HETEROCYCLES, Vol. 57, No. 7, 2002, pp. 1353 - 1365, Received, 20th February, 2002

METHODS FOR PREPARATION OF γ- AND δ-OXO ACIDS AS USEFUL SYNTHONS FOR HETEROCYCLES

Ferenc Csende and Géza Stájer*

Institute of Pharmaceutical Chemistry, University of Szeged, PO Box 121, H-6701 Szeged, Hungary, E-mail: stajer@pharma.szote.u-szeged.hu

Abstract – Numerous synthetic routes have been recommended for the preparation of γ- and δ-oxo acids. The present paper collects methods which need simple starting materials, procedures and conditions. Many examples are presented, comparing the preparations of aliphatic, cycloalkane, aromatic and hetero ring-containing oxo acids from the aspects of yield, regio- and diastereoselectivity.

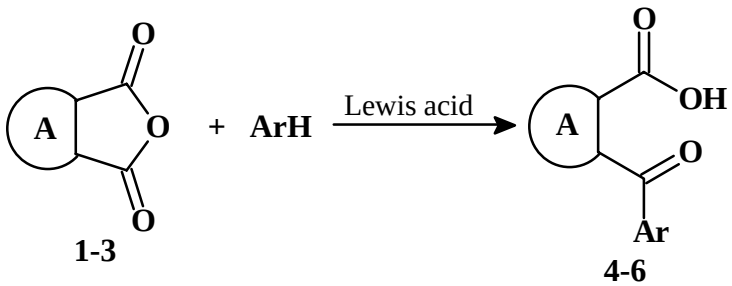
CONTENTS

γ- and δ-Oxo acids and their functionalized derivatives, *e.g.* esters, lactones and ketals, are of great importance in the formation of carbocycles, *e.g.* condensed polycyclic benzene derivatives[1-4] and many heterocycles,[5] in the preparation of drugs[6-8] and natural products[9,10] and as chiral auxiliaries for asymmetric reactions[11-14] in direct condensations or multistep reactions. The most common oxo acids are alicyclic, *e.g.* levulinic acid, but a great number of aromatic, heteroaromatic and cyclic derivatives have been prepared and used in recent decades.

1. STARTING FROM CYCLIC ANHYDRIDES

1.1. PREPARATION BY FRIEDEL-CRAFTS REACTION

The standard and most widely used method involves a Friedel-Crafts reaction of a cyclic anhydride with an aromate in the presence of a Lewis acid, *e.g.* $AlCl_3$, $AlBr_3$ or $FeCl_3$. Succinic, glutaric, maleinic, phthalic and hexahydrophthalic anhydrides (**1**-**3**) are frequently applied as acylating agents (Scheme 1).[15-19]



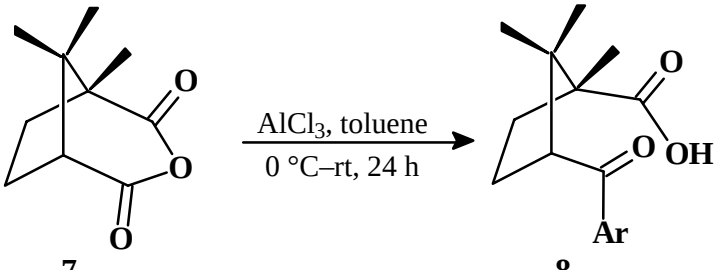
1-3 **4-6**

	Ring **A**	ArH	yield	ref.
1.	–	thiophene	54%	17
2.	benzene	benzene	78%	18
3.	cyclohexane	toluene	92%	19

Scheme 1

In this way, halo-, alkyl-, hydroxy- or alkoxy-substituted benzene-, naphthalene-, phenanthrene-, anthracene- and pyrene-condensed derivatives, partially hydrogenated aromatic compounds containing aliphatic, *e.g.* fluorene, tetraline or heterocyclic rings, such as thiophene and its (di)benzene-fused compounds, thiochromane, carbazole and protected pyrrole derivatives have been acylated.[20,21]

δ-Oxo acids have also been obtained from homologues, *e.g.* glutaric, homophthalic and camphoric anhydrides, but the formation of a small amount of diketone as side-product is observed. With camphoric anhydride (**7**), the acylation proved to be stereo- and regioselective (Scheme 2);[22] the qualitative structure–reactivity relationship has also been studied in detail.[23]



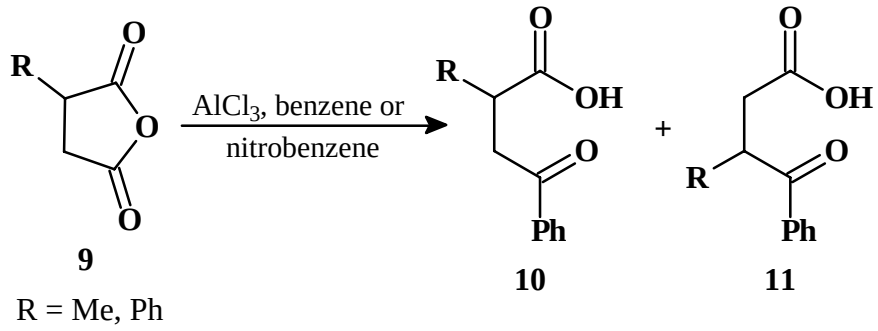
7 **8**

Ar = *p*-tolyl

Scheme 2

With unsymmetrically substituted anhydrides, mixture of regioisomers of substituted oxo acids have been obtained in different ratios. Thus, phenyl- and methylsuccinic anhydride (**9**) furnish α-methyl-β-benzoyl-

propionic acid (**10**) and the β-methyl isomer (**11**, R = Me) (Scheme 3).[24] The β-methyl acid (**11**) can be isolated only with difficulty, because it is formed to a much smaller extent and is well soluble.

