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COMMUNICATION

Direct amide formation in a continuous-flow system mediated by carbon disulfide

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Amide bond is ubiquitous in nature. It can be found in proteins, peptide, alkaloids, etc. and it is used in various synthetic drugs too. Amide bonds are mainly made by the use of (i) hazardous carboxylic acid derivatives, or (ii) expensive coupling agents. Both ways make the synthetic technology less atom economic. We report a direct flow-based synthesis of amides. The developed approach is prominently simple and various aliphatic and aromatic amides were synthetized with excellent yields. The reaction in itself is carried out in acetonitrile, of which is considered as a less problematic dipolar aprotic solvent. The used coupling agent, carbon disulfide is widely available and has a low price. The utilized heterogeneous Lewis acid, alumina is sustainable material and it can be utilized multiple times. The technology is considerably robust and showed excellent reusability and easy scale-up was carried out without the need of any intensive purification protocols.

The amide linkage is one of the most ubiquitous chemical bonds in nature.[1-3] It provides an essential chemical spine-like connection in peptides and proteins. In addition, numerous medicines contain an amide bond from small organic molecules (local anaesthetics, nonsteroidal anti-inflammatory drugs, etc.) through peptides to antibodies, which are considered to be the therapy of the future.[4-8] Furthermore, the amide moiety is also a crucial connecting bond in synthetic polymers.[9] The natural way of amide formation is a very complex process involving the interplay of many macromolecules such as enzymes, protein factors, mRNAs, and tRNAs in a complex molecular machine, known as the ribosome. Ribosomes and associated molecules are also known as the translational apparatus of biological protein synthesis.[10,11]

There are many different synthetic methods to create amide bonds.[12,13] However, there are only a limited number of methods available for direct amidation resulting in amide bonds without coupling reagents or activating agents.[14-16] These processes utilize greater than the stoichiometric ratio of coupling reagents (carbodiimides, *1H*-benzotriazoles, etc.). Furthermore, these are generally expensive and harmful materials, and purification of the crude products is complicated due to a considerable amounts of by-products.[17-21] Therefore, there is a need for a general technique to access amides directly from free carboxylic acids and amines in an uncomplicated, environmentally friendly, and efficient way.

The direct method route, in general, is hampered by a large activation energy, because the complete thermal dehydration reaction between an amine and a carboxylic acid needs harsh reaction conditions. Thus, the direct method usually requires high temperatures for dehydration of the intermediate salt to provide the amide compound.[22,23]

There are several boronic acid derivatives studied as catalysts of the amidation reaction.[24-26] One of them, reported by Yihao Du *et al.*,[27] is a solid-supported arylboronic acid catalyst for direct amidation of a wide range of amine substrates in a continuous-flow system with low yields.

Carbon disulfide has been utilized in the manufacture of viscose rayon,[28] cellophane,[29] and carbon tetrachloride[30] and it is even used as solvent in extraction processes.[31] On laboratory scale, it is a reagent and a powerful building block in preparative synthesis.[32-37] A previous study showed the carbon disulfide might be a possible reagent for amide and peptide coupling synthesis.[38] They produced peptides from unprotected amino acids under prebiotic condition by the use of carbon disulfide as additive. The synthesis of poly-β-peptides has recently been described through the ring-opening polymerization of β-amino acid *N*-thiocarboxyanhydrides, as carbon disulfide derivatives.[39]

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Flow chemistry methods offer many benefits over the use of conventional batch reactors, including improvements in reaction rate and yield, safety, reliability, and energy efficiency.[40,41] During the last decade there has been a significant increase in the use of flow chemistry either in laboratory or industrial scale.[42-50] Herein we show that the use of carbon disulfide with alumina utilized in continuous flow (CF) allowed to develop a novel, atom-efficient, green, and sustainable catalytic method for the direct synthesis of amides. Thus, the CF approach could offer a possibility to accomplish direct amide coupling in new, unique, and efficient way, providing amides with high yields and excellent purity in a single step.

Reactions were carried out in a home-made continuous-flow reactor: a solid catalyst was loaded into an HPLC column, where the reaction takes place and using an organic solution transported by an HPLC pump. The system also contained a GC oven and an in-line back pressure regulator that ensure the required temperature and pressure in the reactor zone, respectively. A schematic outline of the reactor used in this study is shown in Fig. 1.

