University of Nebraska - Lincoln

DigitalCommons@University of Nebraska - Lincoln

Patrick Dussault Publications

Published Research - Department of Chemistry

September 2004

Curtius rearrangement and Wolff homologation of functionalized peroxides

Patrick Dussault
University of Nebraska-Lincoln, pdussault1@unl.edu

Chunping Xu
University of Nebraska - Lincoln

Follow this and additional works at: https://digitalcommons.unl.edu/chemistrydussault

Part of the Chemistry Commons

Curtius rearrangement and Wolff homologation of functionalized peroxides

Patrick H. Dussault* and Chunping Xu

Department of Chemistry, University of Nebraska–Lincoln, Lincoln, NE 68588-0304

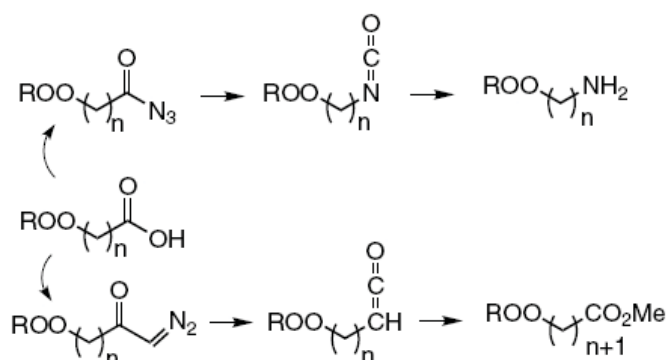**Corresponding author:* pdussault1@unl.edu

Abstract – The Curtius and Wolff rearrangements of peroxide-containing alkanoyl azides and diazoketones provide an efficient entry to peroxy-substituted amines, isocyanates, carbamates, and peroxyalkanoates.

1. Introduction

Synthetic approaches to peroxides are typically constrained by the limited methodology available for introduction of the peroxide functional group.[1] For example, our recent investigations into redox-based enzyme inactivators[2] required preparation of 2-peroxyl and 3-peroxylalkylamines, poorly explored functional motifs.[3] We now report the successful Curtius rearrangement of peroxyalkanoyl azides as a method for synthesis of peroxysubstituted isocyanates, amines, and carbamates. In addition, we discovered that the corresponding Wolff rearrangement of peroxide-containing diazoketones provides a very effective method for homologation of peroxyalkanoates (Scheme 1).

Preparation of peroxyalkanoic acid substrates is illustrated in Scheme 2.[†] The synthesis of substrate **4a** includes the first example of acid-catalyzed intermolecular reaction of a hydroperoxide with a secondary epoxide, a reaction that was found to proceed with only moderate regioselectivity in favor of the more substituted peroxide.[4]

Scheme 1. Curtius and Wolff rearrangements on peroxidic substrates.
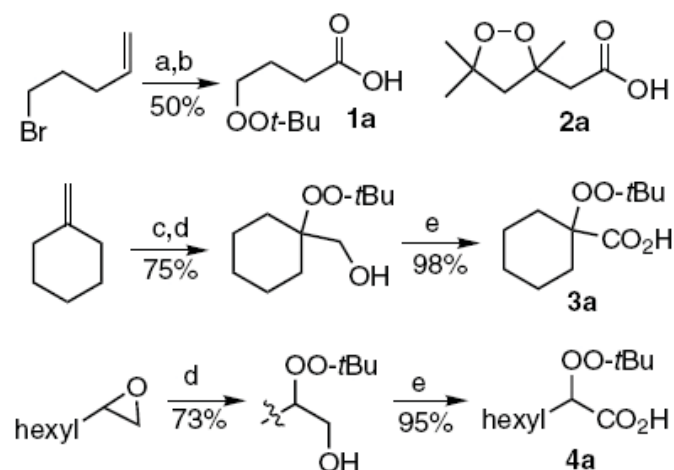
Scheme 2. Substrate preparation. Reagents and conditions: (a) t-BuO$_2$H, CsOH; (b) KMnO$_4$; (c) m-CPBA; (d) t-BuO$_2$H, BF$_3$OEt$_2$; (e) H$_2$CrO$_4$.

[†] All new compounds were purified to homogeneity and characterized by ^{1}H, ^{13}C, IR, and HRMS, except for **1d**–**4d**, where no molecular ions were observed.

