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Amidation by Reactive Extrusion for the Synthesis of Active Pharmaceutical Ingredients Teriflunomide and Moclobemide

Matthieu Lavayssiere¹ and Frédéric Lamaty*¹

¹IBMM, Univ Montpellier, CNRS, ENSCM, Montpellier, France

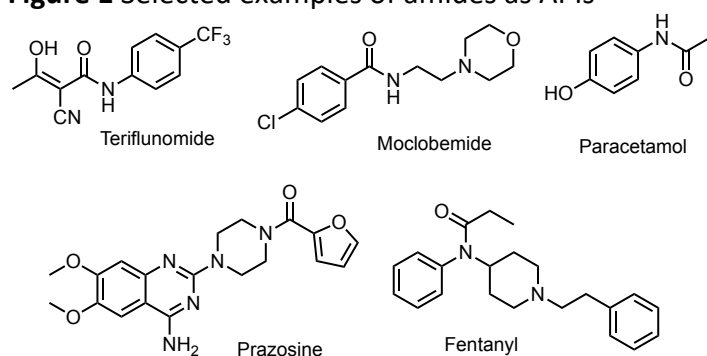
* frederic.lamaty@umontpellier.fr

Abstract: The amidation reaction is a key step for the preparation of a large number of organic molecules, including active pharmaceutical ingredients (APIs), but still challenging from the point of view of its efficiency and sustainability. In this context, the solventless synthesis of an amide, starting from a carboxylic acid and an amine, was performed in a twin-screw extruder (TSE) in the presence of a coupling agent, providing a high yielding and productive method. Reaction conditions were evaluated and successfully used to prepare two APIs, teriflunomide and moclobemide. This complements the synthetic tool box of twin-screw extrusion to prepare organic molecules and opens the way to broader applications, including in an industrial perspective.

Introduction

The amide bond is ubiquitous in nature, structuring biomacromolecules such as proteins and playing a major role in their biological activities. It is involved in numerous interactions (e.g., hydrogen bonding or electrostatic interactions) related to biological processes. Amide bonds are also present in a large number of manufactured molecules such as materials and pharmacologically active compounds. This includes marketed drugs, 25 % of their active pharmaceutical ingredients (APIs) are owning an amide bond,¹ as depicted in Figure 1, with the examples of major drugs.

Figure 1 Selected examples of amides as APIs



While alternative methods to prepare amides are under development,² the amide bond is typically synthesized from a carboxylic acid and an amine.³ However, the synthesis of these compounds, including at the industrial level,⁴ often requires reaction conditions involving hazardous and toxic reagents (coupling agents, bases...) in stoichiometric quantities, source of pollution, including the use of large amounts of solvent to solubilize the reaction medium and purify the synthesized product. To counteract the ecological and economic issues in relation with the use of solvents in the fine chemical industries, research teams have developed solvent-free or solventless methods by ball-milling for the preparation of organic molecules⁵⁻

¹³ including APIs.^{13,14} In 2012, our team reported the first example of solvent-free amide bond synthesis starting from a carboxylic acid and an amine, in a ball-mill, with CDI (1,1'-carbonyl diimidazole)¹⁵ as a coupling agent.¹⁶ This method was applied to the organic-solvent free synthesis of the API teriflunomide.^{16,17} Nearly concomitantly, the group of Štrukil and Margetić reported amidation reaction including EDC.HCl (*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride) as an efficient coupling agent.¹⁸ Recently, further developments were reported with the use of various coupling agents in a ball-mill to prepare an amide.¹⁹⁻²¹ Furthermore, the mechanochemical approach to the synthesis of peptides has pioneered and complemented the evaluation of coupling systems in the absence of solvent.^{11,13,22-24}

