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USE OF ACTIVATION METHODS FOR ORGANOZINC REAGENTS

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CONTENTS

1. INTRODUCTION

Preparation of organo-Zn reagents by an activation method and their uses in organometallic synthesis are discussed. Organozinc reagents are now extensively used due to their synthetic potential.[1] Some recent examples are of the synthesis of ketones from Pd catalyzed coupling of organozinc reagents with acid chlorides,[2a,b] synthesis of arylacetic esters from Ni catalyzed coupling of aryl zinc chlorides with ethyl bromoacetate[2c] and synthesis of α,β-unsaturated ketones from Pd catalyzed coupling of Zn salts of allenic ethers with aryl and alkenyl halides.[2d] Pd catalyzed coupling of organic reagents has been extended to the coupling of alkyl zinc chlorides;[2e,f] perfluoroalkyl zinc iodides;[2g] homoallylic, propargylic and benzylic zinc chlorides[2h] and α-heterosubstituted alkenyl zinc chlorides[2i] with various organic halides. Zn mediated coupling of substituted halogeno esters[2j] and Zn promoted reductive coupling of iminium salts with alkyl halides[2k] are among the numerous synthetic procedures using organozinc compounds. Regio- and stereo-selective addition of allenic Zn reagents to aldehydes[3a] and the reaction of diethylzinc and benzaldehyde catalyzed by a chiral Pd complex[3b] have been reported. Diorganozinc compounds have given rise to clean and selective conjugate additions to α,β-unsaturated aldehydes and ketones catalyzed by nickel acetylacetonate.[3c] Selective and unusual replacement of phenylthio substituent by a methyl group has been achieved only by the use of dimethylzinc.[3d] Carbometallation, which is an extremely attractive method for stereospecific synthesis of alkenyl derivatives, has been succeeded effectively by the addition of allylic Zn compounds to alkynes.[4] Reformatsky reaction is still the most generally applicable procedure for converting aldehydes and ketones to β-hydroxyesters and it has been the subject of extensive synthetic study in recent years.[5–9] Reformatsky reagents have also been found to act as selective nucleophilic reagents towards halogen and oxygen containing electrophiles[10] and Reformatsky type reagents have been used for Pd catalyzed coupling with acid chlorides.[11]

For the preparation of organo-Zn reagents, direct metallation of an organic halide with zinc is known to be difficult[12,13] and transmetallation,[14] which is a two step process from organo-Mg or organo-Li precursors and a zinc halide, is preferred. Organo-Zn compounds, which have found numerous applications in synthesis, were generally obtained by this classical transmetallation method. Recently, physical activation by ultrasound irradiation has been shown to make the transmetallation possible in a one step procedure with increased yields in shorter time. It has been also reported that the formation of allylic, benzylic and perfluoroalkyl zinc halides starting from metallic Zn, Simmons–Smith and Reformatsky reagents can be improved by the use of sonication. However, exceptional reactivity of the chemically activated Zn has been demonstrated by several reactions. The reactive Zn powder can be prepared by Rieke's method, i.e. reduction of a zinc halide by an alkali metal. Classical method is to reduce a zinc halide by potassium in tetrahydrofuran. Two new procedures have been published. Highly reactive Zn is easily prepared by reduction of a zinc halide by Li in glyme in the presence of 10 mole % naphthalene as an electron carrier, or reduction of a zinc halide can be carried out with K–graphite in tetrahydrofuran. In addition, ultrasound irradiation has also been found to accelerate the formation and to increase the reactivity of Zn powder produced by Rieke's method. Use of activated Zn in organic and organometallic synthesis was already surveyed.[12] In this account, activation methods for preparation of organo-Zn reagents since 1970 are reviewed and key papers reporting their use in organometallic synthesis are presented.

2. ACTIVATION METHODS

A variety of organo-Zn reagents can be efficiently and rapidly prepared by using an activation method, either for metallic Zn or for transmetallation. In addition, difficultly accessible, or in some cases unobtainable organo-Zn reagents under normal conditions can be easily prepared by the use of activated Zn. However, it is noteworthy that the use of commercial unactivated Zn for the preparation of organo-Zn reagents has been frequently reported. A recent example is the preparation of allyl zinc bromide[5] by using electrolytic Zn without activation. The form of Zn used and its quality appears to be important in the formation of organozinc reagent and pure electrolytic Zn has been preferably used. Commercial Zn should be used after activation (purification) for Reformatsky or Reformatsky-type reactions and related procedures have been well surveyed.[15,16] Commercial Zn dust is activated[17] by washing it rapidly with dilute sodium hydroxide solution, water, dilute acetic acid, water, ethanol, acetone and ether. It is then dried in vacuum at 100° for 2 h. A modified activation involves[18] washing Zn with aqueous HCl, with water until neutral, with acetone and ether. For the preparation of organo-Zn compounds derived from substituted halogenoesters[2i] and from α-bromonitriles,[19] electrolytic Zn turnings and Zn dust, respectively, have been activated by this procedure. Zn wool has been used after activation for the preparation of Reformatsky reagents.[10,20] Zn dust is also activated by the method of Cava[21] by stirring it with saturated ammonium chloride solution followed by decantation and successive washings with water, ethanol, ether and dimethylformamide. This method of activation has been used in the preparation of Reformatsky reagents[7] and benzylic organo-Zn reagents.[22]