2. Curtius rearrangements

Conversion of the peroxyalkanoic acids to acyl azides was readily achieved via the mixed anhydrides, with the exception of the hindered acid **3a**, which required activation as the acid chloride (Table 1).[5] The azides were stable to extractive isolation but decomposed upon attempted purification. Heating the crude azides with ethanol in refluxing benzene directly furnished the ethyl carbamates **1b**, **2b**, and **4b** as stable products. In the case of the hindered azide derived from **3a**, thermolysis resulted in decomposition with loss of the peroxide functional group.[6]

We also briefly investigated aprotic thermolysis of an azide as an approach to a peroxide-containing isocyanate. Refluxing the acyl azide derived from **2a** in dry benzene furnished a dioxolane isocyanate, which was not isolated but which could be observed by IR (Scheme 3). Hydrolysis of the isocyanate in aqueous acid furnished the aminomethyl dioxolane **5**, which underwent coupling with CBZ-Phe to furnish a peroxide-containing amino acid **6**.
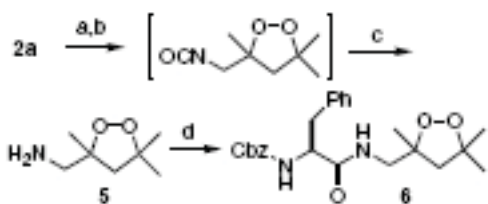
3. Wolff rearrangement

The success of the Curtius rearrangements described above led us to consider the potential of the Wolff rear-

Table 1. Curtius rearrangement of peroxylalkanoyl azides

(a) EtOC(O)Cl then NaN$_3$; (b) (ClCO)$_2$ then NaN$_3$; (c) EtOH, benzene, reflux.

Scheme 3. Synthesis of dioxolane isocyanate and aminomethyl dioxolane. Reagents and conditions: (a) EtOC(O)Cl then NaN$_3$; (b) C$_6$H$_6$, reflux; (c) aq HCl; (d) CBZ-Phe, DCC.

Table 2. Homologation via diazoketones

(a) EtOC(O)Cl then CH2N2; (b) ClCOCOCl then CH2N2; (c) AgOBz (0.1 equiv), Et3N, MeOH; (d) hv, MeOH, HOAc.

rangement for preparation of peroxyalkanoates, a functional motif found in a number of marine natural products.[7] As shown in Table 2, the peroxyalkanoic acids were easily converted, via the mixed anhydrides or the acid chlorides, to isolable diazomethyl ketones. Reaction of diazoketones **1c** or **2c** with silver benzoate and triethylamine in methanol furnished the homologated peroxyalkanoates **1d** or **2d** in excellent yield.[8]

Application of these conditions to substrate **4c** resulted in a poor yield of homologated product, accompanied by significant amounts of the oxodiazoketone, apparently derived from base-promoted decomposition of the starting material (Eq. 1).[9] Photochemical Wolff rearrangement (254 nm, methanol) furnished a much better yield of the homologated peroxyalkanoate **4d**, accompanied by small amounts of 2,3-epoxynonanoate, which presumably arises via intramolecular attack of a developing ester enolate on the peroxide. Performing the photochemical rearrangement in the presence of a trace amount of acetic acid resulted in an improved yield of peroxyalkanoate. The tertiary peroxide substrate **3c**, which failed to give any homologation product in the presence of AgOBz/Et$_3$N, underwent photochemical rearrangement to afford peroxyalkanoate **3d**.
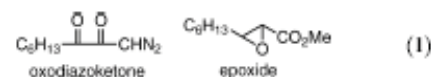
In conclusion, we have demonstrated the ability to employ the Curtius and Wolff rearrangements for synthesis of peroxylamines or homologated peroxyalkanoates. The ability to homologate 2- and 3-peroxyalkanoic acids holds particular promise for synthesis of peroxide natural products while the ability to perform the Curtius rearrangement opens new possibilities for the introduction of natural or unnatural peroxide-containing groups onto polymers and biomolecules.

4. Caution

While we experienced no particular problems, any research involving peroxides, azides, and similar functional groups should be conducted with appropriate precautions against spontaneous exothermic decomposition.

Supplementary data

Experimental procedures and spectral listings for new compounds, and other supplementary data associated with this article (found in the online version at doi:10.1016/j.tetlet.2004.08.059), are presented in the Appendix to this document.

References and notes

1. In: H. Kropf, Editors, *Organische Peroxo-Verindungen*, Georg Thieme Verlag, Stuttgart (1988); P.H. Dussault in C.S. Dussault Foote, J.S. Valentine, A. Greenberg and J.F. Liebman, editors, *Active Oxygen in Chemistry*, Blackie A&P, London (1995), pp. 141–203.

