4) (a) Yin, H.; Xu, L.; Porter, N. A. *Chem. Rev.* **2011**, *111*, 5944. (b) Hazen, S. L. *J. Biol. Chem.* **2008**, *183*, 15527. (c) Pazos, M.; Andersen, M. L.; Skibsted, L. H. *J. Agric. Food Chem.* **2008**, *56*, 11478. (d) Kellerby, S. S.; McClements, D. J.; Decker, E. A. *J. Agric. Food Chem.* **2006**, *54*, 7878. (e) Bieschke, J.; Zhang, Q.; Powers, E. T.; Lerner, R. A.; Kelly, J. W. *Biochemistry* **2005**, *44*, 4977. (f) Zhang, Q. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *45*, 7162.

(5) (a) Mansano, F. V.; Kazaoka, R. M. A.; Ronsein, G. E.; Prado, F. M.; Genaro-Mattos, T. C.; Uemi, M.; Mascio, P. D.; Miyamoto, S. *Anal. Chem.* **2010**, *82*, 6775. (b) Uemi, M.; Ronsein, G. E.; Miyamoto, S.; Medeiros, M. H. G.; Mascio, P. D. *Chem. Res. Toxicol.* **2009**, *22*, 875. (c) Brinkhorst, J.; Nara, S. J.; Pratt, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 12224. (d) Frimer, A. A. *Chem. Rev.* **1979**, *79*, 359. (e) Yamada, T.; Iwahara, Y.; Nishino, H.; Kurosawa, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 609. (f) Qian, C.-Y.; Yamada, T.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1371.

(6) Kornblum, N.; DelaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880.

(7) Some representative examples: (a) Palframan, M. J.; Kociok-Köhn, G.; Lewis, S. E. *Chem.—Eur. J.* **2012**, *18*, 4766. (b) Nicolaou, K.; Totokotspoulos, C. S.; Gigùere, D.; Sun, Y.-P.; Sarlah, D. *J. Am. Chem. Soc.* **2011**, *133*, 8150. (c) Buchanan, G. S.; Cole, K. P.; Tang, Y.; Hsung, R. P. *J. Org. Chem.* **2011**, *76*, 7027. (d) Staben, S. T.; Xin, L.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658.

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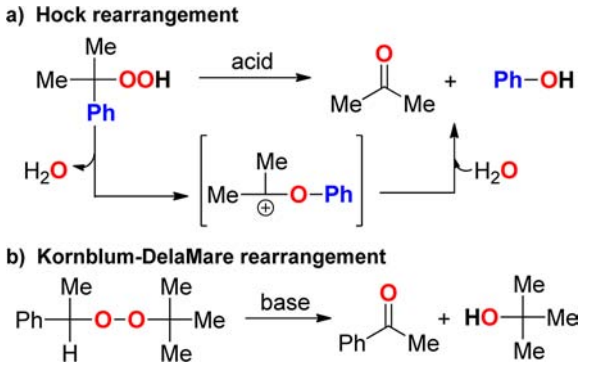
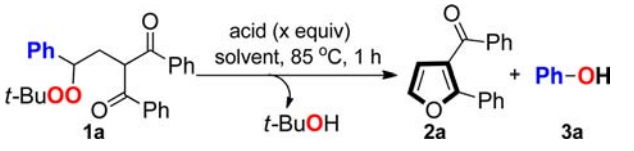
Scheme 1. Rearrangements of Organic Peroxides



products[8] but also their usefulness as building blocks in synthetic chemistry.[9] For these reasons, the exploration of new methods for the synthesis of polysubstituted furans continues to attract the interest of chemists.[10] Herein, we would like to disclose a novel method to construct 2,3-disubstituted furans through an efficient and selective acid-catalyzed 1,2-aryl migration of *tert*-butylperoxides. Base-catalyzed Kornblum–DelaMare rearrangement followed by acid-promoted Paal–Knorr furan formation for the synthesis of 2,3,5-trisubstituted or 2,5-disubstituted furans was also investigated.

