

Making Grignard reaction safer and cleaner in continuous flow synthesis and applying for synthesis of active pharmaceutical ingredients (APIs) and key starting materials (KSMs)

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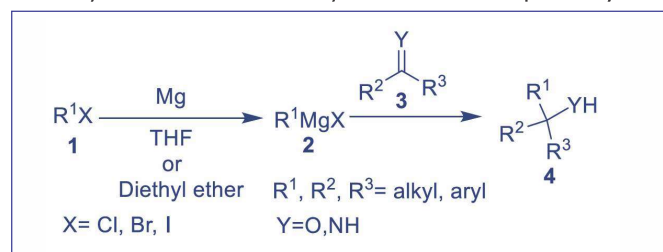
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Grignard reaction was discovered by Victor Grignard. Victor Grignard was awarded Nobel prize in the year 1912. This is an efficient reaction for C-C, C-hetero atom bond formation, for synthesis of several organic building blocks and active pharmaceutical ingredients. The drawback of this reaction is sudden spike in reaction temperature of environment friendly some substrates and slow addition to the substrates. This makes the process time consuming and formation of byproducts. The starting material is converted to product in a few minutes, in continuous flow process. The hazardous, unstable intermediates are well managed in a flow reactor. The safe operation and product with improved purity are the advantages of adopting continuous process in active pharmaceutical ingredients synthesis. This review article highlights recent reported literatures related to generation and applications of Grignard reagents for synthesis of precursors, active pharmaceutical ingredients, using flow reactors.

Introduction

Grignard reagents are the highly predominant reagents used in organic synthesis, for C-C, C-hetero atom bond formation (Scheme 1) and for the synthesis of active pharmaceutical ingredients (API). These are inexpensive and robust organometallic compounds.¹ Victor Grignard discovered the Grignard reaction and he was awarded Nobel Prize in Chemistry in the year 1912. Grignard reagent is denoted as RMgX, the R is an alkyl or aryl functional group, and X is generally a halogen group such as Cl or Br. It is synthesized by reaction of alkyl or aryl halide with Mg metal in tetrahydrofuran or diethyl ether.² The polarity and



Scheme 1. Generation of Grignard reagent and its reactivity with electrophiles.

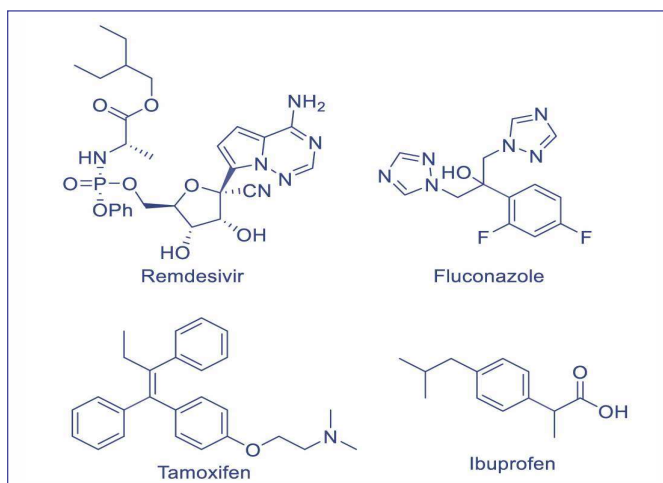


Figure 1. Familiar drug molecules synthesized using Grignard reagents.

electronegativity difference of the C(d⁻)-Mg(d⁺) in the Grignard reagent implies that it reacts as a nucleophile, and facilitates the addition to an electrophilic substrate such as carbonyl, imine, cyano compounds etc.²

The Figure 1 describes the structures of a few

Research Article

essential, highly prescribed drug molecules such as remdesir,³ fluconazole,⁴ tamoxifen,⁵ and ibuprofen,⁶ synthesized using Grignard reagents. Grignard reagents are stored at room temperature. But these are extremely moisture, air sensitive, and should be stored in air tight closed container, as they lose reactivity over time, leading to lower yield. The other drawback is that it takes more time for initiation of the reaction for some substrates and once initiated, the reaction generates a lot of heat quickly, which must be dissipated. In order to control the sudden spike of temperature, the reagent is added slowly in drop-wise manner. This increases the reaction time, and promotes formation of byproducts. In continuous flow synthesis, the entire starting material is converted to product in a matter of minutes. The product purity is improved, and produced amount of product could be tailored to requirements.⁷

