SOME ALTERNATIVE SYNTHETIC ROUTES TO γ- AND δ-OXO ACID DERIVATIVES

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Received 09-05-2002

Abstract

Several simple and special procedures are reviewed for the preparation of alicyclic and cycloalkane condensed γ- and δ-oxocarboxylic acids in this paper. These synthons have great importance in the synthesis of benzene condensed carbocycles, five to seven-membered heterocycles or natural products, therefore formation of oxo acids requires in many cases unusual and peculiar synthetic methods in respect to simplicity, yield, variability of substituents and stereo- or regioselectivity. Besides conventional Friedel-Crafts and Grignard reactions numerous alternatives are recommended in this review.

Introduction

The γ- and δ-oxo acid derivatives (esters, lactones) are often applicated starting compounds for the preparation of benzene condensed polycyclic carbocycles[1,2] (tetralone and its analogues) and different heterocycles.[3] On the other hand oxo acids are also useful synthons in the course of the synthesis of natural products[4,5] and serve as precursors for chiral auxiliary in asymmetric reactions.[6-8]

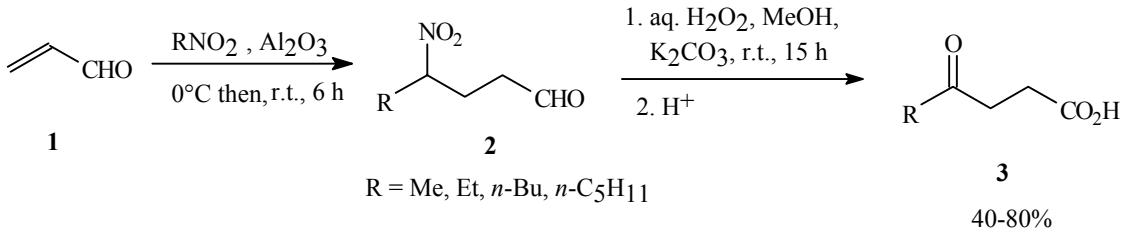
The most common and widely used procedure for synthesis of these oxo acids is based on the Friedel-Crafts reaction, starting from suitable aromatic agents (substituted or condensed benzene, thiophene, or *N*-acyl-pyrrole derivatives) with cyclic anhydrides (*e.g.* succinic, glutaric, maleinic, phthalic anhydride) in the presence of anhydrous Lewis acids ($AlCl_3$, $AlBr_3$ or $FeCl_3$).[9-13] Cycloalkane skeleton anhydrides resulted in 2-aroyl cycloalkanecarboxylic acids diastereoselectively in this way,[14-16] moreover asymmetric cyclic anhydrides (camphoric and alkyl- or phenylsuccinic anhydrides) showed considerable regioselectivity.[17-19]

The Grignard reaction is also useful and well-known method which applies cyclic anhydrides with alkyl-, aryl- or heteroarylmagnesium and zinc halides in tetrahydrofuran or ether solution usually at room temperature. This method allows higher variability regarding the acyl group.[20-23]

Numerous unusual and special methods are presented below, which are suitable for the synthesis of (poly)substituted or cycloalkane skeleton γ- or δ-oxo acid derivatives.

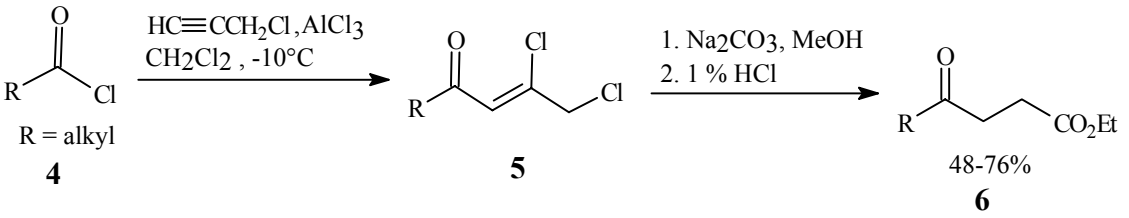
Results and discussion

A simple procedure for the synthesis of the levulinic acid **3** (R = Me) and its analogues is depicted in Scheme 1. Conjugate addition of primary nitroalkanes to acrolein on alumina surface in the absence of a solvent and oxidation of the 4-nitroalkanals **2** thus obtained keto acids **3** with hydrogen peroxyde, then acidification.[24]



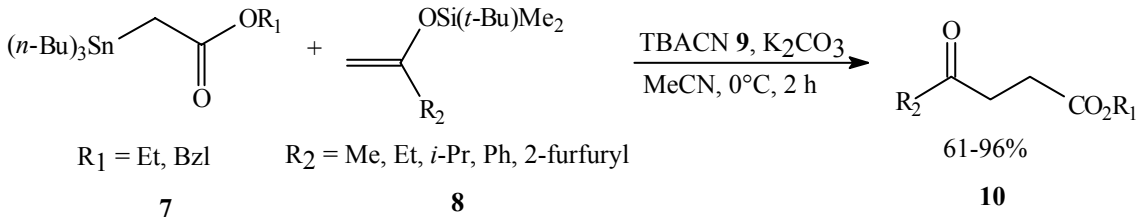
Scheme 1

Methyl 4-oxoalkanoates **6** have benn obtained in good yields by treatment of 1,2-dichloro-2-alken-4-ones **5** with sodium carbonate in methanol followed by acid-catalyzed hydrolysis (Scheme 2) of intermediate 5-alkyl-2,2-dimethoxy-2,3-dihydrofurans.[25] Dichloro ketone **5** was obtained starting from propargyl chloride and acyl chlorides by anhydrous aluminium chloride catalyzed acylation.