To continue our exploration on the synthesis and applications of functionalized organic peroxides,[11] a series of γ-carbonyl peroxides were prepared by the Co-catalyzed three-component reactions of alkenes, *tert*-butyl hydroperoxide (TBHP), and diones or β-ketone esters.[12] Initially, the *tert*-butylperoxyl compound **1a** was selected as a model substrate to investigate the transformation. The furan product **2a** was obtained in 21% yield together with a 54% yield of phenol **3a** by the use of 1.0 equiv of $TsOH \cdot H_2O$ in CH_3CN at 85 °C for 1 h (Table 1, entry 1). Further investigations showed that the efficiency of the furan formation is affected by the acidity of the acids (Table 1, entries 2 and 3) and the use of TfOH led to a 65% yield of **2a** (Table 1, entry 3). To our delight, the yield of **2a** was improved up to 81% in the presence of 0.3 equiv of TfOH (Table 1, entry 5). Other solvents such as toluene, DCE, and DMF retarded this transformation (Table 1, entries 7–9). It should be noted that the yields of phenol **3a** were higher than the yields of the furan **2a** in all cases, indicating that the migration of the phenyl group is prior to the formation of **2a**.

Table 1. Optimization of the Reaction Conditions for Acid-Promoted Rearrangement of **1a**[a]



entry	acid (*x* equiv)	solvent	**2a** (%)[b]	**3a** (%)[b]
1	$TsOH \cdot H_2O$ (1.0)	MeCN	21	54
2	H_2SO_4 (1.0)	MeCN	49	56
3	TfOH (1.0)	MeCN	65	84
4	TfOH (0.5)	MeCN	70	90
5	TfOH (0.3)	MeCN	81(80)	87
6	TfOH (0.1)	MeCN	62	74
7	TfOH (0.3)	toluene	56	70
8	TfOH (0.3)	DCE	47	63
9	TfOH (0.3)	DMF	trace	<5

[a] Conditions: **1a** (0.2 mmol), solvent (2.0 mL), 85 °C, 1 h. [b] NMR yields were determined by ^{1}H NMR using an internal standard; isolated yield was given in parentheses.

Subsequently, the different migration groups were explored for this transformation in the presence of 0.3 equiv of TfOH (Scheme 2). To our delight, we found that a variety of aryl groups could migrate smoothly, and the furan product **2a** and the corresponding phenolic compounds **3** were obtained in good to excellent yields. Substrates with electron-donating (**1b** and **1c**) or electron-withdrawing (**1d** and **1e**) groups on the aryl ring all proceeded well under the optimized reaction conditions. Notably, bulky phenol **3f** could also be obtained in 83% yield through this TfOH catalyzed 1,2-aryl migration reaction. Moreover, 2-naphthyl substituted peroxide **1g** also gave the furan **2a** and 2-naphthol **3g** in good yields.

Encouraged by the successful transformation of **1a** to furan **2a**, we then extended the reaction to a range of substituted γ-carbonyl peroxides, and a variety of 2,3-disubstituted furans **2** were obtained in moderate to good yields (Table 2). Methyl-substituted *tert*-butylperoxide **1h** gave the corresponding furan **2b** in moderate yield (Table 2, entry 1). Both isomers of the expected furans, **2c** and **2c′**, were obtained when the unsymmetric substate **1i** was used (Table2, entry 2). β-Benzoyl ester derived *tert*-butylperoxides **1j**–**1m** all proceeded well and gave the 2-aryl-3-ester furans **2d**–**2g** in good yields (Table 2, entries 3–6). To our satisfaction, 2-alkyl-3-ester furans **2h**–**2k** could also be synthesized smoothly from the corresponding

(8) (a) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

(9) (a) Katritzky, A. R. *Comprehensive Heterocyclic Chemistry III*; Elsevier: Amsterdam; New York, 2008. (b) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076. (c) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; p 231.