Chemical and ultrasonical activation methods are now available to produce organo-Zn reagents. Chemical methods of activation for Zn are the use of iodine as a catalyst, the use of 1,2-dibromoethane for entrainment, the preparation of a Zn–Cu or a Zn–Ag couple and the preparation of reactive Zn powder by reduction of a zinc halide by an alkali metal. In this survey, no attempt has been made to summarize all reactions in which activation of Zn by I_2, by 1,2-dibromoethane or by forming Zn couples have been reported for the preparation of organo-Zn reagents, except for just the past few years.

Iodine has been reported to increase the rate of Reformatsky reagent formation by activating the Zn surface.[15] A mixture of Zn, ethyl α-bromoacetate and an aldehyde or ketone reacts very slowly without I_2 even in the presence of ultrasonic radiation.[7] By using 10 mole % I_2 and stirring, modest yields of β-hydroxyesters has been obtained in the absence of ultrasonic radiation.

A recent example[6] of Zn activation by 1,2-dibromoethane can be found in the preparation of organo-Zn compounds from silylated esters of γ-bromoacids. For the activation of Zn by 1,2-dibromoethane, a mixture of Zn and 1,2-dibromoethane (11 : 1 molar ratio of Zn : 1,2-dibromoethane) in THF has been refluxed for 30 min.

The use of a Zn–Cu couple has been recently reported[11] for the preparation of organo-Zn compounds from β- and γ-iodo ethyl esters. For classical preparation of a Zn–Cu couple,[23] Zn dust is treated with the following solutions: 3% hydrocholric acid, four times; water, five times; 2% copper(II) sulfate, twice; water, five times; anhydrous ether, five times. The couple is then dried in air and then in a vacuum desiccator. One of the most prominent uses of Zn couples has been in Simmons–Smith reactions.[24,25] These will be discussed later.

2.1. *Reduction of a zinc halide with an alkali metal*

The reduction of metal salts with an alkali metal in an hydrocarbon or ethereal solvent produces metal powders, which are far more reactive than the corresponding commercial metal. Rieke who found and developed the procedure has published numerous papers on the preparation and use of highly reactive metal powders.[12,26,27] So far, Mg, Ca, Zn, B, Al, Ga, In, Tl, Ge, Sn, Pb, Ti, V, Cr, Mn, Fe, Co, Ni, Pd, Pt, U and recently Cu[28] and Cd[29] were generated. The methods for preparation of activated Mg and its use in synthesis have been well reviewed.[30] Preparation and reactions of Rieke Zn and Al are the topic of a dissertation.[31]

$$MX_n + nA \rightarrow M^* + nAX \qquad A: K, Li; X: Cl, Br. \tag{1}$$

The basic procedure for preparing finely divided Zn metal involves the reduction of anhydrous zinc chloride or bromide under an inert atmosphere. The reduction can most conveniently be carried out by using K or Li and an ethereal solvent, mostly THF or glyme. The reaction temperature and time have been optimized to carry out the reduction most easily and to produce metallic Zn of highest reactivity. The reduction yields Zn as a fine black powder, which can be immediately used to prepare the organometallic reagent. No attempt is made to remove the alkali metal salts formed in the reactions. In most cases, the organic halide is added directly to the suspension of powdered metal. If necessary, the solvent used for the reduction can be removed and replaced by another solvent in the synthesis without affecting the reactivity of Zn metal.

