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Utilization of Grignard Reagents in Solid-phase Synthesis: A Review of the Literature

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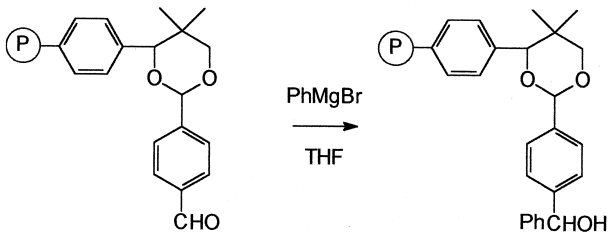
Contents

1. Introduction

Organomagnesium reagents have been used extensively in synthetic organic chemistry. Since their discovery, numerous industrial applications have been reported for these versatile reagents.[1] Grignard reagents can be synthesized from organic halides and they exhibit a high reactivity and good chemoselectivity. Therefore, it is not surprising that it would be convenient to utilize Grignard reagents in reactions at a polymer support, thus giving them applications in combinatorial chemistry.[2,3]

Solution-phase reactions with Grignard reagents have been well documented.[4–6] However, the literature associated with reactions of organometallic reagents with molecules attached to a polymer support has not been reviewed extensively. This report summarizes the literature published until March 1999 describing Grignard reagents involved in reactions performed on a variety of polymer-supported resins. Further details of the experimental conditions are available from the primary literature references. All of the publications cited are from refereed journals and not from patents. A search in *Chemical Abstracts*, using the keyword 'Grignard' combined with other keywords such as 'solid-phase synthesis', 'combinatorial chemistry' and 'solid support', has been performed to ensure that most of the references on the subject have been covered.



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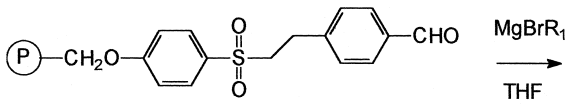
Scheme 1.



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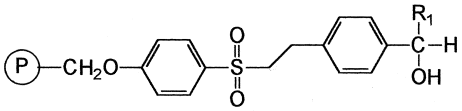

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Scheme 2.

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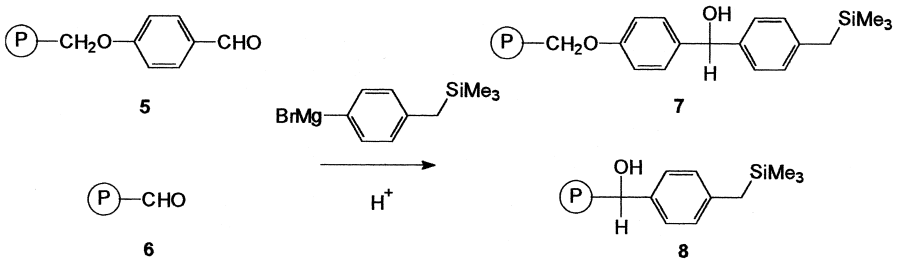


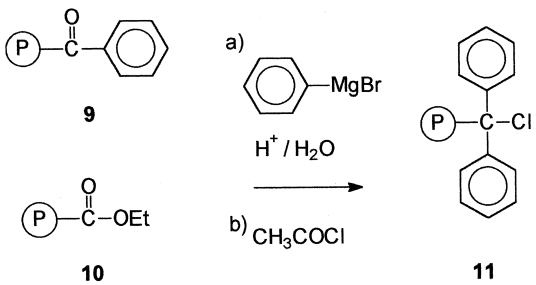
Scheme 3.

2. Reactions of Grignard Reagents with Polymer-bound Aldehydes and Ketones

Probably in part for historical reasons, and in part because of their general utility as preparative methods, addition reactions at the carbonyl double bond have come to be regarded as the 'normal' reactions of Grignard reagents with aldehydes and ketones in solution. In the case of reactions of Grignard reagents with polymer-bound aldehydes and ketones, this is also the most-studied reaction to date. Several reactions have been reported and found to be a convenient approach in the production of molecules on solid support.

In a paper by Qi-Sheng Ren et al.,[7] 1-polystyryl-2,2-dimethyl-1,3 propanediol was prepared and used as a protecting group for one of the aldehydic functions of terephthalaldehyde through the acetal linkage. The unbound aldehydic group of the polymer **1** obtained was reacted with a Grignard reagent, giving the corresponding polymer-bound secondary alcohol **2**. The reaction was performed at ambient temperature in THF (Scheme 1).