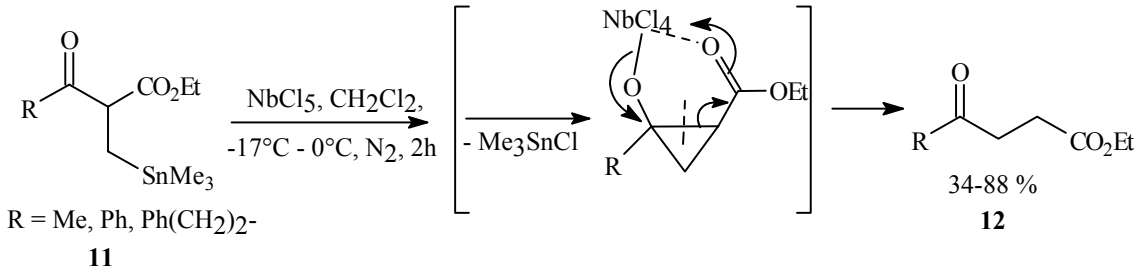
Scheme 2

The oxidation of α-tributylstannyl alkanoates **7** with tetrabutylammonium hexanitratocerate (IV) **9** generated α-radicals of the alkanoates by eliminating the stannylium ion. The thus-formed radicals reacted with various electron-rich olefinic compounds, such as silyl enol ethers **8**, giving addition products (Scheme 3) in good yield. This method formally achieves selective and oxidative cross coupling to prepare γ-keto alkanoates.[26]



Scheme 3

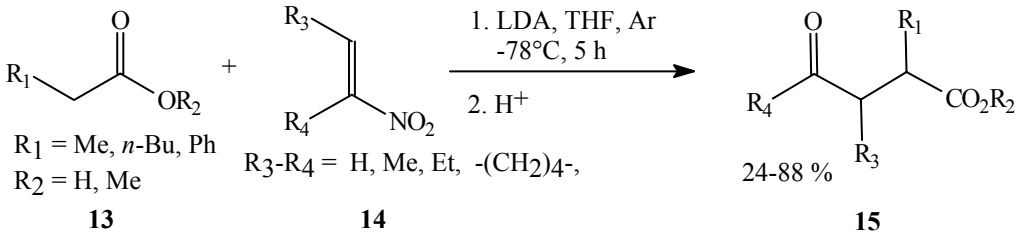
In the presence of niobium(V)chloride an α-trialkylstannylmethyl-β-keto ester **11** was homologated to the corresponding γ-keto ester **12** at low temperature in moderate to good yields (Scheme 4).



Scheme 4

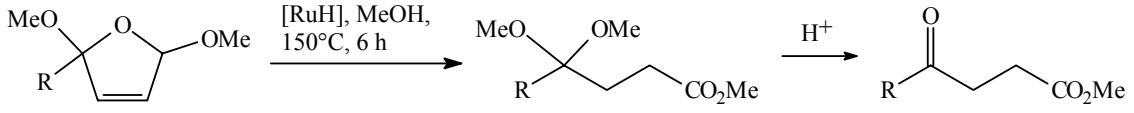
In a plausible mechanism, **11** forms the corresponding cyclopropanol-niobium-complex, which is cleaved at a C-C bond of the cyclopropanol ring. Optimalized temperature is –17 °C, but the reaction also takes place at 0 °C or room temperature, though the yields are then lower.[27] The starting compound **11** was prepared from β-keto ester with iodomethyl tributyltin in dry tetrahydrofuran in the presence of sodium hydride for 2 hours at 45°C.

Base-sensitive conjugated nitro olefins **14** reacted with lithium enolates of esters **13** at a low temperature and subsequent treatment of the Michael adducts with aqueous acid (Scheme 5) yielded 2,3-disubstituted γ-keto acids or esters in a one-pot operation.[28]



Scheme 5

γ-Keto esters are obtained in excellent yields by means of double bond migration of 2,5-dimethoxy-2,5-dihydrofurans **16** (Scheme 6) mediated by a ruthenium hydride complex, $HRuCl(PPh_3)_3(C_6H_5CH_3)$ or $HRuCl(CO)(PPh_3)_3$ and subsequent hydrolysis in acidic media.[29]



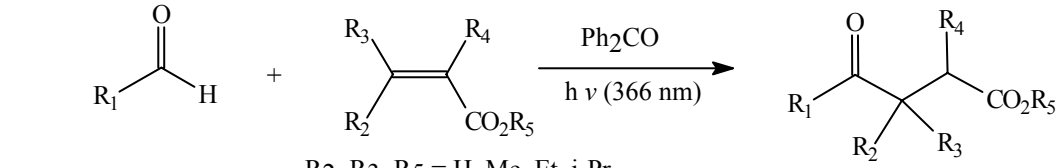
R = H, Me, Bu

16 **17** **18**

77- 91 %

Scheme 6

Facile photochemical synthesis of some polysubstituted γ-oxo alkanoic acids and esters **21** was achieved in a one-step procedure (Scheme 7) by benzophenone-initiated photochemical addition of aldehydes **19** to α,β-unsaturated carboxylic acids and esters.[30]



R_1 = Me, *n*-Pr, *i*- Pr, Ph

R_2, R_3, R_5 = H, Me, Et, i-Pr

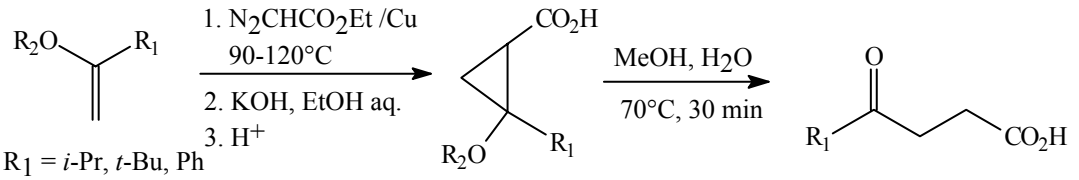
R_4 = H, Me, CO_2Et

10-81 %

19 **20** **21**

Scheme 7

(*Z*/*E*)-2-Alkoxycyclopropanecarboxylic esters were prepared from enol ethers **22** and ethyl diazoacetate. After saponification the corresponding acid was transformed to aliphatic keto acids almost quantitatively (Scheme 8) in water-methanol solution, heating at 70°C.[31]



