# Synthesis of Five- and Six-Membered-Ring Compounds by Environmentally Friendly Radical Cyclizations Using Kolbe Electrolysis

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**Abstract:** Substituted carbocycles, tetrahydrofurans, and tetrahydropyrans can be efficiently obtained from ω-unsaturated carboxylic acids. Our methodology involves a Kolbe decarboxylation followed by an intramolecular radical cyclization and a radical–radical cross-coupling process.

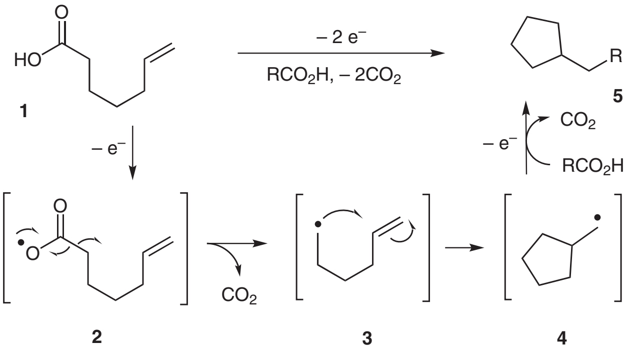
**Key words:** cyclization, electron transfer, green chemistry, heterocycles, radical reactions

Over the past decades, the development and synthetic applications of radical reactions have expanded at a remarkable rate.[1] Nowadays, the generation of five- and six-membered ring compounds using radical cyclization methods has become an efficient, well-established, and reliable synthetic procedure. In many cases, elaborate polycyclic structures can be readily assembled using radical-based technologies.[2] However, in spite of numerous efforts, most of these useful radical-mediated transformations have been carried out using stoichiometric amounts of toxic reagents, such as organostannanes[3] or organomercury derivatives,[4] expensive hydride sources, such as tris(trimethylsilyl)silane,[5] or noxious substrates like the xanthates.[6]

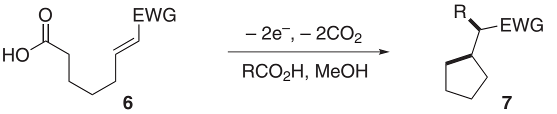
Radical species can be generated by a number of alternative methods, including electrochemistry.[7] Indeed, recent studies have reported the generation of primary radicals by electroreductive techniques usually involving a nickel[8] or cobalt electrocatalysis.[9] Among the oxidative electro-organic reactions, the Kolbe electrolysis is likely the most famous.[10]

This transformation, which involves radical intermediates, has been used as a simple and environmentally friendly procedure to obtain long-chain alkanes from short-chain carboxylic acids.[11,12] Moreover, seminal contributions by Schäfer et al. have demonstrated that cyclic compounds **5** can be obtained by suitable positioning of an unsaturation in the starting material (Scheme 1).[13] It is noteworthy that capture of intermediate **4** by a radical derived from a co-acid leads ultimately to the overall creation of two carbon–carbon bonds.

However, despite obvious synthetic interests, the utility of the Kolbe electrolysis in promoting these cyclizations has been somewhat neglected most probably due to the modest yields observed in these reactions. Indeed, initial attempts to enhance the yield of the ring closure of **1** into **5** proved unsuccessful. We envisioned that this misfortune could be linked to the nucleophilic behavior of radical intermediate **3**[14] and, consequently, that higher yields and wider scope could be obtained by employing substrates such as **6**, bearing an electron-deficient alkenyl substituent (Scheme 2).



**Scheme 1** Proposed mechanistic sequence: Kolbe decarboxylation–radical cyclization–radical capture



**Scheme 2** Electrochemical cyclization of **6**

In this communication, we wish to report the successful implementation of this electrochemically based cyclization strategy. At the onset of our work, it was decided to examine the radical cyclization of the linear substrate **8a** (Figure 1), possessing a carboxylic acid function and a suitably positioned enoate residue. Electrochemically mediated ring closure of **8a** should deliver a substituted cyclopentane derivative. Precursors **8b–d**, containing other electron-withdrawing groups at the ε-position or able to generate a six-membered ring adduct **8e** (Figure 1), will also be investigated.

Substrates **8a–d** were synthesized in a straightforward manner, according to the sequence outlined in Scheme 3. Various electron-withdrawing groups were introduced by Horner–Emmons olefination of aldehyde **13** and hydrogenolysis of benzyl esters **14a–d** proceeded quantitatively and chemoselectively.

