Trimethylaluminium mediated amide bond formation in a continuous flow microreactor as key to the synthesis of rimonabant and efaproxiral†

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Received (in Cambridge, UK) 19th December 2007, Accepted 16th January 2008
First published as an Advance Article on the web 1st February 2008
DOI: 10.1039/b719603b

A safe, functional-group-tolerant and high-throughput version of the trimethylaluminium mediated amide bond formation reaction has been developed in a microreactor system; rimonabant and efaproxiral were prepared to illustrate the utility of the method.

During the drug development process the synthetic route is often altered several times to allow for the efficient synthesis of larger quantities.[1–3] Microreactors may be beneficial for reaction scale-up by taking advantage of higher surface to volume ratios and more precise temperature control than regular reactors.[1,4–7] Small reaction volumes translate into small amounts of potentially hazardous intermediates present, while toxicity issues can be addressed by *in situ* quenching. Rapid transfer from laboratory scale, where the microreactor's low volume is ideal for optimization studies, to larger scale is straightforward.[1,3,8–17]

Amide bond formation is a common transformation in medicinal chemistry laboratories. Starting from esters, a three-step sequence of hydrolysis, activation and treatment with an amine is performed. Transfer of this process to larger scale requires further reaction optimization and safety investigations leads to loss in productivity. Aluminium-mediated amine activation is frequently employed to avoid the three step sequence.[18] Trimethylaluminium, the most commonly used aluminium-reagent, is highly pyrophoric and difficult to handle safely beyond small scale. The aluminium–amide intermediate is unstable at elevated temperatures and is known to result in exotherms even at room temperature.[19] Microreactors will avoid uncontrolled exotherms by forming and reacting the aluminium–amide continuously, and may increase reaction rates. Here, we report microreactor-based aluminium-mediated amide bond formation and its application to the continuous synthesis of two drug substances: rimonabant and efaproxiral.

Microreactors, like microwave reactors, allow for solvent superheating, high pressures and rapid heating. The $AlMe_3$-mediated amide formation that typically requires reaction times between 4 and 16 h with conventional heating were complete within 2 min at 100 °C in toluene and at 130 °C in THF in a microwave reactor (Table 1, methods A and B, respectively). In the microreactor system the reactions were performed at 125 °C with 2 min retention time and equimolar amounts of the three reactants (method C). Toluene was less suitable as solvent due to the formation of surface films or fine precipitates that eventually blocked the flow. The reactions proceeded well in THF, despite the release of methane gas by the reaction of trimethylaluminium and the amine. It was found that a simple T-type mixer gave excellent mixing of reagents, thereby avoiding the use of other more elaborate and clogging-sensitive specialized mixer.[20] The temperature was monitored with a Pt100 sensor and remained constant throughout the reaction. For continuous quenching of unreacted reagents the solution was either collected directly in a HCl-solution (5%) or, more conveniently, by introducing and mixing the HCl-solution at the outlet *via* a HPLC-pump and a T-mixer.

The reactions (Table 1) were typically performed on 8 mmol scale, however, the reaction was scaled to 0.1–0.2 mol (entries 5 and 11) to demonstrate that increased scales can readily be achieved by running the reaction continuously. On larger scale the products were purified by recrystallization in two batches, accounting for the drop in yield. Both aromatic and aliphatic esters were reacted with anilines and aliphatic amines to give amide products in good yield. Amines reacted with substrates with more than one electrophilic centre (entries 15–16 and 22) with good selectivity for the ester. Substrates containing acidic protons (entries 18–19 and 24) worked well, but pressure build-up from the additional equivalent of methane gas made the reactions more sensitive to high concentrations. Reaction with secondary amines proved more difficult under these conditions and unreacted amine could always be recovered. Best results were obtained using 1.5 equivalents of both amine and trimethylaluminium (entry 9), employing one or two equivalents of trimethylaluminium resulted in poor yields (<20%), as did longer reaction times. The chemoselectivity for substrates containing two different esters (Table 1, entry 24 and Scheme 2, compound **34**) was excellent to produce only one amide product.[21] Very polar products, *e.g.* **26** (entry 26), caused blocking of the reactor channels. While addition of TMSCl to temporarily silylate the formed alcohol and aid solubility resulted in a clear solution under microwave conditions (entry 25), it did not resolve the blocking problem in continuous flow.

Rimonabant (SR141716, **31**, Scheme 1) and efaproxiral (RSR13, **36**, Scheme 2), two pharmaceutically active

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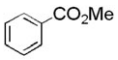
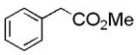
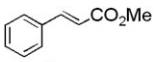
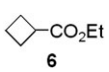
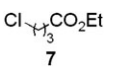
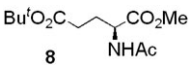
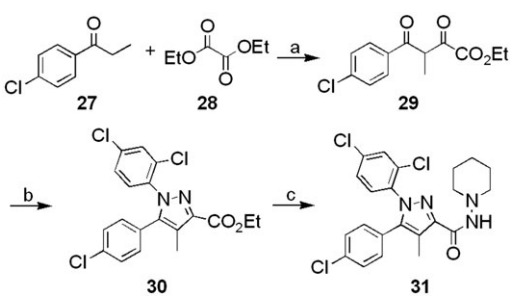
† Electronic supplementary information (ESI) available: Schematic setup of microreactor system, experimental procedures and spectroscopic data of compounds. See DOI: 10.1039/b719603b

Table 1 Trimethylaluminium mediated synthesis of amides in a microwave or continuous flow reactor

