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COMPREHENSIVE REVIEW

$MgCl_2$ and its applications in organic chemistry and biochemistry: a review

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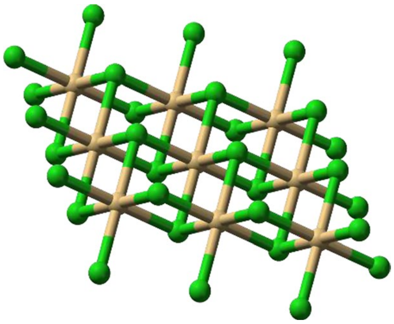
Abstract

$MgCl_2$ has been reported to be a versatile reagent especially as a Lewis acid catalyst in a variety of organic transformations including the preparation of heterocyclic compounds, the protection of functional groups and condensation reaction. Also the use of $MgCl_2$ in the preparation of metallic magnesium and the application of magnesium chloride in biochemistry such as anesthetic for cephalopods, the separation of serum high-density lipoprotein, effect of $MgCl_2$ on rabbit bronchial smooth muscle, antimicrobial properties of magnesium chloride and effect of $MgCl_2$ on the quality of life for patients with fibromyalgia have been reported. Therefore, in this article the use of $MgCl_2$ in organic chemistry and biochemistry is reviewed.

Graphical abstract

$MgCl_2$ has been reported to be a versatile reagent especially as a Lewis acid catalyst in a variety of organic transformations including the preparation of heterocyclic compounds, the protection of functional groups and condensation reaction. Also the use of $MgCl_2$ in the preparation of metallic magnesium and the application of magnesium chloride in biochemistry such as anesthetic for cephalopods, the separation of serum high-density lipoprotein, effect of $MgCl_2$ on rabbit bronchial smooth muscle, antimicrobial properties of magnesium chloride and effect of $MgCl_2$ on the quality of life for patients with fibromyalgia have been reported. Therefore, in this article the use of $MgCl_2$ in organic chemistry and biochemistry is reviewed.

$$Mg(OH)_{2(s)} + 2HCl \rightarrow MgCl_{2(aq)} + 2\,H_2O_{(l)}$$



Keywords $MgCl_2$ · Synthesis · Acylation · Heterocyclic

Introduction

Magnesium chloride, $MgCl_2$, is an inorganic compound including one magnesium and two chloride ions. Magnesium chloride and its variety of hydrate forms, $MgCl_2{\cdot}(H_2O)_x$, are dehydrated at higher temperatures [1]. Magnesium chloride salts are highly soluble in water and utilized in medicine as a source of magnesium ions, which are necessary for many

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$$Mg(OH)_2(s) + 2HCl \longrightarrow MgCl_2(aq) + 2\ H_2O(l)$$

Scheme 1 Preparation of magnesium chloride from magnesium hydroxide

$$NH_4MgCl_3 \ .\ 6H_2O \longrightarrow MgCl_2 + NH_3 + HCl$$

Scheme 2 Preparation of magnesium chloride from $NH_4MgCl_3{\cdot}6H_2O$

cellular activities. Magnesium chloride has also been used as a cathartic and in alloys. Anhydrous $MgCl_2$ is the main source to magnesium metal, which is manufactured on a large scale. Hydrated $MgCl_2$ is the most compound available. Magnesium chloride is utilized for low-temperature deicing of highways, sidewalks and parking lots. When highways are treacherous owing to icy conditions, magnesium chloride helps to prevent the ice bond, allowing snow plows to clear the roads efficiently. Magnesium chloride is employed in nutraceutical and pharmaceutical preparations. It is also an additive in baby formula milk [2].

Also, anhydrous $MgCl_2$ is a low-power Lewis acid. Ziegler–Natta catalysts, used commercially to produce poly olefins, contain $MgCl_2$ as catalyst support [3]. The use of $MgCl_2$ supports raises the activity of traditional catalysts and develops highly stereospecific catalysts for the synthesis of polypropylene [4]. In this communications, herein we interest to review the synthesis and the use of $MgCl_2$ in organic chemistry and biochemistry.

The preparation of magnesium chloride, $MgCl_2$

The hydrated magnesium chloride can be obtained from brine or seawater. In the Dow process, $MgCl_2$ is prepared from magnesium hydroxide using hydrochloric acid (Scheme 1) [5]. It can also be manufactured from magnesium carbonate by a similar procedure.

Hydrated magnesium chloride can be dehydrated via some procedures by heating, and it is impossible to completely dehydrate magnesium chloride by heating in the air due to hydrolytic decomposition. The dehydration should be taken place in hydrochloric acid gas atmosphere accordingly. However, this procedure suffers from many problems, such as hydrochloric acid gas storage, corrosive nature and the use of plenty of hydrochloric acid gas. Many methods have been reported for the synthesis of anhydrous magnesium chloride such as using $NH_4MgCl_3{\cdot}6H_2O$ (Scheme 2). In this route is reported that anhydrous magnesium chloride is manufactured from $NH_4MgCl_3.6H_2O$ at 50-400 °C in 30 min in air atmosphere [6].

$$TiO_2 + C + 2Cl_2 \longrightarrow TiCl_4 + CO/CO_2$$

Scheme 3 Preparation of titanium chloride

$$TiCl_4 + 2Mg \longrightarrow Ti + 2MgCl_2$$

Scheme 4 Preparation of $MgCl_2$ in titanium sponge production

Another method for the preparation of magnesium chloride is the chlorination of the dolomite and obtaining of $MgCl_2$ in titanium sponge production. Osaka Titanium Technologies Co., Ltd (OTC) began manufacturing titanium sponge by the Kroll process in 1952. In this procedure, titanium ore and coke were fed into the chlorinator. Then, chlorine gas was blown into the chlorinator (Scheme 3).

Titanium ore was gotten rid of its oxygen and banded with the chlorine to give crude titanium tetrachloride. Then, the crude $TiCl_4$ was distilled to remove impurities. The highly purified $TiCl_4$ was furnished from ore that contained impurities. The purity standard of pure $TiCl_4$ is 5N (99.999%) grade; therefore, a large amount of impurities is removed in this process. Then molten magnesium is fed into the vessel, and subsequently, liquid titanium tetrachloride is fed into the vessel and a reduction reaction is caused to obtain titanium sponge and magnesium chloride as a by-product is precipitated to the bottom of the vessel due to its heavier density, and is periodically separated by pressurizing the vessel with argon gas [7] (Scheme 4).