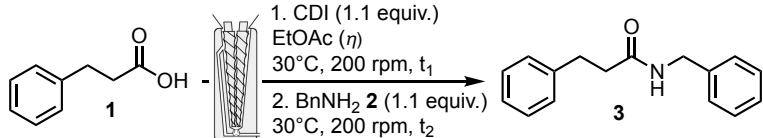
Nevertheless, the ball-milling approach corresponds to a discontinuous batch process and the scaling-up of the corresponding reaction with larger mills, currently employed in the mineral industry, raises problems of safety for organic synthesis. While flow chemistry is currently revolutionizing the processing of chemicals, this approach necessitates large amount of solvent and is not well-adapted to the use of solids or of concentrated mixtures. Recently, it has been demonstrated, including work from our team involving peptide formation,²⁵ that extruders, another mechanochemistry tool, could provide a continuous approach for solvent-free or solvent less organic reactions, involving solids or viscous mixtures,^{26,27} with few reports regarding the preparation of APIs.²⁸⁻³⁰ This approach was also recognized by IUPAC as one of the ten most important chemical innovations that could change our world,³¹ including at the industrial level. In order to fill in the gap of the number of reactions developed by reactive extrusion, further developments are needed to provide chemists with practical tools to synthesize efficiently organic molecules, including the widespread amidation. We now disclose a first report on the continuous synthesis of amides by reactive extrusion including the preparation of two important APIs, teriflunomide and moclobemide.

Results and discussion

Capitalizing on previous results obtained in the synthesis of peptides,^{25,32} the amidation reaction was studied and optimized using a corotating twin-screw extruder (Pharma Melt Extruder (PME) Xplore). This extruder can be used in a continuous mode when reaction time is short, or with a recirculation to increase the residence time in the barrel, corresponding to a longer length of the screw. The previously reported model reaction, used for studying the reaction conditions in a ball-mill,¹⁶ namely the coupling of 3-phenylpropionic acid **1** and benzyl amine **2** was investigated in various conditions including coupling agents and bases/additives if needed. Two important parameters, belonging to the extruder and which could be optimized, if necessary, are the temperature of the barrel and the rotation speed of the screws. Many coupling agents and conditions are available and reported in literature to carry out efficiently an amidation reaction. Among them, a limited number has been effectively used in the pharmaceutical industry for large scale applications.⁴ Selection criteria for choosing a coupling system (including coupling agent, base, additives, solvent) are efficiency, availability, practical handling and ease of purification of the final product, as well as safety, toxicity and environmental impact. We evaluated the toolbox for amidation using an extruder focusing on three coupling agents: CDI, EDC.HCl, and 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminoxy) dimethylaminomorpholino)] uronium hexafluorophosphate (COMU).

Firstly CDI, one of the most employed coupling agents, efficient, cheap and considered non-toxic was explored. CDI generates carbon dioxide and imidazole as a by-product, which can serve as a base when the coupled amine is provided as a salt. The reaction was carried out in two steps, first an activation step of carboxylic acid **1**, for a given mixing time t_1 with CDI, followed by the addition of benzyl amine **2** (Table 1). The reaction mixture was mixed for a further time (t_2). The loading of the experiment was fixed at about 2 g, filling completely the available volume of the barrel equipped with screws (2 mL). A slight excess of acid compared to the amine was used. The temperature of the barrel was set to 30°C and the rotation speed to 200 rpm. Premixing²⁵ or not the starting materials, with a spatula in a beaker, before introduction in the barrel did not change the final result. At the end of the transformation, the output valve was adjusted to recover the crude mixture. In a first experiment (entry 1), when reactants were mixed neat, recirculation did not happen and no conversion was observed. In the next experiment (entry 2), EtOAc was used in a small amount (1.2 mL, $\eta = 0.6 \text{ mL.g}^{-1}$)⁵ as liquid additive (LA) to facilitate the fluidity and the homogeneity of the reaction mixture.³³ The conversion sharply increased to completion towards the expected product. Optimization of quantities of LA and reaction time was realized. Decreasing the amount of EtOAc ($\eta = 0.15 \text{ mL.g}^{-1}$), conversion was still excellent but introduction of reagents was not facilitated and recovery of the extrudate was difficult (entry 3). Increasing to $\eta = 0.3 \text{ mL.g}^{-1}$ solved this problem (entry 4). When the three reaction components were mixed together (entry 5) avoiding a pre-activation time, high conversion was obtained albeit with the formation of about 4% of urea arising from the reaction of CDI with benzyl amine **2** only. Gratifyingly, reducing both activation and reaction time to 1 minute each (entry 6) afforded almost complete conversion. In this case, the extrudate was solubilized in EtOAc, followed by acidic then basic aqueous washings to afford pure expected *N*-Benzyl-3-phenylpropanamide **3** in 81% yield.