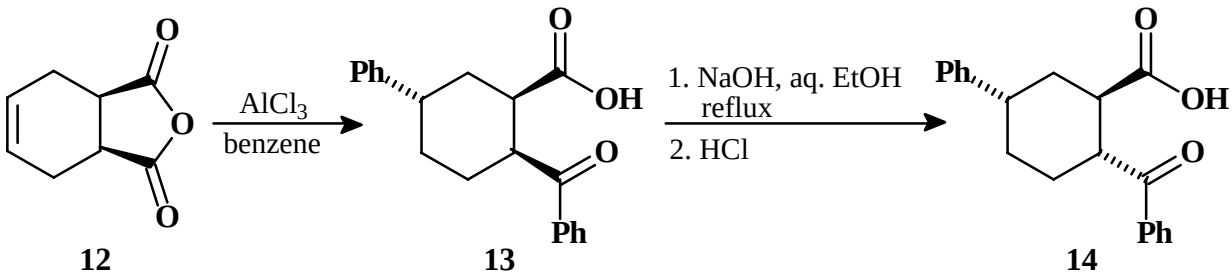


9 R = Me, Ph **10** **11**

Scheme 3

For phenylsuccinic anhydride, the ratio of isomeric α-phenyl and β-phenyl acids depends on the solvent.[25] With an excess of benzene,[26] the two acids are formed in almost equal amounts, but with nitrobenzene, 89% of the products is the α-phenyl acid (**10**, R = Ph) and only 11% the isomer **11**.[27]

From tetrahydrophthalic anhydride with dry benzene and anhydrous $AlCl_3$, *trans*-5-phenyl-*cis*-2-benzoyl-cyclohexane-*r*-1-carboxylic acid (**13**) is obtained in good yield (72%) (Scheme 4).[28]

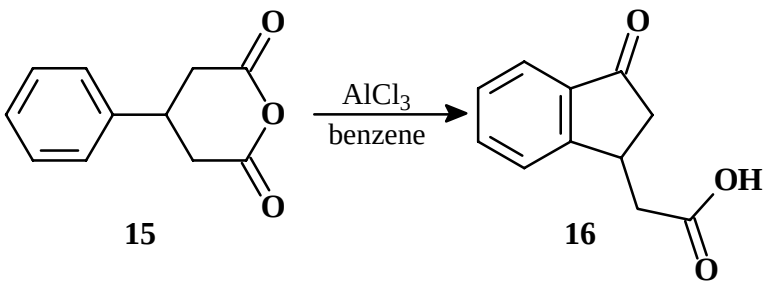


12 **13** **14**

Scheme 4

This oxo acid can be easily converted to the *trans* isomer (**14**) by treatment with NaOH.[29]

The intramolecular $AlCl_3$-catalysed Friedel-Crafts acylation of 3-phenylglutaric anhydride (**15**) gives the cyclic δ-oxo carboxylic acid (**16**) (Scheme 5).[26]



15 **16**

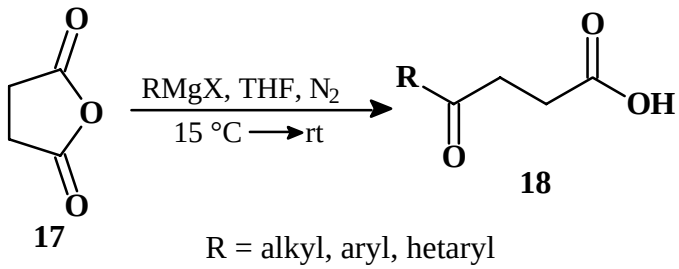
Scheme 5

To summarize: the preparation of oxo acids by the Friedel-Crafts reaction is advantageous because of the good to excellent yields, the high purity of the products and the variability of the aromatic substituent. The

procedure is simple, but alkyl, aralkyl and some heteroaryl, *e.g.* pyridyl and furyl derivatives can not be prepared in this way.

1.2. REACTIONS WITH GRIGNARD REAGENTS

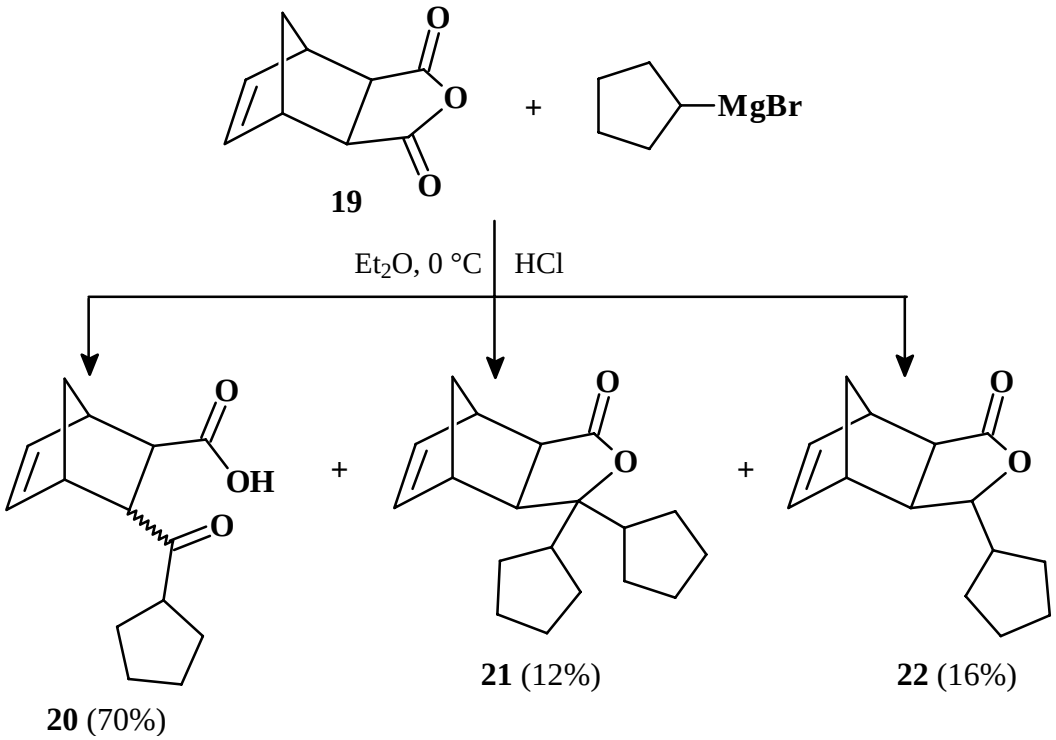
The alkane and cycloalkane oxo acids were first prepared by a Grignard reaction in THF or Et_2O solution of the anhydrides in a short reaction time (0.5–1 h), usually at room temperature (Scheme 6).[30,31]