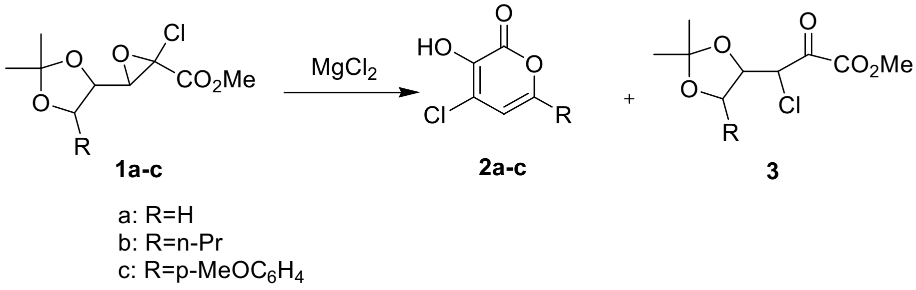
The use of $MgCl_2$ in organic chemistry

The synthesis of heterocyclic compounds

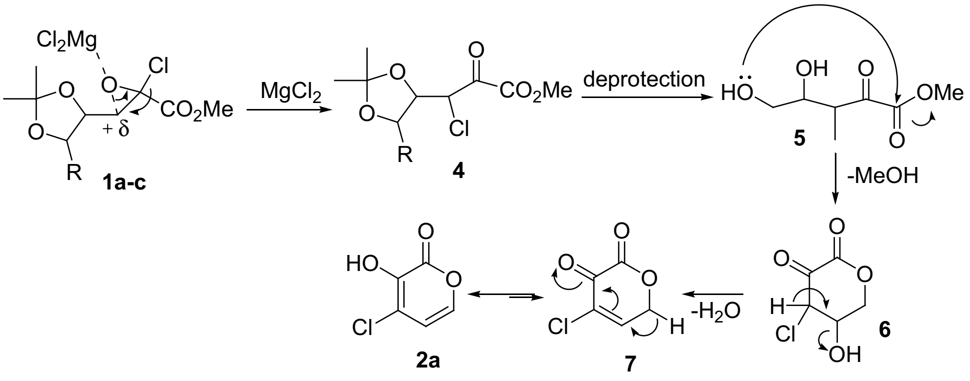
The synthesis of 4-chloro-3-hydroxy-2-pyrone

Komiyama et al. [8] reported the preparation of 4-chloro-3-hydroxy-2-pyrones from the treatment of acetonide-protected 4,5-dihydroxy-2-chloroglycidic ester by magnesium chloride in very good yields (Scheme 5). The results revealed that the reaction was carried out by magnesium chloride as a catalyst. Furthermore, the reaction of 5-substituted glycidic esters **1b,c** with magnesium chloride also resulted in desired compounds **2b,c** in high yields.

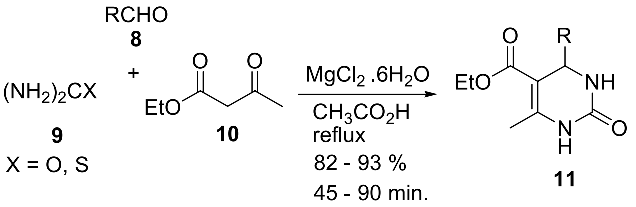
The suggested mechanism in the synthesis of pyrone **2a** from glycidic ester **1a** is shown in Scheme 6. Firstly, 2-chloroglycidic ester **1a** is transformed to 3-chloro-2-keto ester **4** in ring opening of oxirane reaction using magnesium chloride, and the subsequent substitution at the chloroglycidic esters **1a** is not a simple SN_2 mechanism [9]. Nucleophilic addition of hydroxyl group to ester carbonyl carbon **5**



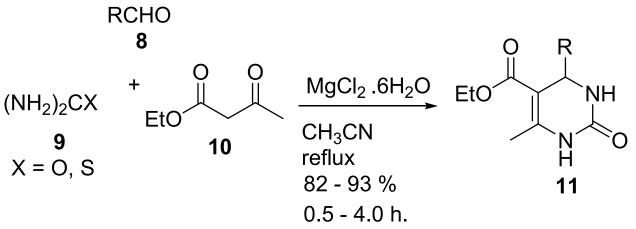
Scheme 5 Preparation of 4-chloro-3-hydroxy-2-pyrones using $MgCl_2$



Scheme 6 Plausible mechanism for the synthesis of 4-chloro-3-hydroxy-2-pyrones using $MgCl_2$



Scheme 7 Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones in acetic acid



Scheme 8 Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones and thiones in acetonitrile

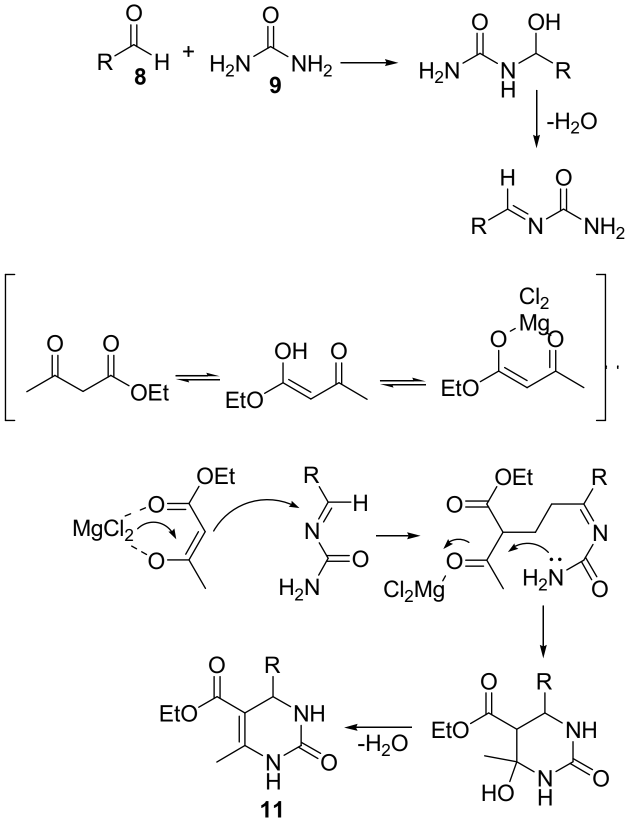
gives **6**. Lately, dehydration and tautomerization produced 4-chloro-3-hydroxy-2-pyrone **2a**.

The synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones

Khaleghi et al. reported facile Biginelli reaction for the production of 3,4-dihydropyrimidin-2(1H)-ones and thiones, in the presence of alkaline earth metal chlorides such as $MgCl_2$ and acetic acid as a solvent in a homogeneous catalytic reaction. The simple separation of the product and the catalyst was the major advantages of this procedure (Scheme 7) [10].

Heravi et al. also reported the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones by $MgCl_2.6H_2O$ as a catalyst in acetonitrile under reflux condition. Several aromatic and aliphatic aldehydes possessing electron donor and acceptor groups underwent the reaction to provide dihydropyrimidinones/thiones in high yields. The experimental procedure was very practical and was applicable for the other functional groups such as methoxy, nitro, halide and olefins under the reaction conditions. The thiourea was also employed instead of urea with similar success to prepare the corresponding 3,4-dihydropyrimidin-2(1H)-thiones in high yield (Scheme 8) [11].

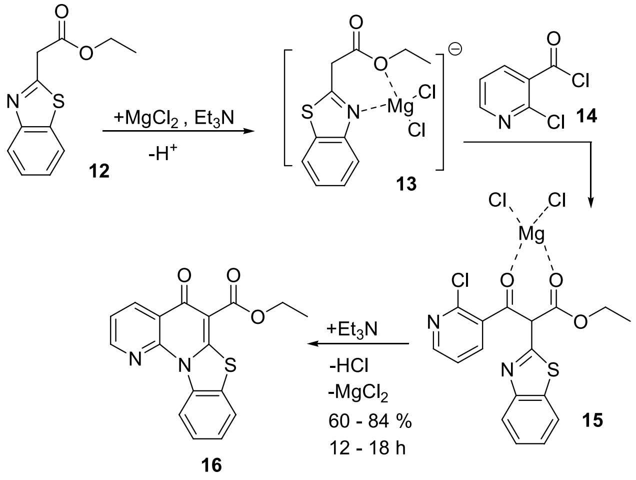
The suggested mechanism also revealed that the first step of the reaction carried out between aldehyde **8** and urea **9** gave Schiff's base on the α-olefinic carbon of the tautomer followed by carbonyl attack on imine carbon to obtain a six-membered heterocyclic compound, in which dehydration led to the target DHPMs **11** (Scheme 9).



