Polish J. Chem., **77**, 1385–1410 (2003) **REVIEW ARTICLE**

Reduction and Reductive Alkylation of 3*H*-Isobenzofuran-1-ones[*]

by A. Bieniek[**], J. Epsztajn and K.K. Kulikiewicz

Department of Organic Chemistry, Institute of Chemistry, University of Łódź,
90-136 Łódź, Narutowicza 68, Poland

(Received May 19th, 2003; revised manuscript June 27th, 2003)

The survey reports the reductive conversion of phthalides into *ortho*-alkylated carboxylic acids. This procedure is the most convenient and effective methodology for regiospecific syntheses of *ortho*-alkylated carboxylic acids. The literature up to the end of 2002 is reviewed.

Key words: phthalides, carboxylic acids, reduction, reductive alkylation, isobenzofuran-1-ones

1. Introduction

The chemistry of 3*H*-isobenzofuran-1-one was first completely reviewed in 1951 [1], although the system of phthalide has been known since the nineteenth century. R.C. Elderfield [1] wrote the article about isobenzofuranes, phthalans and 3*H*-isobenzofuran-1-ones. The part, which concerned phthalides, contained their synthesis and reactions. Since then, some information about 3*H*-isobenzofuran-1-ones was described only in few works [2,3], which were connected with isobenzofurans.

The moiety of phthalide is very often part of important compounds [4], which are commonly used in medicine, printing industry and as cosmetics, indicators. Great interest of 3*H*-isobenzofuran-1-one unit results from possibility of employing of the title compounds in further reactions as well. It must be emphasized that phthalides are very convenient precursors to different biologically active compounds such as antracyclic antibiotics [5–8], alkaloids [9,10], furanonaphthoquinones [11–13] and polycyclic systems [14–18]. It is known from the bibliographic data, that transformation of 3*H*-isobenzofuran-1-ones into *o*-alkylbenzoic acids is frequently used in the synthesis of those complex compounds. In spite of significance of the *o*-alkylbenzoic acids as synthons, it should be pointed out, however, that little systematic work has been done on transformation of 3*H*-isobenzofuran-1-ones into *o*-alkylbenzoic acids. That is why, the review of reductions of phthalides, which give *o*-alkylbenzoic acids and reductive alkylations of 3*H*-isobenzofuran-1-ones will be presented in this paper.

---

[*] Dedicated to Prof. M. Szafran on the occasion of his 70th birthday.

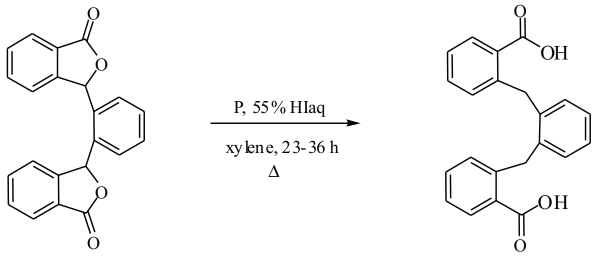
[**] Corresponding author: fax: (4842) 6786583, e-mail: bieniek@uni.lodz.pl

The employed literature is covered up to the mid 2002 and refers mainly to reduction of phthalides with palladium, hydriodic acid, zinc in acidic and basic medium, and ionic hydrogenation. The review was divided for the 9 main groups: Reduction of phthalides with hydriodic acid, Reduction of phthalides in the presence of Me_3SiI, Catalytic reduction of phthalides over palladium, Catalytic reduction of phthalides over zinc in basic medium, Catalytic reduction of phthalides over zinc in acidic medium, Miscellaneous catalytic reductions of phthalides, Ionic hydrogenation of phthalides, Reduction of phthalides with titanium compounds and Reductive alkylation of phthalides.

2. Reduction of phthalides with hydriodic acid

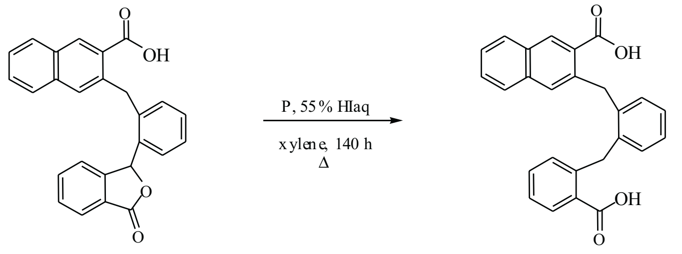
Hydriodic acid, one of the oldest reducing agents of phthalides was used mainly in the form its aqueous solution, which contains 55–57% of hydrogen iodide. Hydrogen iodide dissociates at higher temperatures to iodine and hydrogen, which effect hydrogenation. Carrying out the process of reduction by long-lasting heating 3*H*-isobenzofuran-1-ones with concentrated hydriodic acid was very expensive. Therefore, removal of the free iodine, which can cause side reactions, was necessary. It was accomplished by reaction with phosphorus or hypophosphorus acid H_3PO_2 to form phosphorus triiodide, which decomposed in the presence of water to phosphorus and hydrogen iodide. In that way, by adding phosphorus to the reaction mixture hydrogenating agent was recycled and the reducing efficiency of hydriodic acid was enhanced.

Reductions of phthalides with hydriodic acid were usually accomplished by long-lasting refluxing organic compounds with the azeotropic (57%) acid in organic solvents. For instance, diphthalide **1** was converted to dicarboxylic acid **2** in the presence of red phosphorus and concentrated HI in a xylene solution. The organic solvent helped to gain milder conditions for hydrogenation [19,20].



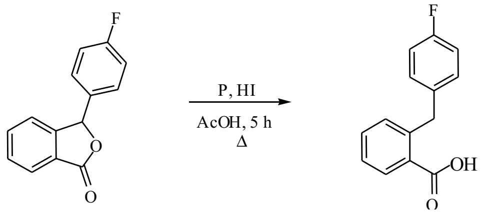
1 **2**

Dicarboxylic acid **4** was obtain in 60% yield from isobenzofuran-1-one **3** by hydrogenation during 140 hours heating of substrate with HI in the presence of red phosphorus in xylene solution [21].



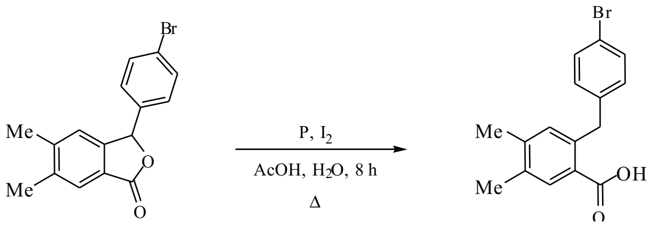
3 **4**

Selective reduction of phthalides, which contain halogen atom [22–24] or methyl group [22] in the molecule, was achieved by treatment with HI in the presence of phosphorus or its derivatives. Sometimes acetic acid was added to increase miscibility of HI with the organic compound. Reduction of 3*H*-isobenzofuran-1-one **5** in acetic acid by HI in the presence of red phosphorus gave acid **6** with 93% yield [24].



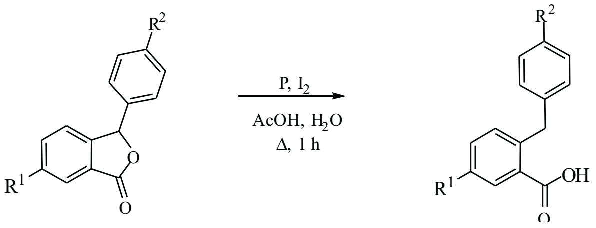
5 **6**

Another example was reaction phthalide **7** in the presence of red phosphorus, iodine in glacial acetic acid and a small amount of water, where desired HI is prepared *in situ*. After 8 h of heating, the yield of the acid **8** was 80% [22].

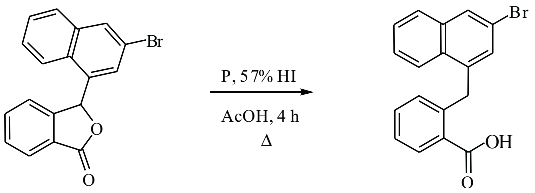


7 **8**

Similarly, 3*H*-isobenzofuran-1-ones **9**, **11** were reduced by heating in the presence of iodine, red phosphorus or hydriodic acid in acetic acid to corresponding benzoic acids **10**, **12** in above 80% [23,25].



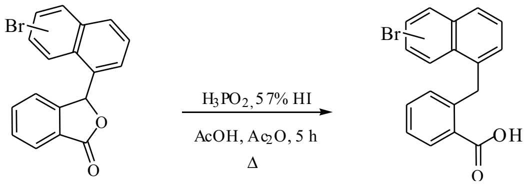
9 $R^1 = H; R^2 = Br, Cl$ **10**



11 **12**

In the case, when substrates do not contain any groups, which are sensitive on activity of H_3PO_2 or when their destruction does not influence further reactions, profitable reduction system is H_3PO_2–HI.

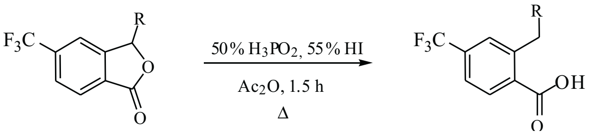
For instance, compounds **13** gave corresponding derivatives of benzoic acid **14** (> 85%) on short refluxing with H_3PO_2 and HI in anhydrous medium of glacial acetic acid [26].



13 **14**

a: 6-Br; **b**: 7-Br; **c**: 8-Br

However, phthalides **15** were converted to acids **16** by hydrogenation at the reflux temperature in acetic anhydride in the presence of H_3PO_2 and 55% HI. Small amount of water, which is present in both acids, was removed by the reaction with acetic anhydride and therefore reaction was accomplished in anhydrous conditions [27].



15 **16**

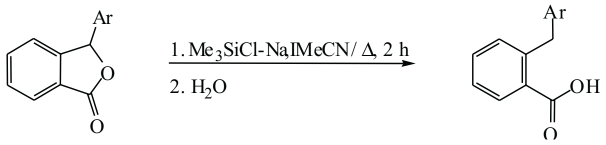
R = naphth-1-yl, naphth-2-yl

Advantage of reduction of 3*H*-isobenzofuran-1-ones with hydrogen iodine was that unreacted reductive agent can be easily separated from the products. However, the method is limited to substrates that do not contain reductible alkoxy, nitro groups and double bonds or when products of reduction of phthalides cannot transform furthermore to polycyclic systems under the reduction conditions. Besides, HI is quite expensive and therefore is used mainly on the laboratory scale.