2.1.1. *Reduction of a zinc halide with potassium in THF.* Activated Zn powder can be prepared by the reduction of zinc chloride or bromide with K in THF by refluxing.[32,33] THF has been found to be the best solvent in which the reduction of zinc halide proceeds most easily. Refluxing time for zinc chloride and bromide has been reported to be 2.5 h[32] and 4 h,[33] respectively. For the preparation of Zn powder,[32] a mixture of anhydrous zinc chloride and K in THF is heated until the reaction starts. Then, heating is stopped and the mixture is stirred, if necessary with cooling. Finally, the mixture is refluxed for 2.5 h with rapid stirring.

$$ZnCl_2 + 2K \xrightarrow[\text{reflux, 2.5 h}]{\text{THF}} Zn^* + 2KCl. \tag{2}$$

2.1.2. *Reduction of a zinc halide with* Li *in* 1,2-*dimethoxyethane in the presence of an electron carrier.* In the preparation of highly reactive Zn, Li and naphthalene (10 mole % based on Li) which acts as an electron carrier, has been used to reduce zinc halide.[34] With regard to the solvent, in which the reduction is carried out, 1,2-dimethoxyethane (glyme) is definitely the best solvent. Use of THF leads to a powder of much reduced reactivity: the reaction does not proceed at all in diethyl ether. Also, the anion of Zn salt has been found to be of critical importance, with chloride being superior. A typical reduction[34] is carried out by adding Li to anhydrous zinc chloride and naphthalene (1.2 : 2.5 : 0.25 molar ratios of $ZnCl_2$: Li : naphthalene) in dimethoxyethane and stirring at room temperature until the reduction is complete (about 15 h).

$$ZnCl_2 + 2Li \xrightarrow[\text{glyme, r.t., 15 h}]{\text{naphthalene}} Zn^* + 2LiCl. \tag{3}$$

2.1.3. *Reduction of a zinc halide with K–graphite in THF.* Activated Zn can be prepared by the K–graphite (C_8K) reduction of a zinc halide.[35] Optimized conditions require the preparation of Zn–graphite from zinc chloride in THF and high reactivity of Zn–graphite allows a quantitative formation of organo-Zn derivative. Preparation of Zn–graphite is as follows:[35] to graphite powder heated at about 150°, K is added (8 : 1 molar ratio of C : K). When the K melts, the mixture is vigorously stirred. This forms C_8K which is covered with THF and anhydrous zinc chloride is added. An exothermic reaction causes the solvent to reflux. When the temperature subsides, the mixture is stirred at 70° for an additional 30 min.

$$8C + K \xrightarrow{150^\circ} C_8K$$
$$ZnCl_2 + 2C_8K \xrightarrow[\text{reflux, 30 min}]{\text{THF}} C_{16}Zn + 2KCl. \quad (4)$$

2.2. *Use of ultrasound radiation*

In recent years, synthetic applications of ultrasound have attracted widespread attention and there has been outstanding success. Ultrasound waves are known to accelerate a number of heterogeneous reactions involving metals. Many applications of ultrasound radiation in organometallic chemistry have been published.[36,37] The use of ultrasound facilitates the formation of transition metal carbonyl anions from transitional metal halides, sodium and carbon monoxide.[38] Ultrasound has been reported to aid the formation of organo-Li and Grignard reagents and also to improve the Barbier reaction,[39,40] and Bouveault–Blanc formylation.[41] The synthesis of lithium organocuprates[42] and coupling of organic halides and organometallic halides with Li[43] has been improved in the presence of ultrasound. The main effect of ultrasound in heterogeneous systems comes from creating surface erosion and pitting,[36,38] which are largely responsible for ultrasound cleaning. Pitting action leads to beneficial results by exposing freshened surface in the presence of reactive metals such as Li, Mg and Zn. The use of ultrasound during the formation and *in situ* reactions of organometallic compounds can offer some advantages: improved yields and selectivity, reduced reaction times and temperatures, and the possibility of using commercial metals without activation. Irradiation by ultrasonic waves can simply be done by using a common ultrasound laboratory cleaner.

Ultrasound irradiation has been found to facilitate the preparation of Zn powder by Rieke's method and to increase its reactivity. Formation of various organo-Zn compounds, either by direct attack of Zn or by transmetallation, are noticeably improved in the presence of ultrasound.

2.2.1. *Sonic preparation of organo-*Zn *reagents from* Zn *metal.* So far, it has been possible to utilise ultrasonic activation in reactions starting from metallic Zn only for the preparation of allylic,[4c] benzylic,[22] and perfluoroalkyl organo-Zn,[44,45] Simmons–Smith,[46,47] and Reformatsky reagents.[7–9] However, reactions of these organo-Zn reagents have been tried in a one pot process by sonication of the halide and Zn metal in the presence of the substrate. They will be discussed later.