2. P.H. Dussault, A.D. George and T.K. Trullinger, *Bioorg. Med. Chem. Lett.* **9** (1999), pp. 3255–3258.

3. H.-G. Brünker and W. Adam, *J. Am. Chem. Soc.* **117** (1995), pp. 3976–3982; S.-i. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi and S. Akutagawa, *J. Am. Chem. Soc.* **112** (1990), pp. 7820–7822.

4. Intermolecular reactions of tertiary epoxides are well established: W.H. Richardson and R.S. Smith, *J. Org. Chem.* **33** (1968), pp. 3882–3885; Y. Higuchi, K. Matsuyama and T. Komai, *Bull. Chem. Soc. Jpn.* **61** (1988), pp. 1821–1823.

5. T. Shioiri in B.M. Trost and I. Fleming, editors, *Comprehensive Organic Synthesis* **Vol. 6**, Pergamon, Oxford (1988), pp. 795–828.

6. L.L. Smith and F.L. Hill, *J. Chromatogr.* **66** (1972), pp. 101–109.

7. D.A. Casteel, *Nat. Prod. Rep.* **16** (1999), pp. 55–73.

8. W. Kirmse, *Eur. J. Org. Chem.* (2002), pp. 2193–2256.

9. H. Kropf and W. Nurnburg In: H. Kropf, Editors, *Methods in Organic Chemistry: Organische Peroxo-Verbindungen* **Vol. E13**, George Thieme Verlag, Stuttgart (1988), pp. 1068–1084; C.W. Jefford, J.C. Rossier and J. Boukouvalas, *J. Chem. Soc., Chem. Commun.* (1986), pp. 1701–1702.

Supplementary data follows:

Experimental/Supporting Information

Curtius rearrangements and Wolff homologations of functionalized peroxides.

Patrick H. Dussault* and Chunping Xu
Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588-0304
pdussault1@unl.edu

General experimental conditions have been described.[1] NMR spectra were acquired in $CDCl_3$ unless otherwise indicated.

4-*tert*-Butyldioxy butanoic acid (1a): To a 0°C solution of $KMnO_4$ (7.32mmole, 1.16g) in 25 mL water were added, in one portion, a solution of 1,1-dimethylethyl 4-pentenyl peroxide[2] (0.268g, 1.83 mmol), acetic acid (2 mL), and a catalytic amount of benzyl triethyl ammonium chloride in 10 mL methylene dichloride. After 5 h, the reaction was quenched by slow addition of sodium sulfite (1.3 g), followed by a solution of concentrated HCl (1.7 mL) in water (3 mL). After 10 min, the mixture was poured into a mixture of CH2Cl2 (40 mL) and water (20 mL). The separated organic layer was washed with water and dried with sodium sulfate. The solvent was evaporated and the residue was purified by 225:25:1 (Hexane/isopropanol/acetic acid) to furnish 215 mg of the peroxyacid (72%): ^1H NMR(500 MHz) 3.95(t, 6.1, 2H), 2.45(t, 7.4, 2H), 1.89-1.94(m,2H), 1.20(s, 9H); ^{13}C (100 Mhz) 80.2, 73.5, 26.3, 25.3, 23.1 (the carboxyl was barely observable even using acquisition delays); IR(NaCl) 3500-3000 (b), 2978, 2933, 1711, 1364, 1243, 1196 cm^{-1}; HR-FAB: calcd. for $C_8H_{16}O_4$ [M+H]$^+$: 177.1128. Found: 177.1119

3,5,5-Trimethyl-1,2-dioxolane-3-acetic acid (2a) was prepared using a reported procedure.[3]

