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UNSATURATED LACTONES: SYNTHESIS AND APPLICATIONS

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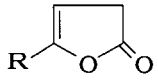
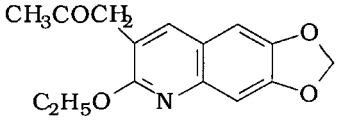
Abstract: An easy approach to the synthesis of substituted unsaturated lactones is described, and the reactions of these compounds with nucleophiles leading to the formation of useful intermediates are reported.

Unsaturated lactones of the 2(3H)-furanone type **1** are useful intermediates in the synthesis of more complex, biologically active heterocyclic compounds. For example, α-angelicalactone **2** is a starting material in a two-step synthesis of compound **3**, a drug used in the treatment of the central nervous system and circulatory disorders (1). α-Angelicalactone and other related unsaturated lactones have been employed in a variety of procedures leading to the formation of heterocyclic systems (2,3).



1

2 **R = CH_3**



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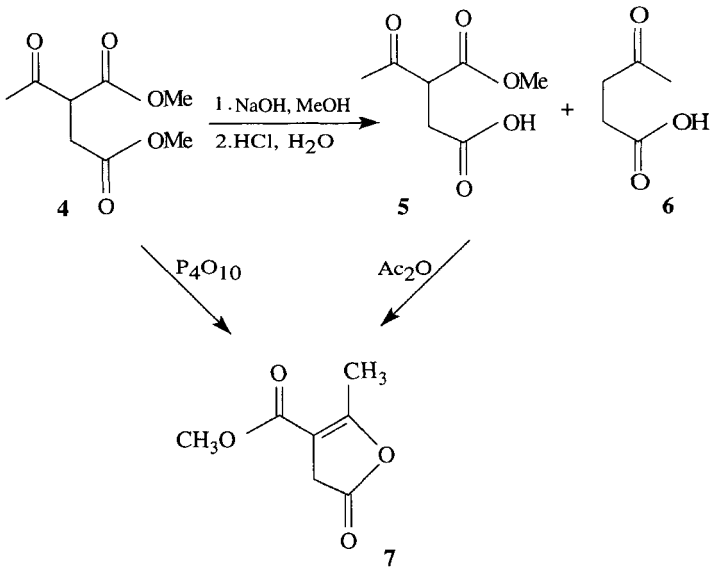
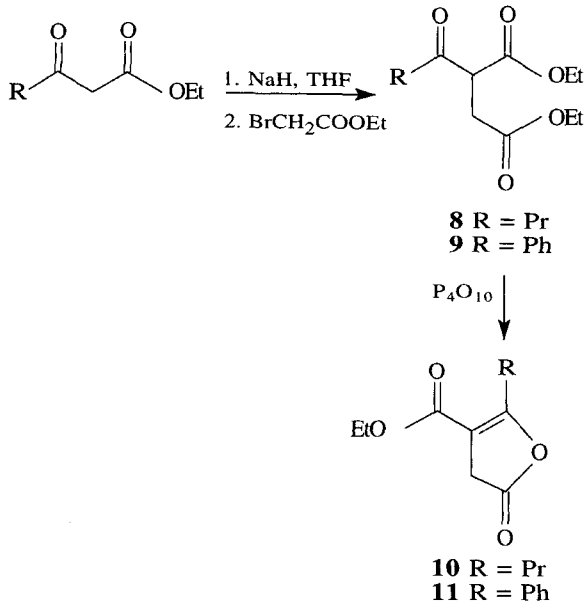
[1] To whom correspondence should be addressed



Scheme 1

A number of procedures for the synthesis of these useful compounds have been developed, most of them with a specific target lactone in mind (4-10). We wish to report an easy, general synthesis of 3,5-substituted 2(3H)-furanones, and their uses as versatile intermediates in chemical synthesis.