Scheme 9 Suggested mechanism for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones using $MgCl_2$

The synthesis of 3-carboxy-4-oxo-1,8-naphthyridines

Chua et al. introduced the synthesis of 5-oxo-6-carboxy naphthyridines in 2008. Activated 3-nicotinic acids **14** readily were acylated by the magnesium anion of 2-(benzothiazol-2-yl) or 2-(benzimidazol-2-yl) acetates **13**. The desired product could next undergo cyclization spontaneously or under very mild conditions to result in the desired naphthyridine products **16**. Only near-stoichiometric ratios of reactants were required for this approach, and the products were separated in pure form after a trituration makes this an efficient process (Scheme 10) [12].



Scheme 10 Synthesis of 3-carboxy-4-oxo-1,8-naphthyridines

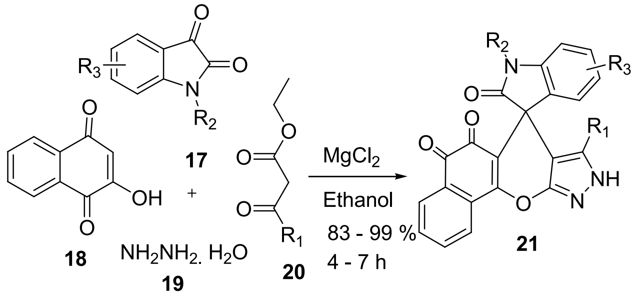
The synthesis of 5H-spiro[benzo [7, 8] chromeno [2,3-c]pyrazole-7,3′-indoline]-2',5,6(9H)-triones

Shen and co-workers presented one-pot synthesis of 5H-spiro[benzo [7, 8] chromeno[2,3-c]pyrazole-7,3′-indoline]-2′,5,6-(9H)-trione derivatives via a multicomponent reaction of hydrazine hydrate, β-keto esters, isatins and 2-hydroxynaphthalene-1,4-dione using $MgCl_2$ in ethanol. This reaction had the advantages of very good yields, environmental-friendly solvent, easy work-up and short reaction time (Scheme 11) [13].

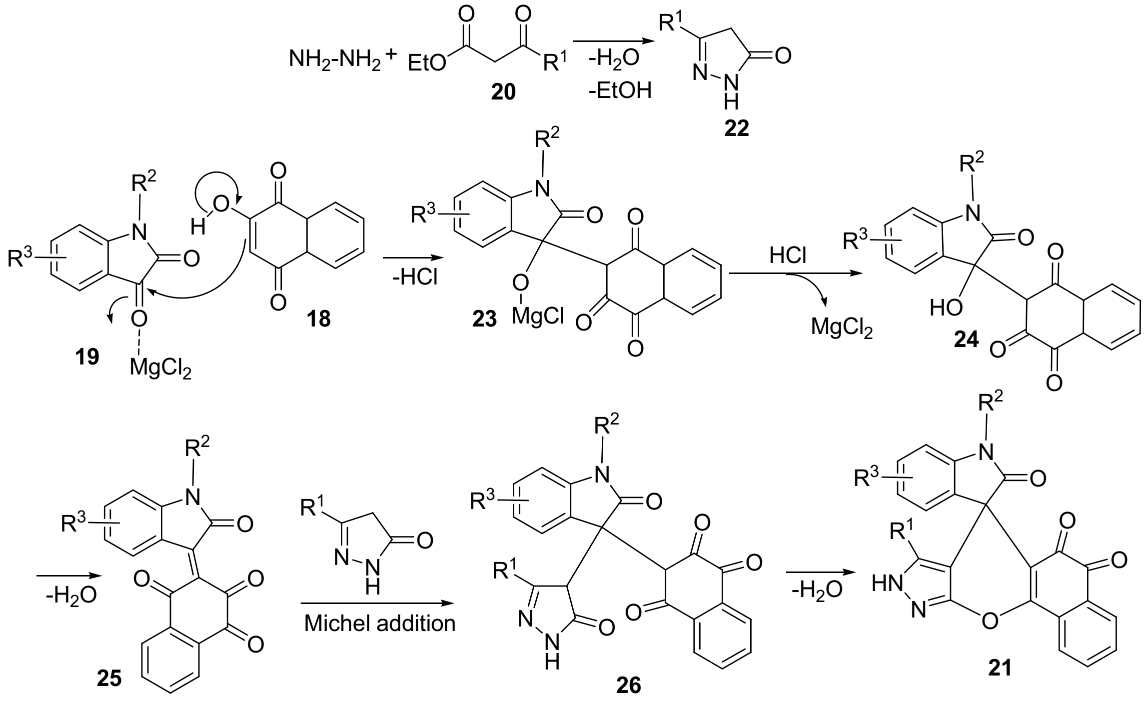
A probable mechanism for the synthesis of products **21** is shown in Scheme 12. Firstly, hydrazine is condensed with β-keto esters **20** to result in the intermediate **22**. Then, compound **19** is produced by the coordination of the isatin **17** with $MgCl_2$. Furthermore, 2-hydroxynaphthalene-1,4-dione **18** attacks compound **19** to form unsaturated ketone **25** with the elimination of HCl, $MgCl_2$ and H_2O. Next, Michael addition of intermediate **22** to unsaturated ketone **25** takes place to provide intermediate **26**, which underwent tautomeric proton shift and intramolecular elimination of H_2O to result in the target product **21**.

The synthesis of 2-substituted-1*H*-benzimidazoles

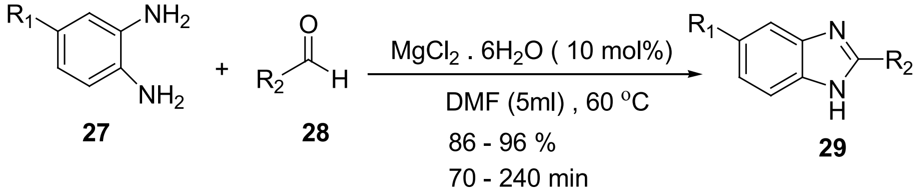
Also, a series of substituted benzimidazoles **29** were prepared by reaction between 1,2-phenylenediamine **27** and aryl, heteroaryl aldehydes **28** using catalytic amount of $MgCl_2 \cdot 6H_2O$. This procedure had some advantages such as high yield, clean reaction profile, the use of green and environmental-friendly catalyst. The protocol was very simple,



Scheme 11 Synthesis of 5H-spiro[benzo [7, 8] chromeno [2,3-c] pyrazole-7,3′-indoline]-2′,5,6(9H)-triones



Scheme 12 Plausible mechanism for the formation of products **21**

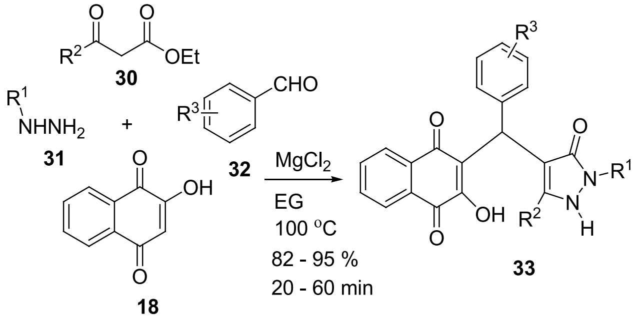


Scheme 13 Synthesis of 2-substituted-1H-benzimidazoles

mild and applicable to aryl as well as hetero aryl aldehydes without significant difference (Scheme 13) [14].