3. Reduction of phthalides in the presence of Me_3SiI generated *in situ*

A practical way to overcome usual drawbacks of the reduction process such as long reaction time, small selectivity and high price of reagent was the use of Me_3SiI as a reducing agents. It was generated *in situ* from inexpensive and readily available Me_3SiCl and NaI in acetonitrile [28].

The reductive cleavage of isobenzofuran-1-ones **17** was performed in refluxing acetonitrile with 3.5 equivalents of Me_3SiI and the products **18** obtained in 1–2 hours with good yields.



17 **18**

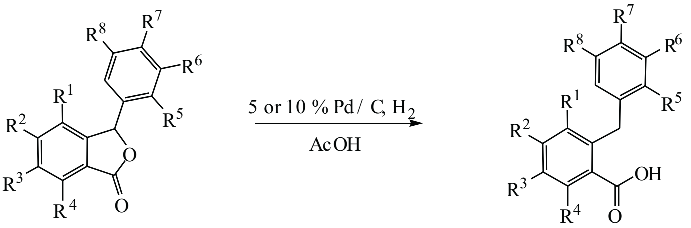
Ar = Ph, thien-2-yl, $C_6H_4Me(4)$, $C_6H_4OMe(4)$, $C_6H_3Br_2(3,4)$, $C_6H_4Br(4)$, CH_2-thien-2-yl, Bn

4. Catalytic reduction of phthalides over palladium

With a few exceptions dihydrogen does not react with organic compounds at temperatures below 480°C and therefore the presence of catalyst is necessary to do the reduction. The reaction between gaseous hydrogen and an organic compound takes place only at the surface of a catalyst, which adsorbs both the hydrogen and the organic molecule and thus facilitates their contact [29].

In order to increase the contact of catalyst with hydrogen and the compound to be hydrogenated, palladium is precipitated on materials having large surfaces such as charcoal. Such supported palladium catalyst, with the contents of 5% or 10% of palladium, (called palladium black) is prepared by hydrogenation of palladium oxide or palladium chloride in aqueous suspensions of activated charcoal or other solid substances, just before the right reduction [29,30].

The reduction of 3*H*-isobenzofuran-1-ones in atmospheric or moderate pressure of hydrogen, in acetic acid and in the presence of supported catalyst, containing 5–10% Pd is well-known method [31–38]. For instance, reaction of various 3-arylphthalides **19**, afforded after several hours in 80–85°C corresponding *o*-substituted benzoic acids **20** with 93-95% yields.

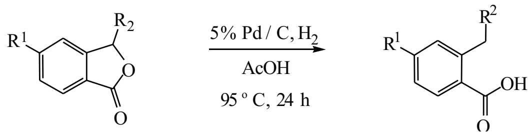


19 **20**

$R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$ = H, OMe, *i*-Pr

Also in the situation, when the phthalide has substituent at C-3 different from phenyl, this method is very convenient and finds application as mentioned below [38–40].

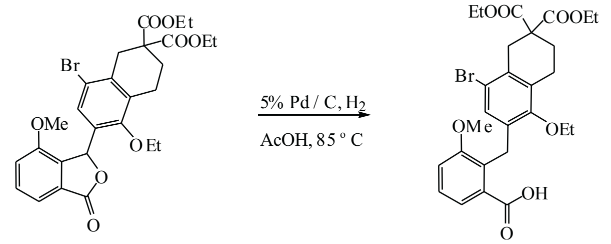
Reduction of 3*H*-isobenzofuran-1-ones **21** was accomplished by catalytic hydrogenation over palladium catalyst after long-lasting reaction [39]. Deactivating effect of substituents probably influenced on decreasing of yield (60–70%). Sulphur, which was present in substituents, might inhibit of catalyst shown in decreasing its activity and in consequence induce onto yield of the reduction.



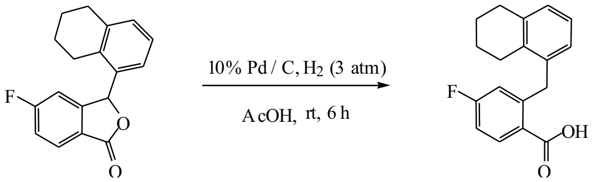
21 **22**

R^1 = H, Me; R^2 = 3-benzo[b]thien-2-yl, 3-benzo[b]thien-3-yl

When bromine, fluorine atoms and ester groups were present in the molecules of phthalides like in compounds **23** and **25**, they did not cause decreasing yield (91%) or selectivity of the hydrogenation [38,40,41].

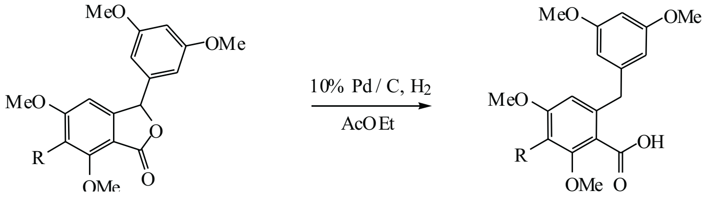


23 **24**



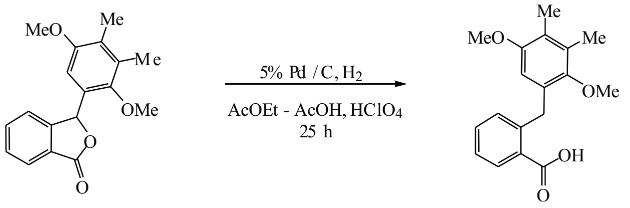
25 **26**

Ethyl acetate [42–45] or mixture of acetic acid and ethyl acetate can be used as solvents in reduction of phthalides **27** and **29** as well [46].



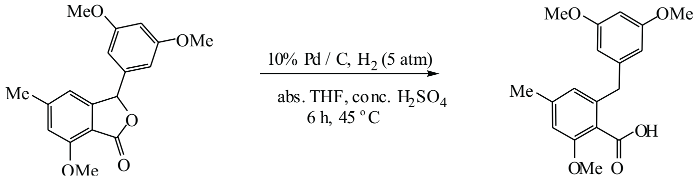
27 **28**

R = H, *i*-Pr



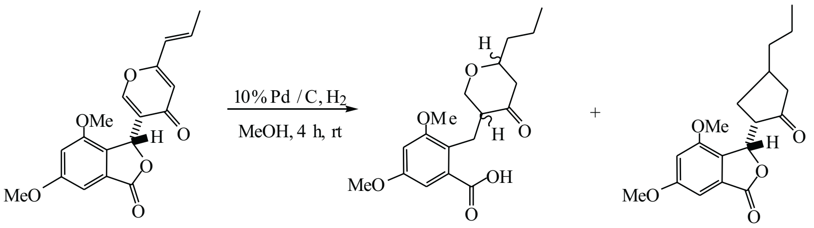
29 **30**

Using activated palladium on charcoal in THF – sulphuric acid, at 45°C during catalytic hydrogenation of 3*H*-isobenzofuran-1-one **31**, allowed to obtain corresponding acid **32** almost quantitatively (96%) [47].



31 **32**

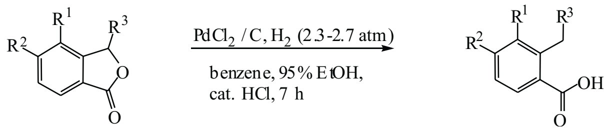
During the hydrogenation over 10% palladium, which was carried out in methanol, at room temperature phthalide **33** was transformed to the mixture of compounds **34a–b** and **35** [48]. Additionally, during the reduction pyran ring was hydrogenated. In the applied conditions part of phthalide **33** was converted onto compound **35**. In this case phthalide ring appeared to be inert reduction.



33 **34 a**: *trans* **35**
34 b: *cis*

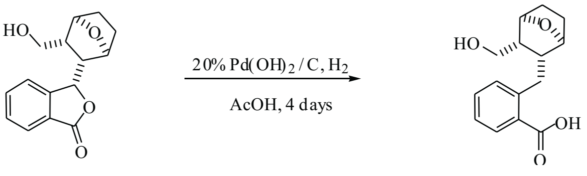
The thermodynamically less favourable *cis* isomer **34b** isomerized slowly into the *trans* isomer **34a** in the solution; after 4 days about 30% conversion was observed.

Besides typical palladium catalyst, which was commonly used in reduction of phthalides, it should be mentioned that Pd(II) salts of such as palladium chloride [49,50] or palladium hydroxide [51] were employed in hydrogenation 3*H*-isobenzofuran-1-ones **36** or **38**.



36 **37**

R^1, R^2 = H, F; R^3 = naphth-1-yl, naphth-2-yl



38 **39**

Main advantage of this method is the ease in separation of the product from the catalyst. Furthermore, the reaction conditions are usually quite mild (gentle): short time of the reaction, low pressure of hydrogen, and temperature below 100°C.

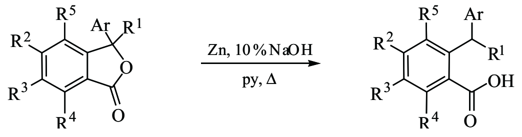
In this kind of hydrogenation a careful consideration should be taken for the carrying out of the reaction. Amount of catalyst, amount of hydrogen needed for the reduction, its pressure, vapour pressure of the solvent as well as kind of employed solvent must be considered. Effect of mixing of solution is very often underestimating factor, which can affect course of the catalytic hydrogenation, because it is reaction between three phases.

Great disadvantage of this method is that reaction yield depends on quality of the catalyst. Efficiency of catalyst is affected by the presence of some compounds, especially of sulphur(II). In addition to this, quite high price of catalyst results in searching different, cheaper routes of reduction of phthalides and use of palladium catalysts is restricted to research in laboratory scale.