R_1 = *i*-Pr, *t*-Bu, Ph

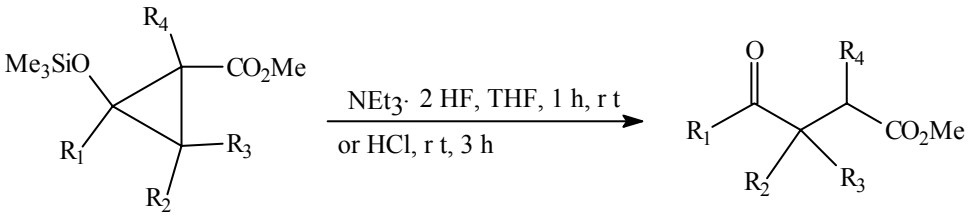
R_2 = Me, Et

89-97 %

22 **23** **24**

Scheme 8

A great variety of methyl 2-(trialkylsiloxy)cyclopropanecarboxylates **25** are cleaved under very mild conditions and with excellent yields providing 2,3,5-trisubstituted 4-oxoalkanoic esters (Scheme 9).[32]



R_1 = H, Me, Pr, *t*-Bu, Ph
R_2, R_3 = H, Me R_4 = H, Me, *n*-Bu, Bzl

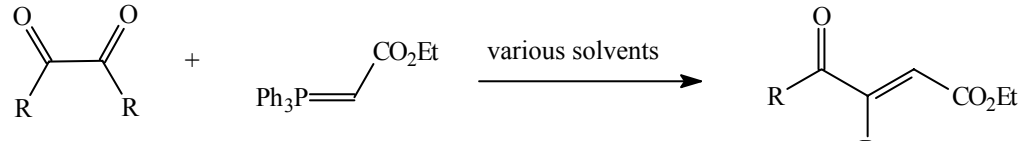
25

63 - 98%

26

Scheme 9

A series of reactions between Wittig or Wittig-Horner (Wadsworth-Emmons) reagents and diketones was studied and several solvents were tested, namely dichloromethane, toluene, ethanol, dimethylformamide, however only pyridine had significant effect on the *Z* : *E* ratio of isomeric products. In this way diketones **27** were reacted with carboethoxymethylene triphenylphosphorane (Scheme 10) in different solvents to obtained unsaturated oxo esters **29** in excellent yield (81-94 %).[33]



R = Me, Et, Ph

27

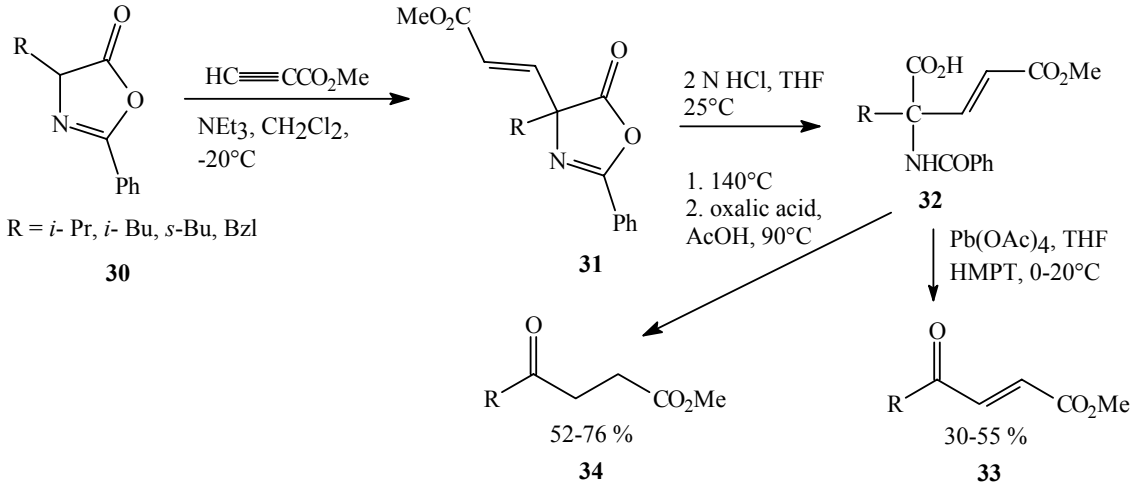
28

81-94 %
Z : *E* = 27:73- 64:36

29

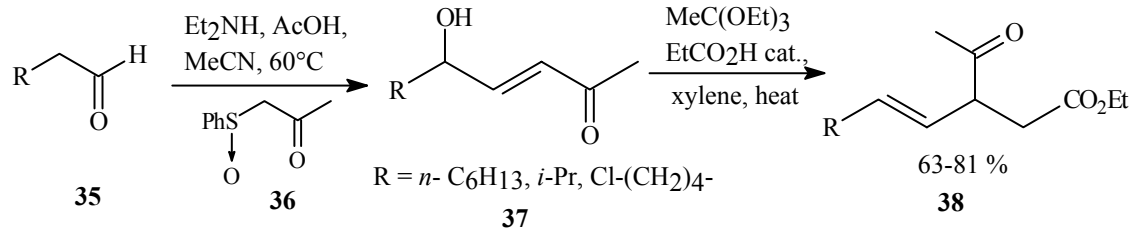
Scheme 10

Base-catalyzed addition of methyl propiolate to oxazolin-5-ones **30** yields mixtures of the diastereomeric acrylate derivatives **31** which may be converted into acylacrylates **33** *via* hydrolytic ring opening and subsequent oxidation with lead tetraacetate. Alternatively, the vinylogous monomethyl malonates **32** was converted into γ-oxo esters **34** (Scheme 11) by thermal decarboxylation followed by hydrolysis with oxalic acid in acetic acid.[34]