In work reported by Baxter et al.,[8] a resin-bound arylsulphonate ester **3** was reacted with two different Grignard reagents in 42 and 50% yield, respectively. The investigation showed that the sulphonate ester moiety was sufficiently stable so that many common reactions, including Grignard reactions, could be conducted (Scheme 2).



Scheme 4.

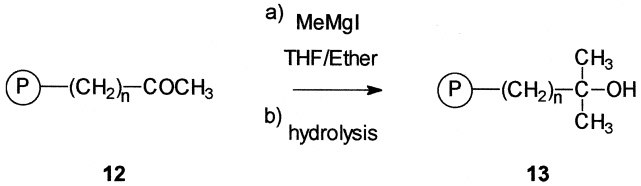
A recent paper by Routledge et al.[9] described the development of new fluoride-labile linkers for solid-phase organic synthesis. Merrifield resin was reacted with the sodium salt of 4-hydroxybenzaldehyde to give the resin-bound aldehyde **5**. A Grignard reaction between 4-bromobenzyltrimethylsilane[10] and either **5** or commercially available formylpolystyrene **6** produced the resin-bound silyl-linkers **7** and **8**, respectively. The yield in these reactions was reported as being >95% (Scheme 3).

In the preparation of trityl chloride functionalized polystyrene, Fréchet[11] reported the addition of phenylmagnesium bromide to the benzoic ester functionalized polymer **9** or to the acetylated polymer **10**. Following acid hydrolysis, the diphenylpolystyrylcarbinol derivative was obtained. The desired product **11** was formed by reaction with an excess of acetyl chloride. A similar reaction has been published by Cramer and Köster[12] and this was utilized in the preparation of dimethoxytrityl chloride resin to be used in the synthesis of oligonucleotides on a polymeric carrier (Scheme 4).

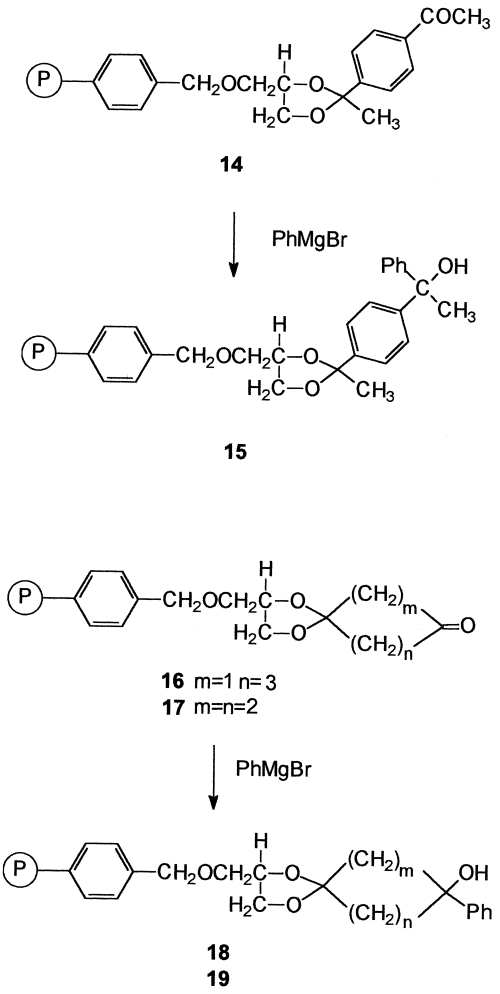
Sreekumar and Pillai[13–15] have reported some conversions of polymer-supported ketones **12** to tertiary alcohols **13** by Grignard reactions with methylmagnesium iodide. The tertiary alcohols have been utilized in the production of spacer-modified polystyrene-supported tertiary hypohalites (Scheme 5).

Xu et al.[16] have similarly shown that the polymer-bound *p*-acetylbenzene monoacetal **14** reacts with phenylmagnesium bromide in THF and that the corresponding polymer-bound alcohol **15** is obtained. The laboratory also reported on the reaction of polymer-bound cyclic ketones with Grignard reagents. Polymer-bound 1,3-cyclohexanedione monoacetal **16** or 1,4-cyclohexanedione monoacetal **17** reacts in THF with phenylmagnesium bromide at room temperature and the corresponding polymer-bound adducts **18** and **19** are obtained, respectively (Scheme 6).