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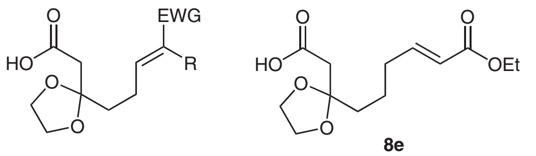
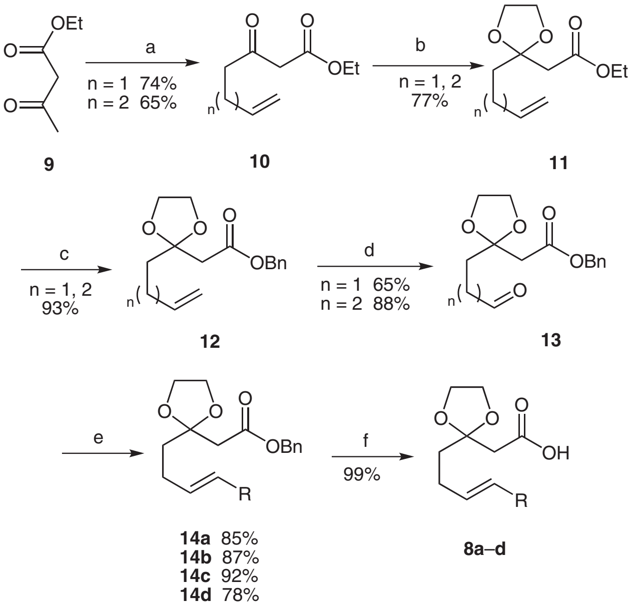


**8e**

**8a** EWG = Boc, R = H
**8b** EWG = CN, R = H
**8c** EWG = Ac, R = H
**8d** EWG = $CO_2Et$, R = Me

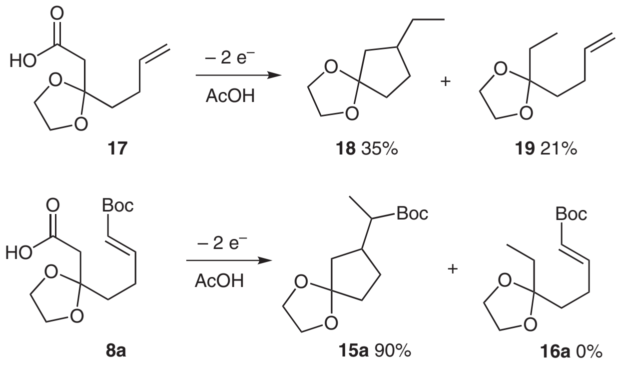
**Figure 1** Five- and six-membered carbocycle precursors



**Scheme 3** Synthetic procedure for substrates **8a**–**d**. *Reagents and conditions*: (a) NaH (1.1 equiv), *n*-BuLi (1.1 equiv), allyl bromide (1 equiv; or butenyl bromide for **8e**), THF, 0 °C; (b) ethylene glycol, PTSA (cat.), benzene, reflux; (c) Ti(O*i*-Pr)$_4$, BnOH, 100 °C, 3 h; (d) $NaIO_4$ (2.5 equiv), $OsO_4$ (1 mol%), THF–$H_2O$, toluene, 1 h; (e) $(MeO)_2P(O)CH_2R$ (1.1 equiv), KO*t*-Bu (1.1 equiv), THF, 0 °C; (f) $HCO_2NH_4$ (2 equiv), Pd/C (10 mol%), MeOH.

With the desired precursors in hand, typical Kolbe conditions[15] were employed initially in the electrochemical step, resulting in modest yields that were rapidly improved by modulating the main parameters pertaining to this reaction. Hence, the current density, which has a significant influence on the overall yield, should be kept between 80 and 120 mA/cm$^2$. Furthermore, the use of smooth platinum electrodes, a weakly acidic medium (partial neutralization of the acids with 5 mol% of KOH), a high dilution in MeOH (40–80 mM in substrate) and an excess of the co-acid (5 equiv) provided the best results. Eventually, it was also noticed that a switching electrical supply was useful in preventing the fading out of the current due to the formation of a layer of black deposit on the electrodes.[16] These optimized conditions were then applied to substrates **8a** and **17**.