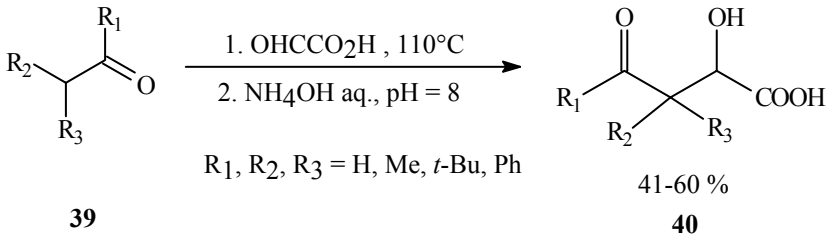
Scheme 11

Claisen-Johnson orthoester rearrangement of γ-hydroxy-α,β-unsaturated ketones **37** undergoing a [3,3] sigmatropic shift when heated at reflux with an excess of trethyl orthoacetate in xylene (Scheme 12) in the presence of a catalytic amount of propionic acid, giving the corresponding oxo esters in good yields and high (*E*) stereoselectivity.[35] Intermediate ketones **37** were prepared from aldehydes reacting with sulfoxide **36** in acetic acid-acetonitrile mixture at 60°C in the presence of diethylamine as basic catalyst.



Scheme 12

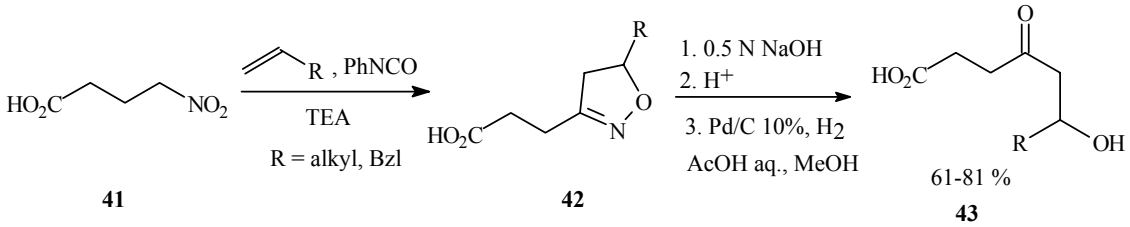
An efficient one-pot preparation of aliphatic γ-oxo acids involves a self-catalysed process *via* an aldol intermediate. Starting from a three-fold excess of ketone **39**, reaction with glyoxalic acid and then treatment with aqueous NH_3 to pH 8 and removal of the excess of ketone by steam distillation or extraction leads to the α-hydroxy-γ-oxobutyric acids **40** (Scheme 13).[36]



39 **40**

Scheme 13

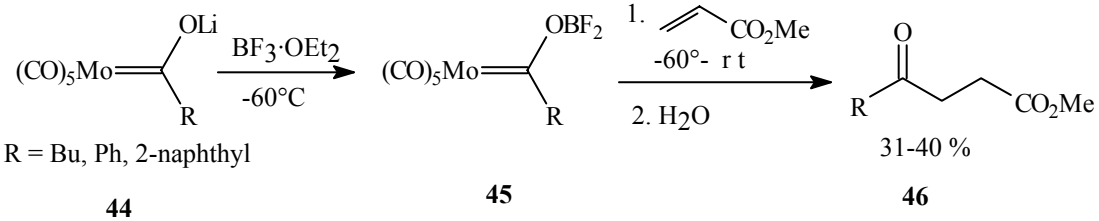
Hydroxy-substituted γ-oxo acids **43** can be obtained through a two-step sequence involving a 1,3-dipolar cycloaddition of nitrile oxide generated *in situ* from methyl 4-nitrobutyrate **41** and alkenes, followed by reductive ring opening of the 4,5-dihydroisoxazolines **42** by catalytic hydrogenation with 10% Pd/C in aqueous methanol–acetic acid solution (Scheme 14). The yield of the hydroxy derivative **43** is high, without detectable elimination products.[37]



41 **42** **43**

Scheme 14

Pentacarbonyl acyl molybdates react with boron trifluoride to give difluoroboroxy Fischer carbene complexes **45**. Decomposition of this complex in the presence of electron-deficient alkenes (Scheme 15) furnishes the two-component coupling product oxo ester by undergoing loss of the methal fragment at room temperature in medium yield.[38]



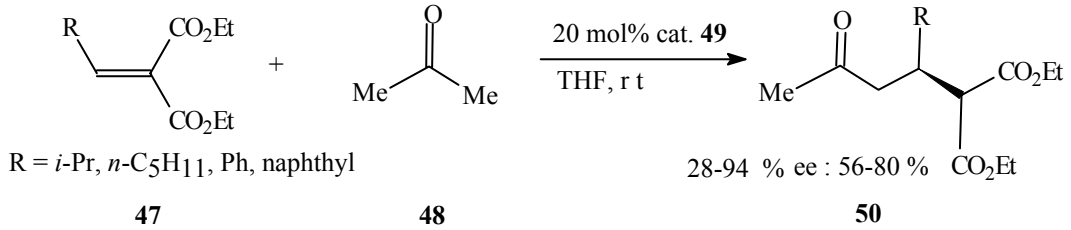
R = Bu, Ph, 2-naphthyl

44 **45** **46**

Scheme 15

Enantioselective direct Michael additions of ketones to alkylidene malonates using (*S*)-1-(2-pyrrolidinylmethyl)-prrolidine **49** as a catalyst (Scheme 16) resulted in γ-oxo

diethylesters **50** under mild and simple conditions with fairly to high enantiomer excess.[39]

