Green Chemistry

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View Article Online
DOI: 10.1039/C6GC02619B

Journal Name

COMMUNICATION

Reformatsky and Blaise Reactions in Flow as a Tool for Drug Discovery. One Pot Diversity Oriented Synthesis of Valuable Intermediates and Heterocycles.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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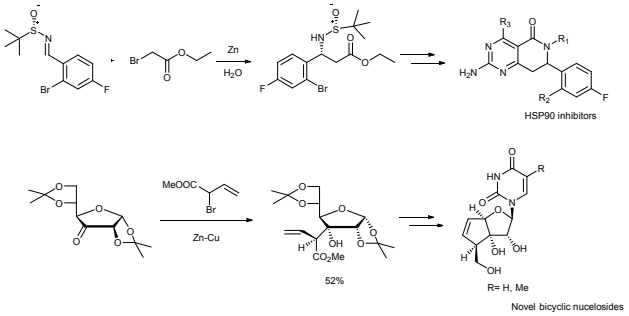
The application of Reformatsky and Blaise reactions for the preparation of a diverse set of valuable intermediates and heterocycles in a one-pot protocol is described. To achieve this goal, a greener activation protocol for zinc in flow conditions has been developed to introduce this metal efficiently into α-bromoacetates. The organozinc compounds were added to a diverse set of ketones and nitriles to obtain a wide range of functional groups and heterocyclic systems.

Diversity Oriented Synthesis (DOS) has recently been identified as a tool for the discovery of novel, biologically interesting small molecules and it increases the likelihood of finding modulators for a broad range of biological targets.[1] A fundamental requirement for DOS is the availability of synthetically versatile starting materials that are capable of undergoing a variety of chemical transformations to convert them into several products with different molecular skeletons through the variation of reagents alone.[2] Thus, diverse syntheses of heterocyclic scaffolds in one-pot protocols prior to further modifications are highly desirable in Medicinal Chemistry.[3]

Suitable procedures for C–C bond formation are key elements in DOS. The Reformatsky and Blaise reactions are very useful tools for this purpose as new C–C bonds are formed under mild conditions and the reactions have good functional group tolerance. For this reason, these reactions have been used in the synthesis of biologically active products (Scheme 1).[4]

However, two main drawbacks limit the application of these reactions in a more general way. The first is the formation of by-products, such as self-condensation of the α-bromoester and retro-aldol condensation of the intermediate β-alkoxyzinc ester in the case of the Reformatsky reaction.[5] The second drawback is safety concerns with these transformations. In both cases, initiation of the reaction requires activation of the zinc metal and this process is usually associated with exothermal runaway issues that can continue during the addition of the corresponding reagents.



Scheme 1. Reformatsky reaction for biologically active products.

In recent years, flow chemistry has become established as an enabling technology that, amongst other advantages, allows very efficient heat transfer, good control of reaction temperature and enhanced mass transfer.[6] These characteristics overcome the problems associated with highly exothermic reactions and dangerous or air- and moisture-sensitive compounds, which are commonly present in Reformatsky and Blaise reactions. Moreover, in continuous flow reactors the levels of hazardous waste are reduced. The ability to optimize a reaction using small quantities of reactants minimises the waste generated during the screening and decrease the volume of waste generated at the clean-up steps. This effect is enhanced by the use of catalysis.[7] These characteristics make this technology a green and sustainable alternative in chemical research and production.

Despite the interest in these transformations only two approaches in flow protocols have been described to date in the literature. The first study was reported in 1974.[8] The authors presented an imaginative solution for the Reformatsky reaction by continuously dropping the reagents through an addition funnel onto the top of a tube containing the zinc metal. The products were collected at the bottom of the tube

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C6GC02619B

in a flask containing refluxing benzene. In this way, benzene was used as both the solvent and the heat source for the whole set up. The authors reported good to excellent yields of the corresponding Reformatsky products, but only eight examples were reported. The lack of control of some reaction parameters, such as residence time, probably limits the applicability of this imaginative approach.