5. Catalytic reduction of phthalides over zinc in basic medium

Zinc in the form of dust or granular is frequently employed as a reducing agent of 3*H*-isobenzofuran-1-ones. However, purity of zinc does not influence the process too much, but generally zinc dust which is used, has got above 75% purity. Activity of the metal depends on degree of its crumbling what can increase real surface of the zinc and in consequence its activity. This metal reductant is frequently covered with a thin layer of products of oxidation and other impurities, which deactivate its surface. This layer can be removed by a proper activation of zinc dust immediately prior to use. For instance, metal can be activated by its treatment with diluted hydrochloric acid for several minutes, then washing with water, ethanol, acetone and diethyl ether. Reduction of 3*H*-isobenzofuran-1-ones with zinc are carried out in aqueous as well as organic solvents and at different pH's either in basic (sodium or potassium hydroxide, ammonia) or acidic (formic, acetic or hydrochloric acid) conditions. Reactions are also carried out in the mixture of organic solvent – water.

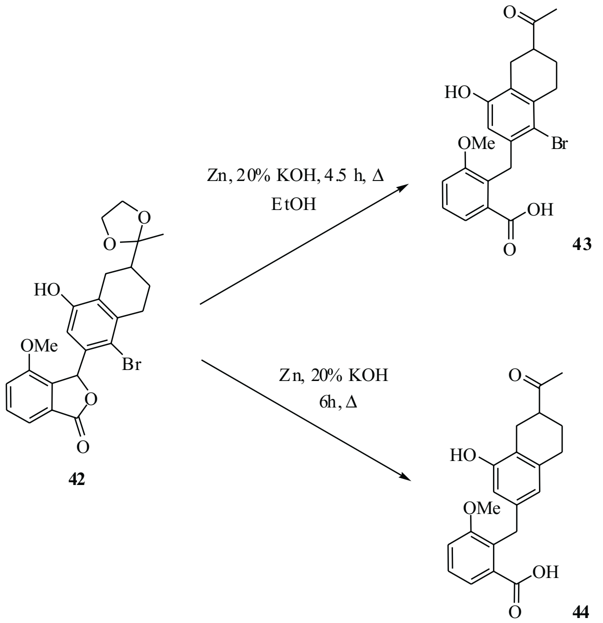
Reductions of phthalides under basic conditions with zinc dust [52–57] is the best carried out in 10% aqueous solution of NaOH with or without addition of pyridine, in hot or refluxing solvents and can take many hours to complete. In that way, 3*H*-isobenzofuran-1-ones **40** were hydrogenolyzed to the corresponding acids **41** with 76–95% yields.



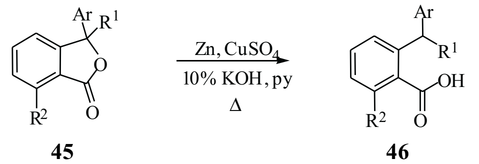
40 **41**

R^1, R^2, R^3, R^4, R^5 = H, Me, OMe; Ar = 6-fluornaphth-2-yl, 2,4,5-trimethoxyphenyl, 3,8-dihydro-4*H*-cyclopenta[*d,e,f*]phenanthr-2-yl, phenanthr-9-yl, 6-acetyl-1-methoxy-5,6,7,8-tetrahydronaphth-2-yl

Reduction of phthalides in the presence of zinc dust under basic conditions not always is selective reaction, especially when there is bromine atom in the molecule. For instance, hydrogenation of bromolactone **42** in 10% aqueous solution of KOH causes reduction of the compound and removal of the bromine atom in the same time. However, when this reaction was carried out in EtOH – H_2O the loss of halogen did not occurred [58,59].

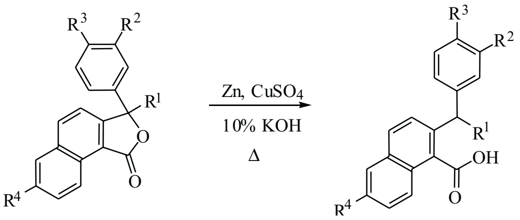


Conversion of zinc into zinc-copper couple by stirring it with copper sulphate in the water solution is way of its activation for the reduction. That hydrogenating system was employed for reduction of phthalides **45** to acids **46** (81–98%). The reaction was accomplished by heating the organic compound for several hours in the 10% aqueous solution of KOH or NaOH with small amount of pyridine [60–65]. The same conditions were used for reduction of phthalides **47** to acids **48** [50,66].



45 **46**

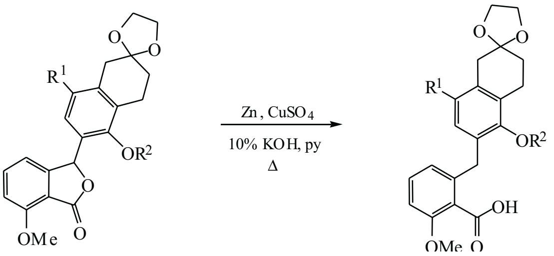
R^1 = Me, H; R^2 = H, Me; Ar = 3-methoxynaphth-1-yl, 7-fluornaphth-1-yl, 4-fluor-6-methoxynaphth-2-yl, 4,8-dimethoxynaphth-2-yl, naphth-1-yl, phenanthr-9-yl



47 **48**

R^1 = H, Me; R^2 = H, CF_3; R^3 = H, F; R^4 = H, OMe

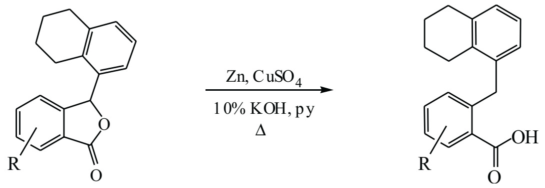
Reductions of 3*H*-isobenzofuran-1-ones **49** with the Zn-Cu couple in 10% KOH gave acids **50** after several hours of heating [67,68].



49 **50**

R^1 = H, OCH_2OMe, Me; R^2 = Me, Et

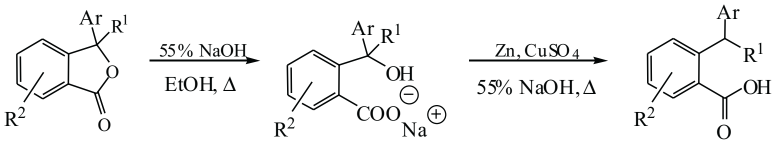
This methodology is effective in the case of the conversion of phthalides **51** to acids **52** as well [38,69,70].



51 **52**

R = 4-F, 6-F, 7-F

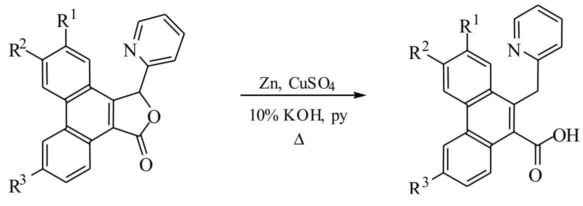
Sometimes, before the reduction, the lactone was hydrolyzed by heating of the 3*H*-isobenzofuran-1-one with concentrated 55% aqueous–alcoholic solution for 20–24 hours. Reduction of phthalides **53** to the acids **55** was achieved by that way [71–73].



53 **54** **55**

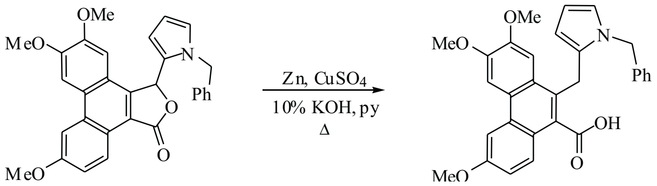
R^1 = H, Me; R^2 = H, 4-F, 7-F, 6-Me; Ar = Ph, naphth-1-yl, 5-methylnaphth-1-yl, 6-methylnaphth-1-yl, 4-methylnaphth-1-yl

Hydrogenation with zinc dust in the presence of $CuSO_4$ in basic solution converted 3*H*-isobenzofuran-1-ones **56** and **58**, which contained heterocyclic ring such as pyridine or pyrrole at C-3, to acids **57** and **59** [74].



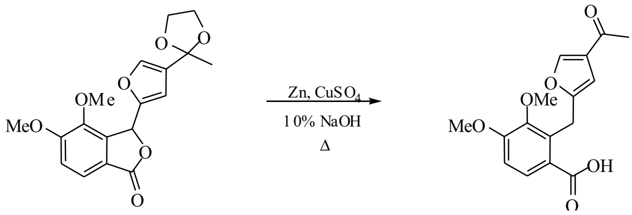
56 **57**

R^1 = H, OMe; R^2 = H, OMe, R^3 = H, OMe



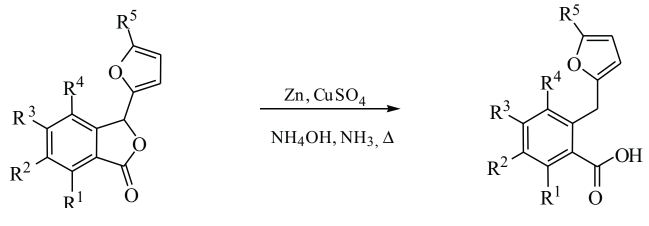
58 **59**

Reduction of phthalide **60**, which contained furan ring, first time was accomplished by employing of standard conditions (Zn, $CuSO_4$, 10% NaOH), but it did not give reproducible results [69].



60 **61**

That is why slightly different way of reduction of this kind of 3*H*-isobenzofuran-1-ones was used. It occurred when phthalides **62** were treated with Zn–Cu couple in the aqueous solution of ammonia with additionally passing through reaction mixture of gaseous ammonia [71–73].



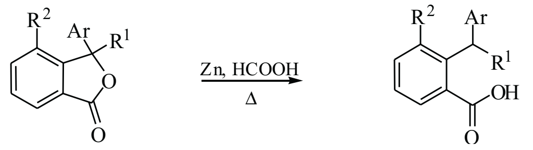
62 **63**

R^1 = H, OMe; R^2 = H, OMe; R^3 = H, OMe; R^4 = H, OMe; R^5 = H, Et, *n*-Pr, *n*-Bu, Ph

6. Catalytic reduction of phthalides over zinc in acidic medium

Conversion of phthalides into *ortho*-alkylated derivatives of benzoic acids can success by reduction with zinc in acidic medium as well, however, there is much less examples of this type reduction of 3*H*-isobenzofuran-1-ones. The way of doing the reaction is similar to that in alkaline solution.