R = alkyl, aryl, hetaryl

Scheme 6

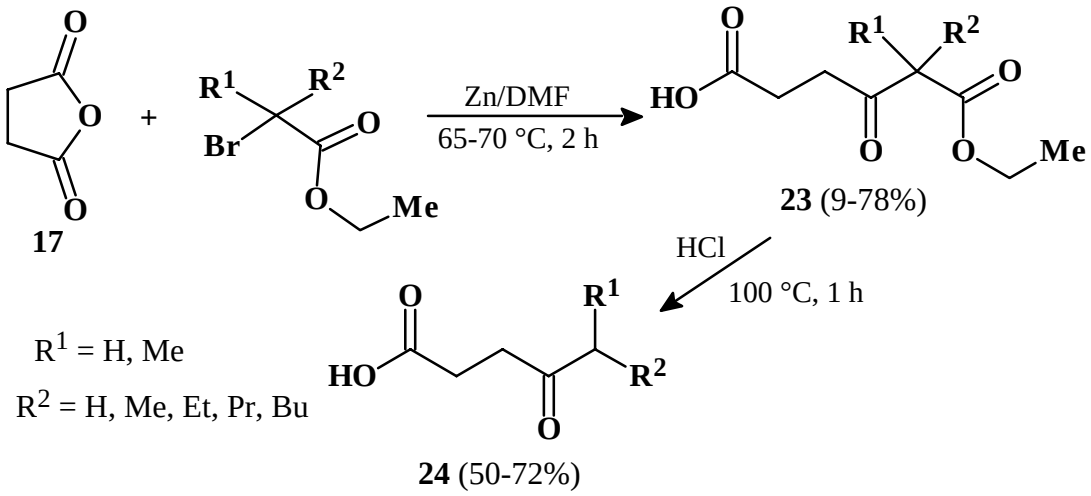
Through the application of different Grignard reagents, this method allows high variability, side-reactions, addition and enolization limit the preparations from bicyclic anhydrides, *e.g.* **19** (Scheme 7).[32]



Scheme 7

1.3. OTHER METHODS

The Reformatsky reaction of ethyl α-bromoalkanoates with succinic anhydride (**17**) in DMF in the presence of zinc results efficiently in γ-oxo acids (**24**) (yield 50-72%) in two steps (Scheme 8). This method is suitable for the large-scale preparation of alkyl derivatives.[33]



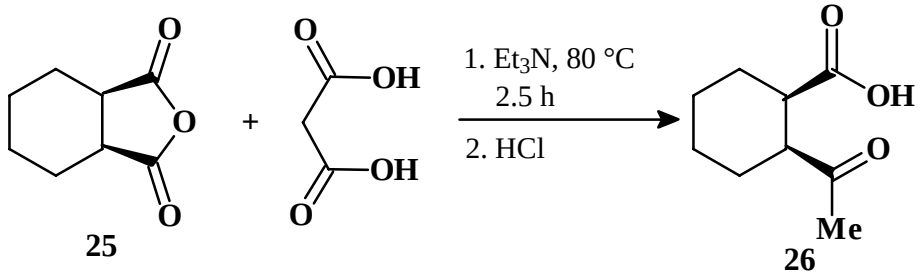
17

23 (9-78%)

24 (50-72%)

Scheme 8

The reactions of phthalic and *cis*-hexahydrophthalic anhydrides (**25**) with malonic acid in Et_3N at 80 °C for 2.5 h result in a condensed 2-acetylpropionic acid (**26**) with gas evolution, in good yield (Scheme 9).[34,35] Unfortunately, in basic medium the *cis*-acid (**26**) readily isomerizes to the *trans* isomer, which also appears in the reaction product.

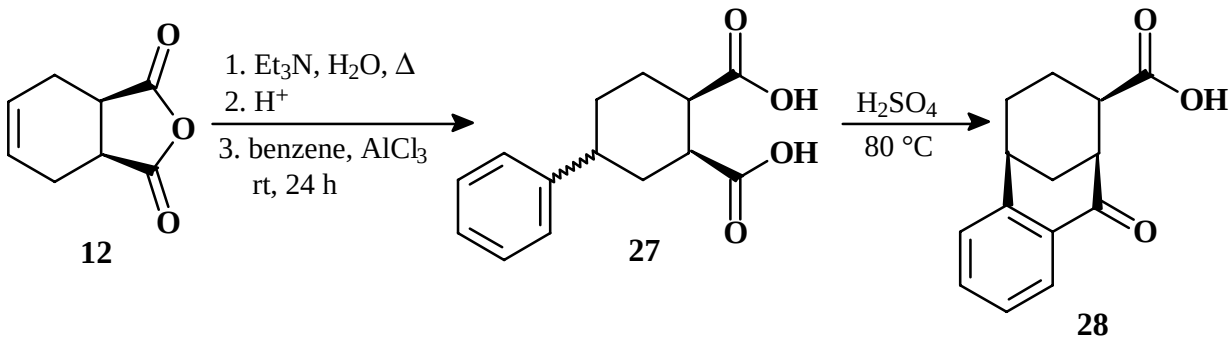


25

26

Scheme 9

On heating with strong acids (PPA or H_2SO_4), the multistep ring closure of the *cis*-tetrahydrophthalic anhydride (**12**) leads stereoselectively to the condensed bicyclic γ-oxo acid (**28**) (Scheme 10).[36]



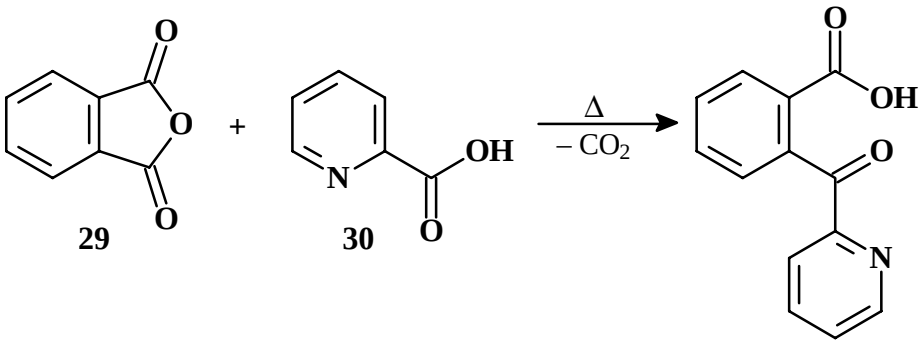
12

27

28

Scheme 10

When picolinic acid (**30**) and phthalic (**29**) or 1,8-naphthalic anhydride are heated together in the absence of solvent, 2-(2-pyridylcarbonyl)benzoic acid derivatives (**31**) are synthesized in moderate yield by the loss of CO_2 (Scheme 11);[37] in nitrobenzene at 160-165 °C, the yield is 38-40%.