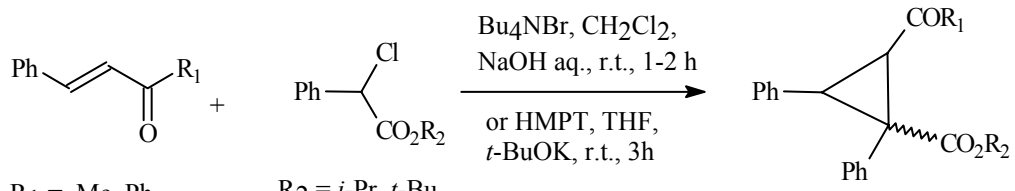


R = *i*-Pr, *n*-C_5H_{11}, Ph, naphthyl

47 **48** **50**

Scheme 16

The stereoselective synthesis of polysubstituted cyclopropyl ketones **53** can be achieved from α,β-unsaturated ketones **51** with phenylchloroacetates by phase-transfer catalysis; the stereoselectivity has been studied at room temperature and at –80 °C with HMPT or the HMPT/THF system as catalyst (Scheme 17). In HMPT, the stereoselectivity is poor, whereas in THF/HMPT (2:1) at –80 °C the reaction is highly stereoselective in all cases.[40]



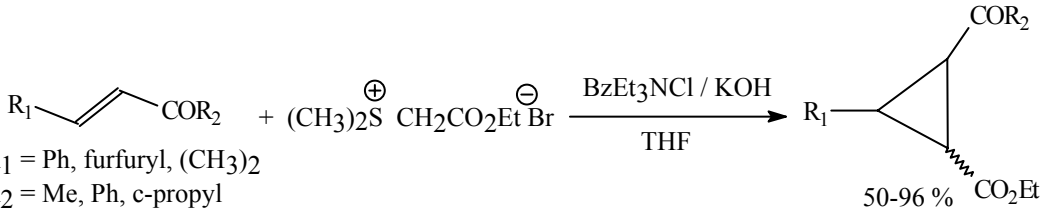
R_1 = Me, Ph

R_2 = *i*-Pr, *t*-Bu

51 **52** **53**

Scheme 17

The derived ylide from carboethoxymethyl dimethylsulfonium bromide does undergo 1,4-addition to enones **54** with formation of oxo cyclopropanecarboxylic esters **56** under phase-transfer conditions (Scheme 18), using benzyltriethylammonium chloride as catalyst.[41]



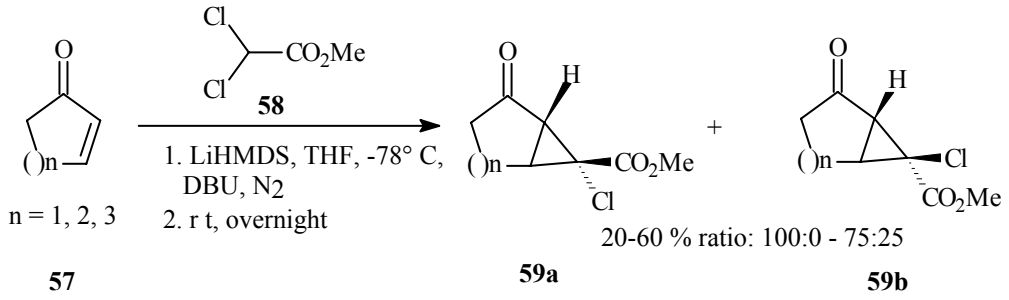
R_1 = Ph, furfuryl, $(CH_3)_2$

R_2 = Me, Ph, c-propyl

54 **55** **56**

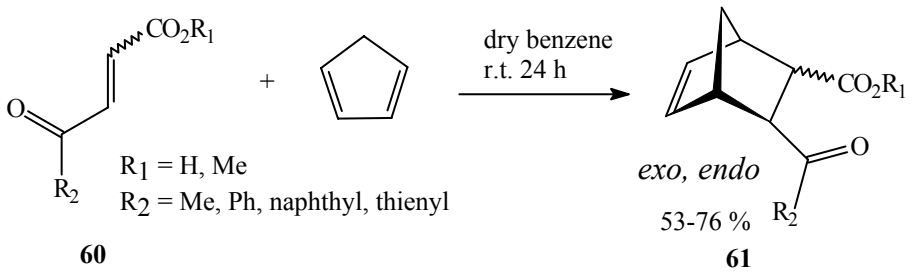
Scheme 18

The reaction of α,β-unsaturated cyclic ketones **57** with methyl dichloroacetate anion (Scheme 19) in the presence of DBU leads to the corresponding bicyclic oxo ester **59a,b** in highly diastereoselective fashion.[42]



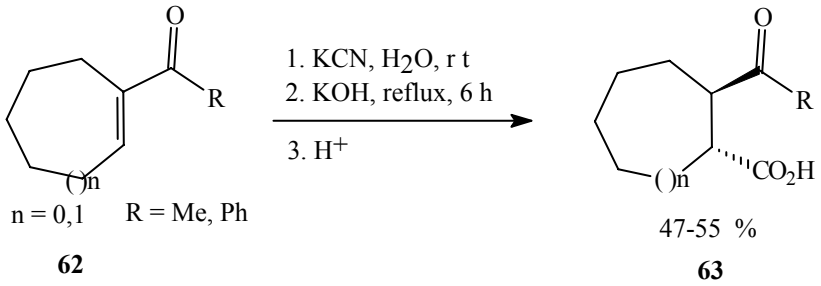
Scheme 19

The Diels-Alder reactions of 1,3-butadiene or cyclopentadiene with *trans*-aroylacrylic acids **60** resulted in mixtures of isomeric cyclohexene or norbornene condensed oxo acids (Scheme 20) in good to excellent (75-98%) yields. A similar preparation was attempted applying furan unsuccessfully. This type of oxo acids is useful for the preparation of unsaturated heterocycles by the retro Diels-Alders reaction.[43-45]



