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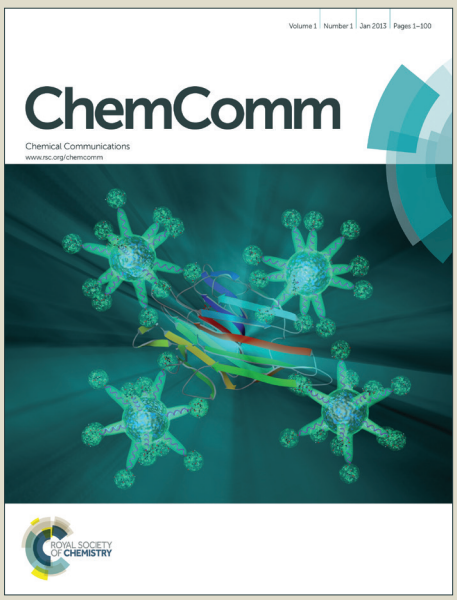

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Practical preparation of challenging amides from non-nucleophilic amines and esters under flow conditions

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A fast and efficient protocol for the formation of amides from low nucleophilic amines and esters in flow is described. Products were obtained in good to excellent yields and with the advantage of simultaneous mixing of all reagents at once, avoiding steps for intermediate formation. The protocol is also suitable to be combined with ester synthesis, resulting in the preparation of amides in-line from haloarenes.

The amide group is one of the most ubiquitous and important functionalities found in natural and synthetic organic compounds. It is omnipresent in high impact drug molecules (antibiotics, antiarrhythmic, sedatives, etc.), in proteins, and related peptide drug products.[1] Consequently, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable identified amide formation as a high priority research field, illustrating the ongoing strong need for simpler, more convenient, inexpensive, and atom economical agents.[2]

The direct aminolysis of esters with amines is attractive for its simplicity, economy, and availability of starting materials. Esters are stable, abundant in nature, usually easily accessible from a synthetic point of view, and hence equally available from commercial suppliers. Different conditions have been reported for the direct amidation of esters.[3] Nevertheless, there is a gap when poor nucleophilic amines are used.

To the best of our knowledge there are only 3 methods described for the direct synthesis of amides from esters and weak nucleophilic amines. First, the enhancement of their low reactivity through pre-formation of metallic amides by strong organometallic bases, such as alkyllithium and Grignard reagents.[4] This procedure is not suitable for molecules bearing sensitive functional groups that may also react in addition to the amine. Second, the preparation of intermediate aluminium amides using organoaluminium reagents, such as trimethylaluminium.[5] However, these reagent are highly pyrophoric, hazardous and potentially thermally unstable. Third, the use of strong inorganic bases, such as potassium tert-butoxide.[6] The procedure is more general, though it makes use of a high concentration of a strong base and, more importantly, it is quite sensitive to the amount of water and oxygen present in the reaction, which may compromise its use at larger scales.

Recently, we have reported a green procedure for amide formation in flow[7] using Grignard reagents, *i.e.* the Bodroux reaction.[8] This method has demonstrated its general applicability and is suitable for primary and secondary, aliphatic and aromatic amines. However, the use of tetrahydrofuran (THF) as the solvent results in a low solubility of most non-nucleophilic heterocyclic amines or precipitation of their corresponding magnesium amides. For instance, even though diluted solutions of 2-aminopyridine could be used, 4-aminopyridine was unsuitable due to its poor solubility in THF.

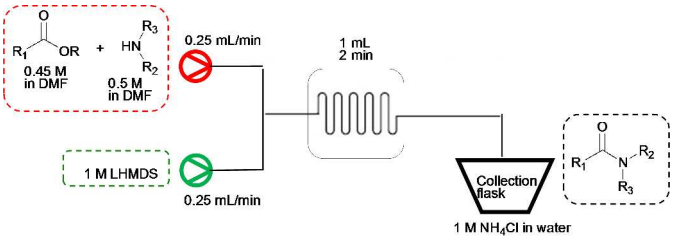


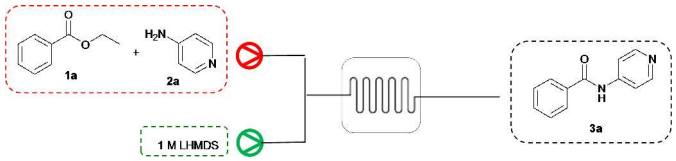
Figure 1 Experimental set up of the flow system.