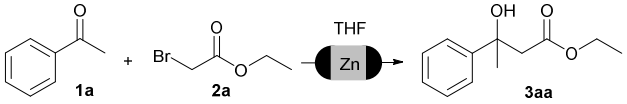
More recently, Ley and co-workers disclosed the use of the Reformatsky reaction between an allylbromide and an Ellman sulfoximine for the preparation of sacubitril.[9]

After our seminal work on the preparation of organozinc reagents in tetrahydrofurane (THF) with a packed zinc column under flow conditions,[10] we decided to explore the insertion of this metal into α-bromoesters. For this purpose we selected the Refomatsky reaction as the starting point and optimized the zinc activation and reaction conditions for ketones and α-bromoesters.

The key factor for the insertion of zinc into a halogenated derivative is the activation protocol. On using the previously reported activation[10] ethyl zincbromoacetate concentrations up to 0.15 M were obtained (see supporting information). This procedure was improved by using a single solution containing both activating reagents (chlorotrimethylsilane and 1-bromo-2-chloroethane) at 40 °C. The reagent solution was introduced directly after activation to obtain the desired organozinc compound at concentrations up to 0.45 M. Not only an higher concentration was obtained, but 1,2-dibromoethane was avoided in the activating protocol and also the amounts of activator and solvent used were reduced by 75%.

Once the activation had been optimized, a solution of acetophenone **1a** and ethyl bromoacetate **2a** was passed through the zinc column at 40 °C with a calculated residence time of 3 minutes (Table 1, entry 1). Reaction did not occur under these conditions and it was decided to increase the temperature and time simultaneously. It was observed that at 60 °C, with a residence time 6 minutes, the product was obtained in an acceptable conversion (entry 2). Further optimization of temperature, time and equivalents of bromoester allowed us to obtain the product in 92% isolated yield (entry 4).

Table 1. Optimization of the Reformatsky reaction.



Entry	T (°C)	Time (min)	**2a** (Equiv.)	Conv.[a] (%)
1	40	3	1.5	No reaction
2	60	6	1.5	56
3	60	10	1.5	82 (78)[b]
4	60	10	2	100 (92)[b]

[a] Conversion by LCMS. [b] Isolated yield in brackets.

These optimized conditions were used to explore the reaction scope using different acetophenones (Figure 1). The Reformatsky reaction has been explored extensively in batch and effort was therefore focused on those substrates that could be of interest from a medicinal chemistry point of view.[11] In this way, ester **3ba**, trifluoromethyl **3ca**, halide **3da**, and methoxy **3ea** groups were compatible with the flow protocol and products could be obtained in good yields. It is worth highlighting that the reaction also tolerated the presence of other reactive groups such as alkyl chlorides (**3ha**), which would allow further modification at that position. The reaction was not limited to aromatic ketones as aliphatic ketones were also well tolerated (**3fa** and **3ga**). The use of heterocycles, such as pyridines, in this reaction has rarely been described in the literature.[11b,12] However, these compounds are quite important for medicinal chemists. On using the current methodology acetylpyridines provided the corresponding β-hydroxyesters (**3ia–3la**) in good to excellent yields at 80 °C with LiCl as an additive in order to complete the reaction and avoid blockage of the system.

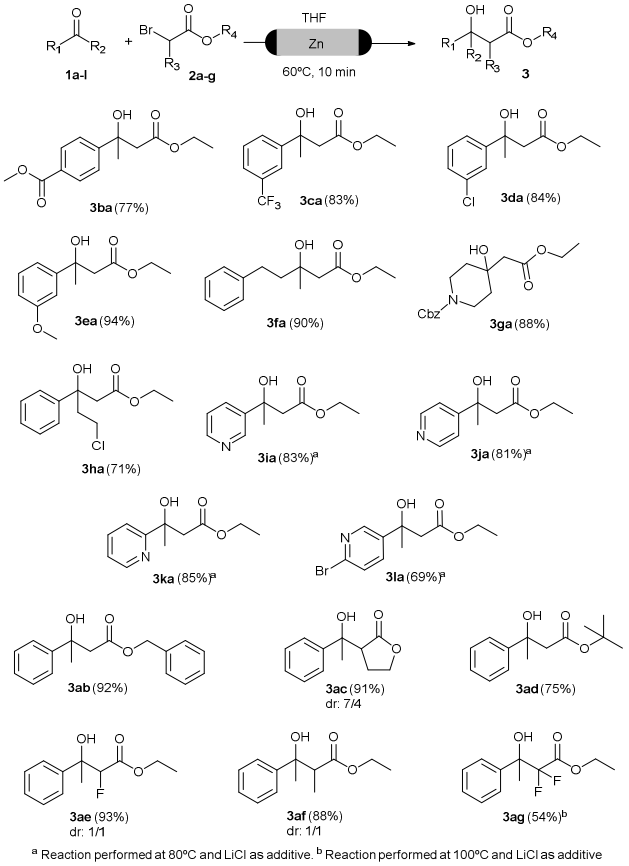


Figure 1. Scope of the Reformatsky reaction.