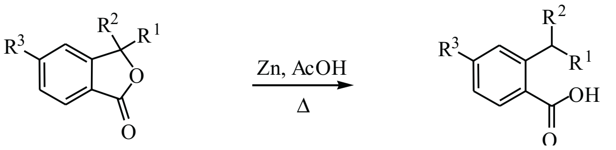
For instance, heated phthalides **64** with activated dust zinc during 10–20 hours in formic acid, underwent into corresponding products **65** [27,75–78].



64 **65**

R^1 = H, Me, Ph; R^2 = H, F; Ar = Ph, naphth-2-yl, naphth-1-yl, 4-methoxynaphth-1-yl, 5-fluoronaphth-1-yl, 6-fluoronaphth-2-yl, 4-methoxynaphth-1-yl, 6-fluoronaphth-1-yl

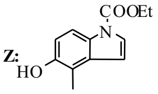
Instead of formic acid, 80–100% acetic acid can be used, what was shown in the transformation 3*H*-isobenzofuran-1-ones **66** into acids **67** [50,66,79].



66 **67**

R^1 = H, Me; R^2 = H, naphth-1-yl, 6-methoxynaphth-1-yl; R^3 = F, Z

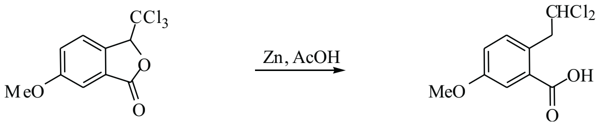
Z:



Sometimes, mixture of concentrated hydrochloric acid and glacial acetic acid can be employed in the reduction of phthalides [80].

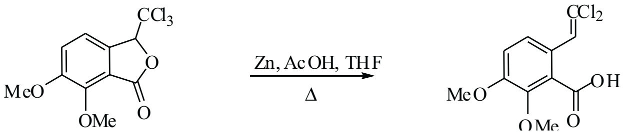
68 **69**

Interesting example of reduction 3*H*-isobenzofuran-1-one with zinc in acidic medium was reaction of 5-methoxy-2-trichloromethylphtalide **70** [81]. The acid **71** was product of hydrogenation of lactone ring and reduction one of the chlorine atom for hydrogen atom. It confirmed, that there is general ease of loss of chlorine atom from the compound in the presence of zinc [82,83].



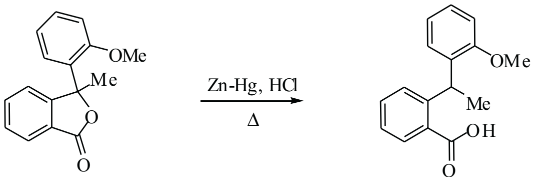
70 **71**

Hydrogenation of 3*H*-isobenzofuran-1-one **72** with zinc in system acetic acid – tetrahydrofurane after 2 hours at 60°C gave acid **73**, in molecule of which there was elimination of chlorine atom as well as forming double bond [84].



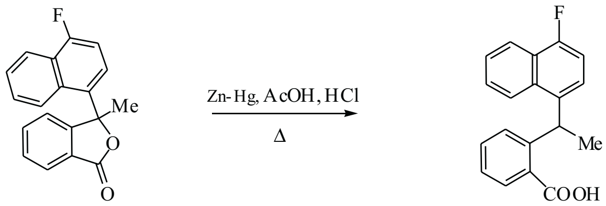
72 **73**

Clemmensen reduction, which employes zinc amalgam in hydrochloric acid solution, was also used in the reduction of phthalides. For instance, 3*H*-isobenzofuran-1-one **74** was transformed into acid **75** upon Clemmensen reduction conditions [85,86].



74 **75**

Hydrogenation of phthalide **76** was accomplished by Clemmensen method with addition of another solvent, which mixed with water, *i.e.* acetic acid [86].

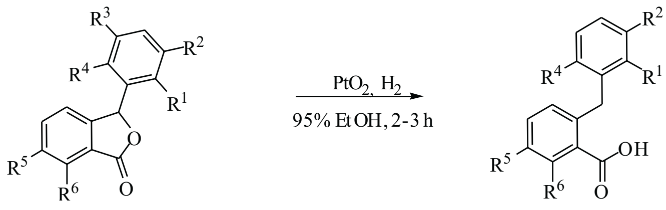


76 **77**

7. Miscellaneous catalytic reductions of phthalides

Besides commonly used palladium as a catalyst in the reduction of phthalides, there are employed platinum, cuprous and molybdenum compounds as well, but high temperature and pressure of hydrogen is often necessary to do hydrogenation of 3*H*-isobenzofuran-1-ones in that way.

Reduction of various bromophthalides **78** was carried out in alcohol, in the presence of platinum oxide and hydrogen under pressure. Unfortunately, during the hydrogenation, the loss of bromine atom took place [87].

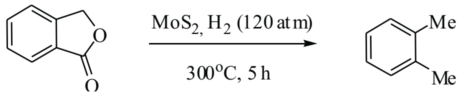


78 **79**

R^1 = OH, OMe; R^2, R^4 = H, Me; R^3 = Br; R^5, R^6 = H, OMe

Sulphides of metals are interesting group of catalyst used in hydrogenation, without deactivation of contact during the reaction [29,30].

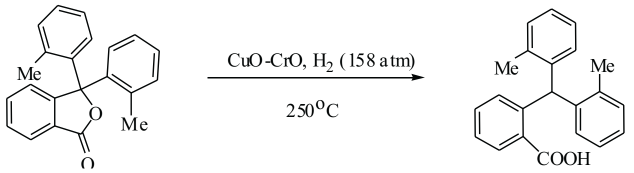
3*H*-Isobenzofuran-1-one **80** was converted to 1,2-dimethylbenzene **81** with the 88% yield by reduction with hydrogen under pressure and at high temperature, in the presence of molybdenum sulphide, which was made from hydrogen sulfide and molybdenum salt [88].



80 **81**

The so-called chromite (Adkins' catalyst) is the mixture of chromium oxide and another ennoble metal such as zinc or copper. It is an example of catalyst, which activity is result of co-existing and co-operating both of oxides. Advantages of chromite catalysts are stability and small sensitivity to deactivators or wetness. However, high temperature and pressure of hydrogen are necessary to effective reaction [29,30].

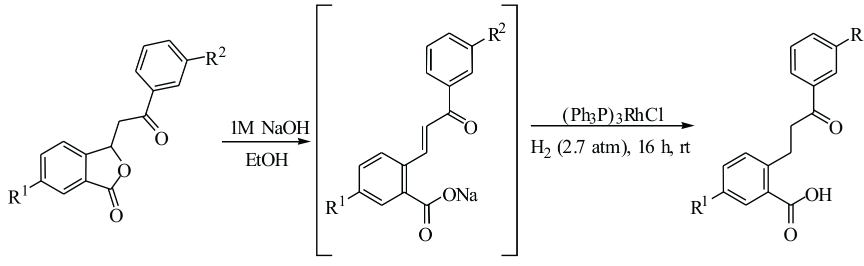
When phthalate **82** was treated with hydrogen in dioxane in the presence of copper chromite, corresponding acid **83** was obtained with 51% yield. If the reaction was carried out without solvent, yield increased to 83% [89].



82 **83**

All the catalysts described so far were used in heterogeneous catalytic hydrogenations. Homogeneous hydrogenation is catalyzed by compounds soluble in organic solvents and takes place in room temperature and atmospheric pressure of hydrogen. It is less effective but more selective than the heterogeneous hydrogenation and is therefore more suitable for selective reductions of polyfunctional compounds. These catalysts are less sensitive to deactivators. The disadvantages of homogeneous hydrogenation are lower availability of catalysts and more complicated isolation of products [29,30].

Example of homogeneous catalyst, which was employed in reduction of phthalides, was complex of noble metal, rhodium tris(triphenylphosphine)chloride (Wilkinson catalyst). Lactones **84** were hydrolyzed in the aqueous-ethanolic solution of NaOH to the salts **85**, and then were treated with hydrogen in the presence of rhodium tris(triphenylphosphine)chloride, which gave ketoacids **86** [90].



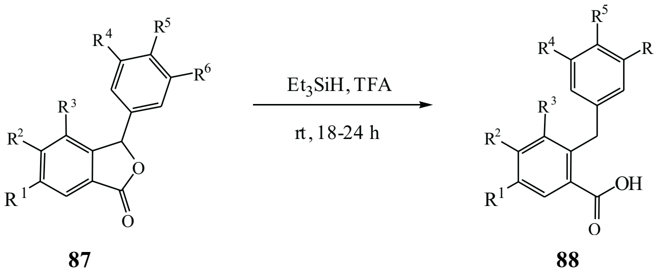
84 **85** **86**

$R^1 = H, Cl; R^2 = OH$

8. Ionic hydrogenation of phthalides

Ionic hydrogenation [91] is another way of reduction of phthalides. In the ionic hydrogenation reaction, the hydrogenating pair consists of a proton donor and hydride ion donor. The components of the hydrogenating pair must not react with each other. Secondly, they should not be involved in side reactions with the substrate. In addition to this, the hydrogenation agents and their conversion products must not hinder the evolution of the reduced compounds. In these respects the pair involving trifluoroacetic acid and organosilanes have proved most useful.

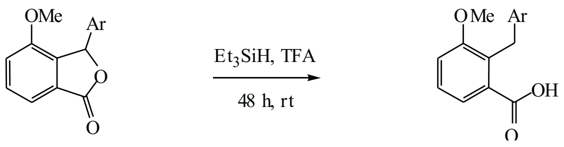
For example, under ionic hydrogenation conditions (TFA – Et_3SiH), phthalides **87** were transformed into acids **88** [92,93].