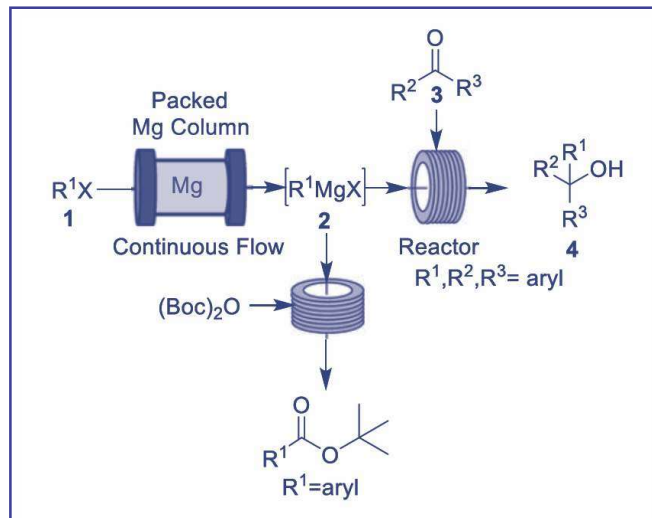
In Flow chemistry, channels or tubing or microreactors are used to carry out a reaction in a continuous stream rather than using a traditional reaction vessel. The solvents, solution of reagents is flown through the reactor using HPLC or peristaltic or other suitable pumps. The solution is pumped with precise flow rate in a controlled manner.⁸ The process is faster, as well as safer to handle hazardous reagents and unstable intermediates.⁸ Hence, flow reactor has got significant attention of academic and industrial synthetic chemists. This review article describes the generation of Grignard reagents in flow reactor, their applications for synthesis of different organic building blocks and API.

Grignard reagent generation in flow reactor

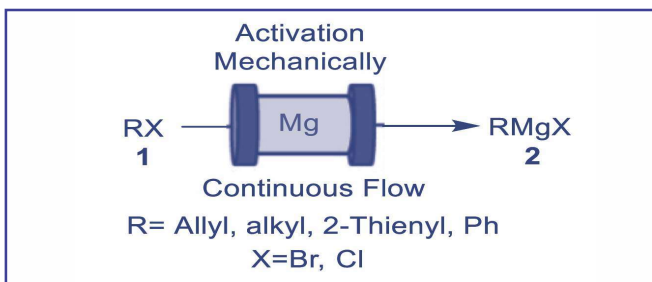
Alcazar and coworkers prepared Grignard reagent in a packed magnesium column in a flow reactor (Scheme 2).⁹ Magnesium metal of 20-230 mesh size was ideal for packing in a column, as it did not generate excess pressure during the reaction. The unwanted oxide layer on Mg surface was removed by passing diisobutylaluminium hydride solution through the column. The Mg metal was activated by flowing a solution of trimethyl silyl chloride in THF and followed by 1-bromo-2-chloroethane in THF. The generated Grignard reagent reacts with electrophiles such as keto compounds, di-tert-butyl dicarbonate [(Boc)₂O] to get alcohols, esters, respectively.

Menges-Flanagan used a jogging motor to activate Mg turning by causing abrasion on its surface, and

Grignard reagent generation in flow reactor

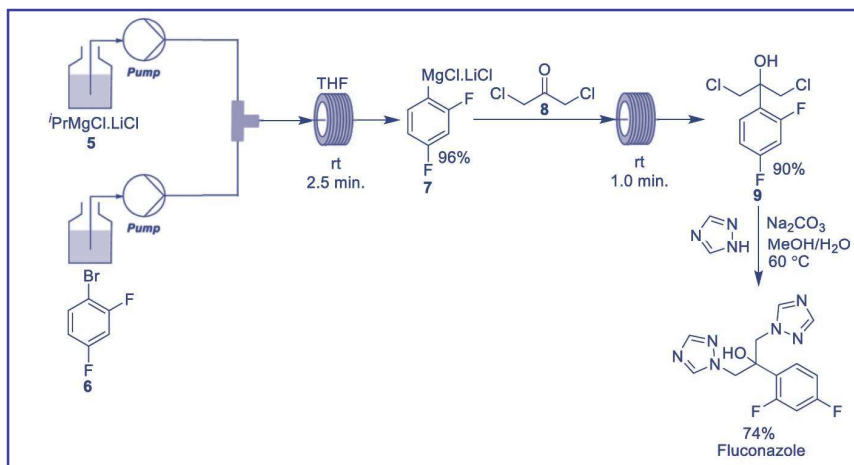


Scheme 2. Generation of Grignard reagent in packed Mg column in flow reactor.