The scope of different α-bromoesters was also studied, including molecules containing substituents in the α-position, such as fluorine, methyl or cyclic ester (**3ab**-**3ag**). Good to excellent yields were obtained in all cases. When an α,α-difluoro-substituted ester was used, compound **3ag** was obtained in an acceptable yield at 100 °C using LiCl as an

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additive. This result is remarkable as it is consistent with others reported the literature, but in our flow protocol there is no need to use other metal catalysts or additives,[13] thus making this approach more sustainable.

It is worth noting that the reaction involving 4-chloro-1-phenylbutan-1-one gave novel 2,2-disubstituted etrahydrofurans **4ma–4me** under very mild conditions (Figure 2). The scaffolds obtained in this ring-closing reaction were quite novel as only a few examples have been reported in the literature to date. The ester motif present in the molecules can be considered as a vector for further derivatization.

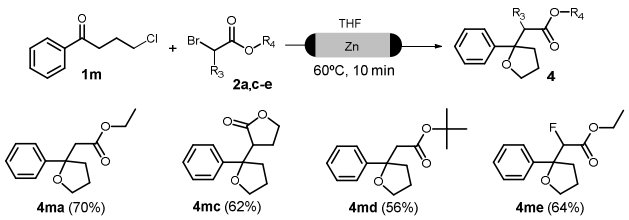


Figure 2. Synthesis of tetrahydrofurans in one step.

Scale-up of the Reformatsky reaction was also studied. For this purpose, the reaction of ketone **1a** and bromoacetate **2a** was allowed to run for several hours through a column filled with 12 g of metal. In this example, the throughput of **3aa** obtained was around 3.5 g/h and the same isolated yield was obtained (92%). Only when 75% of the solid zinc was consumed did the yield drop to 83%. Nevertheless, at this point of the reaction, 22 g of the desired product had been isolated. The remaining metal in the column was not disposed, the column was then refilled, reactivated and used in subsequent experiments. To prove the sustainability of this protocol the space-time yield[6d,14] was calculated and compared to a recent procedure described in batch for the same compound **3aa** in the same solvent[15] (Table 2). Calculations provided a 32 times better outcome for the flow protocol, thus demonstrating the improved sustainability and scalability of the process in flow.

Table 2. Preparation compound **3aa** in batch and flow.

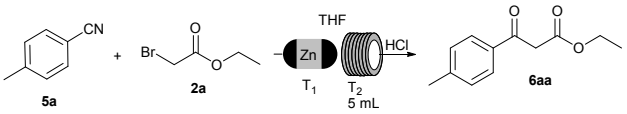
	Flow	Batch[a]
Yield	92%	94%
Reaction Time	10 min	3 h
Product Throughput	10.5 g/3 h	324 mg/3 h
[**1a**]	1.55 M	0.33 M
Space-time Yield[b]	700 mg/h·mL	21.6 mg/h·mL

[a] Batch results from reference 15. [b] Calculated according to references 6d and 14.

Another approach with great potential in medicinal chemistry is the use of nitriles as electrophiles to prepare β-ketoesters, namely the Blaise reaction.[16] This class of compounds has a broad application in the synthesis of biologically active products and, amongst other alternatives, the Blaise reaction appears to be one of the most appealing from a sustainability point of view.[17] For instance, synthesis of β-ketoesters in flow from diazoacetates and aldehydes was recently reported.[18] The use of diazo compounds is potentially hazardous, although the combination with flow chemistry clearly decreases the associated risks.

The initial attempt was based on the previous Reformatsky conditions using nitrile **5a** and ethyl bromoacetate **2a**, but only 47% conversion to compound **6aa** was observed (Table 3, entry 1). An increase in the residence time in the column did not improve the outcome of the reaction (entry 2). For this reason it was decided to add a coil reactor to complete the addition of the organozinc reagent to the nitrile (entry 3). This modification of the setup clearly improved the conversion to product. Refinement of the residence time, temperature and equivalents of bromoacetate **2a** provided the best conditions (entry 6).