In our exploration of novel procedures for amide formation we decided to explore alternative bases for the Bodroux reaction. Our aim is to increase the scope of this reaction especially focused on non-nucleophilic amines as these examples are scarcely reported in literature.[4-6,8] Herein we present a novel procedure for the preparation of synthetically challenging amides under continuous flow conditions mediated by lithium bis(trimethylsilyl)amide (LHMDS). This base was selected due to its high basicity and low

nucleophilicity which would improve functional group tolerance compared to previously described organometallic reagents. Furthermore the use of LHMDS allows for mixing all reagents at the same time without preformation of the metallic amide intermediate. Moreover, flow chemistry would not necessarily require using low temperatures as is the case for batch protocols.[9]

In an initial approach a solution containing the amine and the ester, and a solution of the base were mixed in an LTF (LTF-MX)[10] chip using a dual syringe pump. The outcome was collected in an appropriate quenching solution (Scheme 1). 4-aminopyridine was selected as a model of amine reagent with low nucleophilic activity as it had presented difficulties in our previous protocol.[8] In order to get the amine in solution we decided to use N,N-dimethylformamide (DMF) as solvent.

Table 1 Optimization of Model Reaction in Flow.



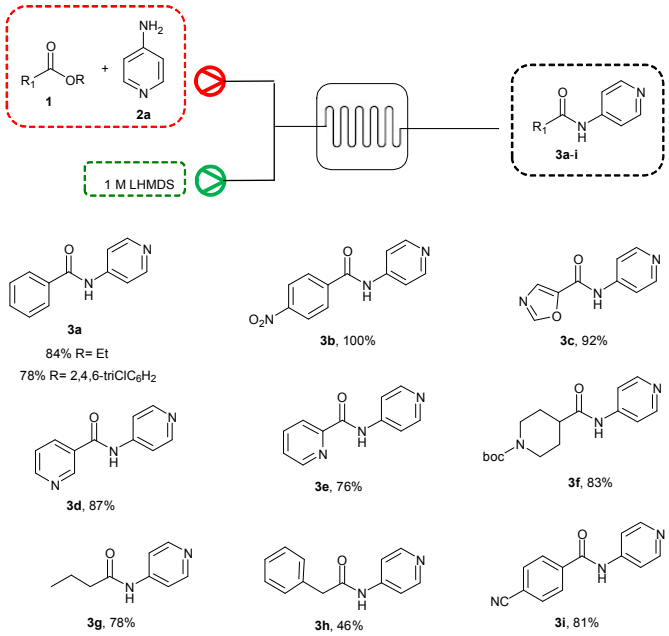
Entry	Eq. **2a**	Eq. LHMDS	*T* /°C	t_R/min	Conv.[a]
1	1.1	1.1	rt	2	36
2	1.1	2.2	rt	2	98 (84)[b]
3	1.1	2.2	rt	1	95
4	1.1	2.2	rt	0.5	92
5	1.1	2.2	40	2	96
6	1.1	2.2	40	1	96
7	1.1	2.2	40	0.25	93
8	1.2	2.4	rt	2	99
9	1.2	2.4	rt	1	96

[a] Conversions determined as percentage by LC-MS. [b]Isolated yield.

The first attempt was performed using 1.1 equivalents of both amine and base. The reagents were allowed to react for 2 minutes at room temperature before the reaction was quenched. The moderate conversion observed was promising because only product and unreacted starting materials were found in the crude mixture (Table 1, Entry 1). The reaction approached completion when simply doubling the amount of base (Entry 2): the reaction required a second equivalent of base as the amide formed is more acidic than the amine, therefore preventing the amine to further react with the ester. Further attempts to reduce reaction time by increasing the temperature or increasing the stoichiometric ratio of amine did not provide remarkable improvement on the reaction outcome (Entries 3-9).