Table 1 CDI-promoted amidation



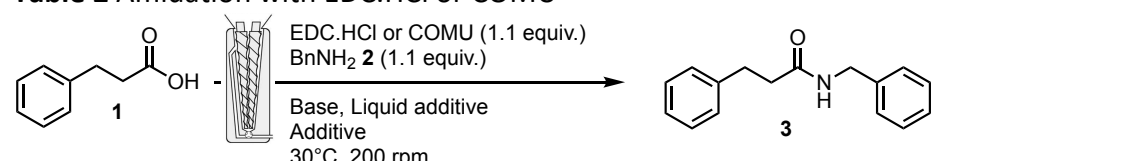
Entry	η (mL.g ⁻¹) of EtOAc	Activation step t_1 (min)	Reaction time t_2 (min)	Conv. into 3 (%) ^a
1	0	5	10	0
2	0.6	5	10	>99
3 ^b	0.15	5	10	>99
4	0.3	5	10	>99
5	0.3	0	5	94 ^c
6	0.3	1	1	98 (81) ^d

^aDetermined by HPLC. ^bIn this case, recovery of the extrudate was incomplete. ^c4% of urea was obtained. ^dIsolated yield.

The efficient use of CDI required a two-step procedure since mixing all reagents together provided urea as side product. To develop a potentially more efficient process, other coupling agents were considered. EDC.HCl is another much employed coupling agent and does not require the use of an additional base unless the amine is used as its salt form. EDC.HCl may be preferred over other carbodiimide type coupling agent because the urea by product thus

obtained can be removed by a simple aqueous work up. To improve the kinetics of the amidation and reduce the potential epimerization of a chiral center present in the starting material, additives have been used to enhance the reactivity of the coupling agent. One of the mostly used additive is 1-hydroxybenzotriazole (HOBT), but its sensitivity to explosion represents some concerns. Recently, other additives were explored more specifically for peptide synthesis, including oximes. One of the mostly used is ethyl cyano(hydroxyimino)acetate (Oxyma), which was investigated in this study.³⁴ Finally, carbodiimides being sensitizing molecules, a carbodiimide-free oxyma-based coupling agent 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminoxy) dimethylaminomorpholino)] uronium hexafluorophosphate (COMU) was also tested.³⁵