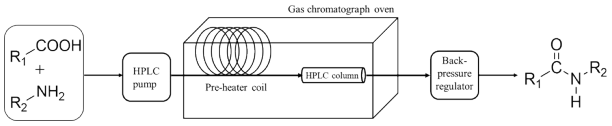


Fig. 1 Schematic illustration of the flow system

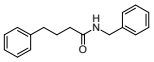
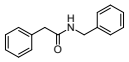
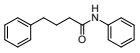
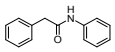
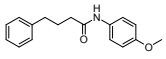
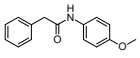
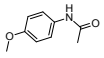
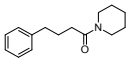
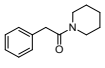
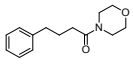
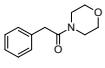
First, a model reaction was selected utilizing benzylamine and 4-phenylbutyric acid as substrates dissolved in acetonitrile to provide a 100 mM solution. Second, the optimization of reaction parameters was carried out. According to our previous study on the acetylation of amines with acetonitrile, high temperature and a modest pressure were used.[51] The first test was performed without either any catalyst or reagent at 200 °C and 50 bar pressure with a flow rate of 0.1 ml min^{-1} and a residence time of 27 min. As expected, no trace of the desired amide product was detected (Table S1, entry 1). A similar result was found when the reaction was repeated under the same conditions in the presence of alumina (Table S1, entry 2). However, a low conversion of 22% was attained when 1.5 equivalent of carbon disulfide was used as an additive along with numerous by-products (Table S1, entry 3). According to literature data, Lewis acids were used in direct amidation reaction as catalysts.[52-56] Thus several Lewis acids were tested too (Table S2). The most promising catalyst was alumina and a significant increase in conversion of 53% was observed with a formation of thioure side product (Table S2, entry 4). At this point the effect of solvent on the reaction outcome was tested. Several solvents were investigated but acetonitrile was found to be the most suitable (Table S3). But in favor of even higher conversion, organic bases, such as triethylamine and pyridine, in catalytic amount were added to the starting substrate mixture. However, this afforded only slight improvements (Table S1, entries 5, 6), although the formation of thiourea side products was not observed.

Finally, with the use of 4-dimethylaminopyridine (DMAP) as organic base full conversion was reached (Table S1, entry 7). The base additive was removed by a simple filtration on a silica gel plug. Conversions were calculated using the relative signal intensities of the carboxylic acid starting compound.

In order to find the optimal condition for the flow synthesis, the effect of temperature on the outcome of the reaction was tested under conditions established previously. In a reaction carried out at room temperature no trace of the desired product was found. The increase of temperature resulted in the increase of conversion and a low 9% was reached at 110 °C. Further temperature increases significantly influenced conversion. The optimal temperature was found to be 200 °C where >99% conversion was obtained. However, reactions at even higher temperatures provided inferior results (Figure S1a). With respect to pressure, tested at 200 °C, the optimal value was found to be 50 bar reaching full conversion. Rising the pressure higher than 50 bar did not influence the conversion (Figure S1b). A similar test about flow rate gave an optimum value of 0.1 mL min^{-1}. Any increase in the flow rate resulted in decreasing conversions (Figure S1c). Analyzing the effect of concentration on reaction outcome indicated full conversions at lower concentrations. The use of higher concentrations of the starting materials, in turn, resulted in lower conversions (Figure S1d). Finally, the results about changing the quantity of carbon disulfide show that the optimal amount is 1.5 equiv.: lower amounts resulted in decreased conversion, whereas higher amounts did not have any significant effect (Table S4).

Inspired by the successful direct amide coupling reaction of the model substrates, we expanded the scope of the reaction testing various aromatic and aliphatic substrates (Table 1).

Table 1 Substrate scope of amide formation with isolated yield data[a]

Substrates	4-phenylbutyric acid	phenylacetic acid	acetic acid
benzylamine	 **3** 98%	 **9** 96%	 **14** 98%
aniline	 **5** 96%	 **10** 95%	 **15** 98%
p-anisidine	 **6** 94%	 **11** 95%	 **16** 97%
piperidine	 **7** 96%	 **12** 97%	 **17** 98%
morpholine	 **8** 97%	 **13** 98%	 **18** 97%

[a]Reaction conditions: CS_2, DMAP, Al_2O_3, 200 °C, 50 bar

Using the optimized protocol (200 °C, 50 bar, 0.1 mL min^{-1}, 27 min residence time), we achieved high yields for 15 different

amides. Reactions were carried out with three different carboxylic acids and five different amines including primary aromatic and aliphatic and secondary aliphatic amines. All reactions were carried out in a single run. After filtration through a silica gel plug and vacuum evaporation of the solvent, the products were analyzed by ^{1}H and ^{13}C NMR spectroscopy without any further purification. This fact makes the technology prominently green and sustainable and the isolation of the products is clearly simple. The synthesized amides and the corresponding isolated yields are shown in Table 1. In all cases, the NMR experiments showed full conversions.