The synthesis of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) (phenyl) methyl) naphthalene-1,4-diones

Fu et al. described [15] an efficient synthetic method for the preparation of 2-hydroxy-3-((5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-diones **33** by a one-pot, four-component reaction of aromatic aldehydes **32,** 2-hydroxy-1,4-naphthoquinone **18** hydrazine derivatives **31** and ethyl acetoacetate **30** using $MgCl_2$ in ethylene glycol (EG). Easy work-up, short reaction time, very good yield and an environmental-friendly catalyst were the major advantages of this route (Scheme 14).



Scheme 14 Synthesis of **33**

In another study, the authors examined the reaction in different conditions for the synthesis of pyran derivatives **38, 40** and **42** (Scheme 13). Unfortunately, when the reaction was set up in different solvents at higher temperatures and longer reaction times, no pyran compounds **38**, **40** and **42** were obtained and instead formed compounds **37** in good yields. In control experiments, aryl aldehydes were replaced with isatin and acenaphthenequinone under the same reaction conditions. Interestingly, the pyran derivatives **40** and **42** were obtained in high yields (Scheme 13). This anomaly may be obtained from the more stability of compounds **37** in enol form and the hydrogen bond action. So far, these two kinds of reactions all obtained good yields when the EG/$MgCl_2$ system was employed (Scheme 15).

The suggested mechanism for this four-component reaction is shown in Scheme 16. Firstly, aryl hydrazine/hydrazine hydrate **31** was reacted with β-keto esters **30** to yield the pyrazolone ring **43**, which was then isomerized to intermediate **44**. Additionally, $MgCl_2$ activated aldehyde **32** carbonyl group to attack of 2-hydroxy-1,4-naphthoquinone **18**. Nucleophilic attacking of 2-hydroxy-1,4-naphthoquinone **18** to activated $MgCl_2$—aldehyde **32**—led to intermediate **45** with C–C bond formation and unsaturated Knoevenagel product **47** was formed with the elimination of $MgCl_2$ and H_2O. Then, Michael addition of intermediate **44** to unsaturated Knoevenagel product **47** occurred to afford intermediate **48**, which underwent tautomeric proton shift to produce the target product **33.**

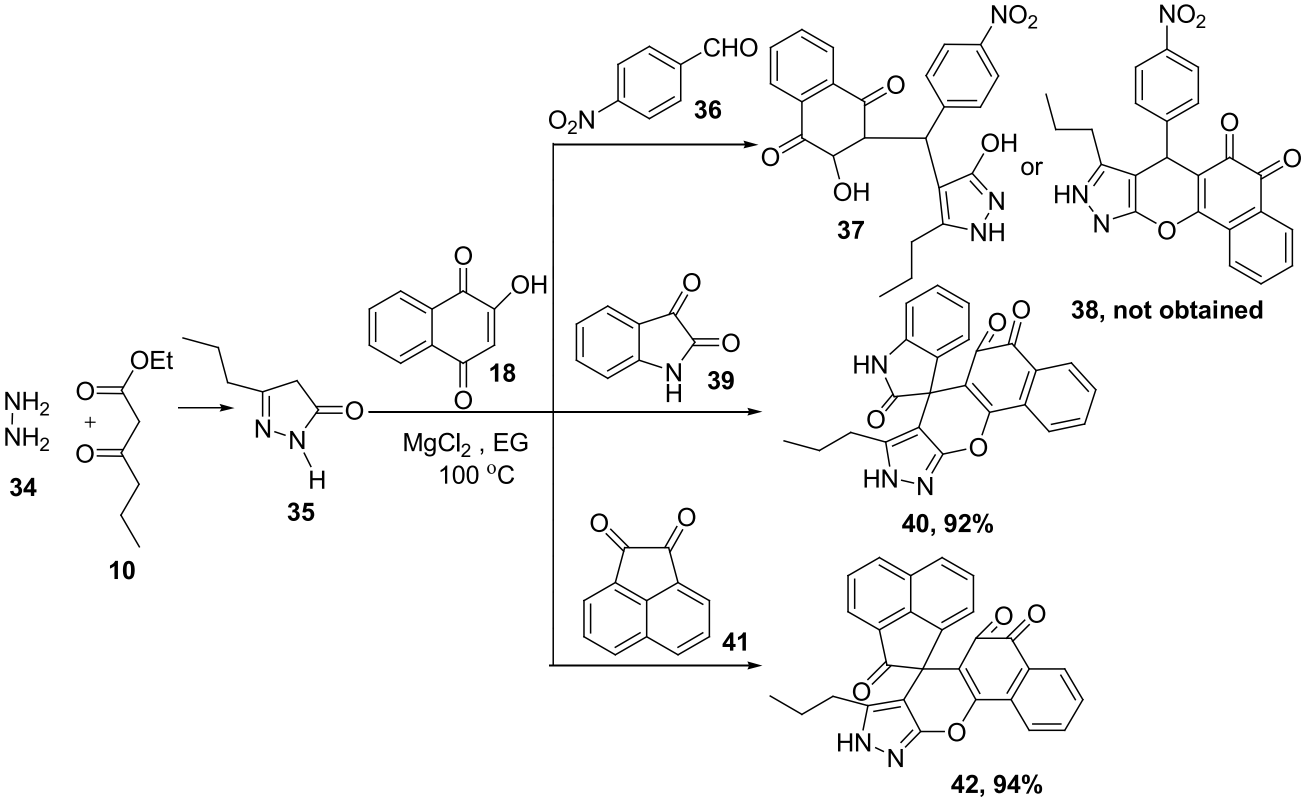
The synthesis of 1,4-dihydropyridines

Asseri et al. reported the preparation of 1,4-dihydropyridines (1,4-DHPs), **51** in the presence of alkaline earth metal chlorides. Typically, the $MgCl_2$ catalyzed the formation of 1,4-DHPs in (69–87%) yields. The Mg^{2+} was used as the Lewis acid catalyst in this reaction, and the proposed mechanism of the synthesis of 1,4-DHPs has been depicted in this manuscript. The advantages of serving $MgCl_2$ as a catalyst are including low cost, availability and simple separation, which has sparked considerable interest in the use of this catalyst in promoting organic reactions [16] (Scheme 17).