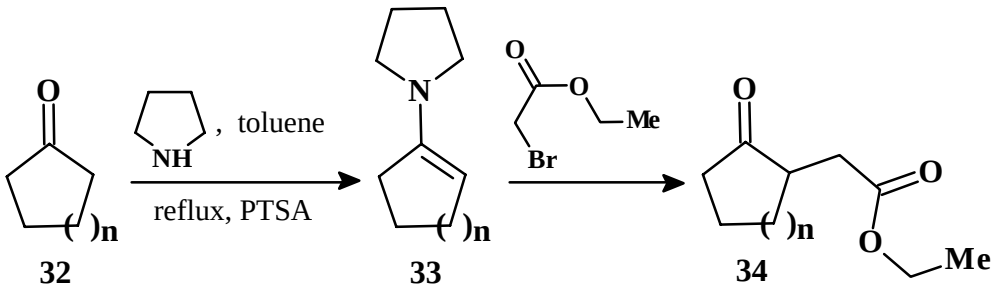


Scheme 11

2. C–C BOND FORMATION

2.1. ENAMINE REACTIONS OF KETONES

Starting from cyclic ketones (**32**) with secondary amines *e.g.* pyrrolidine or morpholine, enamines (**33**) have been prepared, which react with haloalkanoic esters to give (ethoxycarbonyl)methylcycloalkanones (**34**) (Scheme 12).[38-40]



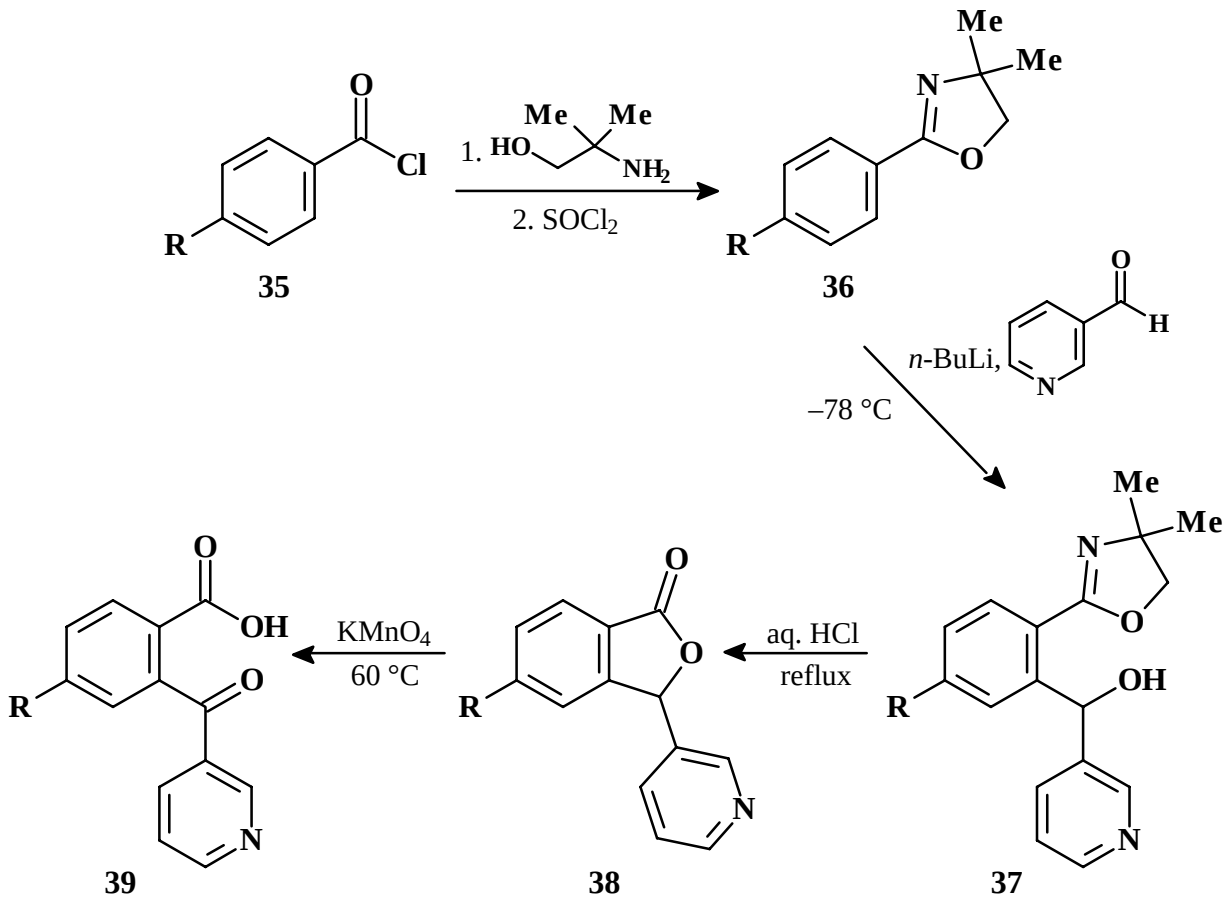
n = 1-4

Scheme 12

2.2. APPLICATION OF ORGANOLITHIUMS AND OTHER ORGANOMETALLICS

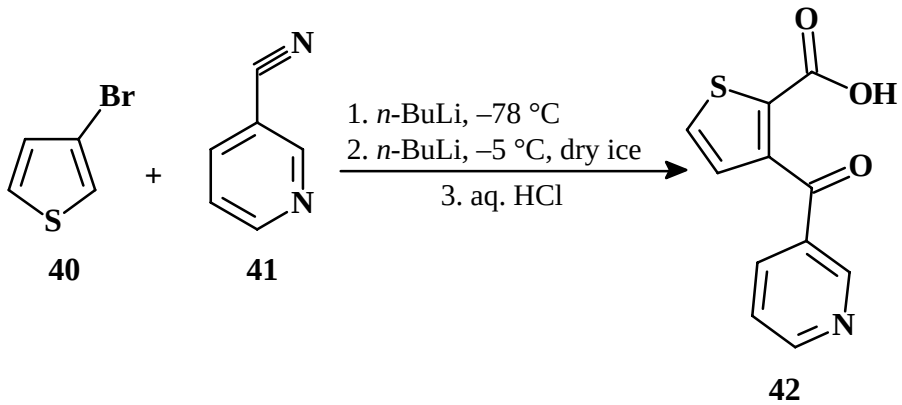
n-BuLi-mediated reactions are often applied for the synthesis of substituted oxo acids, *e.g.* 2-, 3- or 4-pyridyl or 2-furyl derivatives. Thus, 4-substituted benzoyl chlorides (**35**) are converted to the oxazoline (**36**), and their *o*-lithiated derivatives with 3-pyridinecarboxaldehyde give the products (**37**), and then the 5-substituted (3-pyridyl)phthalides (**38**) by hydrolysis and cyclization upon heating with HCl; the alkaline hydrolysis of **38**, followed by $KMnO_4$ oxidation, affords the oxo acids (**39**) (Scheme 13).[41]