87 **88**

$R^1, R^2, R^3, R^4, R^5, R^6 = H, OMe$ $R^4\text{-}R^5 = OCH_2O$

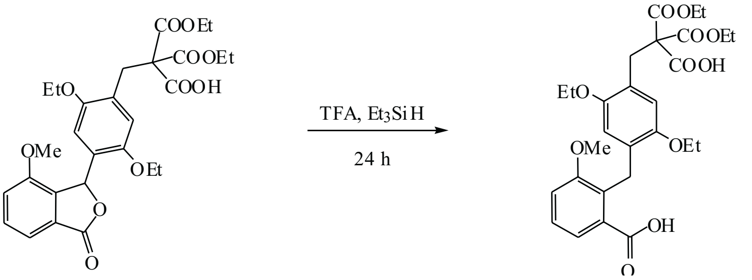
When 3-naphtylphthalides **89** were treated with triethylsilane in the presence of trifluoroacetic acid, corresponding acids **90** were obtained [94].



89 **90**

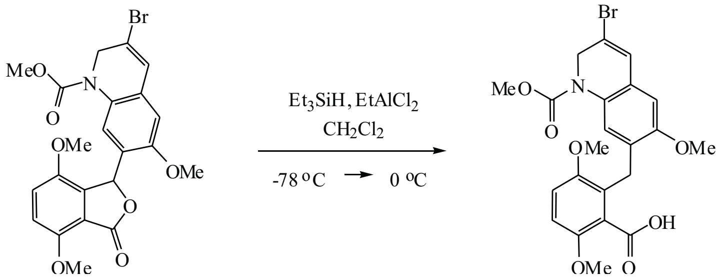
Ar = naphth-1-yl, naphth-2-yl

This kind of reduction can be selective reaction. 3*H*-Isobenzofuran-1-one **91**, which contained carboxylic ester group, after 24 hours was reduced to dicarboxylic acid **92** with 83% yield [95].



91 **92**

Sometimes TFA can be replaced by strong Lewis acid such as $EtAlCl_2$ or $MeAlCl_2$. Additionally, using methylene chloride as a co-solvent, helps to obtain homogeneous medium of the reaction [96,97]. Reduction of the phthalide **93** was achieved in that way.

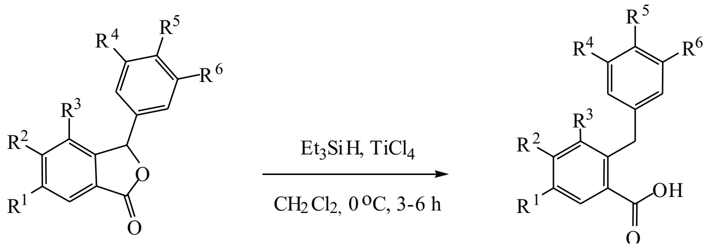


93 **94**

9. Reduction of phthalides with titanium compounds

Another group of reductions of 3*H*-isobenzofuran-1-ones are their transformations in the presence of four valence compounds of titanium.

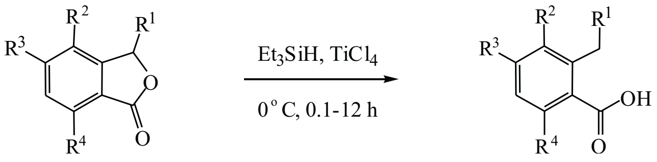
In typical ionic hydrogenation of phthalides **87**, with system TFA – Et_3SiH, trifluoroacetic acid was replaced with titanium tetrachloride, which caused to obtain desired products **88** with good yields in few hours time [92].



87 **88**

$R^1, R^2, R^3, R^4, R^5, R^6 = H, OMe; R^1\text{-}R^2 = OCH_2O; R^4\text{-}R^5 = OCH_2O$

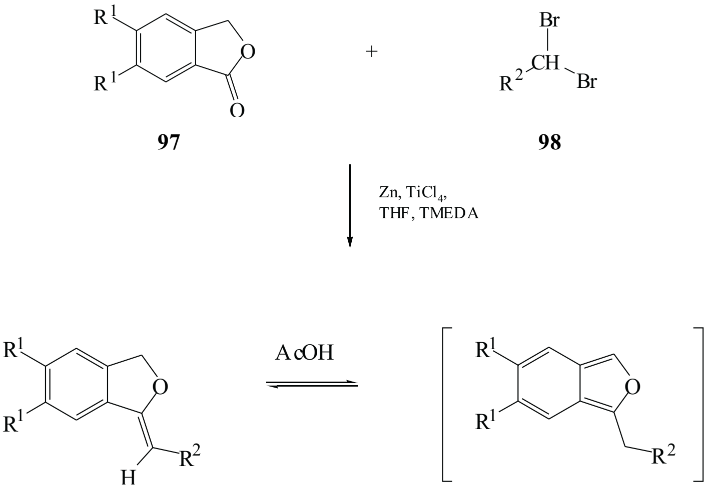
Another example was the synthesis of various chlorobenzoic acids **96** from phthalides **95** at 0°C [98].



95 **96**

$R^1 = C_6H_4$-OMe(2), C_6H_3-(OMe)$_2$(2,3), C_6H_3-(OMe)$_2$(2,4), C_6H_3-(OMe)$_2$(2,5), C_6H_4-Cl(2), C_6H_4-Br(2); R^2 = H, Cl, OMe; R^3 = H; R^4 = H, Cl

Titanium catalyst was employed in reduction of 3*H*-isobenzofuran-1-ones **97** without opening lactone ring [99]. Undefined organotitanium species generated from 1,1-dibromohexane, titanium tetrachloride and zinc dust reacted with phthalides **97** to afford isobenzofuranes **100**. The resulting isobenzofuranes **100** existed in equilibrium with phthalanes **99** in the solution of acetic acid. Isobenzofuranes **100** were very prone to decomposition. Therefore, they were not isolated from the reaction medium, but used in further reactions. Phthalans **99** were isolated in moderate yields (40–50%) but in general those compounds were too unstable and it was better to carry them through the next step without rigorous purification.

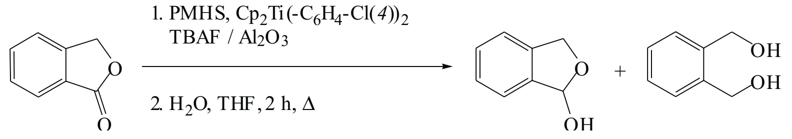


97 **98**

99 **100**

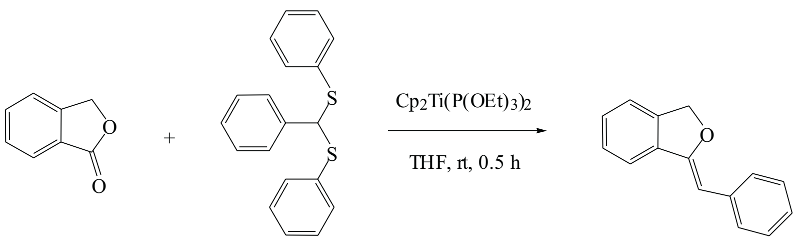
R^1 = H, OMe; R^2 = H, Ph, Bn, $CH_2CH{=}CH_2$, $(CH_2)_2CH{=}CH_2$, $(CH_2)_3CH{=}CH_2$

Titanocenes are stable catalyst, which were employed during the reduction of phthalides [100,101]. Strategy, in which phthalide **101** were transformed into lactol **102** using as reducing agent system Cp_2-Ti(O-C_6H_4-Cl(*p*))$_2$ – polymethylhydrosiloxan. When the reaction was carried out in water and THF in the presence of TBAF, 1-hydroxy-1,4-dihydroisobenzofurane **102** and diol **103** were obtained in the ratio of 5.5 to 1, with overall yield 75%.



101 **102** **103**

Hydrogenation of 3*H*-isobenzofuran-1-one **101** was also accomplished in the presence of titanocene, which gave unsaturated ether of phthalate **105**, mainly Z isomer.

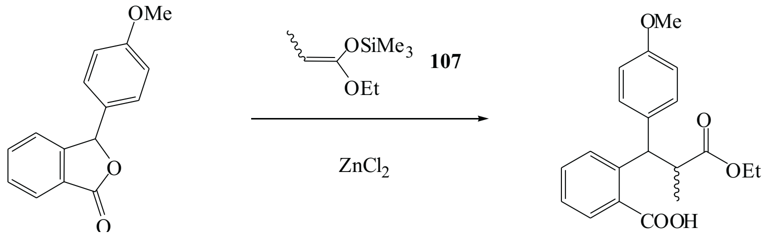


101 **104** **105**

10. Reductive alkylation of phthalides

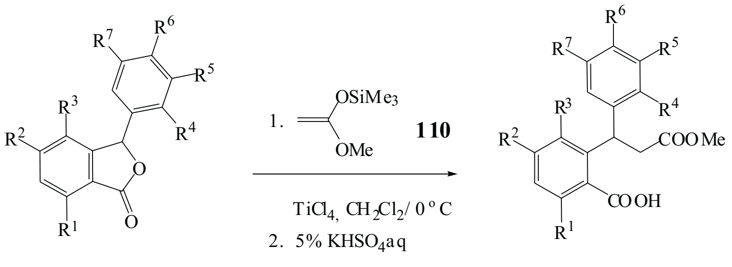
There are only few examples [102–110] of alkylation of esters, including γ-lactones, with silyl enol ethers. Procedures, which were used in those syntheses, employed various catalysts, such as $ZnCl_2$ [102,103], $Ph_3C^+SbCl_6^-$ [104–106], $TiCl_4$ [107–109] and mixture DIBAL-H and $BF_3 \cdot OEt_2$ [111].

In 1990 was published the first paper [103], which referred to the transformation of 3-arylphthalide **106** *via* reaction with trimethylsilyl acetal of ethyl propionate **107** in the presence of $ZnCl_2$ to 2-[1-(4-methoxyphenyl)-2-ethoxycarbonylpropyl]-benzoic acid **108** with 86% overall yield.