The effect of ultrasound waves on the rate of a zinc halide reduction to form reactive Zn powder has been investigated.[37] Reduction of zinc chloride or bromide with Li to produce Zn powder can be carried out in a significantly shorter time with the aid of ultrasound. The reduction is performed with Li dispersion (or powder) and ultrasound in THF at room temperature. Mg, Cr, Fe, Co, Ni, Pd and Pb halides can also be reduced in the presence of Li and ultrasound at a rate faster than that of Rieke's procedure.[26] Naphthalene (10 mole % based on Li) is used in the case of THF insoluble halides as a charge transfer agent. Ultrasound has already been used for the preparation of reactive Cd powder.[29] As a comparison, the reduction time for zinc chloride with K in refluxing THF has been reported to be 2.5 h[32] and the reduction of zinc chloride with Li in the presence of naphthalene is complete after 15 h of stirring at room temperature.[34] When a mixture of zinc chloride (or bromide) and Li in THF is exposed to ultrasound at room temperature, reduction is usually complete within 40 min.[37]

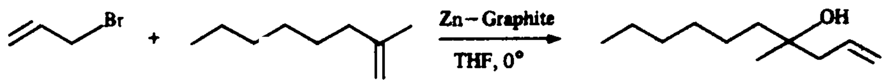
$$ZnCl_2 + 2Li \xrightarrow[\text{THF, r.t., 40 min}]{)))} Zn^* + 2LiCl. \quad (5)$$

2.2.2. *Sonic preparation of organozinc reagents by transmetallation.* Diorgano-Zn compounds can be prepared with great ease and efficiency in a one-pot process by sonication of Li, an organic halide and a zinc halide in ether, THF or THF–toluene mixtures.[3c,48–50] It was found that aryl halides, Li wire and zinc bromide when sonicated in ether or THF yield the corresponding diaryl Zn reagents.[50] The reaction is usually complete within 30–45 min at 0° without any noticeable side reaction. Recently, by changing the technique of sonication,[3c,49] dialkylzinc reagents have also been prepared almost quantitatively by sonication of an alkyl halide, Li wire and zinc bromide in THF–toluene mixtures within 20–40 min at 0°. In comparison, transmetallation with stirring, replacing sonication, takes place much more slowly (1–2 h) with a lower yield by *ca* 25%. Although a THF–toluene mixture would seem less favorable to the formation of organo-Zn derivatives than pure ethers, the sonochemical acceleration of the transmetallation worked well with all the organic halides tested. Organo-Zn reagents prepared by sonic transmetallation are actually diorgano-Zns which transfer only one organic residue. So far, alkyl and aryl bromides (R or Ar : methyl, *t*-butyl, heptyl, cyclohexyl, benzyl, allyl, substituted allyl, phenyl, 2,4-disubstituted phenyl) have been reacted with zinc bromide in the presence of Li and irradiation with ultrasound giving $\mathrm{R(Ar)_2Zn}$ compounds. Experiments run with R(Ar)ZnBr compounds, obtained by the sonication of one equivalent of R(Ar)Br with Li and zinc bromide resulted in a very low yield of organic group transfer. Ultrasound promoted transmetallation was carried out by sonicating a mixture of organic halide, zinc bromide and Li wire in the required solvent at ice-bath temperature.[3c] Irradiation for 30 min gives a black solution of the diorgano-Zn compound.

$$2\mathrm{R(Ar)X} + 4\mathrm{Li} \rightarrow 2\mathrm{R(Ar)Li} \xrightarrow[\mathrm{THF,\ 0°,\ 20\text{–}40\ min}]{\mathrm{ZnX_2,)))}} \mathrm{R(Ar)_2Zn \cdot 4LiX}. \tag{6}$$

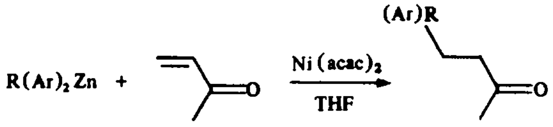
3. USES OF ACTIVATION METHODS

Use of organo-Zn reagents prepared by an activation method results in reduced reaction times and increased yields. Activated zinc prepared by Rieke's methods has been found to be much more reactive towards alkyl and aryl halides than any previously described in the literature.[12] Rieke found that Zn powder reacts rapidly with alkyl bromides in refluxing THF giving quantitative yields of dialkylzinc compounds.[33] The first bifunctional organo-Zn compounds of 1,4-dibromobutane, 1,5-dibromopentane and 1,6-dibromohexane have been prepared by the use of Rieke's Zn.[52] Extraction of the salt mixtures obtained after evaporation of the solvent THF with ether–dioxane mixture yielded the zincacyclopentane, zincacyclohexane and zincacycloheptane. Prior to Rieke's work, there were no reports of the direct reaction of Zn metal with aryl halides. In contrast, activated Zn reacts readily with iodobenzene and even with bromobenzene. Reduction of zinc bromide as in Section 2.1.1, removal of solvent THF, addition of bromobenzene in diglyme, followed by refluxing for 8 hours resulted in preparation of phenyl zinc bromide with a yield of 83%.[33] Use of glyme instead of THF in reduction and starting from zinc chloride leads to a yield of 41% after 18 h of refluxing in glyme.[34] Zn powder prepared as in Section 2.1.2 reacted with bromobenzene in glyme to give 73% of reaction in only 10 h of reflux.[34] Organo-Zn reagents derived from allylic bromides and activated Zn prepared as in Section 2.1.3 reacted with carbonyl compounds giving homoallylic alcohols (65–94% yield).[35]