Table 2 Amidation with EDC.HCl or COMU



Entry	Coupling agent	Base (equiv.)	Liquid additive (η mL.g ⁻¹)/additive	Reaction time (min)	Conv. into 3 (%) ^a
1	EDC.HCl	DMAP (0.3)		10	78
2	EDC.HCl	DMAP (0.3)	EtOAc (0.6)	10	79
3	EDC.HCl		EtOAc (0.6)	10	85
4	EDC.HCl	Ca(OH) ₂ (0.3)	EtOAc (0.6)	10	72
5	EDC.HCl	CaO (0.3)	EtOAc (0.6)	10	87
6	EDC.HCl	KHCO ₃ (0.3)	EtOAc (0.75)	10	90
7 ^b	EDC.HCl	K ₂ CO ₃ (0.15)	EtOAc (0.75)	10	97
8	EDC.HCl	NEt ₃ (0.3)	EtOAc (0.6)	10	93
9	EDC.HCl	DIPEA (0.3)	EtOAc (0.6)	10	98
10	EDC.HCl	DIPEA (0.3)	EtOAc (0.75)/Oxyma	10	81
11	EDC.HCl	DIPEA (0.3)	CH ₃ CN (0.6)/ Oxyma	10	>99
12	EDC.HCl	DIPEA (0.3)	CH ₃ CN (0.3)/ Oxyma	1	96 (86) ^c
13	COMU	DIPEA (1)	EtOAc (0.75)	10	>99
14	COMU	K ₂ CO ₃ (0.5)	EtOAc (0.75)	10	>99 (75) ^c
15	COMU	DIPEA (1)	CH ₃ CN (0.6)	10	>99 (80) ^c
16	COMU	DIPEA (1)	CH ₃ CN (0.6)	3X10	>99 (93) ^c
17	COMU	DIPEA (1)	CH ₃ CN (0.6)	1	94
18	COMU	K ₂ HPO ₄ (1)	EtOAc (0.6)	1	52
19	COMU	K ₂ CO ₃ (0.5)	CH ₃ CN (0.6)	3X1	85(77) ^c

^aDetermined by HPLC. ^bExtruder barrel temperature set at 50°C. ^cIsolated yield.

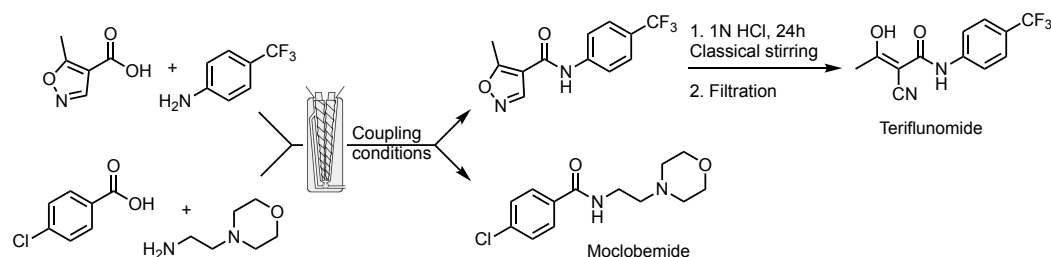
EDC.HCl, widely used together with DMAP as a base, in a catalytic amount, in solution or in solvent-free conditions,^{4,18,36} was investigated. 10 minutes of mixing **1** and **2** in the extruder together with EDC.HCl and DMAP yielded an incomplete conversion towards the expected product (entry 1). Adding EtOAc ($\eta = 0.6$ mL.g⁻¹) did not improve the conversion (entry 2). In the absence of base, conversion was improved but not complete (entry 3). Various less toxic inorganic and organic bases were investigated. Ca(OH)₂, CaO, KHCO₃ did not yield satisfactory conversions (entries 4-6). K₂CO₃ (entry 7) was more effective when the amount of EtOAc was

increased to $\eta = 0.75 \text{ mL.g}^{-1}$ and the temperature raised to 50°C . Triethylamine (entry 8) was more efficient than DMAP, without reaching full conversion. On the other end, diisopropylethyl amine (DIPEA) gave excellent conversion (entry 9). To avoid the need for recirculation in the extruder, the possibility to reduce further the reaction time was explored, adding Oxyma, known to increase the kinetics of amide bond formation. Surprisingly, in a first experiment (entry 10), the conversion decreased, but switching to CH_3CN as liquid additive improved radically the outcome of the reaction, most probably because it provides a more homogeneous reaction mixture in the presence of Oxyma and facilitates the recovery of the extrudate (entry 11). Reaction time could be decreased to 1 min (entry 12), still providing excellent conversion with an isolated yield of 86 % with the same recovery procedure as described above. Noteworthy, in this case, recirculation was not needed and molecule **3** was produced in a continuous mode. With these results in hands the Oxyma-based coupling agent COMU was also tested. Reaction in the presence of DIPEA and EtOAc (entry 13) yielded full conversion in 10 minutes. Switching from DIPEA to less toxic K_2CO_3 did not impact the conversion (entry 14). CH_3CN , for the reasons mentioned above was also used (entry 15) to give a similar result with an isolated yield of 80%. Scaling up the reaction by running the same reaction three times successively in the extruder (entry 16) yielded 99% conversion and an excellent isolated yield of 93% to provide 1.71 g of **3**. Attempt to reduce the reaction time to 1 min (entry 17) was not satisfactory, resulting in a lower conversion. The optimal conditions for amidation reported in literature²¹ in the case of ball-milling, including COMU and K_2HPO_4 as a base, were tested (entry 18) but resulted in a lower conversion, most probably because reaction time was not long enough. Finally, combination of COMU, K_2CO_3 and CH_3CN as liquid assistant (entry 19) was not the best combination regarding conversion but the reaction could be carried out in a continuous mode on a larger scale, providing 1.29 g of **3** (77% isolated yield, 85 % conversion).