1-(tert-Butyldioxy)-cyclohexane carboxylic acid (3a)
1-(tert-Butyldioxy)-cyclohexane methanol: A solution of 11.61g (67.3mmol) mCPBA was dissolved in 80mL dry methylene chloride and cooled to 0 °C. 3.60g (37.4mmol) methylene cyclohexane in 10mL methylene chloride was added slowly. The reaction was stirred at 0°C for 2 hours, the white crystals were filtered and washed with pentane. To a 0 °C solution of the combined filtrates was slowly added *tert*-butyl hydroperoxide (11mL, 5-6M in nonane), followed by BF_3OEt_2 (1mol%). The reaction mixture was slowly brought to RT, stirred for 30 min, and then quenched into 10% aq. KOH. The ether extracts were washed with water and dried with sodium sulfate. The residue obtained after concentration was purified by column chromatography (10-15% EA/hex) to furnish 5.68g (75%) of the peroxide as a colorless liquid: $R_f = 0.55$ (20% EA/hex); ^1H NMR (400 MHz) 3.58(d, 6.34, 2H), 2.24(t, 6.40,1H), 1.26(s,9H), 1.21-1.80(10H); ^{13}C NMR (100 MHz) 81.2, 78.9, 67.7, 30.3, 26.6, 26.0, 21.7; IR(NaCl): 3352(broad), 2931, 2858, 1457,1362, 1196, 1043, 874, 668 cm^{-1}. HREI calc. For $C_{11}H_{22}0_3$ (M+): 202.1569. Found: 202.1562.

To a solution of 2.01 g (9.9mmol) of the *tert*-butylperoxycyclohexane methanol in 30 mL acetone was dropwise added Jones's reagent until the solution no longer remained blue-green. Isopropanol was then added to quench any remaining Cr(VI) and the solution was filtered through Celite. The dried (Na$_2$SO$_4$) solution was concentrated in vacuo and the residue purified by column chromatography using hexane/isopropanol/acetic acid(225:25:1) to furnish 2.10 g (98%) of the acid as white crystals: mp 78-104 (decomposes); R$_f$ = 0.3 (hexane/isopropanol/acetic acid 225:25:1); ^{1}H NMR (500 MHz) 1.35-2.00(10H), 1.32(s, 9H); ^{13}C NMR (125 MHz) 175.4, 84.0, 81.2, 30.5, 26.6, 25.0, 21.1; IR(NaCl) 2977, 2936, 2860, 1714, 1449, 1363, 1247, 1197, 1158, 1066, 885 cm^{-1}.

2-(tert-Butyldioxy) octanoic acid (4a)
2-t-butylperoxyoctanol: To a room temperature solution of 2.1mL (23 mmol) 1,2-epoxyoctane in 20 mL methylene chloride was added *tert*-butyl hydroperoxide (6.0 mL, 35 mmol, 5-6 M in nonane) followed by BF$_3$OEt$_2$ (0.025 mL). After 0.5 h, solvent was removed in vacuo and the residue was purified by column chromatography using 5%EA/hex as eluting solvent to afford 3.71 g (73%) of 2-(tert-butyldioxy)-1-octanol: R$_f$= 0.33(10% EA/hex); ^{1}H NMR (500 MHz) 3.96-3.98(1H), 3.74(dd, 2.8, 12.0, 1H), 3.60(dd, 5.7, 12.0, 1H), 2.47(br s, 1H), 1.22(s, 9H),1.20-1.52(10H), 0.84(t, 6.7 ,3H); ^{13}C NMR (125 MHz) 84.2, 80.4, 64.8, 31.6, 29.3, 29.1, 26.3, 25.7, 22.5, 13.9; IR(NaCl) 3434(br), 2929, 2859, 1462, 1384, 1363, 1196, 1042 cm^{-1}.

To a room temperature solution of 2-*t*-butylperoxyoctanol (2.12 g) in 30 mL acetone was dropwise added Jones' reagent until the red color of Cr(VI) persisted. A small excess of reagent was added and the reaction stirred for an additional 10 min. The reaction was then quenched with isopropanol and filtered through Celite. After drying over Na$_2$SO$_4$, the solution was concentrated under reduced pressure and the residue was purified by column chromatography with hexane/isopropanol/acetic acid(225:25:1) to afford 2.14 g (95%) of acid **4a** as a white solid: mp 39-40°C; Rf = 0.2 (hexane/isopropanol/acetic acid 225:25:1); ^{1}H NMR (400 MHz) 4.43(dd, 4.8, 8.5, 1H), 1.23-1.47(m, 16H), 1.69-1.80(m, 2H),0.86(t, 6.8, 3H); ^{13}C NMR (100 MHz) 177.5, 82.4, 81.6, 31.4, 30.5, 28.9, 26.2, 25.4, 22.5, 14.0; IR(NaCl) 2956, 2930, 2860, 1724, 1461, 1364, 1194 cm^{-1}. HREI calc. For C$_{12}$H$_{24}$O$_4$ (M$^+$): 232.1675; Found: 232.1671.