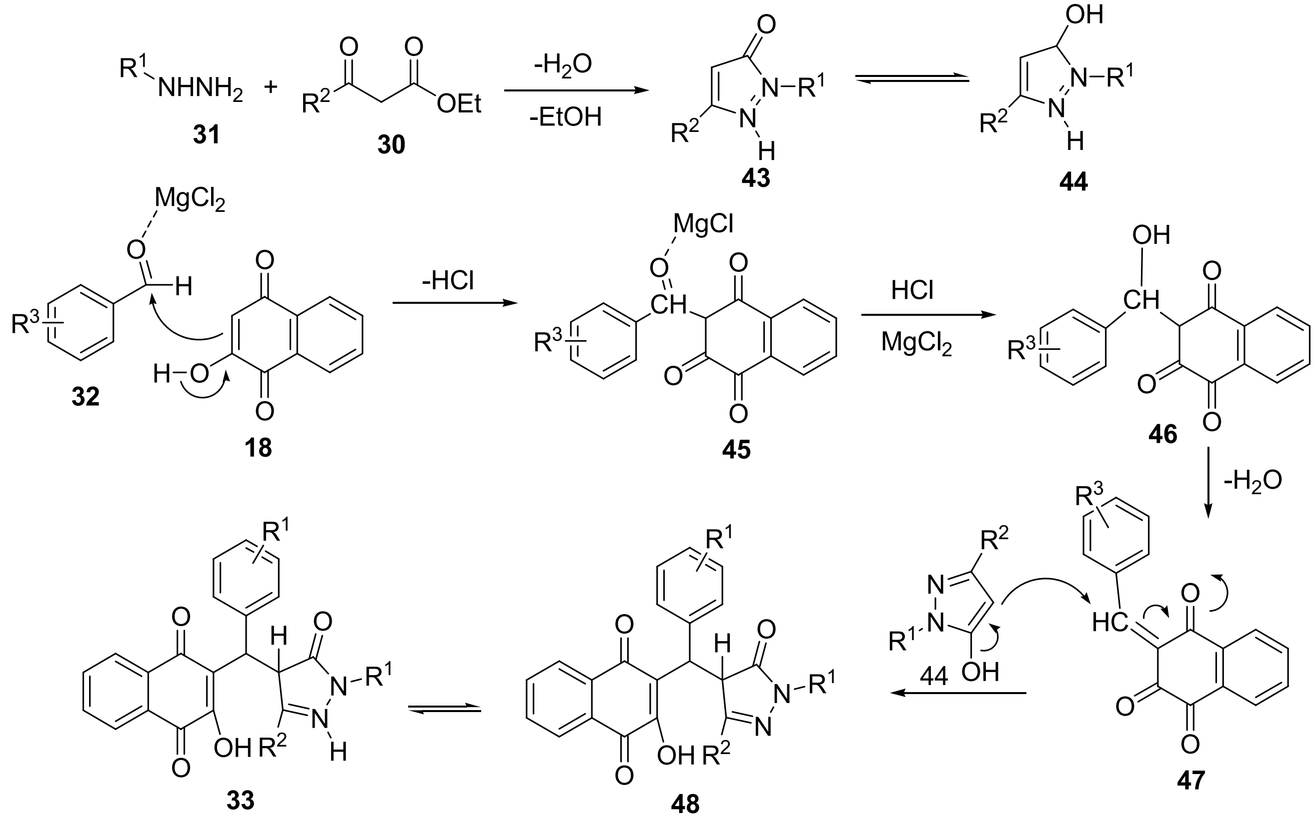
The functionalization of organic molecules

In 2009, Akselsen and Skattebøl reported a convenient method for the selective *ortho*-formylation of oxygenated phenols **52** in good yields (73–97%) using $MgCl_2$, paraformaldehyde and triethylamine in refluxing tetrahydrofuran (THF) under an argon atmosphere for 1–4 h (Scheme 18) [17].

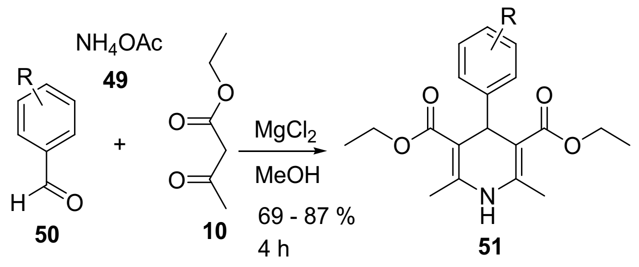
Phenols were also converted to their magnesium salts with the $MgCl_2$–Et_3N base system and subsequently reacted with Eschenmoser's salt, affording *N,N*-dimethyl-substituted benzyl amines in high to excellent yields (Scheme 19). In this method, a series of mono *N*-substituted benzyl amines **57** were produced in one-pot synthesis by *ortho*-formylation of phenols **54** to corresponding salicyl aldehydes **55**, which in turn reacted with amines to imines **56**. The imines were subsequently reduced to mono *N*-substituted benzyl amines **57** [18].



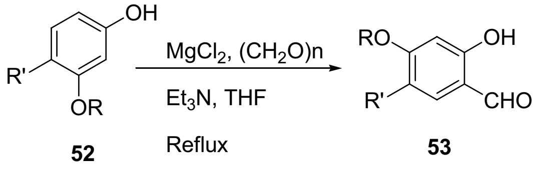
Scheme 15 Synthesis of pyran derivatives **38**, **40** and **42**



Scheme 16 Suggested mechanism for the synthesis of compounds **33**

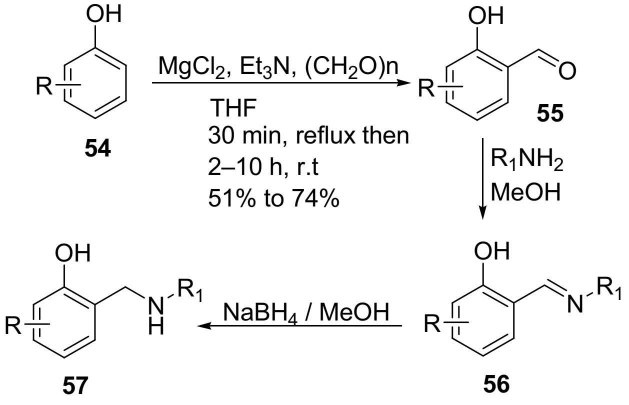


Scheme 17 $MgCl_2$ catalyzed the synthesis of 1,4-DHPs **51**



R = H, Me, Bn, TBS ((tert-butyldimethylsilyloxy),
TDS (thexyldimethylsilyl)
R' = H, Cl, Br

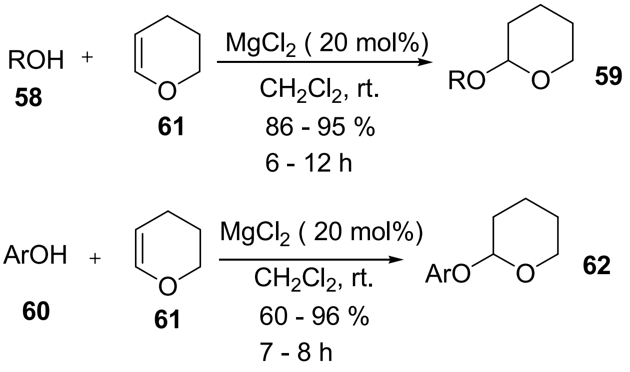
Scheme 18 Akselsen and Skattebøl's approach for the *ortho*-formylation of oxygenated phenols



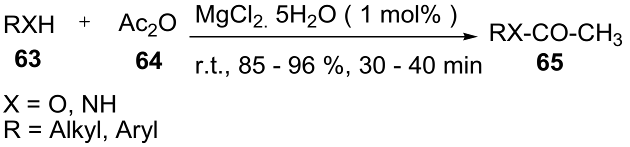
Scheme 19 Aminomethylation phenol using $MgCl_2$-Et_3N to obtain the Mannich product

In another study, an efficient procedure for the synthesis of tetrahydropyranylation of alcohols and phenols were also reported using $MgCl_2$ as a catalyst. In this research, a variety of alcohols **58** and phenols **60** were subjected to synthesize tetrahydropyranyl ethers **59** and **62** (Scheme 20) [19].