106 **108**

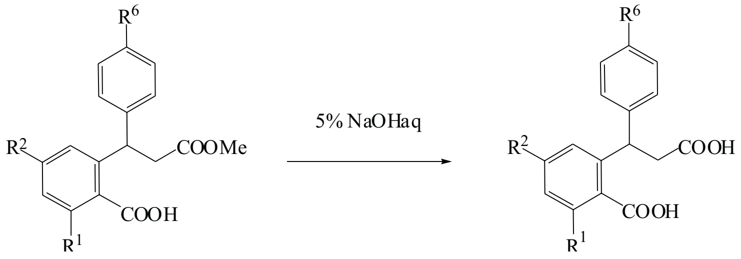
The Mukaiyama procedure conditions [112,113] were chosen for the synthesis of the desired *ortho*-substituted benzoic acids by treatment of phthalides with corresponding methyltrimethylsilyl acetal. The Mukayiama procedure was initially known in the literature as reaction of *O*-silyl enol ethers with aldehydes or ketones in the presence of titanium tetrachloride, which gave aldol condensation, alkylation or Michael addition products. However, it has recently been used for alkylation of acetylated benzyl- and allyl alcohols [102,114] in the presence of Lewis acids. It has been started with a series of 3-arylphthalides **109** and simple 1-methoxy-1-trimethylsilyloxyethene **110** as an alkylating agent [115]. In that way, the corresponding 2-(1-aryl-2-methoxycarbonylethyl)benzoic acids **111** employing titanium tetrachloride as a catalyst and methylene chloride as a solvent were obtain.



109 **111**

R^1, R^3, R^4, R^5, R^6, R^7 = H, OMe; R^2 = H, Cl, OMe

Examination of the data reveals that the only products obtained from the reaction were the corresponding esters **111**. In the cases of two phthalides, the formed products **111** were isolated after basic hydrolysis as the dicarboxylic acids **112a**,**b**.



111 **112a,b**

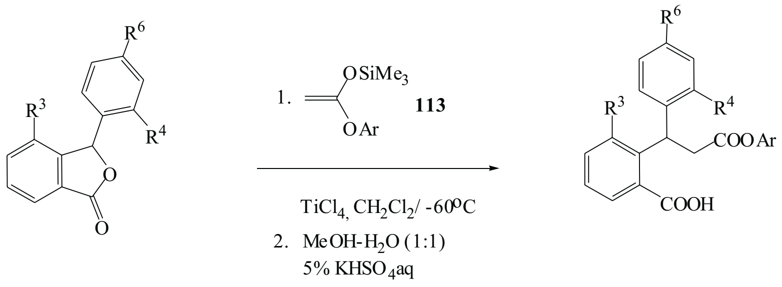
a: R^1 = H; R^2 = OMe; R^3 = H; R^4 = H; R^5 = H; R^6 = OMe; R^7 = H

b: R^1 = OMe; R^2 = H; R^3 = H; R^4 = H; R^5 = H; R^6 = OMe; R^7 = H

The observed yield indicated that the reductive alkylation is significantly affected by the substituents surrounding the reaction center. The reductive alkylation gave good and comparable results, in the cases of phthalides, in which the substituent at position 4 of the molecule is a hydrogen atom. Moreover, the presence of the 2′ methoxy group in the nucleus of phthalide did not produce a meaningful change in the reaction yield. In contrast to these results, replacing the hydrogen atom at position 4 of the phthalide by methoxy group caused decreasing of the output of the process by more than half. This may be attributed to the steric hindrance of the methoxy group at C-4, for the nucleophilic attack of 1-methoxysilyloxyethene on phthalide in this alkylation is assumed. Such a course of the addition *O*-silylating agent **110** to 3-arylphthalide **109** would be consistent with the behaviour of lactones in the reaction with hard acids and soft nucleophilic systems [116]. Molecule of the phthalides contains besides methoxy groups at 4 and 2′, another substituent at 3′ position. The deformation of valency angles of benzene nucleus [117] can be a consequence of additional steric repulsive interactions of the both methoxy groups at 2′ and 3 positions. As a result of the steric hindrance around the reaction center in this phthalide could cause the difficulty in S_{N2}-type nucleophilic attack of 1-methoxysilyloxyethene on it.

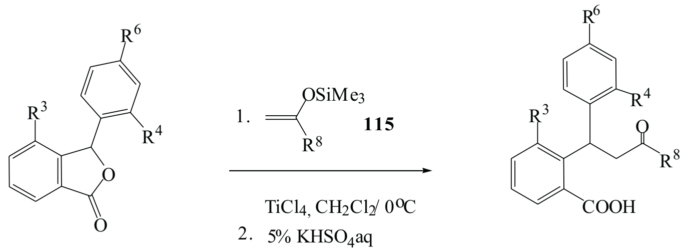
Recently it has been shown that the rate of reaction of diaryl carbenium ions with silyl enol ethers and silyl ketene acetals is effected by their nucleophilicity [124]. Therefore, there appeared intriguing question to what extent the conversion of phthalides into *ortho*-alkylated benzoic acids is effected by the nucleophility of used silyl enol ether or trimethylsilyl ketene acetal. The phthalides **109a**,**b** were selected for testing the reductive alkylation process as considerably different from each other. The reason these compounds were chosen was that it has been shown that reductive alkylation is significantly affected by the neighborhood of reactive center of phthalides.

The reductive alkylation of phthalides **109a,b** with agents **113**, which was carried out in methylene chloride, in the presence of titanium tetrachloride, in temperature –60°C for the silyl ketene acetals **113** gave in the satisfactory yields acids **114**, but in the reaction with silyl enol ethers **115** only in the case of **109a** reaction appeared to be positive [119].



109a,b **114**

a: R^3 = H; R^4 = H; R^6 = OMe; Ar = C_6H_4-OMe(4)
b: R^3 = OMe; R^4 = OMe; R6 = H; Ar = C_6H_4-Me(4)

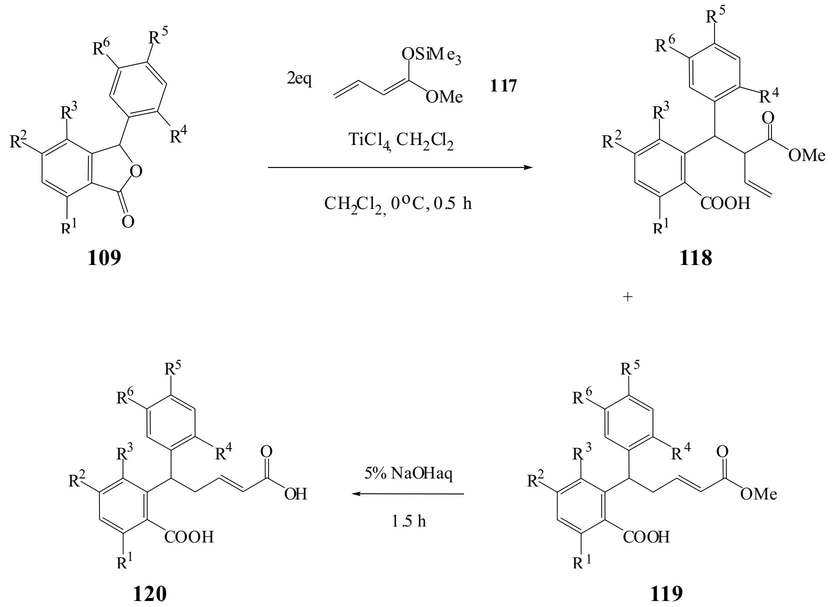


109a,b **116**

The observed yield indicated that two different effects influence on the tested reductive alkylation of phthalides **109**. The first one, which was also seen in the previous reaction of phthalides **109** with 1-methoxy-1-trimethylsilyloxyethene **110**, depends upon the substituents surrounding the reaction center. The larger the steric hindrance is, the more difficult nucleophilic attack [116] of the alkylating agents is and, in the consequence of that the smaller output of the processes is obtained. On the other hand, increasing nucleophilicity of reactants **113** in both series of the phthalides **109a,b** effectively enhances the yield of the addition.

In the case of reaction with the lower nucleophilic activity of the reagent such as **115**, the lower outputs of alkylation products **116** were got. The increase in steric hindrance near the reaction center and poor nucleophilicity of compounds **115** result in forming only traces of acids **116**.

This process was as well extended for the applying as nucleophile 1-methoxy-1-trimethylsilyloxybuta-1,3-diene **117** [120] as a source of a four-carbon atom building block [121]. This method would provide access to a new and effective synthesis as a general transformation of phthalides into alkylated benzoic acid, which contain in the *ortho* position five-carbon atoms chain. It has been demonstrated at the conjugated silyl dienolates such as 1-methoxy-1-trimethylsilyloxybuta-1,3-diene **117**, can be alkylated at the α- or γ-position, and that the γ-selectivity could be enhanced by the increased capacity of alkoxy groups in diene as well as relatively well-stabilized cationic electrophiles [122–126]. The reaction of the phthalide **109** with 1-methoxy-1-trimethylsilyloxybuta-1,3-diene **117** in the presence of titanium tetrachloride in methylene chloride in temperature 0℃, gave the mixture of the corresponding alkylated compounds **118** and **119** [121].



$R^1, R^2, R^3, R^4, R^5, R^6$ = H, OMe

The observed yields suggest that the tested reductive alkylation is significantly affected by the capacity of substituents surrounding the reaction center. Phthalides of **109** with hydrogen atoms at the 4 positions, reacted with 1-methoxy-1-trimethylsilyloxybuta-1,3-diene **117** gave desired γ-adducts **119**, but they were accompanied yet by

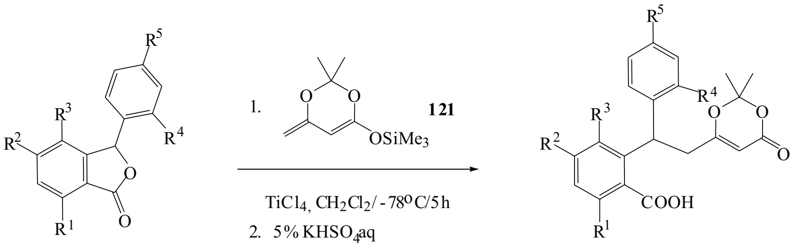
α-adducts **118** with overall quantitative yields. The following tests aimed for improving the degree of γ-selectivity such as variation of the temperature and the reaction time also replacing the titanium tetrachloride for other Lewis acids – $SnCl_4$, $ZnCl_2$, $Ti(OPr)_4$, $TiCl_4$-$Ti(OPr)_4$, BF_3OEt_2 did not affect the ratio of the formed compounds **118:119**. If in the place of 1-methoxy-1-trimethyl-silyloxybuta-1,3-diene **117** more sterically hindered 1-*tert*-butyldimethylsilyloxy-1-*tert*-butoxybuta-1,3-diene was used for the reaction with the phthalide **109** as well any change in the course of the reaction was observed.