Table 3. Optimization of the Blaise reaction in flow.



Entry	T_1 (°C)	T_2 (°C)	Time (min)	Equiv. **2a**	Conv. (%)
1	60	---	3	1.5	47
2	60	---	6	1.5	45
3	40	120	16	1.5	80
4	40	120	16	2.5	82
5	60	120	16	1.5	75
6	60	120	16	2.5	86
7	60	120	20	2.5	81
8	60	120	25	2.5	76
9	80	120	16	2.5	54

These reaction conditions were used to explore the scope of the reaction. Different substituents on the aromatic ring, such as methoxy (**6ba** and **6fa**), trifluoromethyl (**6ca**), and bromine (**6da**), were well tolerated. Different alkyl groups were evaluated to extend the scope of the reaction further. For instance, 4-cyanopiperidine and 5,5,5-trifluorovaleronitrile were employed and compounds **6ga** and **6ja** were obtained in 80% and 56% isolated yields, respectively. The reaction is also compatible with different heterocycles. 2-Thiophenecarbonitrile reacted nicely to produce compound **6ea** in 93% yield. However, in the case of pyridinecarbonitriles **5h–i** the reaction proceeded to product but these precipitated in the coil and clogged the system. The same outcome was observed when other solvents, solvent mixtures and additives, such as dimethylsulphoxide (DMSO), toluene, dimethoxyethane (DME), THF/DMA 1/1, and a 0.5 M solution of LiCl, were screened. Other known alternatives to dipolar aprotic solvents, such as acetonitrile and alkylcarbonate solvents, were not attempted in the Blaise reaction because they can interfere in the reaction. In flow reactions where

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products are insoluble in THF, the best results were obtained with DMA,[‡] which provided the corresponding products **6ha** and **6ia** in high yields. However, as this solvent has been identified as a Substance of Very High Concern, it is clear that there is a strong need for better alternatives to solvents like DMA, DMF. The compatibility of the reaction with different bromoacetates was also explored (compounds **6gb**, **6jb** and **6jf**).

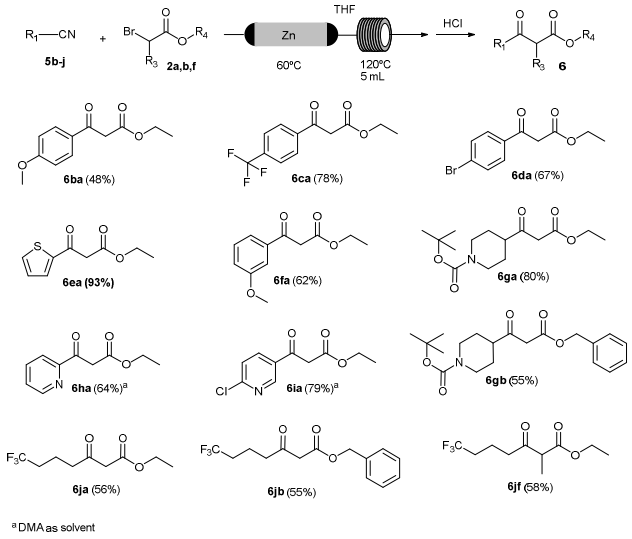
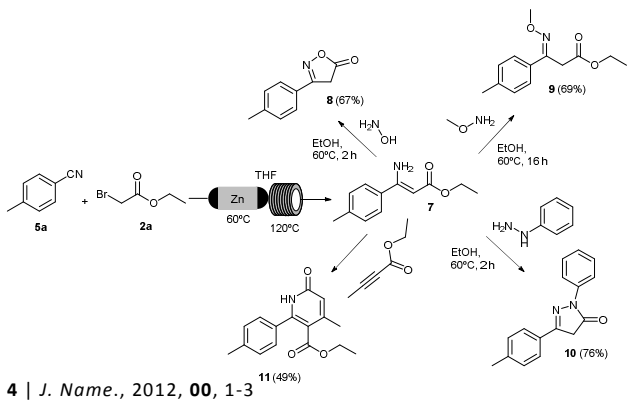


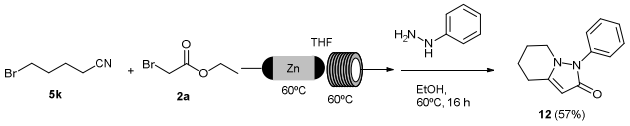
Figure 3. Scope of the Blaise reaction.