Whilst cyclization of **17** proceeded smoothly, affording the substituted cyclopentane **18** in 35% yield, a significant amount of linear product **19** (21%) was also generated in this process. It thus appears that the capture of the intermediate radical (**3**, Scheme 1) by the co-acid competes significantly with the addition of this radical species onto the nonactivated alkene. In stark contrast, Kolbe decarboxylation–radical cyclization of acid **8a**, under identical conditions, afforded exclusively the five-membered ring ketal **15a** in an excellent 90% isolated yield, albeit as a 1:1 mixture of diastereoisomers (Scheme 4). No trace of the linear product **16a** could be detected in this experiment.



**Scheme 4** Kolbe electrolysis–radical cyclization

The other substrates **8b**–**e** were then submitted to these conditions and the results are collected in Table 1. Excellent yields and selectivities are observed for substrates **8a** and **8b** in the presence of various co-acids. As can be seen in entry 1, acetic, propanoic, and isobutyric acids are competent co-acids, leading to adducts **15a**–**c** bearing a methyl, ethyl, and isopropyl substituent, respectively. Whilst the unsaturated nitrile **8b** cyclizes smoothly to **15d** (entry 2), the corresponding enone **8c** only affords the saturated product **21**. This cathodic reduction takes place faster than the desired anodic oxidation because of the much lower reduction potential of the enone **8c** as compared to substrate **8a** (Figure 2).

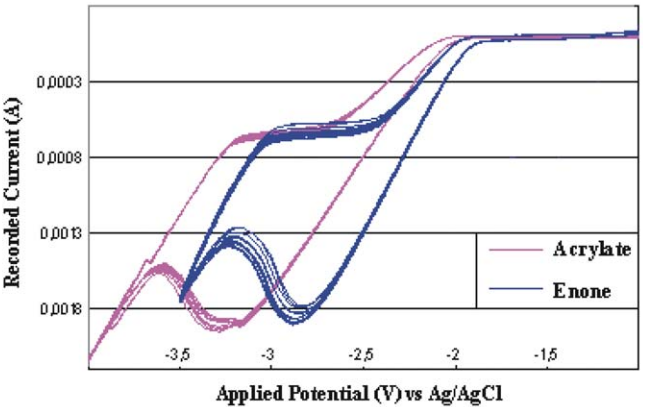
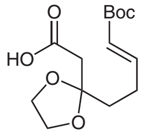
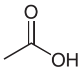
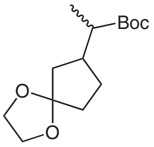
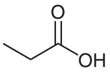
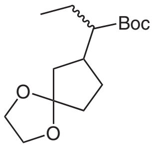
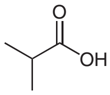
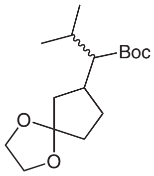
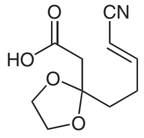
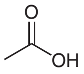
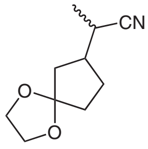
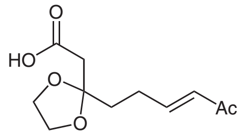
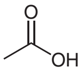
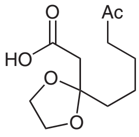
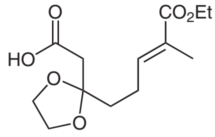
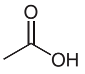
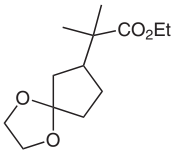
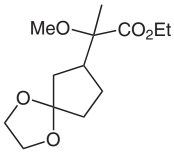
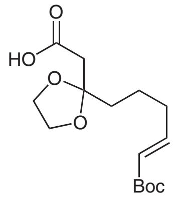
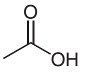
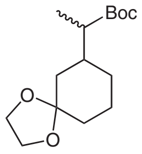
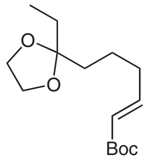


**Figure 2** Reduction potentials of acrylate **8a** and enone **8c**

The Kolbe decarboxylation–radical cyclization of the substituted ester **8d** proceeded efficiently, affording **15e** and **20** in a combined yield of 80%. The methyl ether **20** originates from the oxidation of the intermediate tertiary radical akin to **4**, into the corresponding carbocation, fol-