This optimization study of the reaction conditions on a reactive system with various coupling systems demonstrated that it possible to perform efficiently an amidation reaction in a twin-screw extruder (TSE) on a simple model reaction. The use of CDI does not require the presence of base and is a stepwise activation and coupling reaction. This is not the case of EDC.HCl which efficiency could be enhanced by adding Oxyma to reach shorter reaction time, necessary for a continuous process. Finally, COMU is also well-adapted even if reaction times are longer.

With these tools in hands, the methods were adapted and applied to the preparation of APIs owning an amide bond. Two molecules were chosen, according to their therapeutic and economical value in the pharmaceutical industry, moclobemide and teriflunomide (Figure 1 and Scheme 1). Teriflunomide is an oral disease-modifying therapy for relapsing forms of multiple sclerosis.³⁷ Moclobemide is used to treat depression and social anxiety disorder.³⁸ In the case of teriflunomide, a similar scheme as the one developed in our original work¹⁶ was considered, with the first step (amidation) performed herein in the extruder. Then opening of the isoxazole ring in solution in acidic conditions gave teriflunomide. The isolated yields are reported for the final product recovered by filtration followed by a recrystallization. For moclobemide,³⁹ after the one-step amidation in the extruder, the product was recovered by an extraction and a recrystallization.

Scheme 1 Synthesis of teriflunomide and moclobemide by reactive extrusion



For each of these molecules, the previously evaluated coupling agents were used. The main adjustments consisted in selecting the liquid additive (EtOAc or CH₃CN), the base (DIPEA or K₂CO₃), the temperature of the barrel and the reaction time (Table 3). For teriflunomide, the use of CDI (entry 1) gave a very good result (full conversion for the amidation and 77 % isolated overall yield), provided that CH₃CN was used as liquid additive at a temperature of 50°C. These results compare favorably in term of reaction time to the ones previously obtained by ball-milling (5h).¹⁶ Reaction with EDC.HCl/DIPEA was much slower and increasing the reaction temperature resulted in a mixture of products (entry 2). Adding Oxyma (entry 3) reduced the reaction time and provided a good yield of the expected product. COMU gave similar results but was not as fast (entry 4). Noteworthy, the recovery of teriflunomide from the reaction with CDI is facilitated (simple precipitation in water) because of the absence of a base or additives. In the case of a reaction where Oxyma is present, more careful recrystallization was needed to remove the by-products. In contrast to these results, CDI was not adapted to the preparation of moclobemide. Either with EtOAc or CH₃CN as liquid additive, recirculation was difficult and resulted in lower conversion and yield than in the case of teriflunomide (entry 5). Again, increasing the temperature to accelerate the reaction with EDC.HCl/DIPEA resulted in a mixture of products (entry 6). The presence of Oxyma dramatically improved the results with a complete conversion obtained within 5 min (entry 7). Switching to K₂CO₃ as a base (entry 8) proved to be more practical and faster, and the transformation could be carried out in 1 min in a continuous mode to furnish 87 % yield of moclobemide. Conversion and yields with COMU were excellent but the process needed recirculation (entry 9).