The phthalides **109**, in which one or two methoxy groups are attached at close positions to the centre of the reaction, caused a basic change in the course of the process. In practice solely γ-selectivity was observed, but with a greater or smaller decrease of yields. This may be attributed to the steric hindrance caused by the pivotal methoxy groups for the nucleophilic attack by 1-methoxy-1-trimethyl-silyloxybuta-1,3-diene **117** [116].

Interestingly, introducing methoxy group at the position 5′ drastically decreased output of the process. Although the observed behaviour of that phthalides cannot be unequivocally explained. It should be emphasized that nucleophilic substitution of the hydroxy or alkoxy groups at the benzyl species in the presence of Lewis acids is efficiently enhanced, if there is the electron-donating substituent at the *para* position. It is caused by the stabilizing effect of the benzyl cationic species, which would be generated during the process of substitution [127,128]. Shifting of the methoxy group from the position 5′ into 4′ significantly improved the reaction yield.

The use of 2,2-dimethyl-6-methylene-4-trimethylsiloxy-1,3-diox-4-ene **121** constitutes an interesting alternative to the classic enantioselective Mukaiyama aldol reaction with silyl enol ethers. The interest in the employment of this silyl dienolate **121** is due to the easy manipulation of the dioxinone ring in the aldol adducts to a variety of three carbon units [129,130]. In fact, the masked acetoacetate aldol adducts serve as versatile precursors to optically active δ-hydroxy-β-ketoesters and derived β,δ-diol esters, amides and lactones, key structural subunits in biologically active natural products [131,132].

That is why *ortho*-alkylated benzoic acids **122** were synthesized from phthalides **109**. As it was expected, the reaction of phthalides **109** with 2,2-dimethyl-6-methylene-4-(trimethylsiloxy)-1,3-diox-4-ene **121** provided effectively the desired products **122** after 6 hours in the temperature –78℃ [133].



109 **122**

R^1, R^2, R^3, R^4, R^5, = H, OMe

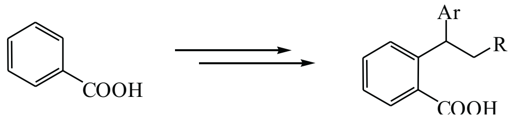
Examination of the data reveals that the only products obtained from the reaction were the corresponding acids **122** together with recovered phthalides. In the cases of phthalides, in which there is no substituent at position 4, the addition gave very good and comparable results. When the hydrogen atom at position 4 was replaced by the methoxy group, the output of the process was slightly decreased.

11. Conclusions

Reduction of phthalides at the carbon atom 3 is very important method for the synthesis of *ortho*-alkylated aromatic carboxylic acids. These kind of aromatic species are important synthons for preparation of numerous *poly*-aromatic compounds incorporating physiologically acitve products [134–139].

As it is shown in this review, the applicability of the methods depend upon the nature and position of substituents at the phthalide nucleus.

Especially valuable is the reductive alkylation of phthalides as a methodology for the preparation of *ortho*-alkylated carboxylic acids with long alkyl chain. This methodology opens possibility of introduction *via* two steps protocol of the chiral carbon atom at the *ortho* position to the aromatic carboxylic acids. However, till now as a racemic mixture.



REFERENCES

1. Elderfield R.C., in "Heterocyclic compounds", (Elderfield R.C., ed.), Vol. 2, p. 68. NY, 1951.
2. Rodrigo R., *Tetrahedron Lett*., **44**, 2093 (1988).
3. Friedrichsen W., *Adv. Heterocycl. Chem*., **26**, 135 (1980).
4. The Merck Index, 11th ed., Rahway 1989.
5. Kende A.S. and Boettger S.D., *J. Org. Chem*., **46**, 2799 (1981).
6. Krapcho A.P., Getahun Z. and Avery K.J., Jr., *Synth. Commun*., **20**, 2139 (1990).
7. Patil M.L., Borate H.B., Ponde D.E., Bhawal B.M. and Deshpande V.H., *Tetrahedron Lett*., **40**, 4437 (1999).
8. Wulff W.D. and Tang P.-C., *J. Am. Chem. Soc*., **106**, 434 (1984).
9. Iwao M., Mahalanabis K.K., Watanabe M., de Silva S.O. and Snieckus V., *Tetrahedron*, **39**, 1955 (1983).
10. Dunsdon S.J. and Martin J.A., *Tetrahedron*, **41**, 2919 (1985).
11. Zani C.L., de Oliveira A.B. and Snieckus V., *Tetrahedron Lett*., **28**, 6561 (1987).
12. Starling S.M., Raslan D.S., de Oliveira A.B. and Zani C.L., *Synth. Commun*., **28**, 3567 (1998).
13. Lopes C.C., Lima L.S., Monteiro A.J. and Costa P.R.R., *Synth. Commun*., **18**, 1731 (1988).
14. Iio H., Zenfuku K. and Tokoroyama T., *Tetrahedron Lett*., **36**, 5921 (1995).
15. Falk H. and Mayr E., *Monatsh. Chem*., **126**, 699 (1995).
16. English D.S., Zhang W., Kraus G.A. and Petrich J.W., *J. Am. Chem. Soc*., **119**, 2980 (1997).
17. Falk H. and Schoppel G., *Monatsh. Chem*., **122**, 739 (1991).
18. Falk H. and Mayr E., *Monatsh. Chem*., **126**, 1311 (1995).
19. Clar E. and Stewart D.G., *J. Chem. Soc*., 3215 (1951).
20. Isola M. and Marsili A., *Tetrahedron*, **23**, 1037 (1967).

21. Marsili A., *J. Org. Chem.*, **32**, 240 (1967).
22. Bergmann E.D., Weiler-Feilchenweld H., Heller A., Britzman C. and Hirschfeld A., *Tetrahedron Suppl.*, **7**, 349 (1966).
23. Fouché J., Blondel J.-C., Horclois R., James C., Léger A. and Poiget G., *Bull. Soc. Chim. Fr.*, **8**, 3113 (1972).
24. Suzuki K., Weisburger E.K. and Weisburger J.H., *J. Org. Chem.*, **26**, 2236 (1961).
25. Newman M.S. and Hussain N.S., *J. Org. Chem*., **47**, 2837 (1982).
26. Newman M.S., Prahbu V.S. and Veeraraghavan S., *J. Org. Chem.*, **48**, 2926 (1983).
27. Newman M.S. and Veeraraghavan S., *J. Org. Chem*., **48**, 3246 (1983).
28. Sabhita G. and Yadav J.S., *Synth. Commun*., **28**, 3065 (1998).
29. Hudlický M., "Reductions in Organic Chemistry", Ellis Horwood, Chichester, 1986.
30. Bartoszewicz R., Miecznikowska-Stolarczyk W. and Oprządek B., "Methods of Reduction of Organic Compounds". Warszawa, 1956, (in Polish).
31. de Silva S.O., Watanabe M. and Snieckus V., *J. Org. Chem.*, **44**, 4802 (1979).
32. Manceron L. and Andrews L., *J. Am. Chem. Soc.*, **110**, 3840 (1988).
33. Sammes P.G., Arnold B.J. and Mellows S.M., *J. Chem. Soc., Perkin Trans. 1*, 1266 (1973).
34. Snieckus V. and Osmund S., *Tetrahedron Lett*., **51**, 5103 (1978).
35. Kelly T.R. and Parekh N.D., *J. Org. Chem*., **47**, 5009 (1982).
36. Falk H. and Mayr E., *Monatsh. Chem*., **126**, 1311 (1995).
37. Nichols D.E., Snyder S.E., Aviles-Garay F.A., Chakraborti R., Watts V.J. and Mailman R.B., *J. Med. Chem*., **38**, 2395 (1995).
38. Witiak D.T., Abdood N.A., Goswami S. and Milo G.E., *J. Org. Chem.*, **51**, 4499 (1986).
39. Castle N., Pratap R. and Tominaga Y., *J. Heterocycl. Chem*., **19**, 865 (1982).
40. Johnson F., Kimball S.D. and Walt D.R., *J. Am. Chem. Soc*., **103**, 1561 (1981).
41. Krapcho A.P., Getahun Z. and Avery K.J. Jr., *Synth. Commun*., **20**, 2139 (1990).
42. Iio H., Zenfuku K. and Tokoroyama T., *Tetrahedron Lett*., **36**, 5921 (1995).
43. Harvey R.G. and Cortez C., *Tetrahedron*, **53**, 7101 (1997).
44. Harvey G. and Cho B.P., *J. Org. Chem.*, **52**, 5668 (1987).
45. Kraus G.A., English D.S. and Petrich J.W., *J. Am. Chem. Soc*., **119**, 2980 (1997).
46. Schultz A.G., McMahon W.G. and Kullnig R.K., *J. Org. Chem*., **52**, 3905 (1987).
47. Falk H. and Schoppel G., *Monatsh. Chem*., **122**, 739 (1991).
48. Proksa B., Uhrinová S., Adamcová J. and Fuska J., *Monatsh. Chem*., **123**, 251 (1992).
49. Newman M.S. and Wiseman E.H., *J. Org. Chem*., **26**, 3208 (1961).
50. Newman M.S. and Kannan R., *J. Org. Chem*., **44**, 3388 (1979).
51. Misra R.N., Brown B.R., Sher P.M., Patel M.M., Hall S.E., Han W.-C., Barrish J.C., Kocy O., Harris D.N., Goldenberg H.J., Michel I.M., Schumacher W.A., Webb M.L., Moshizadegan H. and Ogletree M.L., *J. Med. Chem.*, **36**, 1401 (1993).
52. Newman M.S. and Galt R.H.B., *J. Org. Chem*., **25**, 214 (1960).
53. Birkinshaw J.H. and Gourlay R., *J. Chem. Soc*., 716 (1963).
54. Yang C.-X. and Harvey R.G., *Tetrahedron*, **48**, 3735 (1992).
55. Harvey R.G., Aboshkara E. and Pataki J., *Tetrahedron*, **53**, 15947 (1997).
56. Uemura M., Minami T. and Hayashi Y., *J. Chem. Soc., Chem. Commun.*, **17**, 1193 (1984).
57. Katsuura K. and Snieckus V., *Can. J. Chem*., **65**, 124 (1987).
58. Newman M.S., Cecil J.H. and Hung W.M., *J. Med. Chem*., **15**, 569 (1972).
59. Rama Rao A.V., Reddy K.B. and Mehendale A.R., *J. Chem. Soc., Chem. Commun*., **10**, 564 (1983).
60. Newman M.S. and Tuncay A., *J. Org. Chem*., **45**, 348 (1980).
61. Newman M.S., Sankaran V. and Olson D.R., *J. Am. Chem. Soc*., **98**, 3237 (1976).
62. Sheikh Y.M., Ekwuribe N., Dhawan B. and Witiak D.T., *J. Org. Chem*., **47**, 4341 (1982).
63. Newman M.S. and Kumar A., *J. Org. Chem.*, **51**, 2379 (1986).
64. Mills R.J. and Snieckus V., *J. Org. Chem.*, **54**, 4386 (1989).
65. Newman M.S., *J. Org. Chem*., **48**, 3249 (1983).
66. Harvey R.G. and Cortez C., *Tetrahedron*, **53**, 7101 (1997).
67. Kende A.S. and Boettger S.D., *J. Org. Chem*., **46**, 2799 (1981).
68. Wulff W.D. and Tang P.-C., *J. Am. Chem. Soc.*, **106**, 434 (1984).
69. Witiak D.T., Goswami S. and Milo G.E., *J. Org. Chem*., **53**, 345 (1988).