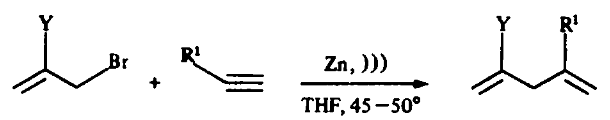
(7)

Diorgano-Zn reagents prepared by sonic transmetallation reacted with α,β-unsaturated ketones[3c] and aldehydes[48] in the presence of nickel acetylacetonate giving 20–90% β-addition products.



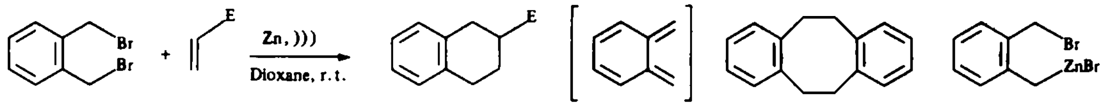
(8)

Carbometallation of alkynes with allylic Zn compounds has been tried under Barbier conditions using ultrasound radiation.[4c] If functionalized allylic bromides (allylic bromoesters and phosphonates) are allowed to react with a terminal alkyne in THF at 45–50° in the presence of Zn and ultrasonic waves, highly functionalized dienes with a yield of 54–81% are isolated in fair to good yields.



Y : COO*t*-Bu(Et), PO(OMe)$_2$ (9)

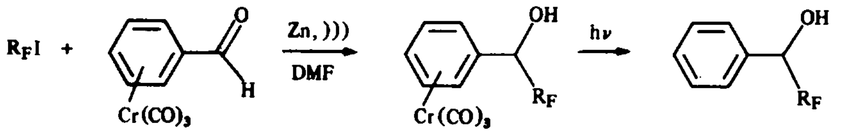
Ultrasound promoted reaction of Zn powder with α,α′-dibromo-*o*-xylene in the presence of activated dienophiles give high yields of cycloaddition products.[22] When a dioxane solution of the benzylic dibromide (1) is treated with Zn and ultrasound in the absence of dienophile, all of 1 is consumed giving mostly polymer and small quantities of 3. These observations are consistent with the formation of *o*-xylylene (2) as an important intermediate in these reactions. Attempts to trap an organo-Zn intermediate (4) were unsuccessful, but some of the dimer (3) was detected.



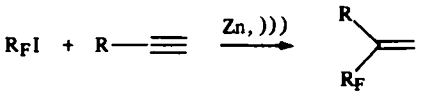
1 E: COOMe, COMe, etc. 2 3 4

(10)

Until now, the only way to synthesize perfluoroalkyl aryl carbinols in good to high yields is the addition of perfluoroalkyl iodide to chiral arene–chromium tricarbonyl complexes using ultrasonically dispersed zinc in dimethylformamide at room temperature.[44] Both enantiomers of the carbinols are obtained. The reaction of perfluoroalkyl iodides with terminal alkynes and ultrasonically dispersed Zn in the presence of copper(I) iodide gave the corresponding perfluoroalkyl olefins.[45] The reactions of perfluoroalkyl iodides with allyl, vinyl or aryl halides and ultrasonically dispersed Zn over a Pd catalyst proceeded smoothly giving the corresponding coupling products.[2g]



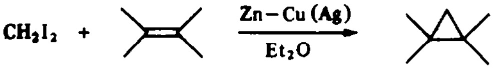
R$_F$: C$_2$F$_5$, *i*-C$_3$F$_7$, C$_6$F$_{13}$ (11)



R$_F$: perfluoralkyl (12)

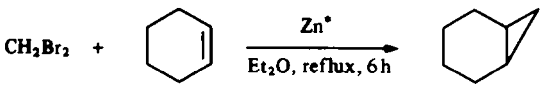
$$R_FI + RX \xrightarrow[\text{Pd catalyst}]{\text{Zn,)))}} R_FR \qquad R: \text{allyl, vinyl, aryl.} \tag{13}$$