Catalyst reusability with 30 mg of the model starting substrates was tested too. Importantly, the activity of the catalyst did not decrease significantly after 30 cycles (Fig. 2). This result opens the way to scale up the reaction using the model reaction. A scale-up reaction was carried out and 2 grams of product were isolated after ca. 13 hours working time and 10 grams after ca. 3 days of operation without significant loss of productivity of the system.

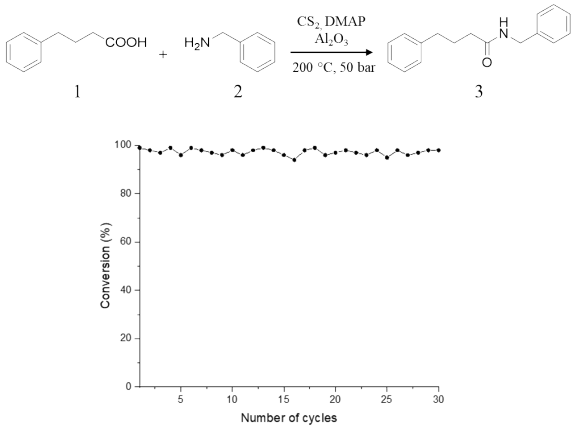


Fig. 2 Robustness of the amide formation reaction was investigated in the reaction of model substrates. The same reaction was repeated 30 times on the same catalyst.

To establish a reaction mechanism, literature data and the results gained by the optimization steps were considered. The first step is the reaction of the amine (**m1**) and carbon disulfide (CS_2).[33,57,58] This provides an N-alkyldithiocarbamic acid (**m2**), which decomposes by releasing hydrogen sulfide (H_2S) and affords an isothiocyanate (**m3**). The formation of H_2S was confirmed by a simple analytical technology. The lead(II) acetate moistened filter paper turned to brown in the gas space of the reaction mixture collecting baker. This fact indicates the formation of PbS by the reaction of lead(II) ions and H_2S. According to literatures,[59-61] we propose that the isothiocyanate (**m3**) is a key element in the direct amidation reaction. In the absence of an organic base, the formation of thiourea side product (**m5**) was observed. However, if DMAP was present in catalytic amount, the formation of the desired amide product (**m7**) was detected. This fact can be explained by the deprotonation of the carboxylic acid providing protonated DAMP and **m4–**. The latter is more nucleophilic and reacts more rapidly with isothiocyanate **m3**, than the amines. The formation of amide product **m7** can be explained by the two mesomeric forms of intermediate **m6**. Furthermore, the necessity to use a catalytic amount of DMAP can be interpreted too, since the last step, when **m7–** transforms to **m7**, is a protonation reaction. We suggest that, as indicated, protonated DMAP (+HDMAP) is involved in the last product-forming step. Then DMAP thus formed is protonated and starts the process again. Therefore, it plays a key role in proton shuffling.

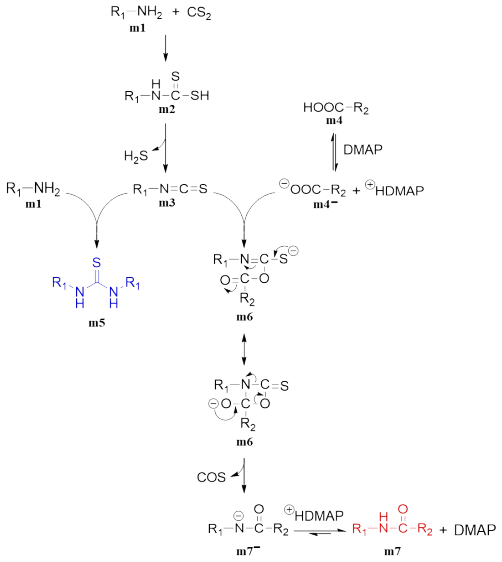


Fig. 3 Plausible mechanism for the alumina-catalyzed amide coupling with carbon disulfide.