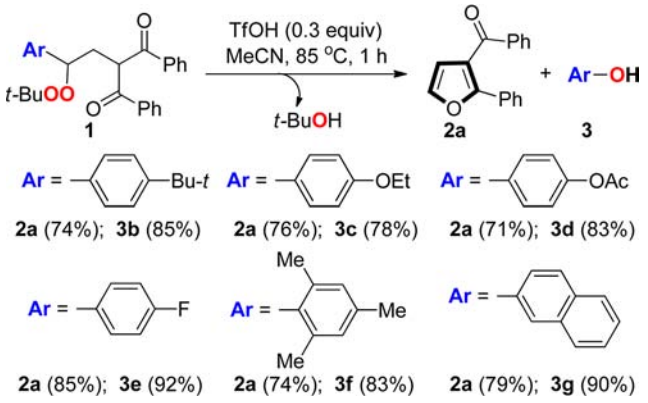
(10) (a) Yang, Y.; Yao, J.; Zhang, Y. *Org. Lett.* **2013**, *15*, 3206. (b) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766. (c) Lenden, P.; Entwistle, D. A.; Willis, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10657. (d) Zhang, M.; Jiang, H.-F.; Neumann, H.; Beller, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1681. (e) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (f) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (g) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850. (h) Xiao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (i) Jung, C.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118. (j) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (k) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386. (l) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285.

(11) (a) Liu, K.; Li, Y.; Liu, W.; Zheng, X.; Zong, Z.; Li, Z. *Chem.—Asian J.* **2013**, *8*, 359. (b) Liu, K.; Li, Y.; Zheng, X.; Liu, W.; Li, Z. *Tetrahedron* **2012**, *68*, 10333. (c) Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756.

(12) See the details of the preparation in the Supporting Information.

β-alkyl ester derivatives **1n**–**1q** (Table 2, entries 7–10). In addition, a cyano group could also be introduced to the furan product **2l** in a reasonable yield (Table 2, entry 11).

Scheme 2. Efficiency of Aryl Migrations[a]



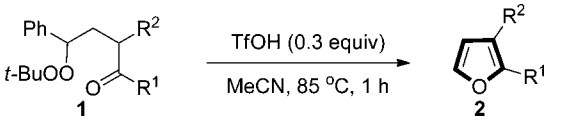
[a] NMR yields were given.

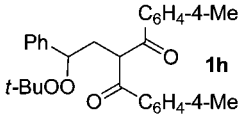
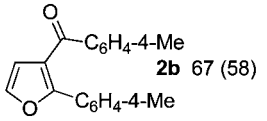
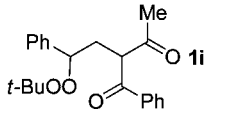
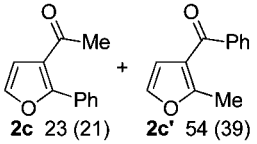
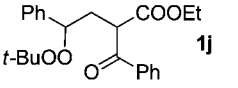
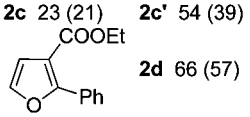
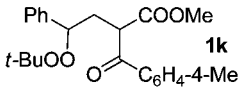
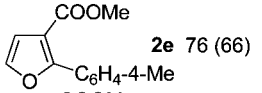
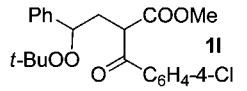
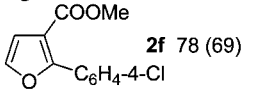
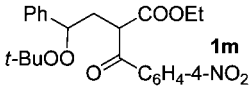
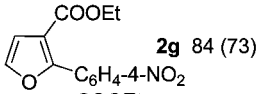
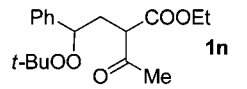
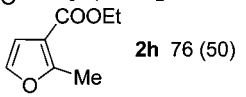
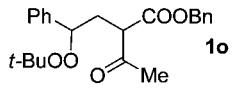
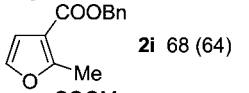
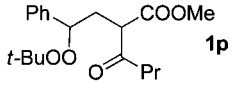
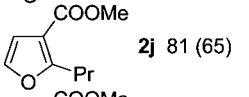
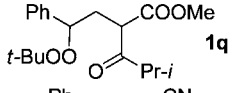
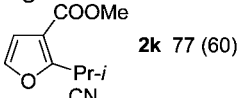
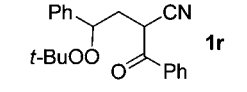
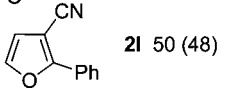
With the success of acid-catalyzed rearrangement/cyclization of the functional peroxides, base-catalyzed Kornblum–DelaMare rearrangement was also investigated (Table 3). The expected 1,4-dicarbonyl products **4** were smoothly obtained from the corresponding peroxides by the use of DBU as a catalyst. Followed by Paal–Knorr furan synthesis,[13] 2,3,5-trisubstituted and 2,5-disubstituted furans **5** were obtained in excellent yields. This sequence protocol provides an additional approach for the synthesis of multisubstituted furans.

