Mechanistic Aspects of Thiyl Radical-Promoted Acyl Radical Cyclization of Formylenoate-Cyclization *versus* Oxidation

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Treatment of formylalkenoates 1 and 7 with 2,2′-azobis(2-methylpropanenitrile) (AIBN) in the presence of dioxygen gave oxygenated carboxylic acids 5, 6, 8, 9 instead of acyl radical cyclization products, through preferential reaction of the corresponding acyl radicals with dioxygen rather than intramolecular attack to an enoate moiety. The reaction of 1 with AIBN in the absence of dioxygen recovered starting 1 in 98% yield.

Key words acyl radical; oxidation; carboxylic acid; ketoester

Direct generation of an acyl radical from a formyl group has been proven to be a versatile methodology for the cyclization of formylalkenes and formylalkenoates to cycloalkanones.[1,2] The reaction developed by us is catalyzed by the combination of a radical initiator and a thiol.[3] For example, the treatment of a formylenoate (**1**) with 0.3 eq of 2,2′-azobis(2-methylpropanenitrile) (AIBN) and 0.3 eq of *tert*-dodecanethiol (R=*tert*-dodecanyl) in refluxing benzene for 19 h gave **4** in 89% yield (Chart 1). This radical cyclization is in sharp contrast to the thiolate-initiated consecutive Michael addition-aldol cyclization of **1**.[4—7] Thiyl radical is supposed to be the agent to abstract hydrogen radical from a formyl group to generate an acyl radical **2**, which undergoes intramolecular addition to a C–C double bond to form a carbon radical **3**.[8,9] Then, the radical **3** abstracts a hydrogen radical from a thiol to provide both **4** and a thiyl radical that enters into the catalytic cycle of the reaction. This scenario seems to be reasonable,[10] however, the generation of an acyl radical **2** by 1-cyano-1-methylethyl radical, produced from AIBN, in place of thiyl radical in the first step, and regeneration of 1-cyano-1-methylethyl radical by the donation of a hydrogen radical from 2-methylpropanenitrile to **3** in the final step are the alternate possibilities. We describe herein that a thiyl radical is essential for this cyclization. Furthermore the presence of dioxygen in the reaction medium alters the reaction pathway to give oxidation products.

Alternate Reaction Pathways in the Presence of Dioxygen Under the strictly deoxygenated conditions (the mixture was degassed by the freeze–thaw procedure three times in advance to heating), a mixture of **1** and AIBN in benzene was stirred under reflux for 22 h to recover **1** in 98% yield (Chart 2). This experiment apparently indicates that 1-cyano-1-methylethyl radical does not generate an acyl radical **2** or 2-methylpropanenitrile does not donate a hydrogen radical to **3**.

Under the open-air conditions, the reaction of **1** with AIBN in refluxing benzene for 21 h gave **4** in 17% yield together with **5** in 63% yield and trace amount of **6** (Chart 3). The structure of **5** was unambiguously determined by the direct comparison with **5** prepared by the reported way.[11] Under the open-air conditions the reaction of **1** with AIBN and *N*-hydroxyphthalimide (NHPI)[12] in toluene at 80 °C for 23 h gave **4** in 20% yield, **5** in 38% yield, and trace amount of **6**. These two reactions indicate that the radical species, probably peroxy radical generated from 1-cyano-1-methylethyl radical and dioxygen, formed an acyl radical **2** that underwent cyclization to **4** *via* **3**, and also oxidation to **5** and **6**.

Established nickel-catalyzed acyl radical generation and its oxidation with dioxygen[13] in 1,2-dichloroethane at room temperature for 48 h gave **5** in 20% yield and **6** in 41% yield (Chart 4). AIBN-mediated nickel-catalyzed oxidation in chlorobenzene at 70 °C for 24 h gave also **5** and **6** in 54% and

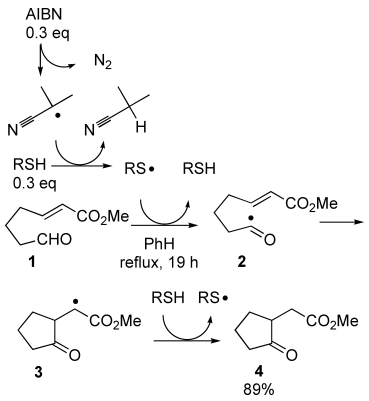

Chart 1. The Acyl Radical Cyclization of **1** to **4** *via* Radicals **2** and **3**