Simmons–Smith cyclopropanation does not proceed readily unless the Zn is first activated. This was accomplished by using iodine promoted Zn or by forming Zn–Cu or Zn–Ag couples.[23–25] The yields of cyclopropanated products using a Zn–Cu couple are in the range of 12–75%.[25] The reaction, however, has often been plagued with poor reproducibility and low yields mainly due to the difficulties in preparing the Zn–Cu couple.[23] A much improved Zn–Cu couple has been prepared by refluxing a mixture of Zn dust and copper(I) chloride in ether.[52] Olefins and diiodomethane were added directly to this mixture and yields of cyclopropanes of greater than 90% were reported. The use of Zn–Ag couple,[53] which appears to be more reactive toward diiodomethane than Zn–Cu couple, gives better yields and requires shorter times. Zn–Ag couple is prepared by adding granular Zn to a stirred hot solution of silver acetate in acetic acid.[53] The mixture is stirred for 30 s and the couple formed is isolated by decantation then washed with acetic acid and ether. It is then stabilized by the addition of a small amount of Ag wool.



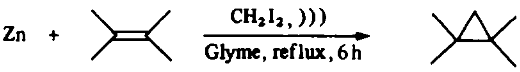
(14)

Activated Zn has been examined for the Simmons-Smith reaction.[34] Zn powder obtained as in Section 2.1.1 reacts rapidly with diiodomethane and if the reaction takes place in the presence of cyclohexane, norcarane is obtained (yield 25–30%). This Zn also reacts with dibromomethane rapidly, and gives the product (yield 5%). In contrast, Zn activated as in Section 2.1.2 gives excellent results. After the preparation of Zn powder, solvent glyme is replaced with ether, cyclohexene is added followed by the addition of dibromomethane with a molar ratio of Zn/cyclohexene/dibromomethane of 1/0.5/1. The reaction solution is refluxed for 6 h (yield 94%). Dichloromethane appears to be unreactive under these conditions and diiodomethane due to its very high reactivity gives somewhat erratic results. For comparison, it should be noted that the use of Zn dust and copper(I) chloride[52] or Zn–Ag couple[53] in the synthesis of norcarane results in a yield of more than 90% after 24 h or 2 h of reaction in boiling ether, respectively.



(15)

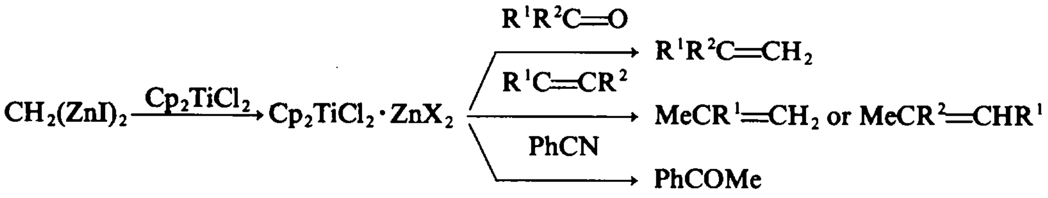
Ultrasound irradiation has been found to activate Zn to such an extent that its reaction with diiodomethane in the presence of olefins proceeds rapidly, but smoothly to give cyclopropanated products (yield 67–97%) in dimethoxyethane in 2–6 h.[46] The advantages of using ultrasound are reproducible reaction times and yields, as well as no chemical activation of zinc by preparing Zn powder or a Zn couple.



(16)

Ultrasound has also been found very useful for the methylenation reaction with Zn–diiodomethane reagents.[47] The method is a very convenient procedure to methylenate ketones (yield 54–73%) by carrying out the reaction with crude Zn at room temperature for 15 min–5 h. Without ultrasound, the reaction does not take place. Previously reported yields using activated Zn–Cu couple for preparing iodomethyl zinc iodide are about 40% after a reaction of 6 h in THF. Another reagent for methylenation has been prepared by treating methylene zinc iodide with titanocene dichloride. The titanocene methylene–zinc halide complex which is obtained readily methylenates ketones, nitriles and alkynes.[54]

$$R_2C{=}O + CH_2I_2 \xrightarrow[\text{THF, r.t., 15 min–5 h}]{\text{Zn,)))}} R_2C{=}CH_2. \tag{17}$$

