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Efficient and scalable synthesis of ketones via nucleophilic Grignard addition to nitriles using continuous flow chemistry

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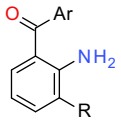
ABSTRACT

In the present Letter we report the development of efficient continuous flow chemistry conditions for the scalable preparation of ketones. This transformation is achieved via nucleophilic addition of Grignard reagents to the corresponding nitriles and imine hydrolysis by means of in-series plug flow reactors.

Ketones in general, and especially arylketones, have been widely used in the agrochemical, fragrance, dye, and pharmaceutical industries.[1] More importantly, they are among the most versatile intermediates available in the synthetic organic toolbox. To address some of the needs of one of our drug discovery programs, we needed ready access to gram-scale intermediates of the general structure **A** to facilitate structure–activity relationship (SAR) studies (Fig. 1).

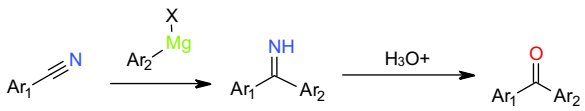
One of the most straightforward methods to prepare these scaffolds consists of the nucleophilic addition of the corresponding Grignard reagent to the nitrile and subsequent imine hydrolysis (Scheme 1).[2] The nitrile substrates are in many cases readily commercially available.

There is a growing interest within the organic synthesis community to find new procedures for translating known transformations from batch to continuous flow.[3] Due to the improved mass and heat transfer that is a key feature of flow technology, the scale-up of the desired reaction is potentially higher yielding, more



A

Figure 1. General structure of SAR key intermediates.



Scheme 1. General preparation of ketones via nucleophilic addition of Grignards to nitriles.

reproducible and safer than a batch process.[4] From our previous experience, the hydrolysis of the intermediate imines is highly exothermic and can be difficult to control during batch scale-up. To overcome this difficulty we envisioned a continuous flow approach in which both Grignard addition and subsequent hydrolysis could be achieved continuously.[5]

As the starting point for our investigation we used 2-aminobenzonitrile (**1**) and phenylmagnesium bromide (**2**) as model reagents for the preparation of imine **3**, to find optimal conditions in flow mode. For comparison purposes, we first ran the reaction in standard batch fashion. The reaction was complete in THF as solvent, at RT in 15 h using 3.5 equiv of PhMgBr. For the hydrolysis step, an inverse addition of the reaction mixture over 6 N HCl at rt was needed to control an exotherm (from rt to 60 °C). Additional stirring at 50 °C for 1 h was required for complete conversion (Scheme 2).

With this batch result in hand, we designed a flow reaction setup for this transformation: a solution of the nitrile in THF was pumped and mixed using a T-union with a solution of Grignard,[6] with reaction taking place in a PTFE-tubular flow reactor (5.5 m, 1 mm ID, total volume 4.32 mL)[7] using standard pressure syringe pumps.[8] After allowing this mixture to react at the selected temperature, the output of the reactor was analyzed by LC–MS (Fig. 2)

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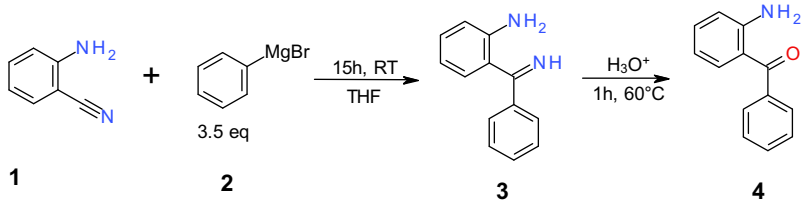

Scheme 2. Model reaction performed in batch mode.

Initially, a small set of flow chemistry conditions was screened, such as reaction temperature, residence time for the Grignard addition, and organomagnesium reagent excess (Table 1). The best conditions obtained were $T = 60$ °C, residence time = 30 min, and 5 equiv of Grignard reagent (entry 5).

The next step was to implement the hydrolysis step in a further continuous process. Thus, a stream of 6 N HCl was pumped and mixed with the output of the first reactor, entering a second flow reactor in which imine hydrolysis took place to afford the final desired ketone. We designed the second reactor with the same parameters as the first one for convenience (5.5 m, 1 mm ID, total volume 4.32 mL) (Fig. 3).