**Table 1** Carbocycle Synthesis

| Entry | Substrate | Co-acid | Products | | Yield (%) |
|---|---|---|---|---|---|
| 1 | <br>**8a** |  | <br>**15a** | | 90 |
| | |  | <br>**15b** | | 78 |
| | |  | <br>**15c** | | 75 |
| 2 | <br>**8b** |  | <br>**15d** | | 65 |
| 3 | <br>**8c** |  | <br>**21** | | 80 |
| 4 | <br>**8d** |  | <br>**15e** | <br>**20** | 50 (**15e**)<br>30 (**20**) |
| 5 | <br>**8e** |  | <br>**15f** | <br>**16e** | 64 (**15f**)<br>16 (**16e**) |

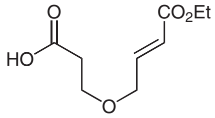
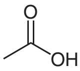
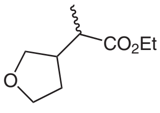
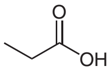
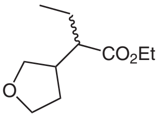
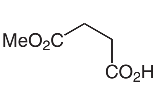
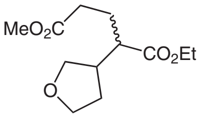
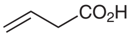
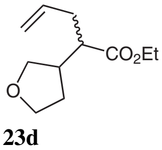
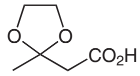
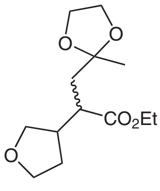
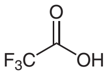
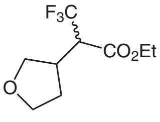
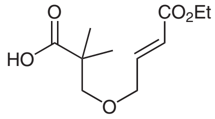
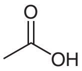
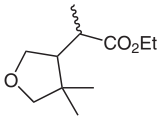
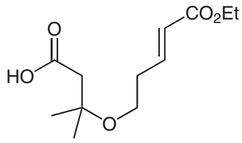
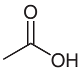
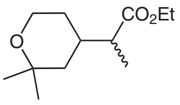
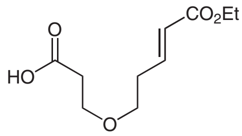
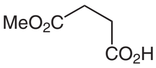
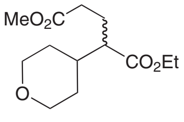
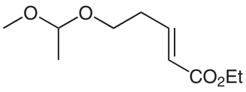
lowed by capture by methanol. Finally, six-membered carbocyles can also be generated under these electrochemical conditions, as shown in Table 1, entry 5. In this case, and for the first time, a small amount of the linear isomer **16e** has also been produced, no doubt due to the lower rate of cyclization.

In order to expand the scope of this electrochemically mediated radical cyclization methodology, we applied these conditions to substrates **22a**–**d**, possessing an ether function (Figure 3).

The ring closure of **22a** and **22b** should lead to substituted tetrahydrofurans whilst **22c** and **22d** should generate the corresponding tetrahydropyrans. Substrate **22b** was selected in order to verify if an electrogenerated tertiary radical would undergo cyclization whereas **22c** would enable us to test the importance of the Thorpe–Ingold effect. Carboxylic acids **22a–d** (Figure 3) were synthesized in 70–80% overall yields, according to general procedures that shall be reported elsewhere.

The carboxylic acids **22a–d** were then submitted to the Kolbe electrolysis under our optimized conditions. The results are collected in Table 2. As can be seen, electrolysis of **22a** proceeded smoothly and delivered the desired tetrahydrofurans **23a–e** in good to excellent yields (entry 1). A wide range of functionalized co-acids could be employed in this transformation, leading to variously substi-

**Table 2** Heterocycle Synthesis

| Entry | Substrate | Co-acid | Products | Yield (%) |
|---|---|---|---|---|
| 1 | <br>**22a** |  | <br>**23a** | 86 |
|  |  |  | <br>**23b** | 72 |
|  |  |  | <br>**23c** | 90 |
|  |  |  | <br>**23d** | 89 |
|  |  |  | <br>**23e** | 87 |
|  |  |  | <br>**23f** | 0 |
| 2 | <br>**22b** |  | <br>**24** | 16–24 |
| 3 | <br>**22c** |  | <br>**25** | 89 |
| 4 | <br>**22d** |  | <br>**26**<br><br>**27** | 57[a] |

[a] Yield of cyclized product **26** (yield of **27**: 35–40%).