Five examples of a 1,2-addition of Grignard reagents to a dihydropyridone scaffold **20** on a solid support have been



Scheme 5.



Scheme 6.

reported by Chen and Munoz.[17] After cleavage from the support **21**, the desired compounds, 2,4-disubstituted pyridines, are obtained as major products or the 2,4-disubstituted-1,2,5,6-tetrahydropyridines as minor products (Scheme 7).

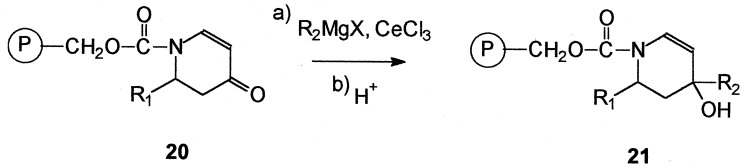
Fraley and Rubino[18] have published the addition of several Grignard reagents to a vinylogous ester resin. The method is useful in the preparation of 2-cyclohexenones from resin-bound 1,3-cyclohexanediones **22**. The yield of the Grignard reaction performed in THF at 0°C averages 34–86% (Scheme 8).

3. Addition of Grignard Reagents to Polymer-bound Esters

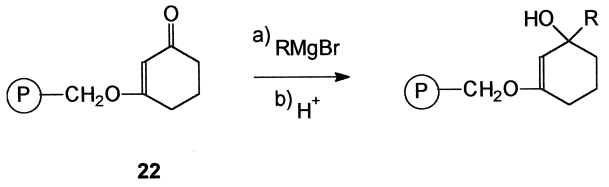
Grignard reagents have been utilized in the preparation of ketones from the corresponding esters on a solid support. In a paper by Wallace,[19] a one-pot procedure for the solid-phase synthesis of ketones from esters, via in situ formation of the *N*-methoxy-*N*-methyl amide is described. Addition of the Grignard reagent to the resin-bound ester **23** and *N*,*O*-dimethyl hydroxylamine hydrochloride at −15°C or at room temperature affords the resin-bound ketones **24** in good yield (Scheme 9).

A resin-bound thioester demonstrated a remarkable selectivity to Grignard reagents. Investigations by Vlattas et al.[20] showed that C-terminal thioesters **25** reacted with Grignard reagents to generate intermediates **26** in solid-phase synthesis (Scheme 10).

In a paper by Hanessian and Xie[21] the resin-bound methyl ester **27** was treated with methylmagnesium chloride in THF



Scheme 7.

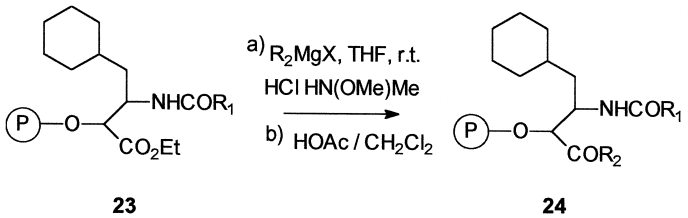


Scheme 8.

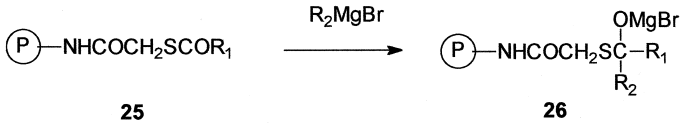
at 0°C to produce the alcohol **28** (Scheme 11).

4. Other Types of Reactions where Grignard Reagents have been Added to Polymer-bound Compounds

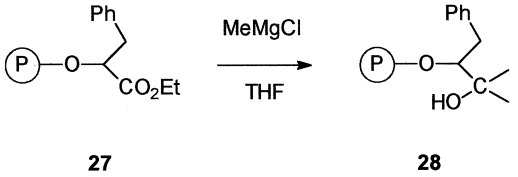
In addition to ‘normal’ Grignard reactions, i.e. with carbonyl double bonds, several other ‘miscellaneous’ reactions have