The substrate scope of both the ester and amine reagent was then studied using the optimized conditions described above (Table 1, entry 2). First, a series of esters was reacted with 4-aminopyridine (Chart 1). After successful conversion of ethyl ester **1a** to its corresponding amide **3a** in 84% isolated yield, the use of its corresponding trichlorophenyl ester gave the same product **3a** in a comparable yield. This result is interesting because the scope of reactivity for previous protocols was limited to alkyl esters.[4-6,8] Nitro compound **3b** was obtained in quantitative yield and easily purified as it precipitated spontaneously upon collection of the reaction mixture in a 1M solution of ammonium chloride. Electron rich and electron deficient heterocyclic esters were also tolerated in the reaction (**3c**, **3d** and **3e**).

Chart 1 Exploration of ester scope.

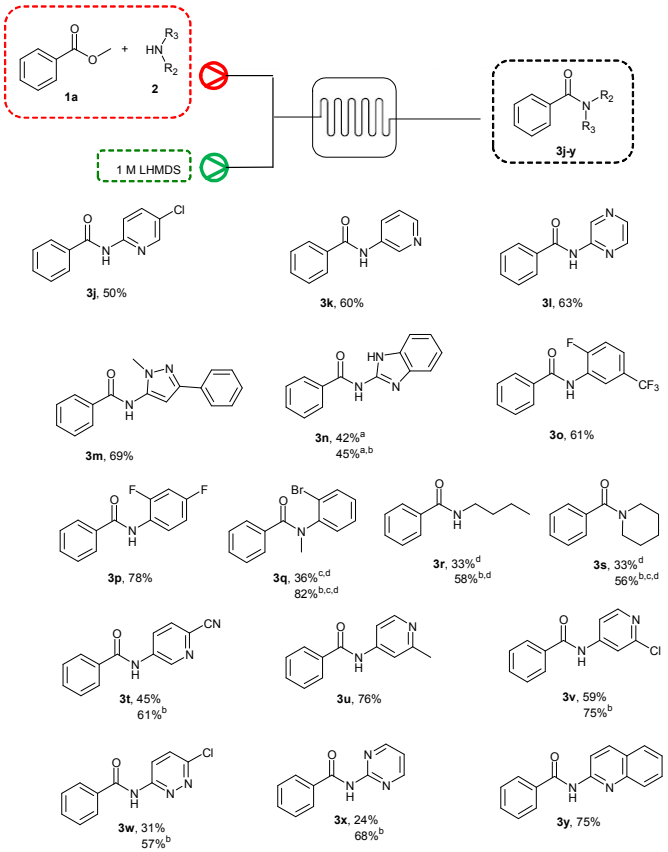


Aliphatic esters also yielded the corresponding products **3f** and **3g**. Notably, the Boc protecting group is permitted under these reaction conditions. However, ethyl phenylacetate proved to be troublesome due to the competing deprotonation at the benzylic position which compromised the conversion of the ester moiety into its corresponding amide **3h**. The low nucleophilicity of the base allows expanding the scope of this reaction to functional groups that would react with organolithium and Grignard reagents.[4,8] This is demonstrated by the preparation of **3i** where the cyano group remained unaltered, corroborating the selectivity of the protocol. Interestingly, in most aforementioned experiments the reaction products were obtained pure after a simple extraction and trituration workup procedure, avoiding the need for chromatography.

Second, the scope of the amines suitable for the reaction was then explored (Chart 2). The coupling of a selection of classical unreactive heterocyclic amines provided the desired products **3j-n** in acceptable to good yields. Both electron deficient and electron rich substrates were found to react surprisingly well. 2-aminobenzimidazole required the use of 3.3 equivalents of LHMDS to be fully deprotonated and provides selectively the amide **3n**. In this example the reaction outcome was slightly improved at 50º C. Low nucleophilic anilines are also suitable for this protocol and compounds **3o** and **3p** were obtained in 61% and 78% yields. However, increasing the sterical hindrance required higher temperatures and amide **3q** was obtained in high yield only at 50° C. Encouraged by the interesting results using (hetero)aromatic amines, the applicability of the reaction protocol on aliphatic amines was then investigated. They proved however to be less reactive, and compounds **3r** and **3s** were only obtained in acceptable yields when the reaction was carried out at 50º C. This notable observation can be understood from the fact that aliphatic amines are generally less acidic than their aromatic counterparts, and hence their deprotonation was probably not fully achieved with LHMDS. In these examples full deprotonation had been achieved using the