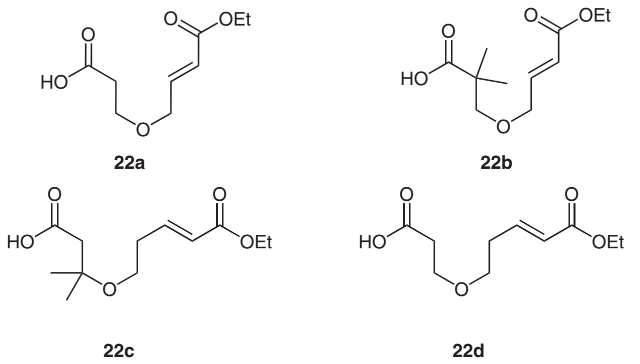


**Figure 3** Five- and six-membered heterocyclic precursors

tuted heterocycles. Only electron-deficient co-acids, such as trifluoroacetic acid, failed to couple with **22a**, most probably because of identical polarity of the in situ generated radicals.

In contrast, the tertiary radical derived from **22b** cyclized only poorly, probably owing to its steric hindrance (Table 2, entry 2). Whereas acid **22c** was smoothly transformed into tetrahydropyran **25** (Table 2, entry 3), the removal of the *gem*-dimethyl substituent resulted in a reduced yield of **26** (entry 4).[17]

In summary, we have developed an efficient electrochemical method for the ecologically benign and safe synthesis of substituted carbocycles, tetrahydrofurans, and tetrahydropyrans from ω-unsaturated carboxylic acids. Our approach embodies a Kolbe decarboxylation followed by a radical cyclization. The intermediate radical is finally captured by another radical, generated by the concomitant decarboxylation of the co-acid, leading to the generation of two carbon–carbon bonds in a single operation. The simplicity, broad functional-group tolerance and good yields, provided by this electrochemical oxidation, makes this procedure an attractive methodology for the synthesis of variously functionalized cyclic structures.

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(16) **Representative Procedure for the Electrochemical Synthesis of Carbocycles and Heterocycles**
In an undivided beaker-type cell (100 mL) bearing two

electrodes of platinum foil (1.3 cm × 1.3 cm × 0.5 mm), acid **22a** (500 mg, 2.47 mmol) and a fivefold excess of AcOH (707 mL, 12.38 mmol) were dissolved in MeOH (50 mL). The acids were partially neutralized by NaOMe to obtain a current density of 100 mA/cm$^2$. The reaction was monitored by TLC or GC and stopped when the pH of the solution changed from 5 to 8; normally 1.2–1.4 F/mol had been consumed. The reaction mixture was then concentrated under reduced pressure. The residue was treated with a sat. aq solution of $NaHCO_3$, and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were collected, dried on $Na_2SO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (PE–$Et_2O$, 4:1) to afford 366 mg of compound **23a** (86%, mixture of two inseparable diastereomers, A/B = 1:1) as a colorless liquid smelling of fruit. GC [60 °C (3 min), 15 °C/min → 290 °C, 290 °C (1 min)]: $t_R$ = 10.90, 11.02 min. IR (neat): 647, 732, 915, 1047, 1076, 1179, 1262, 1377, 1459, 1725, 2873, 2978. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, 3 H, A, *J* = 6.6 Hz), 1.20 (d, 3 H, B, *J* = 6.6 Hz), 1.24 (t, 3 H, A, *J* = 7.2 Hz), 1.26 (t, 3 H, B, *J* = 7.2 Hz), 1.50–1.65 (m, 1 H, A + B), 1.95–2.20 (m, 1 H, A + B), 2.25–2.55 (m, 2 H, A + B), 3.40–3.46 (dt, 1 H, A + B, *J* = 7.8, 2.2 Hz), 3.60–3.95 (m, 3 H, A + B), 4.08–4.18 (m, 2 H, A + B). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 14.20 (A), 14.23 (B), 16.1 (A), 16.2 (B), 30.3 (B), 30.8 (A), 42.39 (A), 42.41 (B), 42.90 (B), 42.93 (A), 60.4 (A + B), 68.0 (A), 68.1 (B), 71.1 (A), 71.9 (B), 175.7 (A + B). MS (APCI): *m/z* (%) = 82.9 (15), 126.9 (95), 144.9 (15), 173.0(10). HRMS (sodium complex): *m/z* calcd: 195.0997; found: 195.0998.

(17) Compound **27** originates from a possible rearrangement of either the primary radical or the derived carbocation. Studies are currently ongoing to elucidate this intriguing transformation.