The intermediates obtained in the Blaise reaction can be considered as examples of versatile tools for DOS purposes in tandem transformations.[3] It has been demonstrated that the enamine form can be trapped with different electrophiles.[19] However, the nucleophilic trapping of the imine form has not been described to date. This kind of trapping would yield different heterocycles and intermediates to the ones obtained by electrophilic reactions. To demonstrate this point, nitrile **5a** and bromoacetate **2a** were allowed to react and the output from the reactor was collected over different reagents to explore the approach in a one-pot procedure (Scheme 2). When the reactor output was collected over hydroxylamine, the isoxazolone **8** was obtained. Collection over *O*-methylhydroxylamine provided oxime **9**. Treatment of the imine-enamine with phenylhydrazine yielded the corresponding *N*-phenylpyrazolone **10**. Electrophilic trapping using propiolates was also possible and this provided the corresponding pyridone **11**.



Scheme 2. Blaise reaction as a tool for DOS.

One of the key advantages of flow chemistry is the possibility of controlling unstable intermediates as they can be reacted as they are formed. In order to explore this opportunity, the Blaise reaction on alkyl bromonitrile **5k** was performed. The enamine intermediate formed in this reaction is reported to follow *in situ* intramolecular *C*- or *N*-alkylative reactivity profiles.[19a,b] On using the flow protocol described here, the enamine intermediate could be trapped using phenylhydrazine as a nucleophile to obtain the corresponding bicyclic pyrazinone **12** in good yield (Scheme 3). Due to the reactivity of the resulting enamine, the temperature of the coil was reduced to 60 °C to avoid the formation of intramolecular alkylation products. In this way, the reactivity profile of these intermediates can be reversed using flow to obtain different compounds to those described previously.



Scheme 3. Controlling reactivity of Blaise reaction using flow.

Conclusions

In summary, a broad-scope flow version of the Reformatsky and Blaise reactions has been developed. The procedure is based on an improved and safe on-column activation of zinc, which produces very pure organozinc derivatives, prior to the one-pot reaction with the corresponding electrophile. The protocols have a broad scope and aliphatic, aromatic and heteroaromatic ketones and nitriles can be used. It is worth highlighting the heteroaromatic examples as they are the most challenging and valuable compounds, which are rarely described in the literature. Different bromoacetates are suitable for the protocol – including α-substituted compounds. When γ-chloroketones were used the corresponding 2,2-disubstituted tetrahydrofurans were obtained directly from the column as potential novel valuable cores for drug discovery. The imine-enamine intermediate obtained in the Blaise reaction was trapped with different nucleophiles and electrophiles to provide several valuable heterocycles and intermediates for medicinal chemistry in a one-pot protocol that combines the capabilities of flow chemistry and parallel batch approach. Up to 8 different compounds have been obtained by flowing compounds through a zinc column followed by appropriate trapping. The scope included 5-membered and 6-membered heterocycles, saturated or unsaturated, bicyclic cores and linear compounds, thus demonstrating the value of this procedure for DOS. The safe use of organozinc compounds, a reduced need for solvents, efficient heat and mass transfer, and simple scale-up all make this procedure a greener alternative to the traditional synthetic protocols.

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DOI: 10.1039/C6GC02619B

Acknowledgements

The authors thank Prof. D. Tyler McQuade, Dr. Nerea Alonso, Dr. Russell Smith and Dr. Miguel Angel Pena Piñon for their assistance in the preparation of this manuscript and Dr. José Manuel Alonso and Mr. José Daniel Martínez for the NMR support.

Notes and references

‡ DMA Warning! May cause respiratory tract irritation. Hygroscopic (absorbs moisture from the air). Causes eye and skin irritation. Combustible liquid and vapour. Harmful if absorbed through skin or if inhaled. May cause harm to the unborn child. Target Organs: Blood, kidneys, central nervous system, liver. Wear appropriate protective eyeglasses, gloves and clothing.

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