3-(3-Pyridoyl)thiophene-2-carboxylic acid (**42**) has been prepared by the sequential *n*-BuLi-mediated reaction of 3-bromothiophene (**40**) in a one-pot procedure. Treatment of **40** with equivalent 3-cyano-pyridine and *n*-BuLi, followed by treatment with another equivalent of *n*-BuLi in dry ice, and hydrolysis with dilute HCl, gives **42** (Scheme 14).[42]



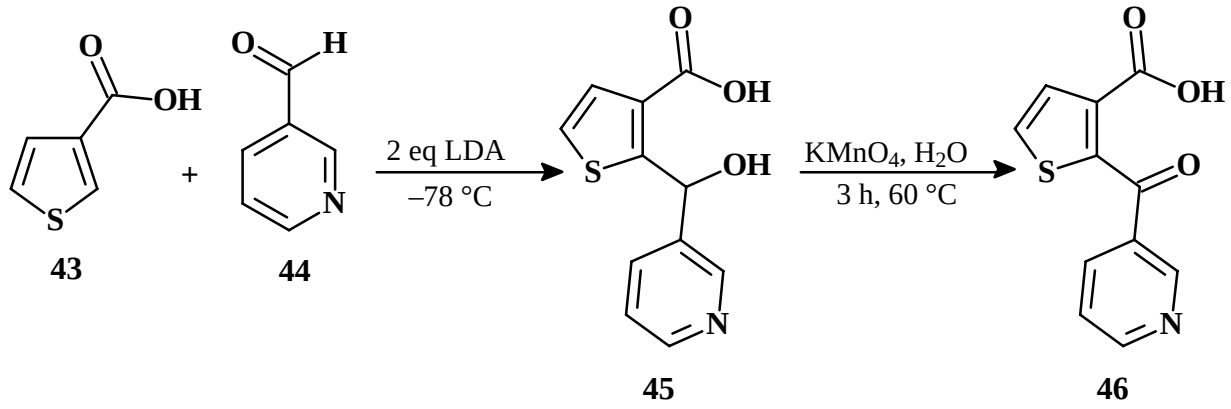
R = F, CF_3, *i*-Pr

Scheme 13



Scheme 14

Because of the poor yield, another synthetic route has been used for the preparation of the isomeric **46**: application of the dianion derived from the readily available thiophene-3-carboxylic acid (**43**). The intermediate hydroxy acid (**45**) can be smoothly oxidized with $KMnO_4$ to give **46** in good (~ 65%) yield (Scheme 15).

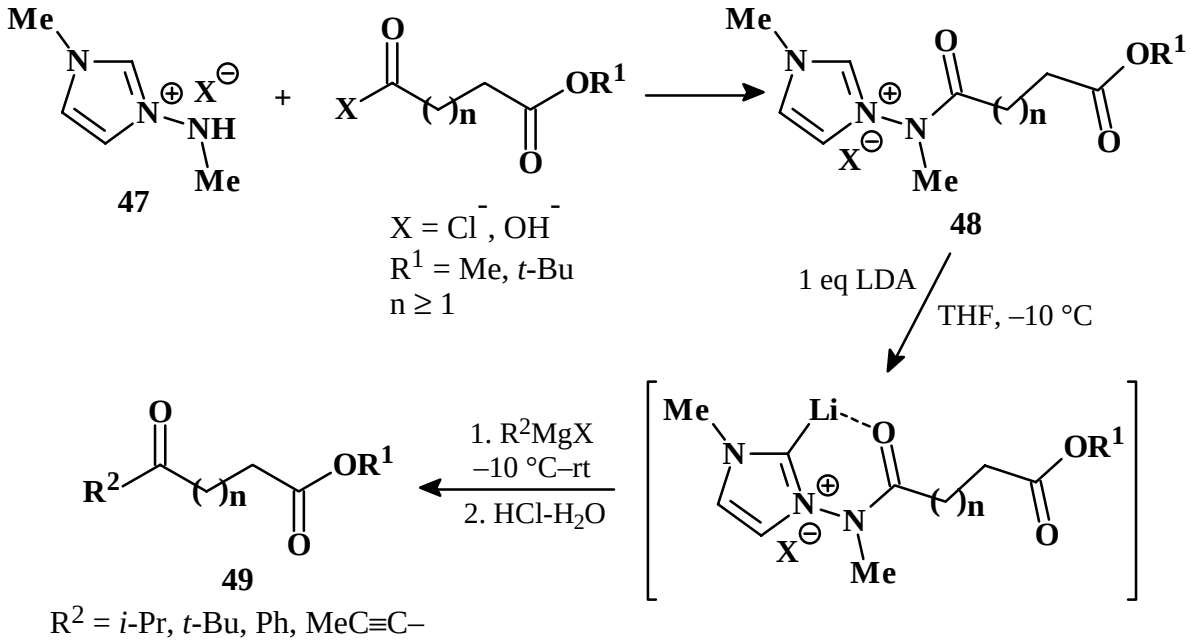


43 **44** **45** **46**

Scheme 15

From the analogous furan-3-carboxylic acid, the initial carbinol is formed similarly, but it resists oxidation with $KMnO_4$ and does not give the expected oxo acid. The oxo acid can be prepared by Swern oxidation with oxalyl chloride in DMSO.

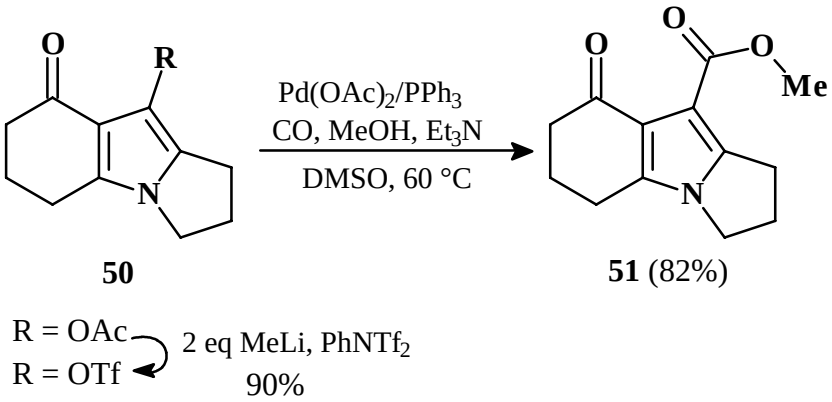
Chemoselective addition of a Grignard reagent to a lithiated alkoxycarbonylalkyl-*N*-imidazolium-*N*-methylamide also results in γ-oxo and homologous esters, in good yields (Scheme 16).[43] The semiester or semichloride of a dicarboxylic acid reacts with the imidazolium derivative (**47**) to give **48**, which has been treated with LDA in THF. Grignard reagent is added to the lithiated amide; the work-up with HCl gives oxo esters (**49**), while the ester group undergoes no reaction with the Grignard reagent.