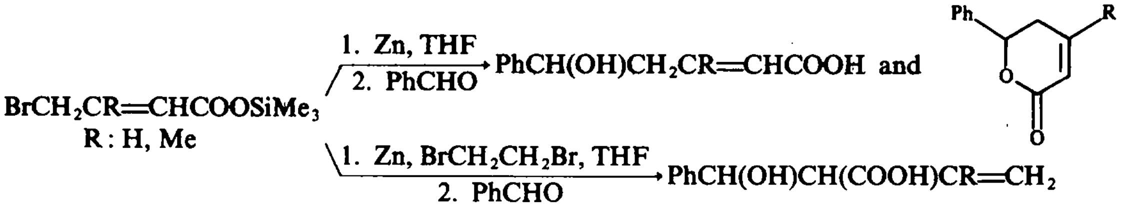


$$CH_2(ZnI)_2 \xrightarrow{Cp_2TiCl_2} Cp_2TiCl_2\cdot ZnX_2 \begin{cases} \xrightarrow{R^1R^2C=O} R^1R^2C{=}CH_2 \\ \xrightarrow{R^1C\equiv CR^2} MeCR^1{=}CH_2 \text{ or } MeCR^2{=}CHR^1 \\ \xrightarrow{PhCN} PhCOMe \end{cases} \tag{18}$$

The reactivity of Zn is especially important in the Reformatsky reaction. Several improvements have been reported in recent years to overcome the drawbacks (the initiation and the control of the very exothermic reaction, variable yields, side reactions, etc.) associated with the original Reformatsky reaction. The yield of β-hydroxyesters in the conventional method[15] using ordinary Zn in refluxing benzene or benzene–ether is 50–89%. The reaction has been shown to produce higher yields (80–90%) if carried out at room temperature in trimethyl borate–THF[55] or in a continuous flow procedure with a Zn column.[56] However, the use of trimethyl borate–THF complicates the procedure and the continuous flow technique still requires refluxing benzene.

$$R^1R^2C{=}O + BrCH_2COOEt \xrightarrow[\text{Benzene, reflux}]{\text{Zn}} R^1R^2C(OH)COOEt \tag{19}$$

Activation of Zn using 1,2-dibromoethane has been reported in the Reformatsky reaction.[6] Silyl ester of a γ-bromo-α,β-unsaturated acid was treated with ordinary Zn at low temperature and subsequently with benzaldehyde giving the γ-hydroxy-acid (yield 37%) and the corresponding lactone (yield 20%). However, the use of activated Zn in a one step reaction gave primarily α-substituted products with 65–100% selectivity.



(20)

Organo-Zn compounds derived from ethyl esters of β- and γ-iodo acids have been prepared by using a Zn–Cu couple and utilized for the Pd-catalyzed coupling reaction with an acid chloride yielding γ- and δ-ketoesters (~100% yield), respectively.

$$\mathrm{I(CH_2)_nCOOEt} \xrightarrow[\text{Benzene}]{\text{Zn–Cu}} \mathrm{IZn(CH_2)_nCOOEt} \xrightarrow{\mathrm{RCOCl}} \mathrm{RCO(CH_2)_nCOOEt} \qquad (21)$$

$$\mathrm{n}: 2, 3$$

Zinc powders have been shown to be very useful in the Reformatsky reaction. Zn powder, prepared as in Section 2.1.1 reacts vigorously with ethyl bromoacetate in THF at −5°.[32] If a 1 : 1 mixture of bromoacetate and aldehyde (or ketone) are reacted with activated Zn at −5° followed by refluxing for various times, β-hydroxyesters are obtained (yield 65%). If the solvent THF is removed after the preparation of activated Zn and replaced by ether, the reaction of bromoester and aldehyde (or ketone) at 0° followed by stirring at room temperature for 1 h gives β-hydroxyesters (yield 80–98%). The ability to use ether at room temperature makes the activated Zn procedure for Reformatsky reactions highly desirable. Zn powder also reacts with ethyl chloroacetate, however, the yield is not as nearly as high (65%). The use of Zn powder prepared as in Section 2.1.2 gives yields (95–98%) in the Reformatsky reaction.[34] When the Zn powder is prepared in glyme then the solvent can be removed and replaced with ether. The reaction is then carried out as above. Ethyl chloroacetate also reacts with the Zn powder and β-hydroxyesters are obtained (yield 85–90%). The use of Zn–graphite gives satisfactory results for the preparation of Reformatsky reagents.[35] Optimized conditions require the preparation of Zn–graphite in THE followed by the addition of a mixture of bromoester and aldehyde (or ketone) and stirring of the mixture at 0° until the carbonyl compound disappears gives β-hydroxyesters (yield 75–90%). For comparison, the yields of the Reformatsky reaction between bromoacetate and cyclohexanone using commercial Zn (56%),[15] Zn powder prepared as in Section 2.1.1 (95%),[32] Zn powder prepared as in Section 2.1.2 (98%)[34] and Zn–graphite (80%)[35] are quoted. Clearly the activated zinc method is superior.