Table 3 Reactive extrusion conditions for the synthesis of teriflunomide and moclobemide

	Entry	Coupling agent	Base (equiv.)	Liquid additive (η mL.g ⁻¹) /additive (equiv.)	T (°C), t (min)	Conv. % ^b (Isolated Yield, %) ^c
Teriflunomide	1	CDI	-	CH ₃ CN (0.6)	50 (10+20) ^a	>99 (77)
Teriflunomide	2	EDC.HCl	DIPEA (0.33)	CH ₃ CN (0.6)	80 (120)	67 ^d
Teriflunomide	3	EDC.HCl	DIPEA (0.3)	CH ₃ CN (0.6)/Oxyma (1)	50 (60)	99 (75%)
Teriflunomide	4	COMU	DIPEA (1.1)	CH ₃ CN (0.6)	30 (120)	85 (80)
Moclobemide	5	CDI	-	EtOAc (0.6)	30 (1+2) ^a	88 (68)
Moclobemide	6	EDC.HCl	DIPEA (0.33)	CH ₃ CN (0.6)	80 (10)	85 ^d
Moclobemide	7	EDC.HCl	DIPEA (0.33)	CH ₃ CN (0.6)/Oxyma (1)	30 (5)	>99
Moclobemide	8	EDC.HCl	K ₂ CO ₃ (0.3)	CH ₃ CN (0.6)/Oxyma (1)	30 (1)	95 (87)
Moclobemide	9	COMU	DIPEA (1.1)	CH ₃ CN (0.6)	30 (10)	99 (95)

^a In the case of CDI, activation + reaction time. ^b Determined by HPLC. ^c In the case of teriflunomide, isolated yield was calculated on the final product after acidic treatment. ^d A mixture was obtained.

As expected, the optimal conditions for the synthesis of the two APIs, teriflunomide and moclobemide, in the TSE are different. They depend on the chemical reactivity of the starting materials (the aniline involved in the reaction of teriflunomide is less reactive than the primary amine in the case of moclobemide) but also on the physico-chemical properties of the reaction medium since in the TSE, it is necessary to obtain a homogeneous mixture which can be extruded at the end of the process. Nevertheless, considering the coupling systems reported herein, and the possibility to adjust various parameters, optimal conditions should be obtained for any coupling reaction. In the case of moclobemide, one reaction could be performed in continuous mode (entry 8) because reaction time was short. In the other cases, longer reaction time required recirculation. With the objective of developing a continuous process, this would require in further studies to switch to a TSE which could accommodate longer length of screws.²⁷

Conclusions

Owing to the importance of the presence of amide bonds in various families of molecules including active pharmaceutical ingredients (APIs), we developed a general amidation method for making these molecules in a twin-screw extruder, in some cases in a continuous mode, starting from a carboxylic acid and an amine. This method was applied to the efficient synthesis of teriflunomide and moclobemide and will complement the toolbox developed for the preparation of APIs by reactive extrusion. It could be also employed for the synthesis of other families of molecules of interest. Furthermore, as it was recently demonstrated,³⁰ drastically decreasing the amount of solvent used, combined with an improved efficiency of the amidation reaction by engaging quasi stoichiometric amount of starting material results in a more sustainable and cost saving approach. This paves the way for the dissemination of the technology of reactive extrusion for organic synthesis in industry.

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Abbreviations:

CDI 1,1'-carbonyldiimidazole

EDC.HCl N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride)

COMU 1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminoxy) dimethylaminomorpholino)]

uronium hexafluorophosphate

HOBt 1-Hydroxybenzotriazole

Oxyrna Ethyl hydroxyiminocyanoacetate

Notes

$\xi\eta$ is defined as the ratio between the volume of liquid (in mL) divided by the total mass of solids (in gram)

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