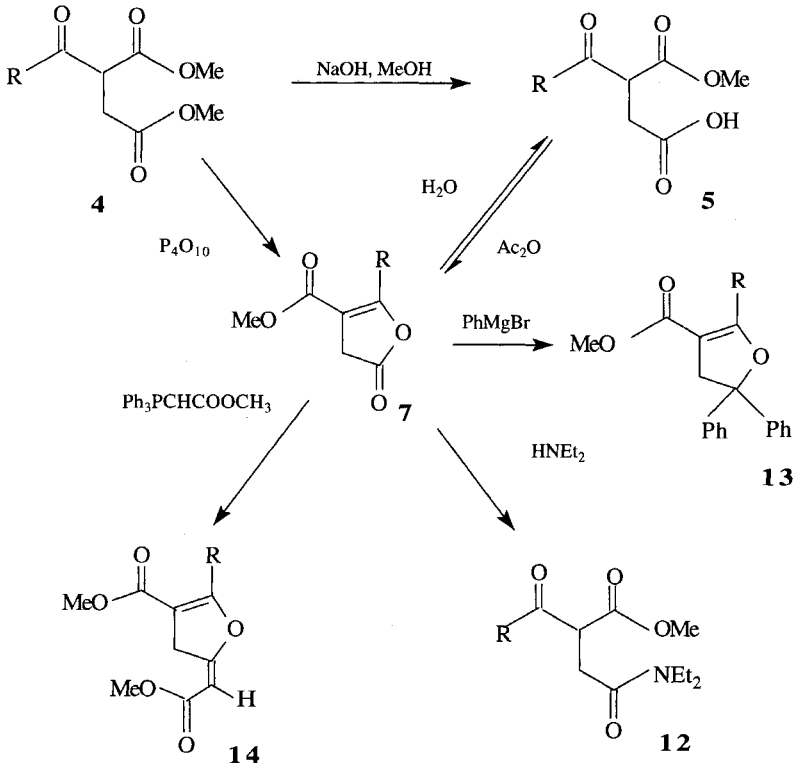
Hydrolysis of dimethyl acetylsuccinate **4** (11) with sodium hydroxide (6N) in methanol yielded monomethyl acetylsuccinate **5** (65%) as the major product (12). In addition, a small quantity (18%) of levulinic acid **6** was also isolated from the reaction mixture. Cyclization of **5** in refluxing acetic anhydride gave lactone **7** in 90% (13) yield. A more direct route to compound **7** was achieved when dimethyl acetylsuccinate **4** on heating with P_4O_{10} under vacuum gave the lactone in 77% yield (14), as illustrated in Scheme 1.



Scheme 2

Further experiments have shown that 2(3H)-furanones with a variety of substituents in position 5 can be prepared, from the readily accessible ß-ketoesters as shown in Scheme 2. Thus, compounds **8** and **9** were converted to diethyl succinates which on heating with P_4O_{10} gave the corresponding 2(3H)-furanones **10** and **11** in reasonably good yields (15).

The unsaturated lactones **7**, **10**, and **11** react readily and cleanly with nucleophiles. Thus, the hydrolysis gives the corresponding monoester succinates such as compound **5**. Similarly, reactions with $HNEt_2$ occur selectively at the carbonyl group in the furanone ring to give the corresponding amide esters **12** (16). Grignard reaction with PhMgBr leads, predictably, to the diphenyl substituted compounds **13** (17), while stabilized



Scheme 3

phosphoranes, such as $Ph_3PCHCOOCH_3$, add to the carbonyl group of the furanone ring to give compounds **14** (18) (Scheme 3).

These preliminary experiments demonstrate a synthetic utility of unsaturated lactones, readily obtainable through the simple procedures described in this communication. Further applications for these compounds are presently explored and will be reported in due course.

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(11) Product **4**: IR ($CHCl_3$, ν cm^{-1}): 1700, 1710; ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H), 2.84 (dd, 2H), 3.02 (dd, 1H), 3.73 (s, 3H), 3.90 (dd, 1H). MS (70eV): m/z 174 (M+).
(12) The hydrolysis of dimethyl acetylsuccinate **4** in sodium hydroxide/methanol was accomplished by stirring overnight at room temperature. The solvent was removed under vacuum at room temperature and the residue was acidified with 6 N HCl to pH 0. The products are extracted with ether. The combined extracts were dried and concentrated. The residue was distilled under vacuum to give **5** as the major product (65% yield). B.p. 110-115°C/0.5 Torr. IR ($CHCl_3$, ν cm^{-1}): 1700, 1710. ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.88 (dd, J=6.53, 17.5, 1H), 3.03 (dd, J=8.16, 17.89, 1H), 3.77 (s, 3H), 3.96 (dd, J=7.82, 6.59, 1H). MS: m/z 174 (M+).
(13) Monoester **5** was converted to **7** in 90% yield by refluxing in acetic anhydride. IR ($CHCl_3$, ν cm-1): 1720, 1740. ^1H NMR ($CDCl_3$): δ 2.40 (t, J=2.4, 3H), 3.43 (q, J=2.4, 2H), 3.771 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 172.8, 163.6, 115.2, 106.0, 51.6, 33.5, 13.7. HRMS: observed: 156.0424, calculated for $C_7H_8O_4$: 156.0422.
(14) A direct conversion to **7** can be accomplished by heating acetylsuccinate with P_4O_{10} in equimolar ratio at 160°C under vacuum for 5 hr. The resulting black mixture can be distilled or sublimed to give unsaturated lactones **7**, **10**, and **11** in 75% to 85% yields.
(15) Compounds **8** and **9** were prepared by the following general procedure: A slurry of sodium hydride (10 mmol) in dry THF (10 mL) was added to a stirred solution of the appropriate ß-ketoester (10 mmol) in dry THF (10 mL) at 4°C. The stirring was continued at room temperature until hydrogen evolution had ceased. At that point a solution of ethylbromoacetate (10 mmol) in THF (5 mL) was added at 4°C and the mixture was stirred for 1 hr at room temperature. The reaction mixture was acidified with 10% HCl until pH 3. The resulting solution was extracted with ether. The ether layer was dried and concentrated to give the product. Product **8** (80% yield): IR ($CHCl_3$, ν cm^{-1}): 1720. ^1H NMR ($CDCl_3$): δ 0.92 (t, J=7.2, 3H), 1.27 (m, 6H), 1.65 (m, 2H), 2.66 (m, 2H), 2.81 (dd, J=6.5, 17.5, 1H), 2.86 (dd, J=8.2, 17.9, 1H), 3.97 (t, J=6.7, 1H), 4.16 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 171.4, 170.7, 168.5, 61.7, 60.9, 54.0, 44.6, 37.5, 32.4, 16.8, 14.1, 14.0. MS:

m/z 244 (M+). Product **9** (81% yield): IR ($CHCl_3$, ν cm^{-1}): 1685, 1735. ^1H NMR ($CDCl_3$): δ 1.16 (m, 6H), 3.00 (d, J=7.6, 2H), 4.07 (t, J=7.8, 4H), 4.82 (t, J=7.4, 1H), 7.43 (m, 3H), 7.98 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 194.2, 171.2, 168.7, 135.9, 133.7, 128.7, 61.8, 61.0, 49.6, 33.3, 14.1, 13.9. MS: m/z 278 (M+).

4-Carboxyethyl-5-propyl-2(3H)-furanone **10** and 4-carboxyethyl-5-phenyl-2(3H)-furanone **11** were prepared by heating the corresponding succinic esters **8** and **9** with P_4O_{10} under vacuum as described above. Compound **10** (85% yield): IR ($CHCl_3$) ν cm^{-1}): 1650, 1700, 1807. ^1H NMR ($CDCl_3$): δ 0.92 (t, J=6.2, 3H), 1.24 (t, J=7.1, 3H), 1.68 (m, 2H), 2.78 (t, J=7.8, 2H), 3.35 (t, J=1.1, 1H), 4.17 (q, J=8.0, 2H). ^{13}C NMR ($CDCl_3$): δ 173.1, 168.5, 163.1, 106.1, 60.9, 33.7, 29.1, 19.9, 14.2, 13.6. MS: m/z 198 (M+, 40%), 152 (M+ - EtOH, 75%), 71(100%). Compound **11** (75% yield): IR ($CHCl_3$, ν cm^{-1}): 1658, 1700, 1808. ^1H NMR ($CDCl_3$): δ 1.21 (t, J=6.1, 3H), 3.59 (s, 2H), 4.07 (q, J=6.1, 2H), 7.27 (m, 3H), 7.81 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 217.8, 172.3, 131.5, 129.4, 128.7, 128.0, 127.3, 60.9, 35.6, 29.7, 14.1. MS: m/z 232 (M+, 45%), 186(52%), 105(100%).

(16) Methyl 2-acetyl-3-(diethylcarbamoyl)propionate **12**: A mixture of **7** (1.7 mmol) and $NHEt_2$ (5mL) was refluxed for 30 min. The solvent was removed to give **12** in 70% yield. IR ($CHCl_3$, ν cm^{-1}): 1630, 1707. 1H NMR ($CDCl_3$): δ 1.22 (t, J=7.2, 3H), 1.69 (t, J=7.1, 3H), 2.41 (s, 3H), 2.84 (dd, J=16.7, 5.6, ^1H), 3.07 (dd, J=16.5, 8.7, ^1H), 3.35 (m, 4H), 3.75 (s, 3H), 4.20 (dd, J=8.6, 5.6, 1H). ^{13}C NMR ($CDCl_3$): δ 203.1, 169.6, 169.1, 54.3, 52.6, 42.0, 40.3, 32.2, 30.6, 14.0, 12.8. MS: m/z 229 (M+, 4%), 198(M+ -OCH_3, 27%), 186(M+ -CH_3CO, 100%), 129(M+ -$CON(Et)_2$, 66%)..

(17) 5,5-Diphenyl-3-methoxycarbonyl-2-methyl-(3H)-dihydrofuran **13** was prepared in 51% yield. IR ($CHCl_3$, ν cm^{-1}): 1650,1700. ^1H NMR ($CDCl_3$): δ 2.78 (s,3H), 3.62 (s,2H), 3.70 (s,3H), 7.35 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 166.7, 145.1, 128.4, 128.0, 127.6, 125.7, 101.5, 91.6, 51.0, 44.1, 14.4. MS: m/z 294 (M+ 7%), 262 (M+ -CH_3OH, 100%), 252 (72%), 247 (55%), 191 (87%).

(18) A mixture of **7** (R=CH_3) (5 mmol) and methyl (triphenylphosphoran-ylidene) acetate (5 mmol) in 20 mL of dry toluene was refluxed for 2 hrs. The solvent was evaporated under vacuum. The residue was purified by chromatography on a silica gel column to give **14** in 68% yield. IR ($CHCl_3$, ν cm^{-1}): 1720, 1741. ^1H NMR ($CDCl_3$): δ 2.55 (s, 3H), 3.63 (s, 2H), 3.73 (s,3H), 3.80 (s, 3H), 6.46 (m, 1H). MS: m/z 212 (M+, 58%), 181 (M+ -CH_3O, 36%), 153 (M+ - CH_3OCO, 100%).

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