47 **48** **49**

Scheme 16

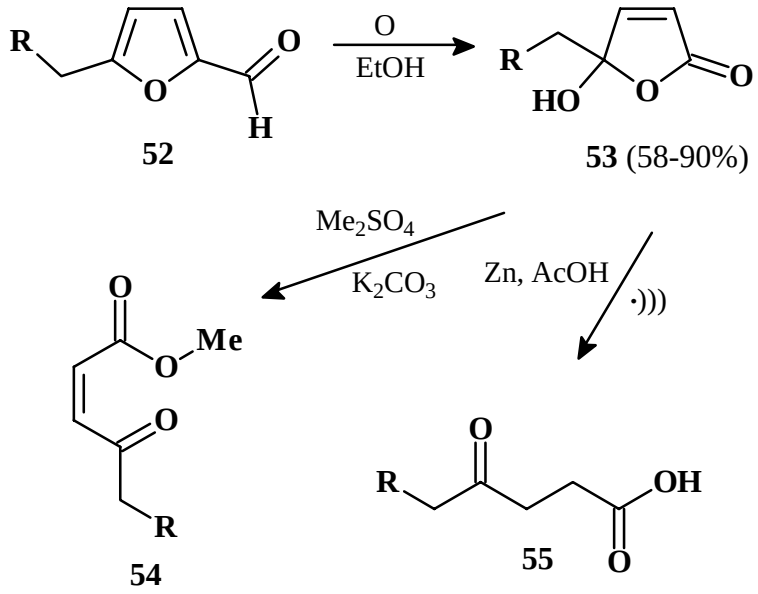
Treatment of the acetoxy compound (**50**) with MeLi at –78 °C, followed by reaction with *N*-phenyltriflimide, affords the triflate in 90% yield.[44] Exposure of the triflate to a modified Pd-catalysed methoxycarbonylation provides the ester (**51**) in good yield (Scheme 17).



Scheme 17

2.5. APPLICATION OF OTHER REACTIONS

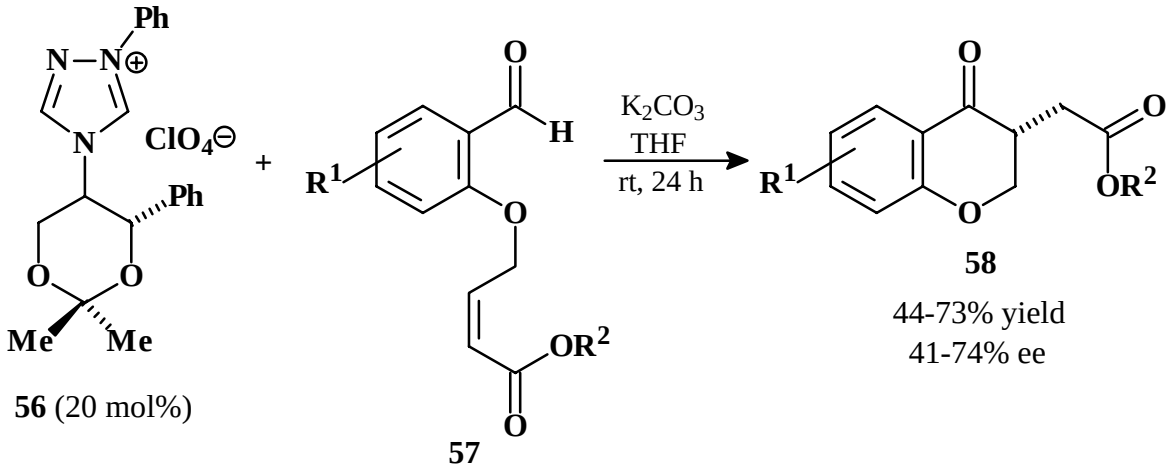
Photooxygenation of the 5-hydroxymethyl-2-furfurals (**53**) leads to the 4-hydroxy-Δ^2-butenolides (**54**) as precursors of α,β-unsaturated γ-oxo esters (Scheme 18). The selective reduction of **53** or its oxo esters with Zn in AcOH under sonication leads to γ-oxo acids (**55**) or γ-esters.[53]



R = OH, OAc, OBz

Scheme 18

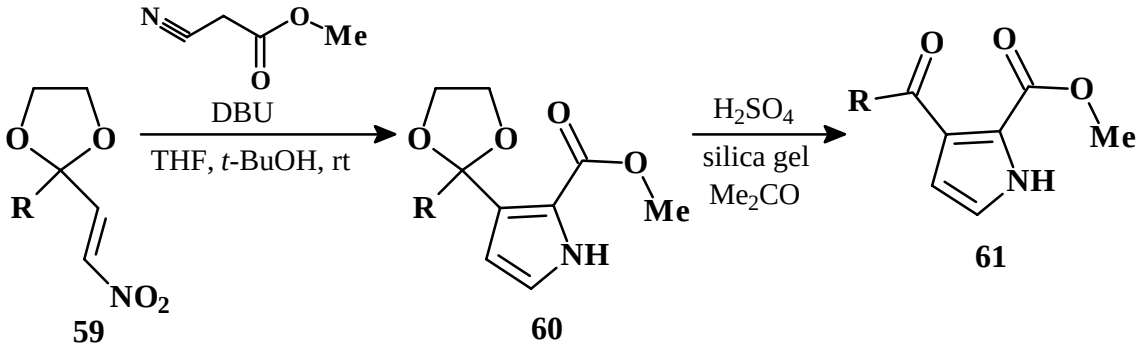
Enantiomerically pure γ-oxo esters with 4-chromanone skeletons (**58**) have been prepared by asymmetric intramolecular Stetter reactions,[46] using the chiral triazolium salt (**56**) as catalyst, which is readily available *via* a large-volume intermediate of the industrial chloramphenicol synthesis (Scheme 19). The actual nucleophilic carbene catalyst formed *in situ* by deprotonation of **56** with K_2CO_3 in the presence of the butenoate (**57**) acts on the formyl function, and the nucleophilic β C-atom on the enamine then attacks the activated C=C bond of the Michael acceptor (**57**).