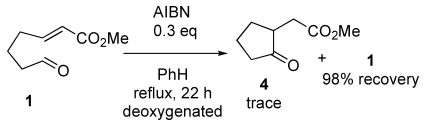

Chart 2. No Reaction under the Deoxygenated Conditions and in the Absence of a Thiol

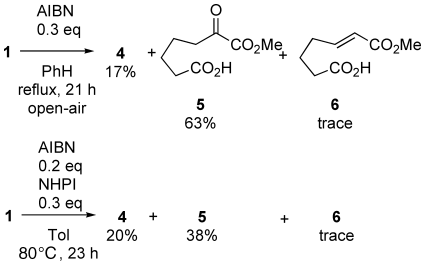

Chart 3. Oxidation Products **5** and **6** from **1** under Open-Air Conditions

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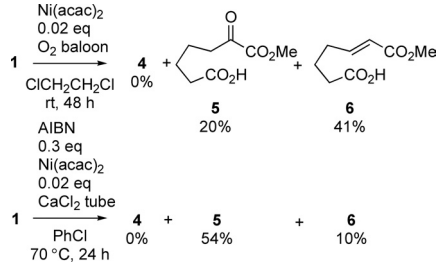


Chart 4. Nickel-Catalyzed Autoxidation Products **5** and **6** from **1**

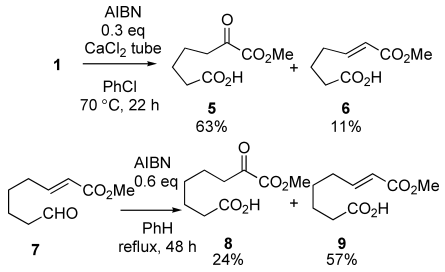


Chart 5. Autoxidation Products **5**, **6** from **1** and **8**, **9** from **7**

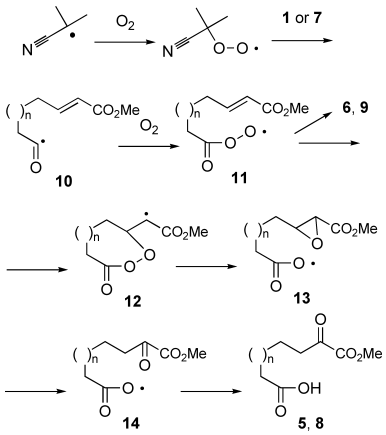


Chart 6. Autoxidation Products **5**, **6** from **1** and **8**, **9** from **7**

10% yields. It is remarkable that cyclization product **4** was not detected in these reactions, suggesting that both **5** and **6** was the direct oxidation products not coming from **4**. It is also important to note that at room temperature **6** is the major product probably derived from initially formed acyl radical.

Interestingly the reaction of **1** with AIBN under open-air conditions ($CaCl_2$ tube) in chlorobenzene at 70 °C for 22 h gave **5** and **6** in 63% and 11% yields (Chart 5). Under the similar conditions **7** was converted to ketoester **8** in 24% yield and acid **9** in 57% yield.

Attempted reaction of **1** with triethylborane-thiol or dimethylzinc-thiol,[14,15] other than diazoanalogues for radical initiator, was unsuccessful, recovering **1** unchanged.

Plausible Way to Carboxylic Acids 5, 6, 8, and 9 The reaction of formylalkenoates **1** and **7** with 1-cyano-1-methylethylperoxy radical produces acyl radical **10**, which reacts with dioxygen to give **11**, because acyl radical **10** reacts with dioxygen faster than cyclization in the present conditions (Chart 6).[16] Reduction of **11** gives carboxylic acids **6** and **9**. When the intramolecular attack of **11** to **12** is easy to take place, epoxide **13** is the major pathway. Its rearrangement to ketone **14** and reduction gives **5** and **8**. Since 7-*exo* cyclization (for **1**) is easier than 8-*exo* cyclization (for **7**), it is reasonably understandable that **1** gave ketoester **5** as a major oxidation product and **7** gave enoate **9** as a major product.[17]

In conclusion, it was demonstrated that both thiyl radical and peroxy radical, which are classified as electrophilic radicals, directly generate an acyl radical from a formyl group, while the nucleophilic 1-cyano-1-methylethyl radical does not. In the absence of dioxygen the acyl radical thus formed undergoes cyclization, however, in the presence of dioxygen it reacts preferentially with dioxygen to produce peracid radical, which attacks an intramolecular C–C double bond when it is easy to take place. We continue our journey to envision atom economical and green radical chemistry.[18—22]

Experimental

NMR (500 MHz for a proton, 125 MHz for a carbon) was measured in $CDCl_3$. Chemical shift values were expressed in ppm relative to internal tetramethylsilane. *J* values were shown in Hz. The IR spectroscopy was presented in cm^{-1} for the wave numbers of maximum absorption peaks.