To assess the scope of the addition and hydrolysis process, a set of aromatic and aliphatic nitriles were reacted with selected Grignard reagents. The results obtained are summarized in tables and discussed under the subheadings below. In some cases, fine tuning of the previously optimized conditions was needed. For the sake of clarity, the methodology developed was categorized in four different condition sets: A, B, C, and D, depending on the values used (residence time and concentration of starting nitrile). These methods were named alphabetically based on harshness (D > C > B > A), (Table 2).

Addition of phenylmagnesium bromides to aromatic nitriles

With the optimized conditions found for the reaction of our model aminobenzonitrile (general method A), we first studied the scope and limitations of this chemical transformation with regard to substitution of the aromatic nitrile. Thus, a new set of substituted aromatic nitriles with differing electronic properties

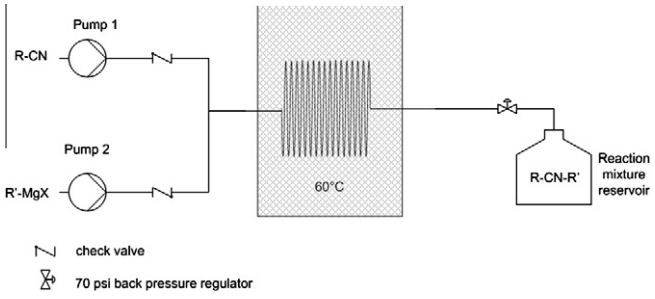

Figure 2. Initial continuous flow Grignard addition.

Table 1
Initial optimization efforts for the Grignard addition to aminobenzonitrile

Entry	T	Residence time (min)	Grignard (equiv)	Conversion (%)
1	rt	5	3.5	20
2	rt	35	3.5	55
3	rt	60	3.5	65
4	60 °C	10	5	60
5	60 °C	30	5	95

Table 2
General methods for continuous flow process

Method	A	B	C	D
Temp (°C)	60	60	60	60
Residence time (min)	5	30	60	240
Nitrile concn (M)	0.1	0.4	0.4	1.2

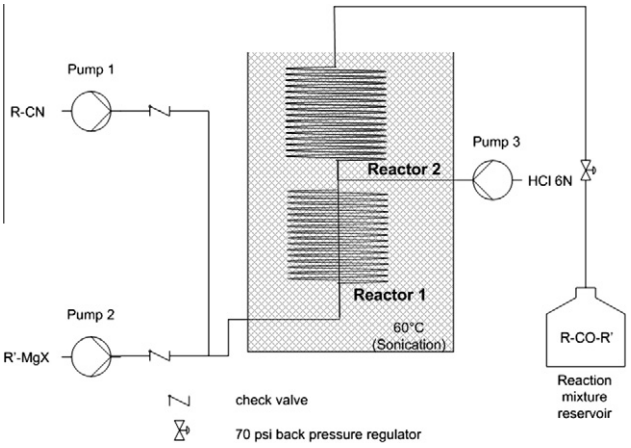

Figure 3. Final flow process set-up.

was chosen to react with the same Grignard reagent (PhMgBr). As it can be seen in Table 3, the reaction is of quite broad scope, using the general method B (Table 2) in the majority of cases. Purities obtained ranged from good to excellent, and the reaction tolerated aminobenzonitriles, as previously described (entry 1), electron-withdrawing substituents in *o*-, *m*-, and *p*-positions (entries 3–5), electron-donating substituents in *o*-, *m*-, and *p*-positions, (entries 6–8) as well as heteroaromatic substitution (entries 9 and 10). In the case of the reaction of 4-methoxybenzonitrile with PhMgBr (entry 8) some precipitation was observed that clogged the tubular reactor during the reaction. We circumvented this problem by placing the reactors in a thermostatic ultrasonic bath that allowed the reaction mixture to flow without any issue.[9] Interestingly, if, during the experiment, the sonication was stopped, the precipitate was formed again, once more clogging the reactor line.[10]

In order to study more extensively the scope of the flow process and once we had investigated the pair Ar-CN and PhMgBr, we decided to test the reaction partners Ar-CN with aliphatic Grignard reagent, aliphatic-CN with PhMgBr, and aliphatic-CN with aliphatic organomagnesium reagents.

Addition of alkyl Grignards to aromatic nitriles

The conversions obtained using these reagent types ranged from excellent to modest. Using 3-methoxybenzonitrile as a model,