General Procedure for generation of acyl azides:

To a solution of 0.23g(1.31mmol) 4-(tert-butyldioxy) butanoic acid (**1a)** in 16.5mL acetone/water(10:1) was added 0.22mL(1.6 mmol) triethylamine. The solution was cooled to between 0 and –5 °C and ethyl chloroformate 0.17g(1.6 mmol) was added dropwise. The reaction was stirred at 0°C for about 10 minutes, after which sodium azide (0.17g, 2.6 mmol) was added slowly in 2mL water. After 40 min the reaction was quenched into ice water (60 mL) and the mixture extracted with diethyl ether(3 x 70 mL). The combined organic layers were dried (Na$_2$SO$_4$); the residue obtained upon concentration was used directly in the Curtius rearrangements.

General procedure for Curtius rearrangement:

The crude acyl azide was dissolved in equal amounts of anhydrous ethanol and dry benzene and the reaction mixture was heated slowly and then held at reflux for 1.5 h. The cooled reaction was then concentrated and the residue purified by flash chromatography.

3-*tert*-Butyldioxypropanamine, ethyl carbamate (1b):

0.23g(1.31mmol) 4-(tert-butyldioxy) butanoic acid **1a** (0.230g, 1.31 mmol) was converted to the azide as described above. Curtius rearrangement as described above furnished 135 mg of peroxycarbamate (47%, two steps) as a colorless liquid: R_f=0.35(20%EA/hex); ^{1}H NMR(400 MHz) 4.93(br s, 1H), 4.05(q, 7.1, 2H), 3.96(t, 6.0, 2H), 3.23(appt. q, 6.3, 2H), 1.77(quint, 6.3, 2H), 1.19(s, 9H); ^{13}C NMR(100 MHz) 156.7, 80.3, 73.9, 60.6, 38.6, 28.3, 25.3, 14.6; IR(NaCl) 3339, 2979, 2934, 2875, 1701, 1534, 1364, 1256, 1197, 1048, 877, 779 cm^{-1}; HR-FAB: calcd. for $C_{10}H_{21}NO_4$ [M+H]$^+$: 220.1550. Found: 220.1540

(3,5,5-trimethyl-1,2-dioxolane-3-methylamine, ethyl carbamates (2b) was prepared as a colorless oil (144 mg, 55%) from the corresponding acetic acid (0.210 g, 1,2 mmol) by the procedures outlined above: R_f=0.2(20%EtOAc/Hex); ^{1}H NMR(500 MHz) 5.13(br, 1H), 4.09(q, 6.9, 2H), 3.34(dd, 5.6,14.0, 1H), 3.26(dd, 6.9, 14.0, 1H), 2.23(d, 12.2, 1H), 2.13(d, 12.2, 1H), 1.35(s, 3H), 1.30(s, 3H), 1.29(s, 3H), 1.21(t, 7.1, 3H); ^{13}C NMR(100 MHz) 85.6, 84.2, 60.8, 54.7, 47.5, 27.0, 25.0, 21.5, 14.6; IR: 3100-3600(br), 2979.50, 2935.65, 1701.93, 1529.99, 1456.38, 1368.96, 1243.65,1176.33, 1036.44; MS: HR-FAB: calcd. for $C_{10}H_{19}NO_4$ [M+H]$^+$: 218.1393 Found: 218.1386

1-(tert-butyldioxy)heptylamine, ethyl carbamates (4b): Conversion of 2-(tert-butyldioxy) octanoic acid (300mg(1.3mmol) to the azide, followed by Curtius rearrangement, furnished 213 mg(60%, two steps) of the ethyl carbamate as a colorless liquid: R_f=0.33(10% EA/hex); ^{1}H NMR (400 MHz) 5.36(m, 1H, CH), 5.07(d, 9.3, 1H, NH), 4.11-4.16(m, 2H), 1.67-1.71(m, 1H), 1.49-1.53(m, 1H), 1.22(s, 9H),1.23-1.40(m, 11H), 0.86(t, 6.9, 2H); ^{13}C NMR (100 MHz) 155.9, 85.4, 80.3, 60.8, 32.6, 31.6, 28.9, 26.3, 24.9, 22.5, 14.5, 14.0; IR(NaCl) 3332, 2958, 2929, 2860, 1714, 1528, 1464, 1364, 1332, 1239, 1196, 1065 cm^{-1}; HR-FAB: calcd. for $C_{14}H_{29}NO_4$ [M+Li]$^+$: 282.2257 . Found: 282.2251.