complementary Grignard reagents as base.[8] Furthermore, this new procedure is more useful when sensitive functionalities are required. In this way compound **3t** was prepared is good yields despite the presence of the cyano group, normally a sensitive group when akyllithium and Grignard reagents are used. Other substituted 4 amino pyridines **3u-v** and quinoline **3y** also proceed very nicely in good yields. To complete the scope for 6 member ring heterocycles pyridazine **3w** and pyrimidine **3x** were explored, providing their corresponding amides in improved yields when the reactor was heated at 50ºC.

Chart 2 Exploration of amine scope.



[a] 3.3 equiv of LiHMDS. [b] Reaction carried out at 50° C. [c] 1.1 equiv of LHMDS. [d] Solvent THF.

Considering the promising result obtained for the conversion of a 2,4,6-trichlorophenyl ester, a typical product of the Manabe reaction,[11] we decided to combine this amidation step with our previous flow carbonylation in a cascade event.[12] This combination would allow to directly prepare amides from low nucleophilic amines and the corresponding aryl halides using an in-line procedure without the need of an external CO source, *i.e.* gas cylinder. This is very convenient as the use of toxic carbon monoxide is becoming more regulated avoiding the need to use it as such, especially in high-pressure reactors. Carbonylation of bromobenzene **4** was performed using compound **8** as CO source following our previously described protocol as 175ºC for 5 minutes in a 2 mL coil reactor. The resulting tricholorophenylester was not isolated and further mixed with amine **2a** and LHMDS solutions by means of two consecutive syringe pumps and T-mixers, allowing them to react for 2 minutes in a 2 mL coil reactor (Figure 2). The outcome of the amidation step was quenched to get **3a** in 65% yield after workup, proving the value of the protocol in the preparation of challenging heterocyclic amides from aryl halides in one cascade event.

Conclusions

A novel protocol for the formation of amides from low nucleophilic heterocyclic amines and esters is described. The combination of LHMDS, a strong non-nucleophilic base, with continuous flow techniques allows for the preparation of these amides under very mild conditions and short reaction times, just combining all reagents at the mixing point. The procedure is compatible with alkyl and aryl esters and tolerant to different functional groups present in both building blocks, especially those sensitive to the use of alkyllithium and Grignard reagents. Furthermore, it is perfectly compatible with our previous carbonylation protocol in flow to obtain the corresponding amides in one cascade event from haloarenes without the use of external carbon monoxide. Further application of this protocol to prepare compounds of pharmacological interest will be presented in future articles.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 For reviews, see: (a) Comprehensive Organic Synthesis, ed. B. M. Trost and I. Fleming, Pergamon Press, New York, 1992, vol. 6; (b) R. C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, New York, 2nd edn, 1999; (c) M. B. Smith, *Compendium of Organic Synthetic Methods*, Wiley, New York, 2001, vol. 9, pp. 100; (d) C. A. G. N. Montalbetti, V. Falque and M. Park, *Tetrahedron*, 2005, **61**, 10827.

2 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.

3 (a) M. B. Smith and J. March, *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001, 510; (b) R. C. Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989, pp. 989–990.

4 (a) B. M. Bhawal, S. P. Khanapure and E. R. Biehl, *Synth. Commun.*, 1990, **20**, 3235; (b) C. A. Faler and M. M. Joullie, *Tetrahedron Lett.*, 2006, **47**, 7229.

5 (a) A. Basha, M. Lipton and S. M. Weinreb, *Tetrahedron Lett.*, 1977, **18**, 4171; (b) M. F. Lipton, A. Basha and S. M. Weinreb, *Org. Synth.*, 1979, **59**, 49; (c) A. Novak, L. D. Humphreys, M. D. Walker and S. Woodward, *Tetrahedron Lett.*, 2006, **47**, 5767; (d) T. Gustafsson, F. Pontén and P. H. Seeberger, *Chem. Commun.*, 2008, 1100.