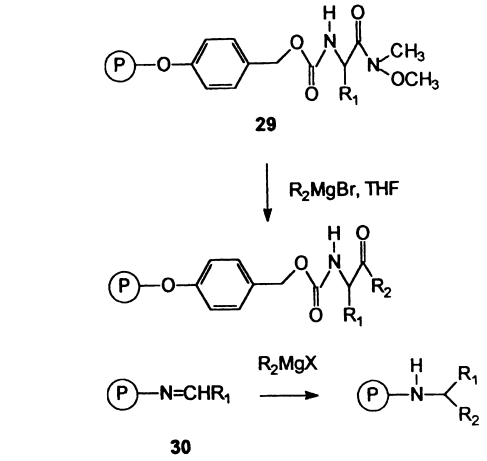
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

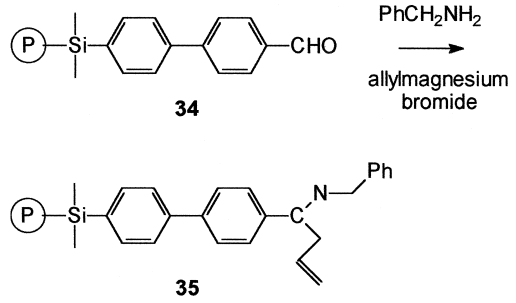
been reported. In these reactions, the Grignard reagent has been added to a polymer-supported carbamate **29**,[22] a resin-immobilized aldimine **30**,[23] an acylpyridium intermediate **31a**[24] or **31b**,[25] or a polymer-bound acyl imidazolide **32**[26] (Scheme 12).

Halogen–magnesium exchange reactions, which include a Grignard reagent, have been performed on a solid support (**33a** and **33b**)[27] (Scheme 13).

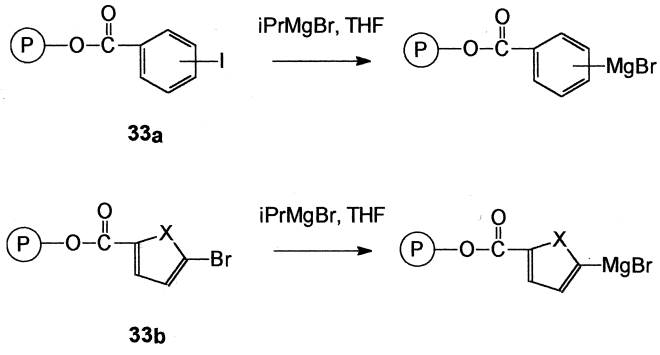
Chenera et al.[28] added allylmagnesium bromide to a Schiff base on a solid support. In this reaction, the Schiff base was prepared from a resin-bound aldehyde **34**. The reaction was performed in toluene/diethyl ether and yielded the polymer-bound adduct **35** (Scheme 14).

Kawana and Emoto[29] have used a Grignard reaction in an asymmetric synthesis procedure on a polymer support, **36**. The reaction yields pure atrolactic acid **37** in 77% yield (Scheme 15).

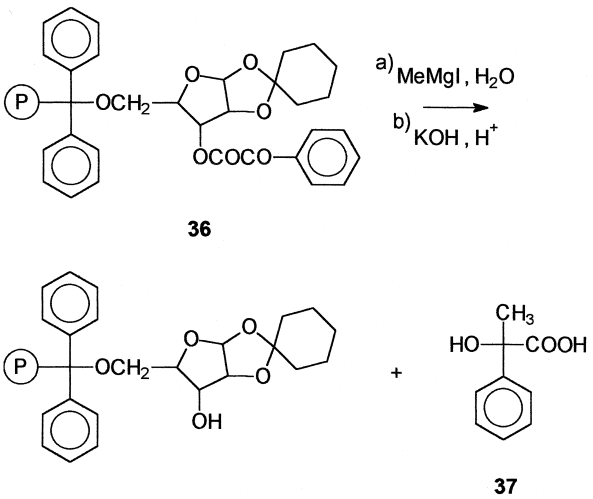
Finally, in a PEG-supported Grignard-activated coupling,[30,31] tertiarybutylmagnesium chloride was used for a stereospecific addition of a deoxynucleoside methylphosphonate.



Scheme 14.



Scheme 13.