In order to gain further insights into the acid-catalyzed rearrangement/cyclization reaction, the functional peroxides **6** and **9** were prepared and submitted to the reaction under the optimized conditions (Scheme 3, eqs 1 and 2). Phenol-tethered furan **7** was obtained together with the elemination product **8** (Scheme 3, eq 1). Interestingly, dihydrofuran[14] **11** was generated in 52% yield along with the desired furan **10** when tertiary peroxide **9** was conducted under optimized reaction conditions (Scheme 3, eq 2).

On the basis of the above results and literature reports, possible pathways of the transformation of the peroxides are proposed (Scheme 4). Both oxygen atoms in the peroxy group could be protonated.[4f] If the oxygen adjacent to the *tert*-butyl group is protonated, the phenyl group will proceed in a 1,2-migration to the oxygen and *t*-BuOH is released simultaneously (Scheme 4, Path a). The intermediate **I** undergoes an intramolecular cyclization to form

Table 2. Examples for Acid-Catalyzed Rearrangement of **1**[a]



entry	1	yield of 2 (%)[b]
1	 **1h**	 **2b** 67 (58)
2[c]	 **1i**	 **2c** 23 (21) **2c'** 54 (39)
3[c]	 **1j**	 **2d** 66 (57)
4[c,d]	 **1k**	 **2e** 76 (66)
5[c,d]	 **1l**	 **2f** 78 (69)
6[c,d]	 **1m**	 **2g** 84 (73)
7[c]	 **1n**	 **2h** 76 (50)
8[c]	 **1o**	 **2i** 68 (64)
9[c]	 **1p**	 **2j** 81 (65)
10[c]	 **1q**	 **2k** 77 (60)
11[c,d]	 **1r**	 **2l** 50 (48)

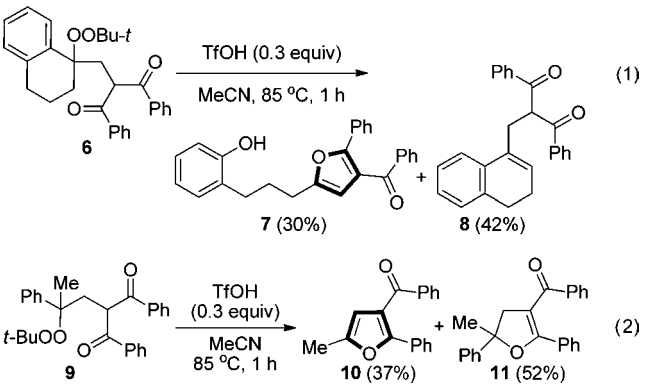
[a] Conditions: **1** (0.2 mmol), TfOH (0.06 mmol), MeCN (2.0 mL), 85 °C, 1 h. [b] NMR yields were determined by ^{1}H NMR using an internal standard; isolated yields were given in parentheses. [c] 1/1 diastereomers. [d] 0.5 equiv of TfOH was used.

the intermediate **II**. Followed by the elimination of phenol and a proton, furan is generated. On the other hand, when the other oxygen atom in the peroxyl group is protonated, a carbocation **III** is generated by the release of TBHP (Scheme 4, Path b). We hypothesized that the generation of a stable tertiary carbocation intermediate drives the reaction in this manner. Dihydrofuran is obtained by an intramolecular cyclization of **III**. In the case of base conditions, hydrogen abstraction leads to 1,4-dione via Kornblum–DelaMare rearrangement (Scheme 4, Path c). Followed by Paal–Knorr furan synthesis, 2,3,5-trisubstituted or 2,5-disubstituted furan is synthesized.