Scheme 20

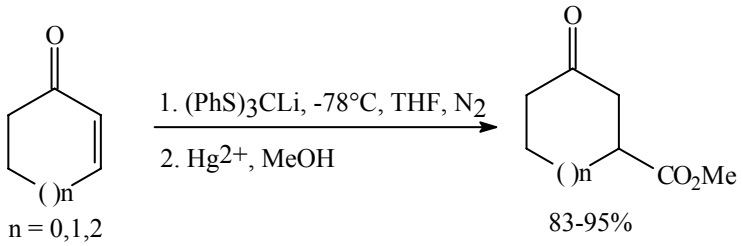
The *trans* oxo acids **64** has been synthesized by the reaction of 1-acylcycloalkenes **62** with hydrogen cyanide giving the corresponding *trans*-2-cyano derivatives by addition, followed by refluxing with potassium hydroxide in water and acidification in good yield, in a large-scale preparation (Scheme 21).[46] Thus *trans*-2-cyano-aroylcyclohexane was prepared starting from cyclohexanone in two steps, which leaded to desired keto acid (n = 0) after hydrolysis.[47]



62 **63**

Scheme 21

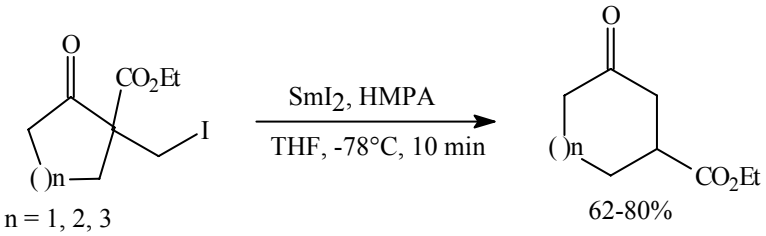
Tris(phenylthio)methyl-lithium, which can be obtained from triphenyl orthothioformate by treatment with *n*-buthyllithium in tetrahydrofuran at –78 °C under nitrogen, reacts in conjugate fashion with unhindered α,β-unsaturated ketones **64** (Scheme 22) producing γ-keto-orthoesters which are turn readily hydrolyzed to keto esters.[48]



64 **65**

Scheme 22

A facile ring expansion of α-halomethyl-β-keto esters **66** mediated with samarium(II)iodide gave above cyclic γ-oxo esters (Scheme 23) in the presence of HMPA in tetrahydrofuran at –78°C after short reaction time.[49]

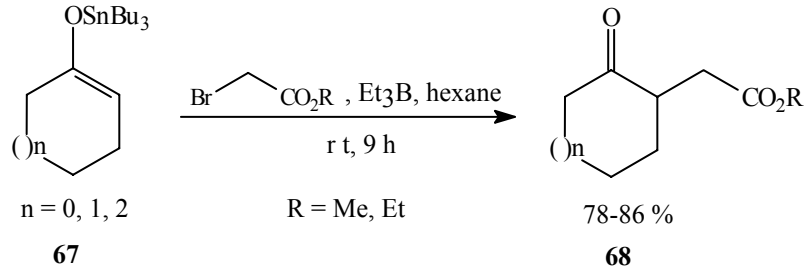


66 **65**

Scheme 23

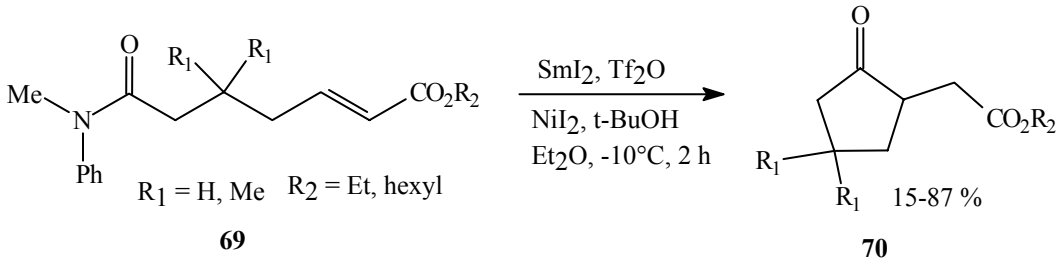
The radical initiated homolytic β-ketoalkylation of haloalkanes with tributylstannyl enolates **67** was described (Scheme 24), where stannyl enolates derived from ketones.

The reactivity of stannyl enolates as radical alkylating agents can be utilized for an efficient two-component coupling reaction.[50]



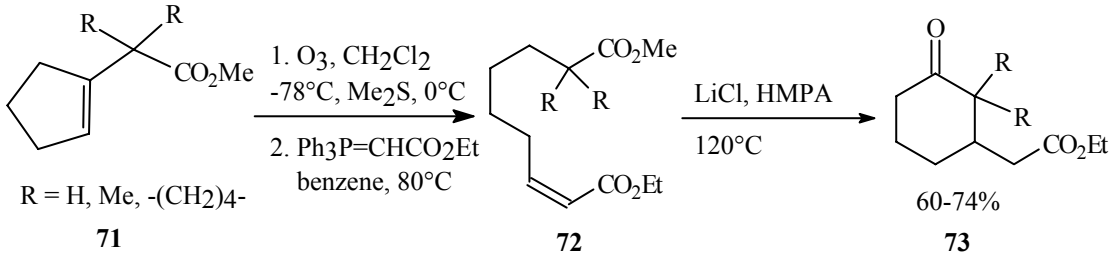
Scheme 24

Unsaturated amide **69** is initially treated with an electrophylic species, such as triflic anhydride, to generate an intermediate iminium triflate. An initial one electron reduction by samarium(II)iodide is thought to generate radical which can then cyclize and further reduction, protonation and rapid hydrolysis upon addition of water affords cyclic γ-oxo ester (Scheme 24).[51]