The Reaction of 1 under the Strictly Deoxygenated Conditions (Chart 1) AIBN (49 mg, 0.3 mmol) was added to a solution of **1** (156 mg, 1 mmol) and *tert*-dodecanethiol (60 mg, 0.3 mmol) in benzene (10 ml). The solution was degassed three times by the freeze–thaw procedure. The mixture was then refluxed under argon atmosphere for 19 h. The crude reaction mixture was directly purified by silica gel column chromatography (hexane/ether 4/1) to give cyclic ketone **4** (139 mg, 89%) as a colorless oil.[3]

7-Methoxy-6,7-dioxoheptanoic Acid (5) and (*E*)-7-Methoxy-7-oxohept-5-enoic Acid (6) (Chart 4) A mixture of **1** (156 mg, 1 mmol) and $Ni(acac)_2$ (5 mg, 0.02 mmol) in 1,2-dichloroethane (1 ml) was stirred under an atmospheric pressure of dioxygen at room temperature for 48 h. The mixture was directly purified by silica gel column chromatography (hexane/ether 3/1) to give **5** (37 mg, 20%) as a colorless oil and **6** (70 mg, 41%) as a colorless oil.

5: ^{1}H-NMR: 1.67—1.72 (4H, m), 2.38—2.41 (2H, m), 2.87—2.90 (2H, m), 3.87 (3H, s). ^{13}C-NMR: 22.0, 23.6, 33.4, 38.6, 52.8, 161.2, 179.0, 193.6. IR (neat): 3100, 1732. EI-MS *m/z*: 188 (M^+). The spectroscopic data were identical with those of **5** prepared by the reported procedure.[11]

6: ^{1}H-NMR: 1.82 (2H, tt, *J*=7.3, 7.3), 2.28 (2H, ddd, *J*=7.3, 7.0, 1.5), 2.40 (2H, t, *J*=7.3,), 3.74 (3H, s), 5.87 (1H, dt, *J*=15.6, 1.5), 6.95 (1H, dt, *J*=15.6, 7.0). ^{13}C-NMR: 22.8, 31.2, 33.0, 51.5, 121.8, 148.0, 167.0, 179.1. IR (neat): 3202, 1728, 1659. EI-MS *m/z*: 173 (M^++H). HR-MS-CI: $[M+H]^+$ Calcd for $C_8H_{13}O_4$, 173.0814; Found, 173.0808.

The Reaction of 1 with AIBN Giving 5 and 6 (Chart 5) A mixture of **1** (156 mg, 1 mmol) and AIBN (49 mg, 0.3 mmol) in chlorobenzene (10 ml) was stirred at 70 °C for 22 h in a round-bottom flask attached with a drying tube filled with $CaCl_2$. The mixture was concentrated and purified by silica gel column chromatography (hexane/ether 3/1) to give **5** (118 mg, 63%) and **6** (19 mg 11%).

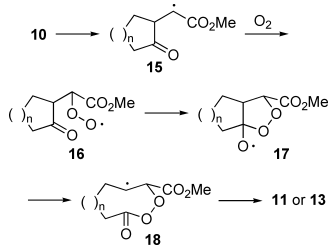
8-Methoxy-7,8-dioxooctanoic Acid (8) and (*E*)-8-Methoxy-8-oxooct-6-enoic Acid (9) (Chart 5) Formylenoate **7** (170 mg, 1 mmol), AIBN (49 mg, 0.3 mmol) and benzene (10 ml) were placed in a round bottom flask fitted with reflux condenser and a drying tube filled with $CaCl_2$. The mixture was refluxed for 24 h. Additional AIBN (49 mg, 0.3 mmol) was added to the mixture which was then refluxed for a further 24 h. The mixture was concentrated and purified by silica gel column chromatography (hexane/ether 2/1) to give **8** (48 mg 24%) as a colorless oil and **9** (106 mg, 57%) as a colorless oil.