$$\mathrm{R^1R^2C{=}O + BrCH_2COOEt} \xrightarrow[\mathrm{Et_2O,\ 0^\circ,\ 1\ h}]{\mathrm{Zn^*}} \mathrm{R^1R^2C(OH)CH_2COOEt} \qquad (22)$$

Sonic acceleration of the Reformatsky reaction starting from ordinary Zn gave beneficial results.[7] High yields and very short reaction times were reported as well as the elimination of the need to prepare activated Zn powder. In the presence of iodine (or potassium iodide) and sonic waves, the reaction times are not only reduced to minutes, but the yields are almost quantitative. Dioxane was found to be better than common Reformatsky solvents, including ether and benzene. Reactions were run at room temperature using 1 : 1.2 : 1.8 : 0.2 mole ratios of $\mathrm{R^1R^2CO : BrCH_2COOC_2H_5 : Zn : I_2}$ and by stirring 5–30 min in the presence of ultrasound radiation. The yields for the Reformatsky reaction between bromoacetate and benzaldehyde by using commercial Zn[15] is 61% after 12 h of reflux, 98% by using Zn powder prepared as in Section 2.1.1[32] and stirring at room temperature for 1 h or by using Zn dust–iodine in the presence of ultrasound[7] and stirring at room temperature for 5 min.

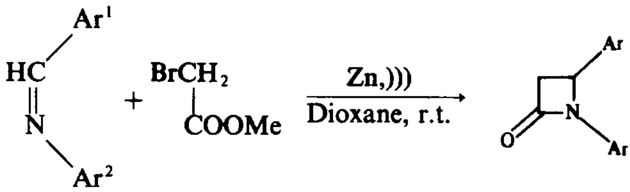
$$R^1R^2C{=}O + BrCH_2COOEt \xrightarrow[\text{Dioxane, r.t., 5–30 min}]{\text{Zn,)))}} R^1R^2C(OH)CH_2COOEt \qquad (23)$$

Zn powder produced from zinc chloride and Li in the presence of ultrasound shows exceptional reactivity in the Reformatsky reaction.[37] For example, Zn produced in this manner reacts (90% yield) with ethyl bromoacetate and benzaldehyde in ether with stirring at room temperature for 1 h. As outlined above, the Reformatsky reaction may also be efficiently performed at room temperature using commercial zinc in the presence of ultrasound instead of preparing ultrasound promoted Zn powder.

$$ZnCl_2 + Li \xrightarrow{)))} Zn^* + 2LiCl$$

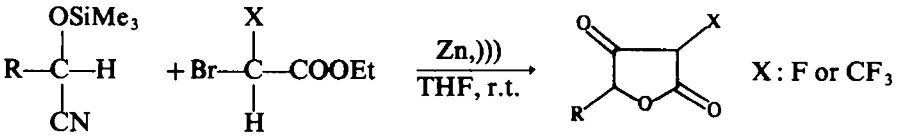
$$PhCHO + BrCH_2COOEt \xrightarrow[\text{Et}_2\text{O, r.t., 1 h}]{\text{Zn}^*} PhCH(OH)CH_2COOEt \qquad (24)$$

Ultrasound promoted Reformatsky type reactions have been reported. The reaction of ethyl bromoacetate and a Schiff base in the presence of Zn and a crystal of iodine as a catalyst proceeded[8] slowly in toluene and β-lactams were obtained with a yield of 25–50%. However, in the presence of ultrasound and with dioxane as solvent, activated (HNO_3 washed) Zn granules and a crystal iodine, gave β-lactams (70–95% yield) in a few hours at room temperature. Unactivated Zn granules gave a lower yield (50–70%).



(25)

A Reformatsky type reaction between *O*-trimethylsilylated cyanohydrins and α-fluoro (or trifluoromethyl) bromoacetate proceeded at room temperature with the assistance of ultrasound radiation.[9] Without ultrasound promotion, the reaction did not proceed at all. Using commercially available unactivated Zn powder in THF, a number of β-keto-γ-butyrolactones (yield 48–69%) were obtained.



(26)

4. CONCLUDING REMARKS

The use of activation methods considerably increases the versatility of organo-Zn reagents. Chemical or ultrasonic activation leads to increased yields and reduced times for organo-Zn reagent formation and improves their reactivities in various reactions. Some organo-Zn reagents which are unobtainable under normal conditions can be prepared using activated Zn. Differences in regioselectivity are observed in some reactions using either unactivated or activated Zn. In addition, some organozinc reagents do not react at all without ultrasound activation. Many possibilities for the use of activation methods in the preparations and reactions of organo-Zn reagents remain to be investigated.

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