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COMMUNICATION

The Application of a Continuous Grignard Reaction in the Preparation of Fluconazole

Sudha Korwar, Somi Amir, Perrer N. Tosso, Bimbisar K. Desai, Caleb J. Kong, Swara Fadnis, Nakul S. Telang, Saeed Ahmad, Thomas D. Roper, B. Frank Gupton*[a]

Abstract: The application of continuous methods in the synthesis of active pharmaceutical ingredients continues to receive significant attention in the academic as well as the industrial research communities. One of the major advantages of continuous methods is the ability to safely access kinetic synthons as well as highly reactive reagents that are typically unavailable through traditional batch methods. In this work, we report the high-yielding, clean formation of an aryl-turbo Grignard and its selective addition to a highly-enolizable 1,3-dichloroacetone, for the continuous synthesis of a key intermediate for fluconazole, a widely-prescribed anti-fungal agent. In addition, process optimization of the final API was also carried out to arrive at a semi-continuous method to this essential medicine.

Introduction

In recent years, flow chemistry has emerged as a vital tool, not only for conducting laboratory scale organic synthesis, but also in the manufacture of active pharmaceutical intermediates (APIs) and molecules of medicinal value[1]. Continuous processes often achieve heightened efficiencies and selectivity as a direct result of the control of critical reaction parameters and enhanced heat and mass transfer properties. Continuous methods can also provide increased access to alternative reaction pathways and/or high energy intermediates that would be inaccessible in batch operations [2]. Furthermore, continuous flow techniques can be exploited to improve the safety profile of chemical processes, making flow chemistry an enabling technology for reactions that would otherwise be too hazardous to be performed on scale[3]. Because the overall quantity of these species is limited in a flow reactor as compared to a bulk solution preparation, the build-up of potentially dangerous or explosive compounds is greatly minimized.

One of the major objectives of our group is to improve the process efficiencies of active pharmaceutical ingredients (APIs) by applying the principals of process intensification which include the integration of continuous flow reactor platforms[4]. In this body of work, we report our efforts to develop a streamlined process for the preparation of fluconazole, a widely prescribed anti-fungal agent. Fluconazole (trade name Diflucan®) was launched in 1988[5] and rapidly became a primary treatment for patients suffering from serious fungal infections. More recently, its use has risen among cancer and HIV-infected patients as well as in support of organ transplants. The drug can be administered either orally or by injection.

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[b] Supporting information for this article is given via a link at the end of the document.

Since its commercialization[5], the process for the preparation of fluconazole has suffered from low overall yields (<35%). Although the synthesis has been re-visited[6] more recently, these efforts have been restricted to conventional batch conditions. Furthermore, these approaches have been confined to the use of expensive organolanthanoid-based reagents.

In this work, we report the development of a continuous process for the formation of a highly reactive turbo-Grignard reagent and its use in the synthesis of fluconazole. Grignard reagents have been widely used on both laboratory and commercial scale and is one of the most common organometallic reagents used for the formation of carbon-carbon bonds. However, its application with highly-enolizable compounds such as 1,3-chloroacetone (**3**) has been previously avoided due to unfavourable side reactions[6a]. In this application, the use of *i*-PrMgCl.LiCl and **4** provided increased yields for both the formation of the corresponding turbo-Grignard reagent and allowed the clean addition to the pivotal intermediate **2**. A significant benefit of this approach for continuous processing was recognized in the ability to carry out both reactions in a single solvent in the absence of solid reactants or by-products

Results and Discussion

In the evaluation of alternative approaches to streamlining the fluconazole synthesis, the focus of our effort turned to intermediate **2** (Figure 1). We considered an approach that would access **2** by employing a Grignard reaction to install the fluorinated aromatic component rather than an alternative organolanthanoid-based reagent (Figure 1). There exists significant precedence for the application of Grignard chemistry in continuous operations[7] and the dihaloketone **3** is a readily available starting material in the chlorinated form.

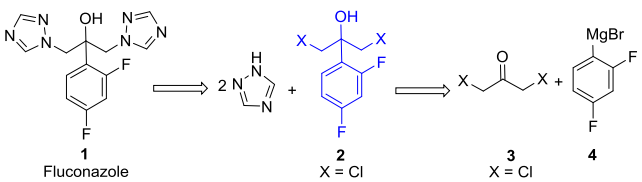
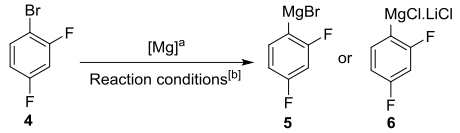


Figure 1. retrosynthesis to fluconazole.

Initially, we explored the formation of the Grignard reagent (table 1) under sub-ambient condition (Table 1, Entry 1) which resulted in a moderate conversion. Further attempts to increase the conversion by increasing the temperature and using diglyme as a solvent did not result in any noticeable improvement. There are several indications that turbo Grignard reagents (*i*-PrMgCl.LiCl) accelerate the halogen magnesium insertion[8]. Hence, we applied this reagent to this system, which provided excellent conversion

to the desired product (**6**) within 15 min (Table 1, entry 4). The observed accelerated reaction rate provided evidence that the reaction could be transferred to a continuous platform.