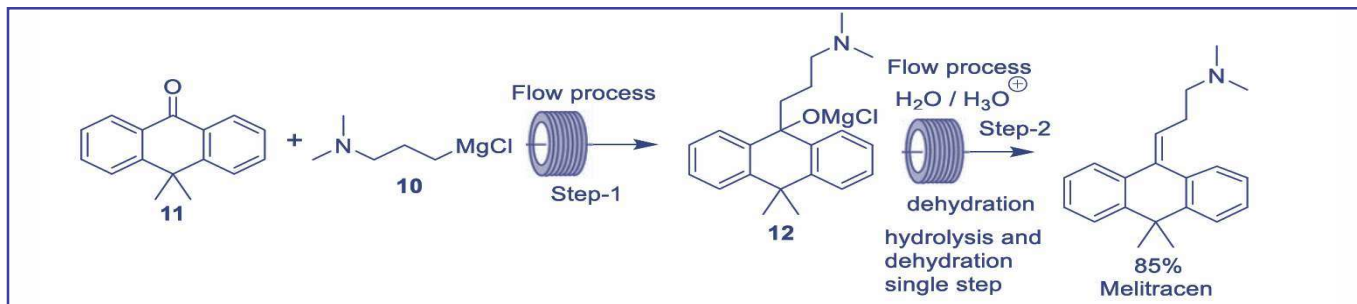


Scheme 3. Activation of Mg mechanically and preparation of Grignard reagent in flow reactor.

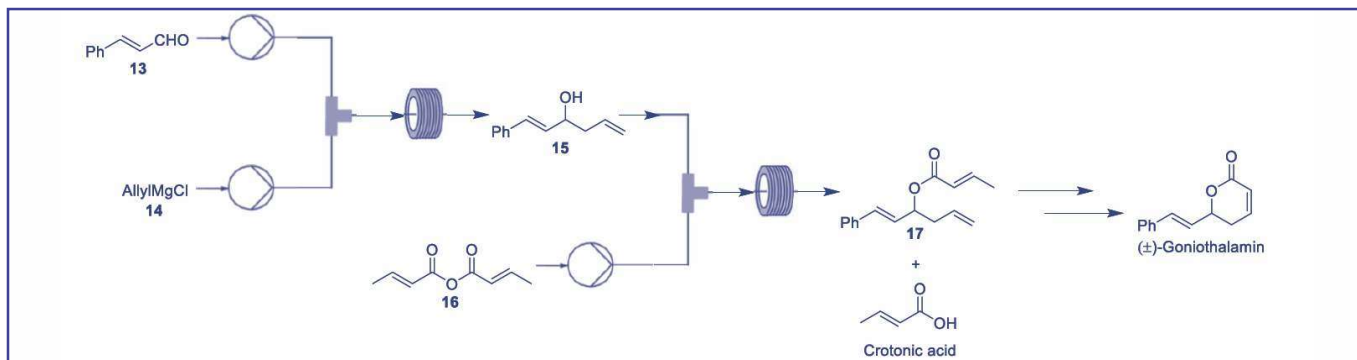
generated Grignard reagent on continuous flow mode (Scheme 3).¹⁰ Excess of Mg (5 to 25 molar) was used for 100% conversion and to prevent formation of unwanted side products. The monitoring of progress of the reaction was performed using inline IR technique. The condition was suitable for preparation of PhMgBr, EtMgBr and AllylMgCl on both



Scheme 4. A standard schematic diagram of continuous flow process for Fluconazole.



Scheme 5. A continuous flow process for synthesis of Melitracen.



Scheme 6. Synthesis of key starting material (KSM) for (±)-Goniathalamin.

the laboratory, as well as pilot scales.

Synthesis of Fluconazole

Fluconazole is an antifungal drug prescribed for treatment of localized and disseminated mycoses.¹¹ The *i*PrMgCl·LiCl (turbo Grignard reagent) which promotes the halogen magnesium insertion was used for conversion of bromo compound **6** to Grignard reagent **7** (Scheme 4).¹² Two separate pumps were used for *i*PrMgCl, bromo compound **6** and mixing of both reagents happens at T-joint and passed through the reactor at rt. There was formation of 96% Grignard reagent **7** and the residence time was only 2.5 min. The obtained compound **7** was reacted with 1,3-dichloro acetone in flow reactor with residence time of 1.0 min. to get 90% of alcohol compound **9**. Finally, treatment of compound **9** with 1,2,4-triazoles provides desired Fluconazole with 74% yield.

Synthesis of Melitracen

Melitracen is a drug used for the treatment of anxiety and depression.¹³ Pedersen reported a continuous flow process for synthesis of Melitracen.¹⁴ In flow process both hydrolysis and dehydration were performed in single step (Scheme 5). The phase separation step was also eliminated and only tetrahydrofuran (THF) was used as a solvent in comparison to the batch process, which requires toluene-THF solvent mixture. The both Grignard reaction (step 1), hydrolysis and dehydration (step

