

Continuous Flow Reaction of Grignard Reagents with Carbonyl Compounds

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Introduction

Flow technologies are becoming more and more popular not only for large scale production of high quantities of chemicals but also for the small scale synthesis of compounds utilized in drug discovery. Established advantages of flow chemistry include:¹

- precise control of reaction conditions (temperature and pressure)
- enhanced safety
- easy scale-up

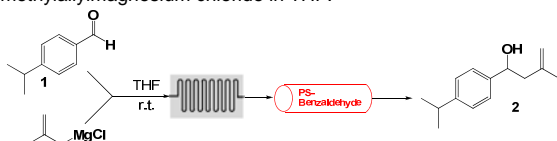
Grignard reagents are broadly applied in organic synthesis and represent an important tool for the formation of carbon-carbon bonds.² Their reactivity often needs to be controlled by operating at low temperature. Flow synthesis is an innovative way to control such reactivity since its homogeneous mixing and heat transfer narrows the temperature distribution and restricts the reaction output to the target product.

Aim of the project was the investigation of the reaction of Grignard reagents with aldehydes and ketones using the **Vapourtec Flow Reactor**.³



Set-up of optimal reaction conditions and scale-up

The reaction set-up was optimized using reference aldehyde (1) and 2-methylallylmagnesium chloride in THF.



Entry	Grignard (eq)	T (°C)	Residence Time (min)	Flow Rate (ml/min)	Conversion
1	2	-78	66	0.15	95%
2	2	-78	33	0.30	96%
3	2	0	33	0.30	94%
4	2	r.t.	33	0.30	97%
5	1.2	r.t.	33	0.30	98%
6	1.2	r.t.	120	batch	29%
7	2	-20	50	batch	95%

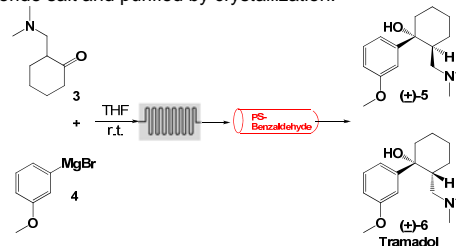
- Temperature of stored solutions can be raised from -78°C to r.t.
- Grignard equivalents can be decreased from 2 to 1.2
- Excess of Grignard reagent was scavenged with PS-benzaldehyde
- Reaction conducted in batch conditions at r.t.: conversion drops to 29%
- Two grams of 2 were produced with an OUTPUT = 0.9 g/h

Optimized protocol:⁴ The solutions of Grignard reagent (1.2 eq) and carbonyl compound, stored under nitrogen at r.t., are pumped through the flow apparatus at 0.3 mL/min (33 min residence time); the reaction stream is directly passed into a column filled with PS-benzaldehyde to scavenge excess of Grignard reagent.

Flow synthesis of Tramadol

The optimized protocol was applied to the synthesis of Tramadol,⁵ a well known centrally active analgesic used for treating moderate to severe pain.

Suitable intermediates 3 and 4 were reacted in the flow system obtaining, after chromatographic purification, the diastereomeric mixture of 5 and 6 in 96% yield, with significant improvement over reported batch conditions.⁶ The same 8/2 diastereomeric ratio reported for the batch process was obtained. Tramadol 6 was converted into its hydrochloride salt and purified by crystallization.



Screening of Grignard reagents

The scope of this protocol was validated using different Grignard reagents on 4-isopropylbenzaldehyde (1) and on acetophenone.

Grignard Reagent	Product (Yield %)*	Product (Yield %)*

*Isolated yield, purity > 95% (UPLC/MS)

Screening of carbonyl compounds

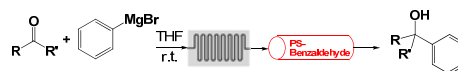
Optimized reaction conditions were successfully applied to the preparation of a small collection of secondary and tertiary alcohols using 4-chlorophenylmagnesium bromide on different aldehydes and ketones.

Carbonyl compound	Product (Yield %)*	Carbonyl compound	Product (Yield %)*

*Isolated yield, purity > 95% (UPLC/MS)

Selectivity over nitriles

The possibility to perform selective addition of Grignard reagents to aldehydes and ketones in the presence of the nitrile function was then investigated. Using slightly modified conditions (1 eq. of Grignard, r.t., 10 min of residence time) selective addition of phenylmagnesium bromide to the carbonyl moiety was observed, with no products of double addition, or deriving from Grignard reaction on the nitrile group.



Carbonyl compound	Product	Yield %
		94
		85
		89

Conclusions

- Fast optimization of the addition of Grignard reagents (aryl, alkyl, allyl) to carbonyl compounds in an efficient and safe manner
- Mild reaction conditions avoiding cryogenic temperatures
- Simple scale-up
- Preparation of a small collection of secondary and tertiary alcohols in high yields using different carbonyl compounds (aryl, alkyl, heteroaryl)
- Improved synthesis of analgesic compound Tramadol
- Selective reaction of aldehydes and ketones over nitriles

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