Table 1: Optimization of activation and reaction conditions in batch

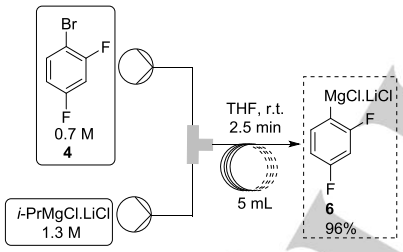


Entry	Temp. (°C)	[Mg]	Solvent (reaction)	Conv[c] (%)
1	0	Mg	THF	56[d]
2	60	Mg	Diglyme	63[d]
3	80	Mg	Diglyme	27[d]
4	0	*i*-PrMgCl.LiCl	THF	97[e]

[a] Mg turnings or *i*-PrMgCl.LiCl, [b] **4** (1 equiv.), 1.3M *i*-PrMgCl.LiCl (1.1 equiv.), 0 °C, 15 min. [c] conversion determined by HPLC; product quenched by MeOH, [d] refers to **5**, [e] refers to **6**.

Given the success with the batch Grignard reactions, we inspired from the previous studies[7] to optimize the chemistry in flow (Table 2). At room temperature, the reaction progressed with moderate conversion at a residence time of 1 min (Table 2, Entry 1). Increasing the residence time to 2.5 min led to an increase in the Grignard formation (Table 2, Entry 2). Finally, the best conversion was realized when using 1.8 equiv. of the turbo Grignard (Table 2, Entry 4) to deliver a conversion of 96%. Increasing the temperature did not provide any measurable advantage. This result demonstrated that under continuous flow conditions, this chemistry could be carried out with significant reduction in the reaction time.

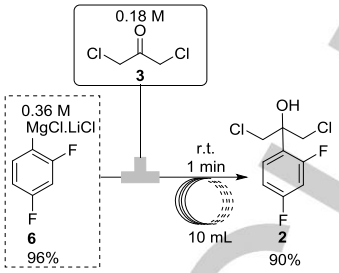
Table 2. Optimization of the flow process for **6** using turbo Grignard reagent**.**



Entry	*i*-PrMgCl.LiCl [equiv.]	Temp (°C)	t_R = min	Conv[a] (%)
1	1.1	r.t.	1	55
2	1.1	r.t.	2.5	80
3	1.4	r.t.	2.5	85
4	1.8	r.t.	2.5	96
5	1.8	50	2.5	96

[a] conversion determined by HPLC; product quenched by MeOH

Table 3. Optimization of preparation of **2** in flow.

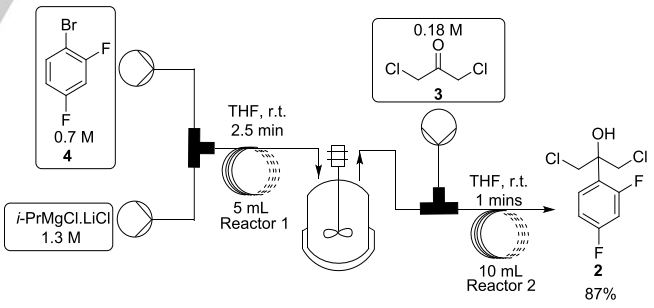


Entry	Equiv. of **6**	Equiv. of **3**	t_R =min	Lewis acid	Conv. to **2** (%)[a]
1	1.1	1	1	-	65[a]
2	2	1	2	-	71[a]
3	2	1	0.7	-	84[b]
4	2	1	1	-	90[b]
5	2	1	1	BF_3OEt_2	73[a]

[a] conversion determined by HPLC. [b] isolated yield.

With the preparation of organomagnesium reagent optimized, the solution of the Grignard reagent collected was further streamed in-line with the 1,3-dichloroacetone **3** to obtain the intermediate **2**. Our initial results were modest (Table 3, Entry 1), however, by attenuating residence time and increasing the relative input of our Grignard, we were able to maximize conversion and obtain an isolated yield of 90% for this transformation (Table 3, Entries 2-4). We also evaluated BF_3-OEt_2 as a Lewis acid catalyst, but with no measurable increase in conversion or rate enhancement. (Table 3, Entry 5).

Table 4. Telescope of **4** to the intermediate **2.**



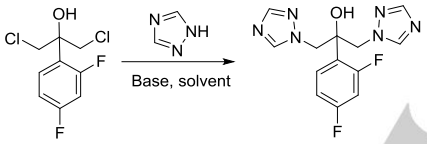
Entry	t_R = min		Yield (%)
	Reactor 1	Reactor 2	
1[a]	1	1	72
2[a]	2.5	1	70
3[a]	2.5	2.5	74
4	2.5	1	87

[a] reactions were streamlined without the continuous stirring tank reactor.