Conclusions

In summary, direct amide synthesis from cheap and easily available carboxylic acids and amines was carried out in CF. The developed technology is time and cost efficient and applies acetonitrile as solvent, which is a relatively cheap industrial side-product. The utilized additives, alumina and carbon disulfide, are broadly used in several industrial processes too. The scope of the reaction was extended to the preparation of 15 diverse amides. Reactions were carried out with three different carboxylic acids and five amines, including primary and secondary aliphatic and primary aromatic amines. In general, full conversions and excellent yields were achieved under the optimized conditions, without the need of any intensive purification step. Catalyst reusability was tested too. The same catalyst bed could be recycled in 30 runs without any significant loss of activity. Additionally, the reaction was successfully scaled up to a 2-gram quantity performed in ca. 13 hours. This methodology could become broadly applicable for direct amide synthesis utilizing the industrially reliable continuous technology.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471-479.
2 K. Scheidt, *Nature*, 2010, **465**, 1020-1022.
3 B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027-1032.
4 D. Aldeghaither, B. Smaglo and L. Weiner, *Journal of clinical pharmacology*, 2015, 55 Suppl 3, S4-S20.
5 P. Chames, M. Van Regenmortel, E. Weiss and D. Baty, *British journal of pharmacology*, 2009, **157**, 220-233.
6 A. Davenport, C. Scully, C. de Graaf, A. Brown and J. Maguire, *Nat. Rev. Drug Disc., 2020,* **19**, *389-413*.
7 D. J. Drucker, *Nat. Rev. Drug Disc.*, 2020, **19**, 277-289.
8 J. Lau and M. Dunn, *Bioorg. Med. Chem.,* 2018, **26**, 2700-2707.
9 J. M. García, F. C. García, F. Serna, J. L. de la Peña, *Prog. Polym. Sci.*, 2010, **35**, 623-686.
10 C. Our Cell Biology, *Nature*, 1969, **222**, 224-224.
11 D. Mazia and D. M. Prescott, *Nature*, 1955, **175**, 300-301.
12 C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.,* 2011, **40**, 3405-3415.
13 E. Valeur and M. Bradley, *Chem. Soc. Rev.,* 2009, **38**, 606-631.
14 H. Xu, X. Qiao, S. Yang and Z. Shen, *J. Org. Chem.,* 2014, **79**, 4414-4422.
15 R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, **2013**, 7453-7465.
16 C. A. G. N. Montalbetti and V. Falque, *Tetrahedron,* 2005, **61**, 10827-2350.
17 J. Dunetz, J. Magano and G. Weisenburger, *Org. Proc. Res. Dev.*, 2016, **20**, 140–177.
18 B. Mahjour, Y. Shen, W. Liu and T. Cernak, *Nature*, 2020, **580**, 71-75.
19 M. Sabatini, L. Boulton, H. Sneddon and T. Sheppard*, Nature Catal.*, 2019, **2**, 10-17.
20 X. Wang, *Nature Catal.,* 2019, **2**, 98-102.
21 K. Wehrstedt, P. A. Wandrey and D. Heitkamp, *J. Hazard. Mat.,* 2005, **126**, 1-7.
22 H. Sigel and R. B. Martin, *Chem. Rev.,* 1982, **82**, 385-426.
23 J. A. Mitchell and E. E. Reid, *J. Am. Chem. Soc.,* 1931, **53**, 1879-1883.
24 N. Gernigon, R. M. Al-Zoubi and D. G. Hall, *J. Org. Chem.* 2012, **77**, 8386-8400.
25 H. Charville, D. Jackson, G. Hodges and A. Whiting, *Chem. Commun.,* 2010, **46**, 1813-1823.
26 R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem. Int. Ed.,* 2008, **47**, 2876-2879.
27 Y. Du, T. Barber, S. E. Lim, H. S. Rzepa, I. R. Baxendale and A. Whiting, *Chem. Comm.,* 2019, **55**, 2916-2919.
28 C. Tian, L. Zheng, Q. Miao, C. Cao and Y. Ni, *Cellulose,* 2014, **21**, 3647-3654.