(13) (a) Paal, C. *Chem. Ber.* **1884**, *17*, 2756. (b) Knorr, L. *Chem. Ber.* **1884**, *17*, 2863. (c) Sundberg, R. J. In *Comprehensive Heterocylic Chemistry*; Katritzky, A. R.; Rees, C. W. Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 329.

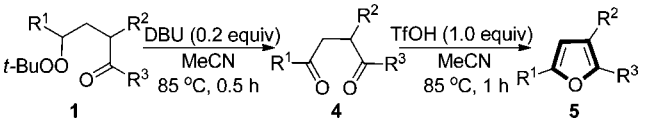
(14) (a) Ye, Y.; Wang, L.; Fan, R. *J. Org. Chem.* **2010**, *75*, 1760. (b) Shen, R.; Zhu, S.; Huang, X. *J. Org. Chem.* **2009**, *74*, 4118. (c) Ma, S.; Zheng, Z.; Jiang, X. *Org. Lett.* **2007**, *9*, 529. (d) Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. *Eur. J. Org. Chem.* **2005**, 4929. (e) Walker, L. F.; Bourghida, A.; Connolly, S.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 965. (f) Feldman, K. S.; Wrobleski, M. L. *J. Org. Chem.* **2000**, *65*, 859. (g) Alonso, M. E.; Morales, A. *J. Org. Chem.* **1980**, *45*, 4532.

Scheme 3. Acid-Catalyzed Rearrangement of **6** and **9**[a]



[a] NMR yields were given.

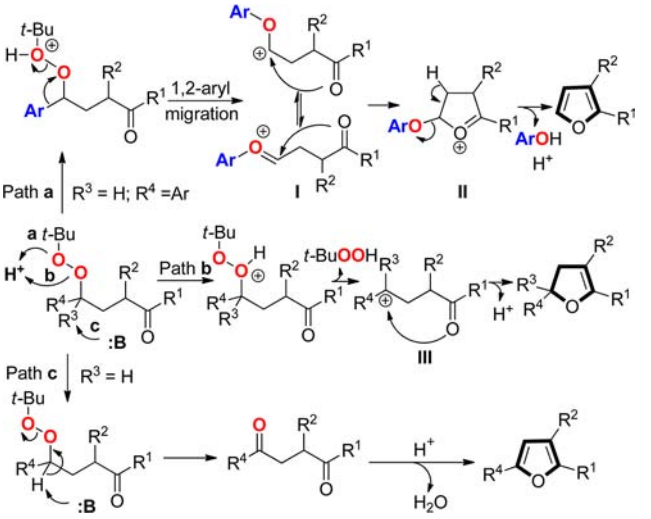
Table 3. Base-Catalyzed Rearrangement/Acid-Promoted Condensation for Multisubstituted Furan Formation[a,b]



entry	yield of **4** (%)[c]	yield of **5** (%)[c]
1	**4a** 93 (85)	**5a** 98 (93)
2	**4b** 93 (87)	**5b** 86 (80)
3	**4c** 81 (75)	**5c** 89 (75)
4	**4d** 82 (80)	**5d** 96 (90)

[a] Conditions of step 1: **1** (0.5 mmol), DBU (0.1 mmol), MeCN (2.0 mL), 85 °C, 0.5 h. [b] Conditions of step 2: **4** (0.2 mmol), TfOH (0.2 mmol), MeCN (2.0 mL), 85 °C, 1 h. [c] NMR yields were determined by ^{1}H NMR using an internal standard; isolated yields were given in parentheses.

Scheme 4. Possible Pathways for Synthesis of Furans from *tert*-Butyl Peroxides



In summary, we demonstrated a novel acid-catalyzed 1,2-aryl migration/intramolecular cyclization reaction of functional peroxide, which provides a direct and efficient tool for the synthesis of 2,3-disubstituted furans as well as 2,3-dihydrofuran in one step. In addition, the functional peroxides could also be efficiently transformed into 2,3,5-trisubstituted or 2,5-disubstituted furans via a sequence of base-catalyzed Kornblum–DelaMare rearrangements and acid-promoted Paal–Knorr furan syntheses. Further understanding and applications of the transformation of functionalized organic peroxides are underway in our laboratory.

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Supporting Information Available. Representative experimental procedure, characterization of all new compounds, and ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.