1-(3,5,5-Trimethyl-1,2-dioxolanyl methylamine (5): To a solution of the dioxolane acetic acid (0.504 g, 2.87mmol) in 27.5mL acetone/H$_2$O(10/1) was slowly added 0.32g (3.2 mmol) triethylamine. The solution was cooled to between 0 and –5 °C, whereupon 0.34g(3.13mmol) of ethyl chloroformate was added dropwise. The reaction was stirred at 0ºC for 10 minutes, followed by slow addition of 0.374g (5.75mmol) sodium azide. After an additional 0.5 h, the reaction was found to be complete (TLC) and was poured into 60 mL ice water and extracted with diethyl ether(3x100mL). The combined organic layers were dried with sodium sulfate and concentrated. The residue was redissolved in dry benzene (15 mL) and held at reflux for 6 h. The reaction was cooled to 40-50ºC, whereupon concentrated hydrochloric acid, (4 mL) was added. After stirring for 0.5 h,

the reaction was cooled to RT and the benzene layer was separated and washed with water. The combined aqueous layers were treated with aq. NaOH (6 N) to achieve a pH of 13 and the solution was extracted with ether (5x20mL). The combined organic layers were dried and concentrated to less than 10 mL volume. Treatment with concentrated HCl led to precipitation of white crystals which were filtered and dried: mp 100-106°C (decomposes as red liquid); ^{1}H NMR (500 MHz, D$_2$O) 3.32 (d, 13.5, 1H) 3.07(d, 13.5, 1H), 2.49 (d, 12.8, 1H), 2.43(d, 12.8, 1H) 1.49(s, 3H), 1.46(s, 3H), 1.42(s, 3H); ^{13}C NMR(125 MHz, DMSO) 83.9, 83.2, 54.7, 444, 26.9, 24.4, 20.8; HR-FAB: calcd. for C$_7$H$_{15}$NO$_2$ [M+H]$^+$: 146.1182   Found: 146.1182

{2-phenyl-1-[(3,5,5-trimethyl-[1,2]-dioxolane-3-methyl)-carbamoyl]-ethyl}-carbamic acid benzyl ester (6): To a solution of 114.2mg(0.381mmol) Cbz-Phe-COOH and 62 mg (0.46 mmol) 1-hydroxybenzotriazole in 10ml distilled THF was added 77mg (0.53 mmol) 3-aminomethyl-3,5,5-trimethyl-1,2-Dioxolane. The mixture was cooled to 0 °C, whereupon 94.3 mg(0.457mmol) of DCC was added. The reaction was stirred 30 min at 0°C and then warmed to RT and stirred overnight. The precipitate was removed by filtration and the filtrate concentrated. The residue was was purified by flash chromatography (50% EtOAc/Hex) to afford 138mg (85%) of the amide **6**:
R$_f$=0.39 (50% EA/hex); ^{1}H NMR (500 MHz) 7.14-7.32(10H), 6.49 (bs, 0.5H), 6.41 (bs, 0.5H); 5.39-5.41(1H), 4.99-5.06(2H), 4.46(br, s, 1H **)**, 3.26-3.42(2H), 3.04-3.11(2H), 2.01-2.12(2H), 1.32(s,1.5H),1.31(s,1.5H), 1.21(s, 3H), 1.20(s,1.5H), 1.10 (s,1.5H); ^{13}C NMR (125 MHz), 171.2, 171.1, 155.9, 136.4, 136.3, 136.1,129.27,129.25,128.70,128.66, 128.5,128.1,128.00,127.98, 127.04, 127.02, 85.22, 85.18, 84.2, 67.0, 56.4, 54.90, 54.87, 45.8, 38.6, 27.01, 26.95, 24.95, 24.92, 21.5, 21.3; IR: 3100-3600(br), 1654.80, 1540.96, 1455.66, 1259.38668.67, 650.14 cm^{-1}; MS: HR-FAB: calcd. for C$_{24}$H$_{30}$N$_2$O$_5$ [M+Li]$^+$: 433.2315   Found: 433.2299