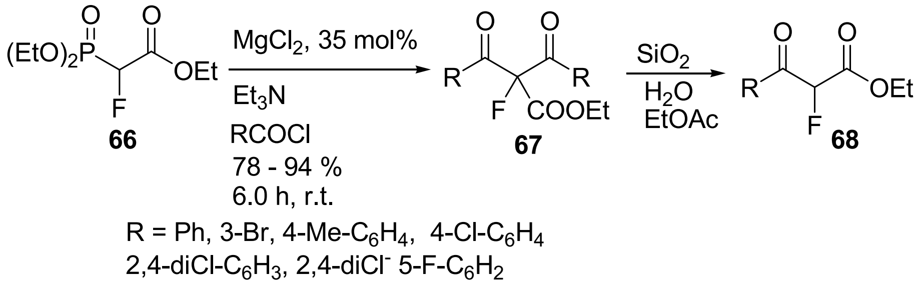
$MgCl_2$ was also employed as a heterogeneous catalyst for the acylation of a variety of aryl amines, alcohols and



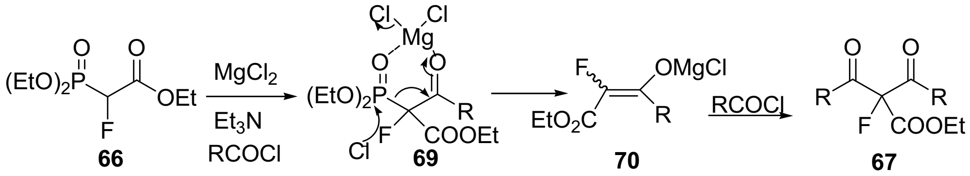
Scheme 20 Tetrahydropyranylation of alcohols and phenols using $MgCl_2$



Scheme 21 Acylation of amines, alcohols and phenols using $MgCl_2$



Scheme 22 Synthesis of α-fluoro β-keto esters using magnesium chloride–triethylamine



Scheme 23 Evidence mechanism for the synthesis of α-fluoro-β-keto esters using magnesium chloride–triethyl amine

phenols **63** using acetic anhydride **64** under solvent-free conditions at ambient temperature. This procedure described $MgCl_2.5H_2O$ as an efficient catalyst for the acylation of amines, alcohols and phenols. The others advantages of this protocol included inexpensive, availability of the catalyst, the use of catalytic amount of $MgCl_2$ (0.1 mol%), mild reaction conditions, short reaction time, high yields and solvent-free condition (Scheme 21) [20].

Kim et al. [21] described a facile formation of α-fluoro β-keto esters **68**, via diacylation reaction of diethyl (ethoxy carbonyl) fluoromethyl phosphonate **66** with aromatic carboxylic acid chlorides in the presence of magnesium chloride–triethyl amine followed by deacylation of compound **67**. Some of the advantages of this procedure were high yields of the product and the mild reaction conditions (Scheme 22).

The isolation of α-fluoro-β-keto esters **68** from the reaction of **69** with NH_4Cl in the presence of $MgCl_2$-triethyl amine proved the mechanism shown in Scheme 23.

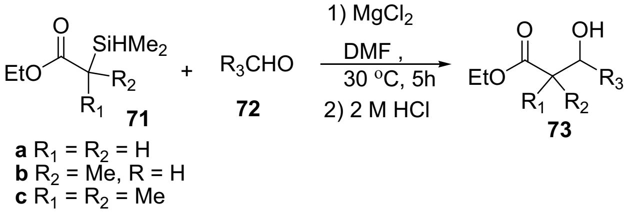
Condensation reactions

Aldol reaction of α-dimethyl silyl esters with aldehydes, ketones and α-enones

In this method, the aldols **73** were synthesized using a catalytic amount of $MgCl_2$, α-dimethyl silyl esters (α-DMS-esters) **71** smoothly with aldehydes **72** at 30 °C in very good yields (Scheme 24) [22].

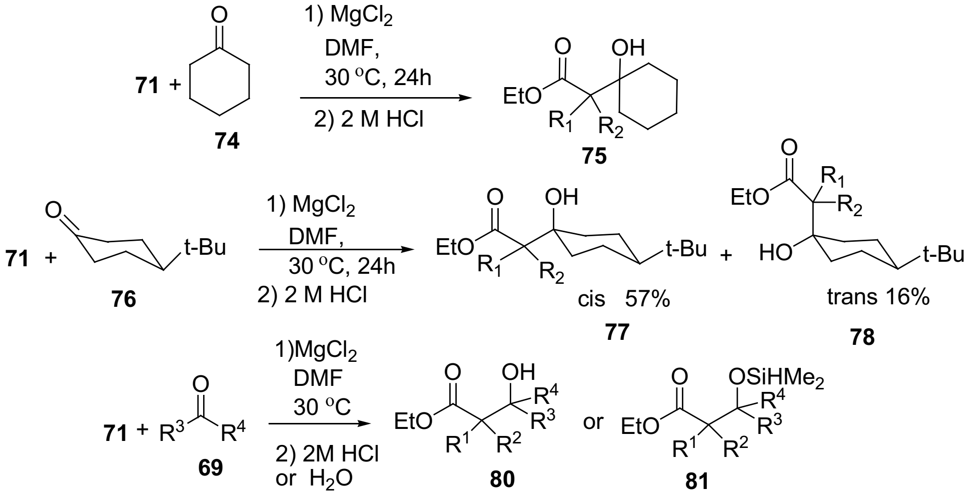
Also, the aldol reaction with ketones was effectively accelerated using $MgCl_2$ (Scheme 25).

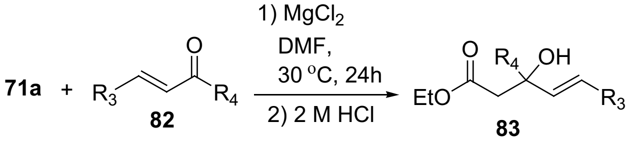
Also, an equimolar amount of LiCl or $CaCl_2$ induced the aldol reaction; however, the rate-accelerating ability



Scheme 24 Aldol reaction using α-DMS-esters

Scheme 25 Aldol reaction with ketones





Scheme 26 Addition of α-DMS-esters **67a** to α-enones

was not high enough to realize a successful aldol reaction. In contrast, $MgCl_2$ was an effective promoter and accelerated addition of **71a** at the carbonyl carbon or β-carbon **82** to give β-hydroxy esters **83** (Scheme 26).

The application of $MgCl_2$

Magnesium is used in making a number of alloys which are used in automobile industry, making of aircrafts and optical instruments. Magnesium powder mixed with potassium chlorate is used for flash bulbs in photography. It has also been used as deoxidizer for removing last traces of oxygen from copper, steel, etc. It is utilized in making Grignard reagents which are used for the synthesis of large number of organic compounds. Also, it is applied in the extraction of boron, silicon, etc. [23].

$MgCl_2$ is also employed for the dust control, soil stabilization and wind erosion mitigation. When magnesium chloride is applied to roads and bare soil areas, both positive and negative performance issues occur which are related to many application factors [24].

The preparation of metallic magnesium

Magnesium chloride is the major starting material to produce metallic magnesium. In a protocol, the magnesium is prepared by electrolysis [25, 26] that is applicable on a substantial scale (Scheme 27).

$$MgCl_2 \longrightarrow Mg + Cl_2$$

Scheme 27 Preparation of metallic magnesium from $MgCl_2$

However, approximately 80% of the world demand for magnesium is currently supplied by China and nearly 95% of the primary magnesium output of China is produced using the Pidgeon process mainly due to low labor and energy costs and lax environmental act. In the Pidgeon process, magnesium metal is produced from calcined dolomite under vacuum at high temperatures using ferrosilicon as a reducing agent. In this process, the finely crushed dolomite is fed into kilns where it is calcined and then pulverized in a mill prior to mixing with finely ground ferrosilicon. After weighing and homogenizing, the calcined dolomite and ferrosilicon mixture is made into briquettes which are charged in a retort and placed in the reduction furnace. The reduction operation is a batch process releasing magnesium in vapor form, which is condensed in the cooled end of the retort outside furnace wall. After removal from the furnace, the magnesium "crown" is separated from the sleeves (Scheme 28) [27].