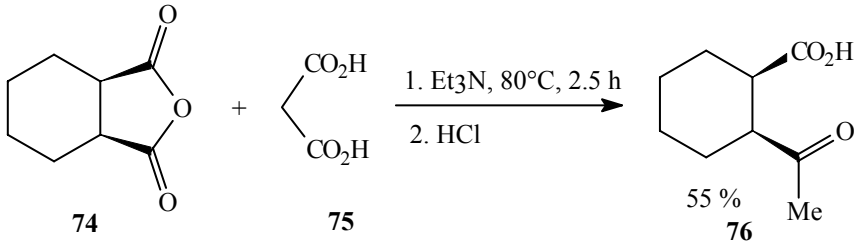
Scheme 24

A three-step procedure involving ring expansion has been developed to convert methyl α,α-dialkyl-1-cyclopenteneacetate **71** to highly functionalized cyclohexaneacetic esters **73**, based on the tandem dealkoxycarbonylation–Michael addition reaction (Scheme 25). The enolate carbanion conjugate addition of the dicarboxylic esters **72** in the presence of lithium chloride furnishes the cyclic δ-oxo esters **73** in good yields.[52]



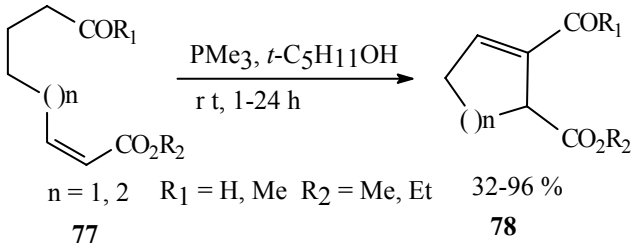
Scheme 25

The reactions of phthalic or *cis*-hexahydrophthalic anhydride **74** with malonic acid in triethylamine at 80 °C for 2.5 hours resulted in a 2-acetyl-cyclohexanecarboxylic acid **76** with gas evolution, in good yield (Scheme 26).[53,54] Unfortunately, in basic medium the *cis*-acid **76** readily isomerizes to the *trans* isomer, which also appears in the reaction product.



Scheme 26

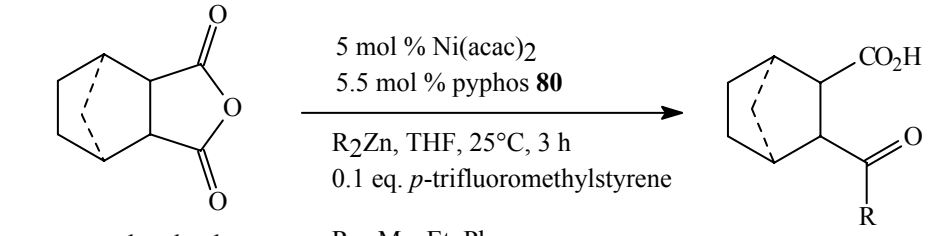
A new variant of vinylogous intramolecular Morita-Baylis-Hillman reaction has been developed for the synthesis of substituted cyclopentenes and cyclohexenes (Scheme 27) by trialkylphophine-catalyzed cyclization of diactivated 1,5-hexadienes or 1,6-heptadienes **77** respectively, at room temperature in *t*-amyl alcohol having high regioselectivity.[55]



Scheme 27

A mild, efficient and highly diastereoselective nickel-catalyzed alkylative and arylative monofunctionalization of cyclic anhydrides **79** was achieved with dialkyl- or diarylzinc respectively (Scheme 28), in the presence of different pyridine ligands and an alkene (*p*-trifluoromethylstyrene) at room temperature. This reaction extremely sensitive to ligand, optimal ligands proved to be 2,2′-bipyridyl and (2-diphenyl-phosphino)ethylpyridine **80** (pyphos). A variety of cyclic anhydrides undergo successful

monoalkylation and alkylzinc halides are also acceptable partners for this reaction, although they proceed in somewhat lower yields (53-67%).[56]



cis, trans, diendo, diexo

79

81

Scheme 28

Conclusions

Numerous alternative synthetic routes were collected and suggested in this paper, which methods are suitable for construction of mono- or polysubstituted aliphatic and cyclic γ- and δ-oxo carboxylic acids as important synthons. This review refers to yields, conditions of reactions and their regio- or diastereoselectivity.

References and Notes

1. Cook, J. W.; Hewett, C. L. *J. Chem. Soc*. **1933**, 398-405.
2. Fieser, L. F.; Novello, F. C. *J. Am. Chem. Soc*. **1942**, *64*, 802-809.
3. Csende, F.; Stájer, G. *Heterocycles* **2000**, *53*, 1379-1419.
4. Lopes, C. C; Lopes, R. S. C.; Pinto, A. V.; Costa *J. Heterocyclic Chem*. **1984**, *21*, 621-622.
5. Ishizaki, M.; Hoshino, O.; Iitaka, Y. *J. Org. Chem*. **1992**, *57*, 7285-7295.
6. Romo, D.; Meyers, A. I. *Tetrahedron* **1991**,*47*, 9503-9569.
7. Resek, J. E.; Meyers, A. I. *Synlett* **1995**, 145-146.
8. Meyers, A. I.; Brengel, G. P. *Chem. Commun*. **1997**, 1-8.
9. Fieser, L. F.; Fieser, M. *J. Am. Chem. Soc.* **1935**, *57*, 1679-1681.
10. Berliner, E. *Organic Reactions*;Vol 5; ed. by Adams, R; John Wiley & Sons Inc, New York, 1952, pp 229–289.
11. Heaney, H. *Comp. Org. Syn*. **1991**, *2*, 733-768.
12. Schellhammer, C.-W. *Houben-Weyl*, Ketone I; VII/2a, ed. Müller, E., Georg Thieme Verlag Stuttgart, 1973, pp 332-374.
13. Olah, G. A. *Friedel-Crafts and Related Reactions*, *Vol.1-4*; Interscience, New York, 1963-1965.
14. Csende, F.; Szabó, Z.; Stájer, G. *Heterocycles*, **1993**, *36*, 1809-1821.
15. Stájer, G.; Csende, F.; Bernáth, G.; Sohár, P.; Szúnyog, J. *Monatsh. Chem*. **1994**, *125*, 933-944.
16. Klika, K. D.; Tähtinen, P.; Dahlqvist, M.; Szabó, J. A.; Stájer, G.; Sinkkonen, J.; Pihlaja, K. *J. Chem. Soc., Perkin Trans. 2*, **2000**, 687-692.
17. Chevallet, P; Orzalesi, H. *Bull. Soc. Chim. Fr*. **1985**, 947-958.
18. Csende, F.; Szabó, Z. *Heterocycl. Commun*. **1996**, *2*, 453-461.
19. Mayer, F.; Stamm, G. *Ber.* **1923**, *56*, 1424-1433.
20. Bergmann, E.; Blum-Bergmann, O. *J. Am. Chem. Soc*. **1937**, *59*, 1572-1573.
21. Canonne, P.; Kassou, M.; Akssira, M. *Tetrahedron Lett*. **1982**, *23*, 3785-3788.