5-(*tert*-Butyldioxy)-1-diazo-2-pentanone (1c): A solution of 4-(tert-butyldioxy) butanoic acid (0.53g, 3mmol) in 20mL methylene chloride was cooled to –5°C. Triethylamine (0.63mL, 1.5eq.) was added dropwise, followed by ethyl chloroformate(0.49g, 1.5eq.). The reaction was stirred for 1hour at –5°C, followed by dropwise addition of ethereal diazomethane (10 mL, about 10mmol) The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Solvent was removed under reduced pressure and the residue was purified by flash chromatography with 20% EA/hex as eluting solvent to afford 470 mg (78%) of the diazoketone as a yellow liquid: R$_f$=0.46 (40%EA/hex); ^{1}H NMR(500 MHz) 5.26(br s,1H), 3.96(t, 6.1, 2H), 2.40 (br s, 2H), 1.94(quint, J =6.8, 2H), 1.23(s, 9H); ^{13}C NMR(125 MHz) 194.3, 80.2, 73.8, 54.4, 37.4, 26.3, 23.5; IR(NaCl) 2978, 2103,1642,1363,1195 cm^{-1}; HR-FAB: calcd. for C$_9$H$_{16}$N$_2$O$_3$ [M+H]$^+$: 201.1240. Found: 201.1244

1-(3,5,5-Trimethyl-1,2-dioxolan-3-yl)-3-diazo-2-propanone (2c) was prepared as a yellow liquid (93 mg, 82%) from acid **2a** by the standard procedure described above: R$_f$= 0.30(30% EA/hex); ^{1}H NMR(400 MHz) 5.43(br s, 1H), 2.73(d, 13.8, 1H), 2.56(d, 13.8, 1H) , 2.46 (d, 12.3, 1H), 2.21(d, 12.3, 1H) 1.41(s, 3H), 1.36(s, 3H), 1.32(s, 3H); ^{13}C NMR(125 MHz) 192.1, 84.8, 84.1, 57.1, 56.2, 50.2, 27.1, 25.6, 23.9; IR(NaCl) 2978,

2105, 1638, 1367, 1311 cm^{-1}; HR-FAB: calcd. for C$_9$H$_{14}$N$_2$O$_3$ [M+H]$^+$: 199.1083 Found: 199.1079

2-(1-*tert*-Butyldioxy)cyclohexyl)-1-diazo-2-ethanone (3c): To a solution of 200mg (0.9mmol) 1-(tert-butyldioxy)-cyclohexane carboxylic acid in 15 mL dry methylene chloride at room temperature was dropwise added 0.16mL (1.85mmol) oxalyl chloride, followed by one drop of DMF. The reaction was stirred at RT for 4 h, and then concentrated. The residue was redissolved in 15mL dry methylene chloride, cooled downed to 0°C, and 10mL(about 3mmol) ethereal diazomethane was added slowly. The reaction solution was stirred at 0°C for 30 min, brought to RT, and the concentrated. The residue was purified by flash chromatography (5% EA/hex) to afford 167 mg (75%) of diazoketone as a yellow oil: R$_f$= 0.44(10% EA/Hex); ^{1}H NMR (500 MHz) 5.75(br, s, 1H), 1.51-1.87(m, 10H), 1.28(s, 9H); ^{13}C NMR (125 MHz) 199.3, 86.6, 79.5, 52.1, 30.3, 26.7, 25.2, 21.3; IR(NaCl) 2978, 2938, 2860, 2102, 1643, 1448, 1338, 1195, 1146, 1009, 968, 883, 809; HR-FAB: calcd. for C$_{12}$H$_{20}$N$_2$O$_3$ [M+H]$^+$: 241.1553 . Found: 241.1546

3-(tert-Butyldioxy-1-diazo-2-nonanone (4c) was prepared as a yellow liquid (154 mg, 70%) from 2-(tert-butyldioxy) octanoic acid (200mg, 0.86mmol) by a similar procedure as for diazoketone **3c**.: R$_f$=0.45 (10%EA/hex); ^{1}H NMR (400 MHz) 5.78(br s, 1H), 4.30(m, 1H) 1.24-1.70(m, 19H), 0.87(t, 6.70, 3H); ^{13}C NMR (100 MHz) 196.9, 88.2, 81.2, 52.6, 31.5, 31.3, 29.1, 26.3, 25.6, 22.5, 14.0; IR (NaCl) 2929, 2859, 2105, 1642, 1354, 1193 cm^{-1}; HR-FAB: calcd. for C$_{13}$H$_{24}$N$_2$O$_3$ [M+H]$^+$: 257.1866. Found: 257.1873.