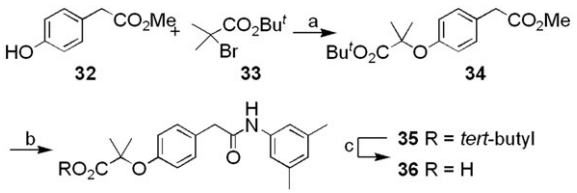
$RCO_2R^1 + R^2R^3NH + AlMe_3 \rightarrow RCONR^2R^3$

Entry	Ester[a]	Amine[a]	Product	Method[b] (%)
1	 **1**	$BnNH_2$	**10**	A (92)
2		$BnNH_2$	**10**	C (96)
3		$PhNH_2$	**11**	A (98)
4		$PhNH_2$	**11**	B (95)
5		$PhNH_2$	**11**	C (91)[c]
6		c-C_6H_{11}	**12**	C (85)
7		Piperidine	**13**	C (37)
8		BnNHMe	**14**	B (56)[d]
9		BnNHMe	**14**	C (61)[d]
10	 **2**	$BnNH_2$	**15**	C (98)
11		$BnNH_2$	**15**	C (80)[e]
12		$PhNH_2$	**16**	C (92)
13		$BuNH_2$	**17**	C (84)
14	 **3**	$BnNH_2$	**18**	A (95)
15		$BnNH_2$	**18**	C (94)
16		$BuNH_2$	**19**	C (88)
17	 **4**	$BnNH_2$	**20**	B (70)
18		$BnNH_2$	**20**	C (78)
19		$PhNH_2$	**21**	C (78)
20	 **5**	$BnNH_2$	**22**	C (86)
21	 **6**	$BnNH_2$	**23**	C (65)
22	 **7**	$BnNH_2$	**24**	C (70)
23	 **8**	$BnNH_2$	**25**	A (64)
24		$BnNH_2$	**25**	C (80)
25		$BnNH_2$	**26**	B (89)[f]
26	 **9**	$BnNH_2$	**26**	C (nd)[fg]

[a] All reagents were used as 0.3 M solutions. [b] Method A: microwave reactor, toluene, 100 °C, 2 min, 0.3 mmol scale; method B: microwave reactor, THF, 125 °C, 2 min, 0.3 mmol scale; Method C: continuous flow microreactor, THF, 125 °C, 2 min retention time, 8 mmol scale unless noted otherwise. [c] 0.1 mol scale, purified by recrystallization. [d] 1.5 eq. of amine and $AlMe_3$. [e] 0.2 mol scale, purified by recrystallization. [f] 1 eq. of TMSCl was added. [g] Blocked flow, yield not determined.



Scheme 1 Continuous flow synthesis of rimonabant. *Reagents and conditions*: (a) LiHMDS, THF, rt, 1 min, then **28**, THF, 50 °C, 10 min, then 5% HCl (70%); (b) 2,4-dichlorophenylhydrazine·HCl, AcOH, 125 °C, 16 min (80%); (c) $AlMe_3$, 1-aminopiperidine, THF, 125 °C, 2 min (88%).



Scheme 2 Synthesis of efaproxiral combining batch and flow regime. *Reagents and conditions*: (a) K_2CO_3, DMF, 75 °C, 16 h (75%); (b) $AlMe_3$, 3,5-dimethylaniline, THF, 125 °C, 2 min (77%); (c) HCO_2H, 90 °C, 4 min (89%).

substances, were synthesized in a continuous flow microreactor to apply the method. Rimonabant is an anti-obesity drug that acts as a central cannabinoid receptor antagonist,[22,23] and synthetic routes are established.[24,25] The last step of the synthetic sequence, the union of an acid chloride and 1-aminopiperidine, may be replaced by direct amide formation. The entire sequence to **31** was performed in a microreactor starting with treatment of ketone **27** with LiHMDS at room temperature (1 min retention time), followed by ethyl oxalate at 50 °C in a second reactor (10 min retention time, 70% yield). While the synthesis of **29** or its lithium salt can be accomplished in batch reactors, the microreactor method avoids cooling that otherwise requires some effort on scale. After work-up and purification, **29** was treated with the HCl salt of 4-chlorophenylhydrazine in AcOH at 125 °C for 16 min to provide pyrazole **30** in 80% yield. Finally, rimonabant **31** was conveniently synthesized in gram quantities in 49% overall yield, using the amidation reaction.

Efaproxiral, a structurally simple but pharmaceutically active substance, is developed by Allos Therapeutics for the enhancement of radiation therapy.[26,27] Efaproxiral can be synthesized from ester **32** or its free carboxylic acid by first forming an amide with 3,5-dimethylaniline, followed by alkylation of the phenol. Phenol alkylation relies on heterogenous mixtures of inorganic bases in organic solvents, rendering this step less suitable for microreactors. Therefore, the phenol was first alkylated using the *tert*-butyl ester of 2-bromo-2-methylpropionic acid (**33**).[28] The methyl ester was converted to the corresponding amide with complete selectivity over the *tert*-butyl ester. The *tert*-butyl ester was removed in the final step using formic acid at 90 °C in continuous flow with a throughput of 24 mmol h^{-1} of efaproxiral **36**.

In conclusion, we report the use of microreactors to safely and conveniently perform trimethylaluminium mediated direct amide formation reactions. Rapid reactions resulted in an efficient process with a throughput of about one mol day^{-1}. A range of substrates containing polar or acidic functional groups works well in this reaction provided that precipitates can be avoided. The syntheses of two pharmaceutically active substances, rimonabant and efaproxiral, were achieved using direct amide formation. These examples demonstrate the potential microreactors hold for reaction and process development for the production of pharmaceutically active substances.

We thank the ETH Zürich, Switzerland and AstraZeneca R&D, Mölndal, Sweden for financial support.

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