Ion hydration and associated defects in hydrogen bond network of water in the aqueous solutions of $MgCl_2$

In this study, the ion effects, at medium to high concentrations, on dynamical properties of H_2O molecules were investigated via classical molecular dynamics simulations by using two well-known non-polarizable water models. Simulations showed that $MgCl_2$-induced perturbations in the hydrogen bond network of water led to the formation of bulk-like domains with "defect sites" on boundaries of

$$2(\mathrm{CaO.MgO})_{(s)} + (x\mathrm{Fe})\mathrm{Si}_{(s)} \longrightarrow 2\mathrm{Mg}_{(s)} + 2(\mathrm{CaO.SiO_2})_{(s)} + \mathrm{Fe}_{(s)}$$

Scheme 28 Pidgeon process for the synthesis of magnesium metal

such domains; H_2O molecules at such defect sites have less number of hydrogen bonds than those in bulk water. Reorientational autocorrelation functions for dipole vectors of such defect water molecules were computed at various concentrations of ions compared with system of pure water. Earlier experimental and simulation studies depicted significant differences in reorientational dynamics for H_2O molecules in the first hydration shell of many dissolved ions. The results of this investigation offered that $MgCl_2$ concentration was effective on defect water molecules, which were beyond the ion shells of the first hydration, and experience significant slowing of reorientation times. Also, the addition of cesium chloride to water does not perturb the hydrogen bond network of water even at higher concentrations. This difference in behavior between $MgCl_2$ and CsCl is consistent with the well-known Hofmeister series [28].

The application of $MgCl_2$ in biochemistry

Magnesium chloride as an esthetic for cephalopods

In this study, $MgCl_2$ was as an anesthetic drug for a range of individual cephalopods of different sexes, ages and sizes and relative to five kind genera effectively at varying temperatures from 13 to 22 °C. The results shown that $MgCl_2$ must be rated an excellent "off the shelf" anesthetic for cephalopods. Some advantages of this method were cheap, stable, non-toxic, simple preparation of the solution and usable for worldwide, in the laboratory or on a research vessel, used routinely to narcotize and relax cephalopods prior to fixation. Lately, it appeared to act with minimal trauma to the animal, unlike urethane or ethanol [29].

The separation of serum high-density lipoprotein (HDL) for cholesterol determination

In this investigation, two procedures for the isolation of serum high-density lipoprotein were evaluated: the use of sodium phosphor tungstate and $MgCl_2$ to precipitate selectively and the use of sodium chloride solution under ultracentrifugation condition. Then cholesterol content of fractions resulted from each protocol was compared. Reference intervals for high-density lipoprotein cholesterol in subpopulations were also categorized by age and sex on the basis of data obtained from volunteer blood donors [30].

The effect of $MgCl_2$ on rabbit bronchial smooth muscle

To investigate effect of magnesium ion on the relaxing of rabbit bronchial smooth muscle, a study was designed in vitro model using bronchial rings from New Zealand white rabbits stimulated to contract by electrical stimulation, histamine or bethanechol. In order to show merit, magnesium chloride in various concentrations such as 1, 6, 16, 36 and 86 mM was induced to each tissue bath and resting tension was measured. Electrical stimulation 100 V/100 ms, histamine 10 rnM or bethanechol 6.25 mM was added to wash tissues to induce contraction. Then magnesium chloride 5, 10 and 50 mM was added, and the response of bronchial smooth muscle was measured. The results shown that magnesium chloride 1, 6, 16, 36 and 86 mM decreased the mean ± SEM resting tension of bronchial rings by 40 ± 16, 100 ± 11, 110 ± 10, 170 ± 9 and 275 ± 22 mg, respectively. Electrical stimulation of 100 V/100 ms was raised the mean ± SEM resting tension by 168 ± 52 mg. Magnesium chloride 5, 15 and 50 mM added to the tissue bath decreased the response to 100 V/100 ms to 65 ± 27, 40 ± 23 and 1 ± 0 rag, respectively. Histamine 10 mM increased mean ± SEM resting tension by 490 +/121 mg. Magnesium chloride 5, 15 and 50 mM decreased the histamine response by 80 ± 56, 250 ± 74 and 475 ± 131 mg, respectively. Bethanechol 6.25 mM increased the mean ± SEM resting tension by 495 ± 74 mg. Magnesium chloride (5, 15, 50 mM) decreased bethanechol-induced tension by 52 ± 18, 184 ± 26 and 506 ± 64 mg. Therefore, $MgCl_2$ produced dose-dependent relaxation of bronchial smooth muscle at rest, when stimulated by histamine, bethanechol or electrical impulse. $CaCl_2$ was unable to significantly reverse magnesium-induced relaxation. These data supported the hypothesis that magnesium relaxed smooth muscle and dilates bronchial rings [31].

The comparison of the reaction of bone-derived cells to enhanced $MgCl_2$-salt concentrations

In this study, magnesium-based implants exhibited various advantages such as biodegradability and potential for enhanced in vivo bone preparation. To determine whether high local magnesium concentrations could be osteoconductive and excluded other environmental factors that occur during the degradation of magnesium implants, $MgCl_2$ was utilized as a model system. As cell lines were preferred targets in the studies of non-degradable implant materials, the authors performed a comparative study of three osteosarcoma-derived cell lines (MG63, SaoS2 and U2OS) with primary human osteoblasts. The correlation among cell count, viability, cell size and several $MgCl_2$ concentrations were utilized to study the influence of magnesium on proliferation in vitro. Moreover, bone metabolism alterations during proliferation were investigated by analyzing the expression of genes involved in osteogenesis. It was revealed that for all cell types, the cell count decreased at concentrations above 10 mM $MgCl_2$. However, detailed analysis showed that $MgCl_2$ had a relevant but very diverse influence on proliferation and bone metabolism, depending on the cell type. Only for primary cells was a clear stimulating effect yielded. Therefore, reliable results demonstrating the osteoconductivity of magnesium implants could only be achieved with primary osteoblasts [32].

Multisite ion model in concentrated solutions of divalent cations: osmotic pressure calculations

It is known that precise force field parameters for ions are essential for meaningful simulation studies of proteins and nucleic acids. Currently accepted models of ions, especially for divalent ions, do not necessarily reproduce the right physiological behavior of Ca^{2+} and Mg^{2+} ions. Saxena and Sept [33] reported known the multisite ion model, instead of treating the ions as an isolated sphere. The charge was divided into multiple sites with a partial charge. This model provided accurate inner shell coordination of the ion with biomolecules and predicted better free energies for proteins and nucleic acids. In another study, Saxena and García revealed and refined the multisite model to describe the behavior of divalent ions in concentrated $MgCl_2$ and $CaCl_2$ electrolyte solutions, eliminating the unusual ion–ion pairing and clustering of ions which occurred in the original model. The authors also calibrated and improved the parameters of the multisite model by matching the osmotic pressure of concentrated solutions of $MgCl_2$ to the experimental values and then use these parameters to test the behavior of $CaCl_2$ solutions. Also, the concentrated solutions Ca^{+2} and Mg^{+2} ions exhibited the experimentally observed behavior with correct osmotic pressure, the presence of solvent-separated ion pairs instead of intimate ion pairs and no aggregation of ions. The improved multisite model for Ca^{2+} and Mg^{2+} ions can also be employed in classical simulations of biomolecules at physiologically relevant salt concentrations [34].