R^1 = OMe, Cl, H; R^2 = Me, Et

Scheme 19

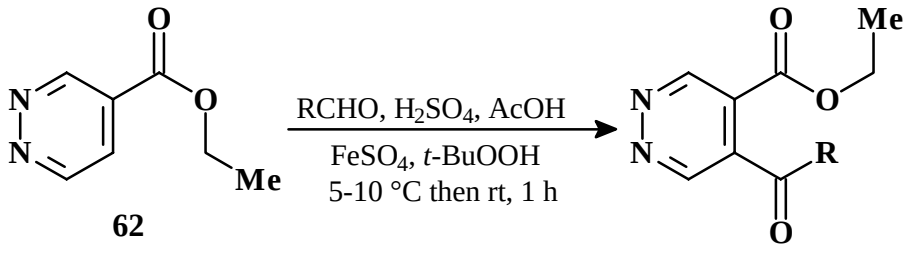
α-Isocyanoacetates condense smoothly with nitroalkenes (**59**) in the presence of DBU in THF–*t*-BuOH to give the acetals (**60**) (Scheme 20). Hydrolysis of the latter with a catalytic amount of concentrated H_2SO_4 yields the 3-alkanoylpyrrole-2-carboxylates (**61**).[47]



R = Me, Et

Scheme 20

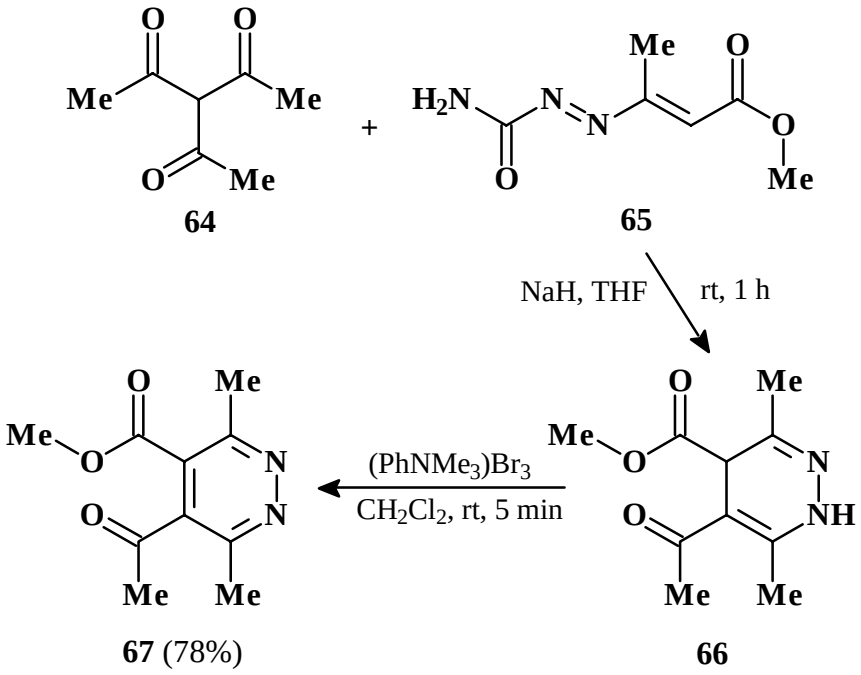
For the preparation of other pyridazine oxo acids, *e.g.* **63**, a homolytic substitution has been successfully applied by introduction of an acyl or aroyl group at position 5 of ethyl 4-pyridazinecarboxylate (**62**) (Scheme 21).[48,49]



R = Me, Et, cyclohexyl, Ph

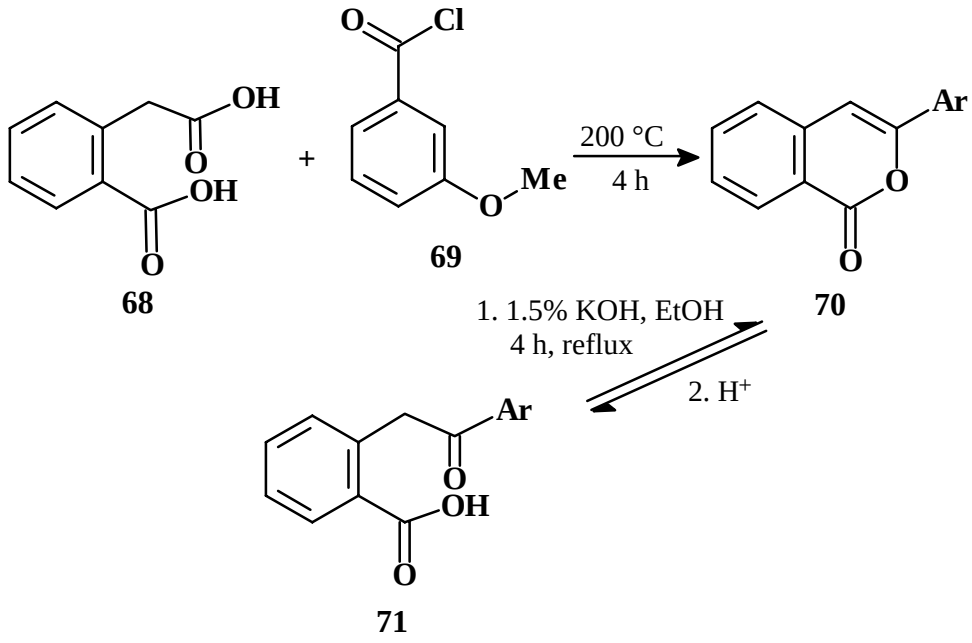
Scheme 21

The reaction of triacetylmethane (**64**) with the diazo compound (**65**) results in the dihydropyridazine oxo ester (**66**), which, after dehydrogenation with phenyltrimethylammonium tribromide, gives the pyridazine (**67**) (Scheme 22).[50]



Scheme 22

The reactions of homophthalic acid (**68**) with aroyl chlorides, *e.g.* **69**, result in the unsaturated lactone (**70**), which, by hydrolysis with alcoholic KOH, and then acidification, furnishes the δ-oxo acid (**71**) (Scheme 23).[51]



Scheme 23

ACKNOWLEDGEMENTS

The authors are indebted to OTKA (grant T-37204) for financial support and to Mrs. E. Csiszár-Makra for the typing of the manuscript.