29 J. Brasier, *Mater. Des.,* 1986, **7**, 65-67.
30 J. F. Devlin, D. Müller*, Environ. Sci. Technol.,* 1999, **33**, 1021–1027.
31 R. Cucciniello, A. Proto, F. Rossi, N. Marchettini and O. Motta, *Anal. Meth.,* 2015, **7**, 4811-4815.
32 M. Gholinejad, *Eur. J. Org. Chem.,* 2013, **2013**, 257-259.
33 W.-D. Rudorf, *J. Sulfur Chem.,* 2007, **28**, 295-339.
34 N. Azizi, B. Pourhasan, F. Aryanasab and M. Saidi, *Synlett*, 2007, **8**, 1239–1242.
35 P. Svoronos and T. Bruno, *Ind. Eng. Chem. Res.,* 2002, **41**, 5321–5336.
36 N. Kihara, Y. Nakawaki and T. Endo, *J. Org. Chem.,* 1995, **60**, 473-475.
37 R. J. Ferm, *Chem. Rev.,* 1957, **57**, 621-640.
38 L. J. Leman, Z.-Z. Huang and M. R. Ghadiri, *Astrobiology*, 2015, **15**, 709-716.
39 M. Zhou, X. Xiao, Z. Cong, Y. Wu, W. Zhang, P. Ma, S. Chen, H. Zhang, D. Zhang, D. Zhang, X. Luan, Y. Mai and R. Liu, *Angew. Chem. Int. Ed.,* 2020, **59**, 7240-7244.
40 P. Watts, The Application of Flow Chemistry in the Use of Highly Reactive Intermediates and Reagents: Methods and Applications, in Sustainable Flow Chemistry: Methods and Applications, Wiley-VCH, 2017, pp. 193-217.
41 T. Noel, V. Hessel, Chemical Intensification in Flow Chemistry through Harsh Reaction Conditions and New Reaction Design, in Microreactors in Preparative Chemistry, Wiley-VCH, 2013, pp. 273-295.
42 M. L. Contente, S. Farris, L. Tamborini, F. Molinari and F. Paradisi, *Green Chem.,* 2019, **21**, 3263-3266.
43 C. Gomez, G. Hallot, A. Pastor, S. Laurent, E. Brun, C. Sicard-Roselli and M. Port, *Ultrason. Sonochem.,* 2019, **56**, 167-173.
44 T. Ichitsuka, N. Suzuki, M. Sairenji, N. Koumura, S.-y. Onozawa, K. Sato and S. Kobayashi, *ChemCatChem,* 2019, **11**, 2427-2431.
45 H. Koo, H. Y. Kim and K. Oh, *Org. Chem. Front.,* 2019, **6**, 1868-1872.
46 G. Laudadio, G. Fusini, G. Casotti, C. Evangelisti, G. Angelici and A. Carpita, *J. Flow Chem.,* 2019, **9**, 133-143.
47 V. R. L. J. Bloemendal, S. J. Moons, J. J. A. Heming, M. Chayoua, O. Niesink, J. Hest, T. J. Boltje and F. Rutjes, *Adv. Synth. Catal.,* 2019, **361**, 2443–2447.
48 M. Shang, V. Hessel, Synthesis and Application of H_2O_2 in Flow Reactors, In Sustainable Flow Chemistry, Wiley-VCH, 2017; pp. 43-72.
49 A. Piskun, J. de Haan, E. Wilbers, H. van de Bovenkamp, Z. Tang and H. J. Heeres, *ACS Sustainable Chem. Eng.,* 2016, **4**, 2939–2950.
50 A. Hafner and S. Ley, *Synlett,* 2015, **26**, 1470-1474.
51 G. Orsy, F. Fülöp and M. I. Mándity, *Molecules*, 2020, **25**, 1985.
52 Y. Du, T. Barber, S. Lim, H. Rzepa, I. Baxendale and A. Whiting, *Chem. Comm.,* 2019, **55**, 2916-2919.
53 N. Gernigon, R. Al-Zoubi and D. Hall, *J. Org. Chem.*, 2012, **77**, 8386–8400.
54 R. Lanigan and T. Sheppard, *Eur. J. Org. Chem.,* 2013, **20**, 7453-7465.
55 M. Sayes and A. Charette, *Green Chem.,* 2017, **19**, 5060-5064.
56 H. Xu, X. Qiao, S. Yang and Z. Shen, *J. Org. Chem.,* 2014, **79**, 4414–4422.
57 F. E. Critchfield and J. B. Johonson, *Anal. Chem.,* 1956, **28**, 430-436.
58 N. Sun, B. Li, J. Shao, W. Mo, B. Hu, Z. Shen and X. Hu, *Beilstein J. Org. Chem.,* 2012, **8**, 61-70.
59 V. Delaveau, Z. Mouloungui and e. A. Gaset, *Synth. Commun.*, 1996, **26**, 2341-2348.
60 R. N. Ram, P. Kumar and A. K. Mukerjee, *J.Chem. Educ.,* 1983, **60**, 508.
61 W. R. Vaughan, M. V. Andersen, H. S. Blanchard, D. I. McCane and W. L. Meyer, *J. Org. Chem.,* 1955, **20**, 819-822.