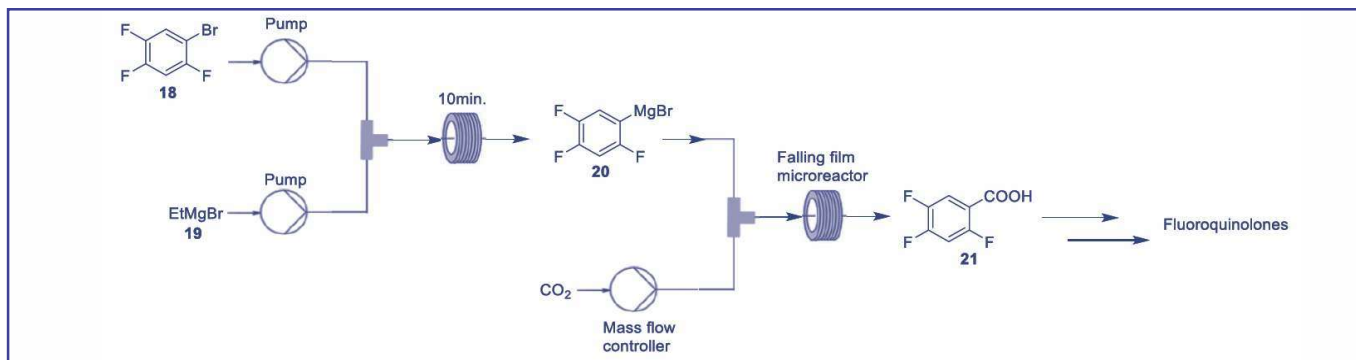
2) were performed at ambient temperature, whereas the batch process reaction happens at 50 °C.

Goniathalamin Precursor synthesis

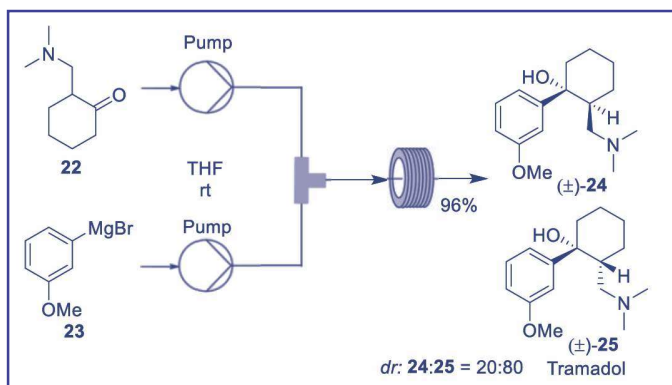
Goniathalamin is obtained from Goniothalamus species, which shows anticancer activity against breast cancer.¹⁵ A continuous flow gram scale process reported for synthesis of (±)-goniathalamin, by Pilli and Ley (Scheme 6).¹⁶ The continuous flow 1,2-addition reaction of allylmagnesium chloride with aldehyde **13**, followed by an acylation using compound 16 provided compound 17, the KSM for goniathalamin, with an output of 7 g·h⁻¹.

Preparation of KSM for Fluoroquinolones

Fluoroquinolones are considered as broad spectrum antibiotics, used for treatment of Gram-negative, as well as Gram-positive bacilli infections.¹⁷ Ciprofloxacin is the first generation fluoroquinolone and the next generation fluoroquinolones are levofloxacin, sparfloxacin, moxifloxacin, gatifloxacin etc. Many fluoroquinolones could be synthesized from the KSM 2,4,5-trifluorobenzoic acid. Deng synthesized 2,4,5-trifluorobenzoic by a continuous flow method (Scheme 7).¹⁸ The aryl-Grignard reagent **20** is unstable in nature. The Grignard reagent **20** is generated from bromo compound **18** using EtMgBr. The generated Grignard reagent **20** reacts with CO₂ (delivered through a mass flow-controller). The falling film microreactor helps in



Scheme 7. Synthesis of precursor for Fluoroquinolones.



Scheme 8. Synthesis of tramadol in continuous flow process.

thorough gas-liquid mixing, and facilitates biphasic reaction of compound **20** with CO₂ at atmospheric pressure efficiently. The increase in reaction temperature to 50°C, improved the yield to 93%. The batch process of the same reaction occurs at low-temperature and slow controlled addition is required, which makes the process expensive and inefficient.

Synthesis of Tramadol

Tramadol is an analgesic drug used for management of moderate to severe pain.¹⁹ Tramadol was synthesized with improved yield (96%) in a continuous flow reactor (scheme 8),²⁰ in comparison to traditional batch process.²¹ The reaction between (3-methoxyphenyl)magnesium bromide **23** and (±)-2-((dimethylamino) methyl)-cyclohexanone **22** generated tramadol with good diastereoselectivity (dr: 80:20).

Conclusion

Grignard reagents generation in a safer way and with good yield in continuous flow process have been reported in recent literatures. Several APIs and KSMs were synthesized using Grignard reagents in continuous flow synthesis ally magnesium chloride.

This technology will help in manufacturing of API, KSM with improved purity and safe operation of hazardous chemicals.

Conflicts of interest

The authors declare no conflict of interest.

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