REFERENCES

1. J. W. Cook and C. L. Hewett, *J. Chem. Soc*., 1933, 398.
2. L. F. Fieser and F. C. Novello, *J. Am. Chem. Soc*., 1942, **64**, 802.
3. E. Bergmann and O. Blum-Bergmann, *J. Am. Chem. Soc*., 1937, **59**, 1572.
4. G. Stájer, F. Csende, G. Bernáth, P. Sohár, and J. Szúnyog, *Monatsh. Chem*., 1994, **125**, 933.
5. F. Csende and G. Stájer, *Heterocycles*, 2000, **53**, 1379.
6. J. H. M. Lange, J. C. de Jong, H. J. Sanders, G. M. Visser, and C. G. Kruse, *Bioorg. Med. Chem. Lett*., 1999, **9**, 1055.
7. Rexall Drug and Chem Co., Neth. Appl. 6, 606, 390 (*Chem. Abstr*., 1967, **66**, 55535w).
8. P. Aeberli, P. Eden, J. H. Gogerty, W. J. Houlihan, and C. Penberthy, *J. Med. Chem*., 1975, **18**, 177.
9. C. C. Lopes, R. S. C. Lopes, A. V. Pinto, and P. R. R. Costa, *J. Heterocycl. Chem*., 1984, **21**, 621.
10. M. Ishizaki, O. Hoshino, and Y. Iitaka, *J. Org. Chem*., 1992, **57**, 7285.
11. D. Romo and A. I. Meyers, *Tetrahedron*, 1991, **47**, 9503.
12. J. E. Resek and A. I. Meyers, *Synlett*, 1995, 145.
13. G. P. Brengel and A. I. Meyers, *Chem. Commun*., 1998, 1.
14. S. M. Allin, C. J. Northfield, M. I. Page, and A. M. Z. Slawin, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1715.
15. L. F. Fieser and M. Fieser, *J. Am. Chem. Soc*., 1935, **57**, 1679.
16. F. D. Carter, J. L. Simonsen, and H. O. Williams, *J. Chem. Soc*., 1940, 451.
17. L. F. Fieser and R. G. Kenelly, *J. Am. Chem. Soc*., 1935, **57**, 1611.
18. C. Friedel and J. M. Crafts, *Ann, Chim. Phys*., 1888, **14**, 447.
19. F. Csende, Z. Szabó, and G. Stájer, *Heterocycles*, 1993, **36**, 1809.
20. W. A. Lindley and D. W. H. MacDowell, *J. Org. Chem*., 1982, **47**, 705.
21. M. Kakushima, P. Hamel, R. Frenette, and J. Rokach, *J. Org. Chem*. 1983, **48**, 3214.
22. F. Csende and Z. Szabó, *Heterocycl. Commun*., 1996, **2**, 453.
23. P. Chevallet and H. Orzalesi, *Bull. Soc. Chim. Fr*., 1985, 947.
24. F. Mayer and G. Stamm, *Ber*., 1923, **56**, 1424.
25. R. Anschütz, C. Hahn, and P. Walter, *Ann*., 1907, **354**, 150.
26. A. Ali, R. D. Desai, R. F. Hunter, and S. M. M. Muhammad, *J. Chem. Soc.*, 1937, 1013.

27. M. A. Wali, A. K. Khalil, R. L. Bhatia, and S. S. Ahmad, *Proc. Indian Acad. Sci.*, 1941, **14A**, 139 (*Chem. Abstr.*, 1942, **36**, 1598).
28. G. Stájer, A. E. Szabó, G. Bernáth, and P. Sohár, *Heterocycles*, 1994, **38**, 1061.
29. K. D. Klika, P. Tähtinen, M. Dahlqvist, J. A. Szabó, G. Stájer, J. Sinkkonen, and K. Pihlaja, *J. Chem. Soc., Perkin Trans. 2*, 2000, 687.
30. P. Canonne, M. Kassou, and M. Akssira, *Tetrahedron Lett*., 1986, **27**, 2001.
31. G. Lhommet, S. Freville, V. Thuy, H. Petit, and J. P. Celerier, *Synth. Commun*., 1996, **26**, 3897.
32. P. Canonne, M. Akssira, and G. Lemay, *Tetrahedron Lett*., 1982, **23**, 3785.
33. H. Schick and R. Ludwig, *Synthesis*, 1992, 369.
34. M. S. Newman, S. Venkateswaran, and V. Sankaran, *J. Org. Chem*., 1975, **40**, 2996.
35. F. Csende and Z. Szabó, *J. Chem. Res. (S)*, 1994, 262.
36. F. Miklós, F. Csende, G. Stájer, P. Sohár, R. Sillanpää, G. Bernáth, and J. Szúnyog, *Acta Chem. Scand*., 1998, **52**, 322.
37. G. A. Karlivan and R. E. Valter, *Zh. Org. Khim*., 1984, **20**, 665.
38. A. Mondon, *Chem. Ber*., 1959, **92**, 1461.
39. F. Csende, G. Bernáth, Zs. Böcskei, P. Sohár, and G. Stájer, *Heterocycles*, 1997, **45**, 323.
40. B. Umezawa, O. Hoshino, S. Sawaki, S. Sato, and N. Numao, *J. Org. Chem.*, 1977, **42**, 4272.
41. M. Yamaguchi, T. Koga, K. Kamei, M. Akima, N. Maruyama, T. Kuroki, M. Hamana, and N. Ohi, *Chem. Pharm. Bull*., 1994, **42**, 1850.
42. M. Yamaguchi, N. Maruyama T. Koga, K. Kamei, M. Akima, T. Kuroki, M. Hamana, and N. Ohi, *Chem. Pharm. Bull*., 1995, **43**, 236.
43. M. A. Heras, J. J. Vaquero, J. L. Garcia-Navio, and J. Alvarez-Builla, *Tetrahedron Lett*., 1997, **38**, 1817.
44. E. D. Edstrom, *Tetrahedron Lett.*, 1995, **36**, 7035.
45. L. Cottier, G. Descotes, L. Eymard, and K. Rapp, *Synthesis*, 1995, 303.
46. D. Enders, K. Breuer, J. Runsink, and J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1899.
47. J. Boelle, R. Schneider, P. Gerardin, and B. Loubinoux, *Synthesis*, 1997, 1451.
48. G. Heinisch and J. Kirchner, *Monatsh. Chem*., 1979, **110**, 365.
49. G. Heinisch, J. Kirchner, I. Kurzmann, G. Lötsch, and R. Waglechner, *Arch. Pharm*.,1983, **316**, 508.
50. O. A. Attanasi, P. Fillipone, C. Fiorucci, and F. Mantellini, *Synlett*, 1997, 1361.
51. K. Zamani, *J. Heterocycl. Chem*., 2000, **37**, 1651.