5- *tert*-Butyldioxy pentanoic acid, methyl ester (1d): To a solution of 40 mg (0.20 mmol) 5-t-butyldioxy-1-diazo-2-pentenone in 5mL methanol and under nitrogen was added triethylamine (0.03mL, 0.21mmol), followed by silver benzoate (5 mg, appx. 0.1 equiv.) The reaction was stirred at RT for 0.5 h, filtered through Celite, and concentrated. The residue was purified by column chromatography (10% EA/hex) to afford 40 mg (>95%) of the methyl ester as a colorless liquid: R$_f$= 0.65 (20% EA/hex); ^{1}H NMR(500 MHz) 3.91(t, 6.3 , 2H), 3.64(s, 3H), 2.31(t, 7.3, 2H), 1.62-1.68(m, 4H), 1.20(s, 9H); ^{13}C NMR(125 MHz), 173.9, 80.1, 74.4, 51.5, 33.8, 27.4, 26.3, 21.8; IR(NaCl) 2977, 2952, 1740, 1362, 1242, 1197, 1169 cm^{-1}.

3-(3,3,5-Trimethyl-1,2-dioxolan-3-yl) propanoic acid, methyl ester (2d) was prepared as a colorless liquid (20 mg, >95%) from diazoketone **2c** by a similar procedure as for **1d**: R$_f$= 0.50 (25% EA/hex); ^{1}H NMR (400 MHz) 3.67(s, 3H), 2.34-2.48(2H), 2.21(d, 12.1, 1H), 2.15(d, 12.1, 1H) 2.14(ddd, 6.0, 10.4, 14.1, 1H) 1.86(ddd, 6.0, 10.4, 14.1, 1H), 1.36(s, 3H), 1.33(s, 3H), 1.30(s, 3H); ^{13}C NMR (125 MHz) 173.9, 85.1, 83.8, 57.5, 51.7, 34.2, 29.3, 26.8, 26.0, 23.5; IR(NaCl) 2975, 2930, 1739, 1453, 1367, 1304, 1244, 1197, 1167 cm^{-1}.

2-[1-(tert-Butyldioxy)cyclohexyl] acetic acid, methyl ester (3d): A solution of 100mg 1-(1-tert-butyldioxy)cyclohexyl)- 2-diazo-ethanone and 0.5 mL acetic acid in dry methanol (15 mL) was irradiated for 4 h (254 nm, Rayonet circular reactor) in a quartz tube. The solvent was removed in vacuo, and the residue was purified by column chromatography (5% EA/hex) to afford 76 mg (75%) of methyl ester as a colorless oil:

R_f=0.46 (10% EA/Hex); ^{1}H NMR (400 MHz) 3.64(s, 3H), 2.59(s, 2H), 1.42-1.95(m, 10H), 1.21(s, 9H); ^{13}C NMR (100 MHz) 171.8, 79.4, 78.4, 51.2, 43.3, 33.1, 26.6, 25.5, 21.8; IR(NaCl) 2977, 2934, 2861, 1740, 1440, 1362, 1198, 1129, 1016, 885 cm^{-1}.HREI calc for M[+]: 244.1675; Found: 244.1665.

3-(*tert*-Butyldioxy)-nonanoic acid, methyl ester (4d) was prepared as a colorless liquid (34 mg, >80%) from) 3-(tert-butyldioxy)-1-diazo-2-nonanone (40mg, 0.156mmol) by a similar procedure as for **3d** except that irradiation was conducted for only 3 h: R_f= 0.44 (10% EA/hex); ^{1}H NMR (400 MHz); 4.36(m, 1H), 3.67(s, 3H), 2.76(dd, 6.7, 15.1, 1H), 2.38(dd, 5.7, 15.1, 2H), 1.23-1.57(m, 12H), 1.21(s, 9H), 0.87(t, 6.7, 3H); ^{13}C NMR (100 MHz) 172.4, 80.19, 80.17, 51.5, 38.9, 32.9, 31.7, 29.3, 26.3, 25.5, 22.6, 14.1; IR(NaCl) 2954, 2930, 2858, 1742, 1436, 1362,1246, 1197, 1167 cm^{-1}.

References:

[1] Dussault, P. H.; Eary, C. T.; Lee, R. J.; Zope, U. R. *J. Chem. Soc., Perkins Trans. 1* **1999**, 2189-2204.

[2] Bourgeois, M. J.; Maillard, B.; Montaudon, E. *Tetrahedron* **1986**, *42*, 5309-5320.

[3] Dussault, P. H.; Liu, X. *Org. Lett.* 1999, *1*, 1391-1393.