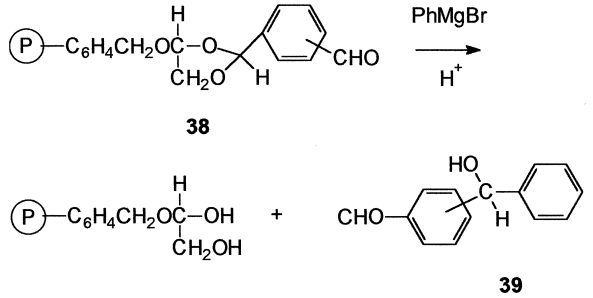
Scheme 15.

5. Grignard Reagents Utilized for Cleavage of Resin-bound Molecules

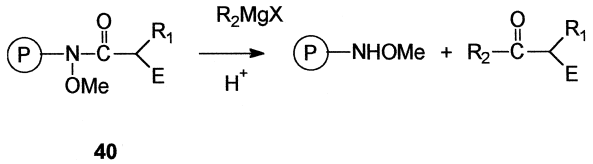
An interesting feature of Grignard reactions has been the discovery of their utilization for the cleavage of products from the solid support. Leznoff and Wong[32] used this property when phenylmagnesium bromide was added to a polymer-bound aldehyde **38**. The reaction yielded (formylphenyl)phenylcarbinol **39** in quantitative yield (Scheme 16).

Dinh and Armstrong[33] reported several examples of an N–O bond cleavage of polymer-supported *N*-methoxy-*N* methylamides **40** by Grignard reagents in 16–78% yield (Scheme 17).

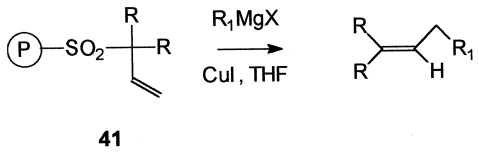
In a paper by Halm et al.,[34] nine examples of S_N2 nucleophilic displacement of, and cleavage from, polymer-supported sulphinates **41** using Grignard reagents were reported (Scheme 18).



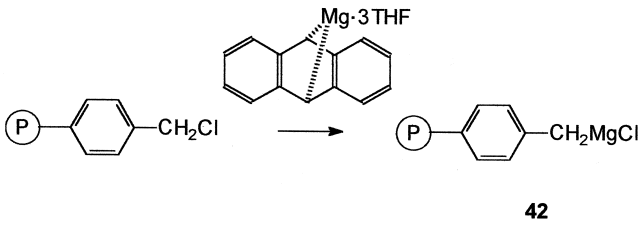
Scheme 16.



Scheme 17.



Scheme 18.



Scheme 19.

6. Grignard Reagents on an Insoluble Polymer

A Grignard reagent has also been prepared on an insoluble polymer. Fréchet at al.[35] described the applications of a polymer-bound Grignard reagent in, for example, asymmetric syntheses, as a regenerable polymeric protecting group, as a supernucleophilic catalyst or as a polymeric separation medium for HPLC. In the preparation of the insoluble Grignard reagent, **42**, a magnesium anthracene–THF complex was used as the metallating species, and an excellent yield of the insoluble polymer-bound benzylic Grignard species was obtained (Scheme 19).

7. Conclusion

Grignard reagents are extraordinarily useful and versatile organometallic compounds and react with a wide variety of electrophiles. From this point of view, it is very important to review the literature on the utilization of these reagents in reactions performed on a solid support.

This review encompasses most of the Grignard reactions performed on solid supports starting from 1960. Although mostly polymer-bound aldehydes and ketones have been reacted with Grignard reagents, a limited number of examples of other reactions have additionally been published. No reported data could be found on Grignard reactions with for example, polymer-bound quinones, lactones, carbonyl halides, nitriles, cyano compounds, carboxylic anhydrides, epoxides, ethers, acetals and ketals. An allylic rearrangement of a Grignard reaction on a solid support is still to be explored.

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Biographical Sketch

Robert G. Franzén (1966) received his PhD in organic synthesis from Åbo Akademi University, Finland in 1995, and then worked as a postdoctoral fellow in the field of bio-organic chemistry in Tsukuba, Japan. In 1997 he returned to Finland (Helsinki University) to work in the field of drug discovery. He is at present responsible for developing solid phase organic chemistry, combinatorial chemistry and automated synthesis in the medicinal chemistry group.