8: ^{1}H-NMR: 1.37—1.43 (2H, m), 1.64—1.70 (4H, m), 2.37 (2H, t, *J*=7.4), 2.86 (2H, t, *J*=7.1), 3.87 (3H, s). ^{13}C-NMR: 22.4, 24.1, 28.1, 33.6, 38.9, 52.8, 161.4, 179.7, 194.0. IR (neat): 3200, 1732, 1717, 1713. EI-MS *m/z*: 202 (M^+). HR-MS-EI: [M^+] Calcd for $C_9H_{14}O_5$, 202.0841; Found, 202.0838.

9: ^{1}H-NMR: 1.50—1.56 (2H, m), 1.64—1.70 (2H, m), 2.24 (2H, dt, *J*=7.0, 7.0), 2.38 (2H, t, *J*=7.4), 3.73 (3H, s), 5.84 (1H, dt, *J*=15.6, 1.5), 6.96 (1H, dt, *J*=15.6, 7.0). ^{13}C-NMR: 24.0, 27.2, 31.7, 33.6, 51.4, 121.2, 148.9, 167.2, 179.6. IR (neat): 3200, 1724, 1659. EI-MS *m/z*: 187 (M^++H), 169 (M^+−OH). HR-MS-CI: $[M+H]^+$ Calcd for $C_9H_{15}O_4$, 187.0970; Found, 187.0975.

References and Notes

1) Recent review: Kim S., *Adv. Synth. Catal.*, **346**, 19—32 (2004).
2) Chatgilialoglu C., Crich D., Komatsu M., Ryu I., *Chem. Rev.*, **99**, 1991—2069 (1999).
3) Yoshikai K., Hayama T., Nishimura K., Yamada K., Tomioka K., *J. Org. Chem.*, **70**, 681—683 (2005).
4) Nishimura K., Tsubouchi H., Ono M., Hayama T., Nagaoka Y., Tomioka K., *Tetrahedron Lett.*, **44**, 2323—2326 (2003).
5) Ono M., Nishimura K., Tsubouchi H., Nagaoka Y., Tomioka K., *J. Org. Chem.*, **66**, 8199—8203 (2001).
6) Ono M., Nishimura K., Nagaoka Y., Tomioka K., *Tetrahedron Lett.*, **40**, 6979—6982 (1999).
7) Nishimura K., Ono M., Nagaoka Y., Tomioka K., *J. Am. Chem. Soc.*, **119**, 12974—12975 (1997).
8) Ryu I., Kusano K., Hasegawa M., Kambe N., Sonoda N., *J. Chem. Soc., Chem. Commun.*, 1018—1019 (1991).
9) Thioester synthesis by aryldisulfide trap has been reported. Nambu H., Hata K., Matsugi M., Kita Y., *Chem. Commun.*, 1082—1083 (2002).
10) Dang H.-S., Roberts B. P., *J. Chem. Soc., Perkin Trans. 1*, **1998**, 67—75 (1998).
11) Magnus P., Gazzard L., Hobson L., Payne A. H., Rainey T. J., Westlund N., Lynch V., *Tetrahedron*, **58**, 3423—3443 (2002).
12) Tsujimoto S., Sakaguchi S., Ishii Y., *Tetrahedron Lett.*, **44**, 5601—5604 (2003).
13) Yamada T., Rhode O., Takai T., Mukaiyama T., *Chem. Lett.*, **1991**, 5—8 (1991).
14) Yamamoto Y., Yamada K., Tomioka K., *Tetrahedron Lett.*, **45**, 795—797 (2004).
15) Yamada K., Yamamoto Y., Tomioka K., *Org. Lett.*, **5**, 1797—1799 (2003).
16) Brown C. E., Neville A. G., Rayner D. M., Ingold K. U., Lusztyk J., *Aust. J. Chem.*, **48**, 363—379 (1995).
17) Alternative pathway to **11** or **13** involves **18** coming from the dioxygen trap of **15** to **16**, and cyclization to **17** followed by β-fission.



18) Yamada K., Yamamoto Y., Tomioka K., *J. Synth. Org. Chem., Jpn.*, **62**, 1158—1165 (2004).
19) Yamamoto Y., Maekawa M., Yamada K., Tomioka K., *Tetrahedron*, **61**, 379—384 (2005).
20) Yamada K., Yamamoto Y., Maekawa M., Chen J., Tomioka K., *Tetrahedron Lett.*, **45**, 6595—6597 (2004).
21) Yamada K., Yamamoto Y., Maekawa M., Tomioka K., *J. Org. Chem.*, **69**, 1531—1534 (2004).
22) Yamada K., Fujihara H., Yamamoto Y., Miwa Y., Taga T., Tomioka K., *Org. Lett.*, **4**, 3509—3511 (2002).