6 (a) B. R. Kim, H. G. Lee, S. B. Kang, G. H. Sung, J. J. Kim, J. K. Park, S. G. Lee and Y. J. Yoon, *Synthesis*, 2012, 42; (b) R. S. Varma and K. P. Naicker, *Tetrahedron Lett.*, 1999, **40**, 6177.

7 (a) L. Vaccaro, D. Lanari, A. Marrocchi and G. Strappaveccia, *Green Chem.* 2014, **16**, 3680. (b) J-I. Yoshida, Y. Takahashi, A. Nagaki, *Chem Commun* 2013, **49**, 9896. (c) V. Hessel, D. Kralisch, N. Kockmann, T. Noël and Q. Wang, *ChemSusChem* 2013, **6**, 746. (d) T. Noël and S. L. Buchwald, *Chem Soc Rev.* 2011, **40**, 5010. (e) D. Webb and T. F. Jamison, *Chem Sci*. 2010, **1**, 675.

8 J. de M. Muñoz, J. Alcázar, A. de la Hoz, A. Díaz-Ortiz and S.-A. Alonso de Diego, *Green Chem.*, 2012, **14**, 1335.

9 As a recent example, see: T. P. Petersen, M. R. Becker and P. Knochel, *Angew, Chem. int. Ed.* 2014, **53**, 7933.

10 For futher information about LTF instrumentation visit the web: www.ltf-gmbh.com

11 (a) T. Ueda, H. Konishi and K. Manabe, *Org. Lett.*, 2012, **14**, 3100; (b) T. Ueda, H. Konishia and K. Manabe, *Org. Lett.*, 2013, **15**, 5370, (c) T. Ueda, H. Konishia and K. Manabe, *Tetrahedron Lett.*, 2012, **53**, 5370; (d) T. Fujihara, T. Hosoki, Y. Katafuchi, T. Iwai, J. Terao and Y. Tsuji, *Chem. Commun.*, 2012, **48**, 8012.

12 N. Alonso, J. de M. Muñoz, B. Egle, J. L. Vrijdag, W. M. de Borggraeve, A. de la Hoz, A. Díaz-Ortiz and J. Alcázar, *J. Flow. Chem.*, DOI: 10.1556/JFC-D-14-00005.

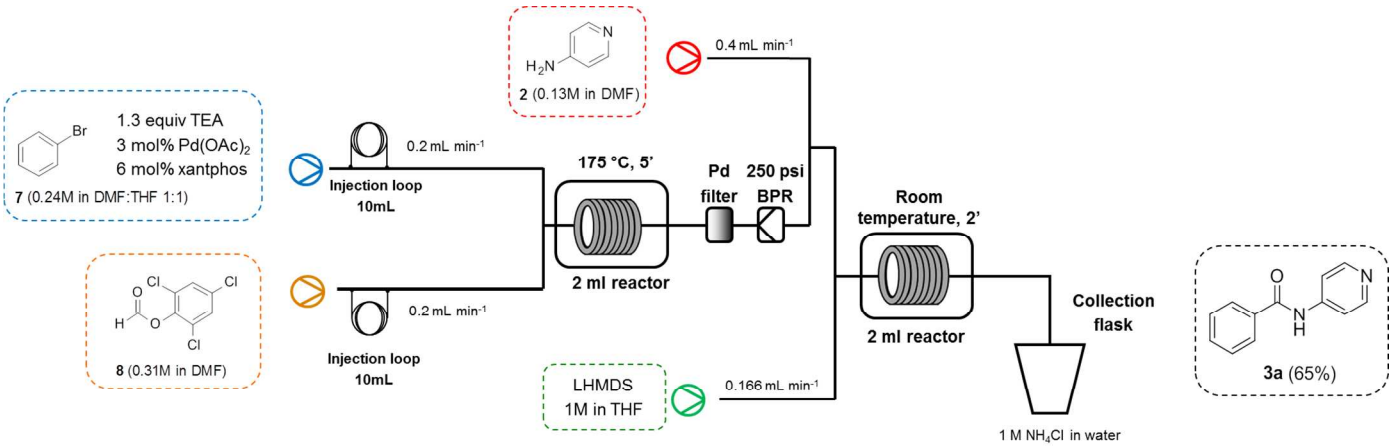

Figure 2 Experimental set up of the combination of carbonylation and amide formation on line.