We then attempted to consolidate the process by telescoping **4** to **2** over two reactors (table 4). When the reaction was streamlined, a moderate yield of 74 % yield was realized (entry 3). The yield was further improved to 87% yield when introducing a continuous stirred tank reactor (entry 4). We are currently investigating the benefits of this dual reactor system in similar applications. In order to quantify the efficiency of this system, we calculated the volume-time output (VTO), the throughput of a reaction relative to its reactor space. For the addition of the turbo-Grignard into 1,3-chloroacetone the VTO for the continuous reaction was 8.962 x 10^{-7} m^3 h kg^{-1}. For reference, process chemists aim for a VTO <1 for a chemical step[9]

With the flow optimization of the key intermediate **2** at hand, we sought to investigate the last synthetic step towards fluconazole. We recognize that prior efforts to carry out this step required significantly long reaction times (up to 16h)[6a], which precludes the application of flow chemistry in this instance. For this reason we elected to confine our research effort towards developing optimum batch conditions for the conversion from **2** to **1**. Process optimization began with screening organic or inorganic bases, taking into account the pKa value of the 1,2,4-triazole, in particular, to circumvent the possibility of having isomers derived by reaction of N-4 atoms of the 1,2,4-triazole. Initially, MeOH was chosen as the reaction solvent screen across organic bases under batch conditions. Although this helped with the solubility of the reactants, it gave very poor conversion to fluconazole (table 5, entries 1-2). Subsequently, we attempted inorganic bases (entries 3-7), which converted moderately to the desired product. In the case of DMF as the solvent, increasing temperature did not provide any significant improvement (entry 6). Interestingly, when using MeOH:H_2O mixture, a slight improvement was realized due to increased solubility. These conditions delivered a 74% conversions within 4.5 hr of reaction.

Table 5. Base and solvent screening for optimization of reactions to fluconazole.



2 **1**

Entry	Base	Solvent	Temp. (°C)	Conv (%)[a]
1	NEt_3	MeOH	60	8[b]
2	DIPEA	MeOH	60	17[b]
3	LiOH	MeOH	60	60
4	K_2CO_3	MeOH	60	65
5	K_2CO_3	ACN	60	70
6	K_2CO_3	DMF	120	55
7	Na_2CO_3	ACN	60	0
8	Na_2CO_3	MeOH/H_2O (90%)	60	74

Reaction condition: **5** (1 equiv.), base (5 equiv.), 1,2,4-triazole (3 equiv.)
[a] conversion determined by HPLC,

Conclusion

This work reports the formation and application of a turbo-Grignard reagent to cleanly access a key intermediate towards fluconazole, with high-throughput using continuous flow technology. Not only were the efficiency gains realized by the process quantified with a remarkably low VTO of 8.962 x 10^{-7} m^3 h kg^{-1}, but the safety concerns involved with organometallic reagents were addressed through a continuous flow approach. In doing so, it should be noted that the optimized process conditions that were established clearly demonstrates the enhanced window of operability provided by continuous method development that would have been otherwise unattainable in batch mode. The elaboration of this intermediate was further optimized using low-cost starting materials to deliver fluconazole. Future work will include closing the gap in this final process to find conditions amenable to a fully-continuous process as well as applying these principles and technologies to other active pharmaceutical ingredients.

Acknowledgments

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Keywords: Fluconazole • flow • continuous • turbo Grignard

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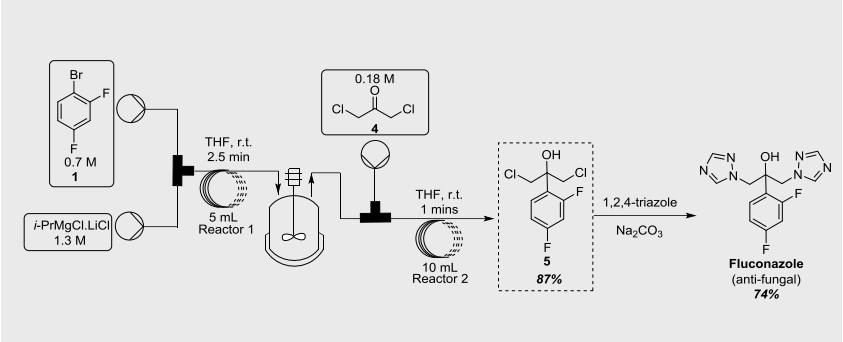

Continuous flow chemistry

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Page No. – Page No.

The Application of a Continuous Grignard Reaction in the Preparation of Fluconazole

This work describes the semi-continuous synthesis of the anti-fungal agent fluconazole via high-yielding and clean formation of an aryl-turbo Grignard followed by its selective addition to a highly-enolizable 1,3-dichloroacetone in a continuous operation to form the precursor to the API.

*Fluconazole