22. Lhommet, G.; Freville, S.; Thuy, V.; Petit, H.; Celerier, J. P. *Synth. Commun.* **1996**, *26*, 3897-3901.
23. Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed*. **2002**, *41*, 1057-1059.
24. Ballini, R.; Petrini, M. *Synthesis* **1986**, 1024-1026.
25. Kulinkovich, O. G.; Sorokin, V. L. *Synthesis* **1994**, 361-362.
26. Kohno, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 322-329.
27. Yamamoto, M.; Nakazawa, M.; Kishikawa, K.; Kohmoto, S. *Chem. Commun*. **1996**, 2353-2354.
28. Miyashita, M; Yamaguchi, R.; Yoshikoshi, A. *J. Org. Chem*. **1984**, *49*, 2857-2863.
29. Hirai, K.; Suzuki, H.; Kashiwagi, H.; Moro-Oka, Y.; Ikawa, T. *Chem. Lett*. **1982**, 23-26.
30. Cerfontain, H.; van Noort, P. C. M. *Synthesis* **1980**, 490-492.
31. Kunz, H.;Linding, M. *Chem. Ber*. **1983**, *116*, 220-229.
32. Kunkel, E.; Reichelt, I.; Reiβig, H.-U. *Liebigs Ann. Chem*. **1984**, 802-819.
33. Mawaziny, S.; Lakany, A. M. *Phosph. Sulf. Silicon* **2000**, *163*, 99-120.
34. Wegmann, H.; Schulz, G.; Steglich, W. *Liebigs Ann. Chem*. **1980**, 1736-1743.
35. Giardina, A.; Marcantoni, E.; Mecozzi, T.; Petrini M. *Eur. J. Org. Chem*. **2001**, 713-718.
36. Coates, W. J.; McKillop, A. *Synthesis* **1993**, 334-342.
37. Baraldi, P. G.; Chiarini, Leoni, A; Manfredini, S.; Simoni, D.; Zanirato, V. *J. Heterocyclic Chem*. **1990**, *27*, 557-561.
38. Barluenga, J.; Rodriguez, F.; Fañanás, F. J. *Chem., A Eur. J*. **2000**, *6*, 1930-1937.
39. Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, III, C. F. *Tetrahedron Lett*. **2001**, *42*, 4441-4444.
40. Artaud, I; Seyden-Penne, J.; Viout, P. *Synthesis* **1980**, 34-36.
41. Tolstikov, G. A; Galin,F. Z.; Iskandarova, V. N.; Khalilov, L. M.; Panasenko, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim*. **1985**, 2287-2292.
42. Escribano, A.; Pedregal, C.; González, R.; Fernández, A.; Burton, K.; Stephenson, G. A. *Tetrahedron* **2001**, 57, 9423-9427.
43. Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc*., **1988**, *110*, 3693-3697.
44. Miklós, F.; Stájer, G.; Sohár, P.; Böcskei, Zs. *Synlett* **2000**, 67-68.
45. Fieser, L. F.; Fieser, M. *J. Am. Chem. Soc*. **1935**, *57*, 1679-1681.
46. Ayres, D. C.; Raphael, R. A. *J. Chem. Soc*. **1958**, 1779-1789.
47. Caamano, O.; Eirin, A.; Fernandez, F.; Garcia, G.; Uriarte, E. *An. Quim. , Ser. C* **1987**, *83*, 257-258.
48. Manas, A.-R. B.; Smith, R. A. J. *J. Chem. Soc., Chem. Commun*. **1975**, 216-217.
49. Chung, S. H.; Cho, M. S.;Choi, J. Y.; Kwon, D. W.;Kim, Y. H. *Synlett* **2001**, 1266-1268.
50. Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A.*Org. Lett*. **2001**, 2591-2594.
51. McDonald, C. E.; Galka, A. M.; Green, A. I.; Keane, J. M.; Kowalchick, J. E.; Micklitsch, C. M.; Wisnoski, D. D. *Tetrahedron Lett*. **2001**, *42*, 163-166.
52. Bunce, R. A.;. Schilling III, C. L. *J. Org. Chem* **1995**, *60*, 2748-2752.
53. Newman, M. S; Venkateswaran, S.; Sankaran, V. *J. Org. Chem*. **1975**, *40*, 2996-2997.
54. Csende, F;. Szabó, Z. *J. Chem. Res. (S)*, **1994**, 262-263.
55. Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc*. **2002**, *124*, 2404-2405.
56. Bercot, E. A.; Rovin, T. *J. Am. Chem. Soc*. **2002**, *124*, 174-175.

Povzetek

Pregledni članek obravnava nekaj enostavnih in posebnih primerov priprave alicikličnih in cikličnih kondenziranih derivatov γ- in δ- okso kislin. Tovrstni sintoni so velikega pomena v sintezi aril kondenziranih karbocikličnih sistemov, pet do sedemčlenskih heterociklov in naravnih spojin. Zato so za izvedbo mnogokrat potrebne posebne in nenavadne sintezne poti the kislin, posebno glede na izkoristek, raznovrstnost substituent ter stereo- in regioselektivnost. Poleg konvencionalnih Friedel-Craftsovih in Grignardovih reakcij so opisane tudi številne alternativne metode.