70. Patil M.L., Borate H.B., Ponde D.E., Bhawal B.M. and Deshpande V.H., *Tetrahedron Lett.*, **40**, 4437 (1999).
71. Bentov M. and Bergmann E.D., *Bull. Soc. Chim. Fr.*, 1316 (1961).
72. Pataki J., Duguid C., Rabideau P.W., Huisman H. and Harvey R.G., *J. Med. Chem.*, **14**, 940 (1971).
73. Bentov M. and Bergmann E.D., *Bull. Soc. Chim. Fr.*, 963 (1963).
74. Iwao M., Mahalanabis K.K., Watanabe M., de Silva S.O. and Snieckus V., *Tetrahedron*, **39**, 1955 (1983).
75. Newman M.S. and Blum S., *J. Org. Chem.*, **29**, 1414 (1964).
76. Newman M.S. and Naiki K., *J. Org. Chem*., **27**, 863 (1962).
77. Letsinger R.L., Jamison J.D. and Hussey A.S., *J. Org. Chem*., **26**, 97 (1961).
78. Newman M.S. and Seshardi S., *J. Org. Chem*., **27**, 76 (1962).
79. Dunsdon S.J. and Martin J.A., *Tetrahedron*, **41**, 2919 (1985).
80. Bistrzycki A. and Krauer J., *Helv. Chim. Acta*, **6**, 763 (1923).
81. Berner E., *Acta Chem. Scand.*, **10**, 1208 (1956).
82. Ryer A.I. and Gebert W.H., *J. Am. Chem. Soc*., **74**, 41 (1952).
83. Schubert W.M., Rabinovitch B.S., Larson N.R. and Sims V.A., *J. Am. Chem. Soc*., **74**, 4590 (1952).
84. Koseki Y. and Nagasaka T., *Chem. Pharm. Bull.*, **43**, 1604 (1995).
85. Topp A., Boldt P. and Schmand H., *Liebigs Ann. Chem*., 1167 (1974).
86. Bergmann E.D. and Blum J., *J. Org. Chem.*, **27**, 527 (1962).
87. Brubaker M.M. and Adams R., *J. Am. Chem. Soc*., **49**, 2279 (1927).
88. Moldawski B.L. and Turetzkaya L.E., *Zh. Ob. Khim.*, **16**, 445 (1946).
89. Bartlett P.D. and Jones J.E., *J. Am. Chem. Soc*., **64**, 1837 (1942).
90. Larsen R.D., Corley E.G., King A.O., Carroll J.D., Davis P., Verhoeven T.R. and Reider P.J., *J. Org. Chem*., **61**, 3398 (1996).
91. Kursanov D.N., Parnes Z.N. and Loim N.M., *Synthesis*, 633 (1974).
92. Joshi R.R. and Narasimhan N.S., *Synthesis*, 943 (1987).
93. Gore V.G. and Narasimhan N.S., *J. Chem. Soc., Perkin Trans. 1*, 481 (1988).
94. Newman M.S. and Kanakarajan K., *J. Org. Chem*., **45**, 2301 (1980).
95. Kimbal S.D., Kim K.S., Mohanth D.K., Vanotti E. and Johnson F., *Tetrahedron Lett*., **23**, 3871 (1982).
96. Tauton J., Wood J.L. and Schreiber S.L., *J. Am. Chem. Soc*., **115**, 10378 (1993).
97. Chikashita H., Porco J.A., Stout T.J., Clardy J. and Schreiber S.L., *J. Org. Chem*., **56**, 1692 (1991).
98. Epsztajn J., Bieniek A. and Kowalska J.A., *Monatsh. Chem*., **127**, 701 (1996).
99. Meegalla S.K. and Rodrigo R., *Synthesis*, **12**, 924 (1989).
100. Verdauguer X., Berk S.C. and Buchwald S.L., *J. Am. Chem. Soc*., **117**, 12641 (1995).
101. Horikawa Y., Watanabe M., Fujiwara T. and Takeda T., *J. Am. Chem. Soc*., **119**, 1127 (1997).
102. Reetz M.T, Wolz P., Hübner F., Hüttenheim S.H., Heimbach H. and Schwellnus K., *Chem. Ber.*, **117**, 322 (1984).
103. Hunt J.T., Malley M.F. and Gougoutas J.Z., *Heterocycles*, **31**, 1359 (1990).
104. Homma K., Takenoshita H. and Mukaiyama T., *Bull. Chem. Soc. Jpn*., **63**, 1898 (1990).
105. Mukaiyama T., Homma K. and Takenoshita H., *Chem. Lett*., **10**, 1725 (1988).
106. Homma K. and Mukaiyama T., *Chem. Lett.*, 1989, 893.
107. Brownbridge P., Chan T.H., Brook M.A. and Kang G.J., *Can. J. Chem*., **61**, 688 (1983).
108. Chan T.-H. and Brownbridge P., *J. Chem. Soc. Chem. Commun*., **1**, 20 (1981).
109. van Oeveren A. and Feringa B.L., *J. Org. Chem*., **61**, 2920 (1996).
110. Kita Y., Segawa J., Haruta J., Yasuda H. and Tamamura Y., *J. Chem. Soc. Perkin Trans. 1*, 1099 (1982).
111. Kiyooka S.-I. and Shirouschi M., *J. Org. Chem.*, **57**, 1 (1992).
112. Mukayiama T., Narasaka K. and Banno K., *J. Am. Chem. Soc*., **96**, 7503 (1974).
113. Mukayiama T., *Angew. Chem., Int. Ed. Engl*., **16**, 817 (1977).
114. Grieco P.A. and Handy S.T., *Tetrahedron Lett*., **38**, 2645 (1997).
115. Epsztajn J., Bieniek A., Kowalska J.A. and Kulikiewicz K.K., *Synthesis*, **11**, 1603 (2000).
116. Node M., Nishide K., Ochiai M., Fuji K. and Fujita E., *J. Org. Chem*., **46**, 5163 (1981).
117. Streitweiser A., Jr., Ziegler G.R., Mowery P.C., Lewis A. and Lawler R.G., *J. Am. Chem. Soc*., **90**, 1357 (1968).
118. Burfeindt J., Patz M., Müller M. and Mayr H., *J. Am. Chem. Soc*., **120**, 3629 (1998).
119. Bieniek A., Epsztajn J. and Kulikiewicz K.K., *Synth. Commun.*, **4**, 667 (2003).
120. Casiraghi G., Zauardi F., Appendino G. and Roussou G., *Chem. Rev.*, **100**, 1929 (2000).

121. Bieniek A., Epsztajn J. and Kulikiewicz K.K., *Monatsh. Chem.*, in press.
122. Mukaiyama T. and Ischida A., Chem. Lett., 319 (1975).
123. Mukaiyama T. and Ischida A., *Chem. Lett.*, 1201 (1975).
124. Mukaiyama T. and Ischida A., *Chem. Lett.*, 467 (1977).
125. Fleming I. and Lee T.V., *Tetrahedron Lett.*, **22**, 705 (1981).
126. Chow H.F. and Fleming I., *J. Chem. Soc. Perkin Trans 1*, 2651 (1998).
127. Angle S.R. and Louie M.S., *Tetrahedron Lett.*, **30**, 5741 (1989).
128. Angle S.R. and Louie M.S., *J. Org. Chem.*, **56**, 2853, (1991) and references therein.
129. Kaneko C., Sato M., Sakaki J. and Abe Y., *J. Heterocyclic Chem*., **27**, 25 (1990).
130. Clemens R.J. and Witzeman J.S., *J. Am. Chem. Soc.*, **111**, 2186 (1989).
131. Singer A.R. and Carreira M.E., *J. Am. Chem. Soc.*, **117**, 12360 (1995).
132. Sato M., Sunami S., Sugita Y. and Kaneko C., *Chem. Pharm. Bull*., **42**, 839 (1994).
133. Bieniek A., Epsztajn J. and Kulikiewicz K.K., in preparation for press.
134. Hall S.E., *Med. Res. Rev.*, **11**, 503 (1991).
135. Ohkawa S., Terao T., Terashita Z., Shibouta Y. and Nishikawa K., *J. Med. Chem.*, **34**, 267 (1991).
136. Ohkawa S., Terao S., Murakami M., Matsumoto T. and Goto G., *Chem. Pharm. Bull.*, **39**, 917 (1991).
137. Bhagwat S.S., Gude C., Cohen D.S., Lee W., Furness P. and Clarke F.H., *J. Med. Chem*., **34**, 1790 (1991).
138. Soyka R., Heckel A., Nickl J., Eisert W., Müller T.H. and Weisenberger H., *J. Med. Chem.*, **37**, 26 (1994).
139. Miki I., Kishibayashi N., Takeda M., Suzuki K., Obase H. and Ishiii A., *Arzneim.-Forsch.*, **45**, 1066 (1995).