Antimicrobial properties of $MgCl_2$ at low pH in the presence of anionic bases

Magnesium is a necessary element for life and is found ubiquitously in all organisms. The various cations play important roles as enzymatic cofactors, as signaling molecules and in stabilizing cellular components. It is not surprising that magnesium salts in microbiological experiments are typically associated with positive effects. In 2014, Oyarzúa and coworkers investigated Listeria monocytogenes as a model organism, on the usefulness of magnesium (in the form of $MgCl_2$) as a stress enhancer. $MgCl_2$ did not affect bacterial viability at near-neutral pH. It was found to strongly compromise culture ability and redox activity when cell suspensions were exposed to the salt at acidic pH. The principle was confirmed with a number of gram-negative and gram-positive species. The magnesium salt dramatically increased the acidity to a level that was antimicrobial in the presence of anionic bases such as phosphate, lactate or acetate. The antimicrobial activity of $MgCl_2$ was much stronger than that of NaCl, KCl or $CaCl_2$. No effect was observed with $MgSO_4$ or when cells were exposed to $MgCl_2$ in phosphate buffer with a $pH \geq 5$. Acid stress was reinforced by an additional, salt-specific effect of $MgCl_2$ on microbial viability that needed further examination. Apart from its implications for surface disinfection, this observation might support the commonly stated therapeutic properties of $MgCl_2$ for the treatment of skin diseases and could contribute to understanding why salt from the Dead Sea, where Mg^{2+} and Cl^{-1} are the most abundant cation/anion, has healing properties in a microbiological context [35].

The effects of $MgCl_2$ on in vitro cholinesterase and ATPase poisoning by organophosphate

Ajilore et al. studied the benefits of magnesium ion as $MgCl_2$ in organophosphorus poisoning targeting its ability to interact with substrates and membrane enzymes. Blood samples collected from the volunteered healthy adult by venipuncture into anticoagulant test tubes containing EDTA were isolated into plasma and red blood cell and divided into three groups including: normal, pesticide only (0.25–2.0 mom/L chlorpyrifos) and pesticide (0.25–2.0 mmol/L chlorpyrifos) + 0.1 mol/L $MgCl_2$. Acetylcholinesterase, Na^+/K^+ ATPase and Ca^{2+} ATPase activities were evaluated. The results showed that chlorpyrifos significantly ($P < 0.5$) reduced the levels of cholinesterase both in plasma and on red blood cells. Red blood cells Na^+/K^+ ATPase and Ca^{2+} ATPase were also significantly ($P < 0.5$) reduced by chlorpyrifos, while $MgCl_2$ counteracted effects of chlorpyrifos with significant ($P < 0.05$) increase in the levels of cholinesterase, Na^+/K^+ ATPase and Ca^{2+} ATPase. The authors resulted that $MgCl_2$ neutralized the effects of chlorpyrifos by increasing normal ATPase activities and inhibiting release of acetylcholine from the cell [36].

The effects of transdermal $MgCl_2$ on the quality of life for patients with fibromyalgia

Fibromyalgia is a syndrome of chronic pain, fatigue, depression and sleep disturbances symptoms. Its main cause is unclear. Several studies have reported decreased intracellular magnesium levels in patients with fibromyalgia and have found a negative correlation between magnesium levels and fibromyalgia symptoms. Engen and co-workers gathered preliminary data on whether transdermal magnesium could improve the quality of life for women who had fibromyalgia. Forty female patients with the diagnosis of fibromyalgia were enrolled. Each participant was provided a spray bottle containing a transdermal magnesium chloride solution and asked to apply four sprays per limb twice daily for 4 weeks. This pilot study suggested that transdermal magnesium chloride applied on upper and lower limbs might be beneficial to patients with fibromyalgia [37].

The removal of dyestuff

Color removal from dye-containing wastewater

Magnesium salts have been reported to be an efficient alternative to conventional coagulants and can enhance the removal of impurities or pollutants from wastewater [38, 39]. Color removal by $MgCl_2$ when treating synthetic waste containing pure dyes was studied. The color removal efficiency of $MgCl_2/Ca(OH)_2$ was compared with that of $Al_2(SO_4)_3$, polyaluminum chloride (PAC) and $FeSO_4/Ca(OH)_2$. The mechanism of color removal by $MgCl_2$ was also investigated. The experimental results showed that the color removal efficiency of $MgCl_2$ was related to the type of dye and depended on the pH of the waste and the dosage of the coagulants used. The treatment of waste containing a reactive dye or dispersed dye with $MgCl_2$ yielded an optimum color removal ratio when the pH of the solution was equal to or above 12.0. For both the reactive and dispersed dye wastes, $MgCl_2/Ca(OH)_2$ was shown to be superior to $MgCl_2$/NaOH, $Al_2(SO_4)_3$, PAC and $FeSO_4/Ca(OH)_2$ for color removal. A magnesium hydroxide precipitate formed at pH values greater than 12.0, which provided a large adsorptive surface area and a positive electrostatic surface charge, enabling it to remove the dyes through charge neutralization and an adsorptive coagulating mechanism. So, the $MgCl_2/Ca(OH)_2$ system found a viable alternative to some of the more conventional forms of chemical treatment, especially for treating actual textile waste with high natural pH [40].

The removal of dyes and industrial dye wastes

Magnesium chloride, as compared to alum and polyaluminum chloride (PAC), is a less commonly used coagulant in the field of wastewater treatment, with a cost in between alum and PAC. It has been used in this study as a coagulant to investigate the effectiveness of the chemical precipitation method for the removal of coloring matters. The color concentration of dye solutions was measured by visible spectrophotometry. Parameters such as the effect of pH, the effect of coagulant and coagulant aid dosages and the effect of different coagulants have been studied. The results showed that $MgCl_2$ was capable of removing more than 90% of the coloring material at a pH of 11 and a dose of 4 g $MgCl_2$/l of the dye solution. $MgCl_2$ was shown to be more effective in removing reactive dye than alum and PAC in terms of settling time and the amount of alkalinity required. Optimal operating conditions such as pH value, coagulant dose and the effect of polyelectrolyte have been determined. Wastewaters of a dying and printing mill on different days have been treated by $MgCl_2$ aqueous solution in bench scale. The treatment of industrial waste has shown a reduction of 88% in COD and 95% of suspended solids [41].

Conclusions

This review has reported production and the applications of magnesium chloride in organic chemistry and biochemistry including the synthesis of heterocyclic compounds, the protection of functional groups, condensation reaction, the preparation of metallic magnesium, as an anesthetic for cephalopods, the separation of serum high-density lipoprotein, effect of magnesium chloride on rabbit bronchial smooth muscle, antimicrobial properties of magnesium chloride, effect of magnesium chloride on the quality of life for patients with fibromyalgia and color removal from dye-containing wastewater and industrial dye wastes. Therefore, this versatile reagent can be easily prepared, can be used in organic transformation and can be employed in the synthesis of heterocyclic compounds. We believe that magnesium chloride can be examined in the other organic reactions and biochemistry process that have not still searched. Also, this review paper can be used for researchers in all field of sciences, especially for chemistry, biochemistry and sewage treatment researchers.

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