Accessing Amides Quickly, Cleanly and on Multi-Gram Scales with DABAL-Me_3

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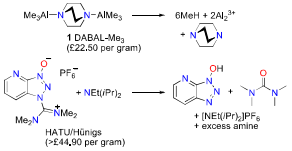
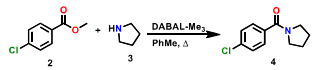
1. Introduction

Amide formation is one of the most commonly used transformations used in API synthesis today. A large range of commercially available coupling reagents exist at present, however many of these are expensive and produce a considerable amount of by-products and environmental waste at the end of the reaction. The ideal reagent that covers a broad coupling scope, that is inexpensive and produces little to no environmental waste currently does not exist. DABAL-Me_3 **1** is an air stable adduct of $AlMe_3$ and DABCO which was developed in the Woodward group, it is a viable "mid-table" option in terms of cost and environmental impact (Scheme 1). With this in mind, DABAL-Me_3 seems like an attractive option for both pre-clinical and kilo scale couplings; however previous attempts to scale the reaction beyond 1 mmol have been met with a stall in reactivity and longer reaction times.[1] Herein we report the successful scale up of DABAL-Me_3 promoted amide couplings utilizing batch and continuous flow scale up methodologies.



Scan the QR Code to link to the Periodic Table of Elements video that demonstrates the handling of pyrophoric $AlMe_3$ versus the stabilised DABAL-Me_3!

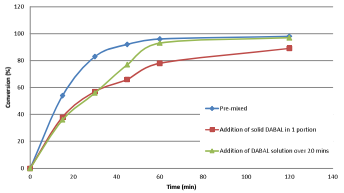
2. Scale-up in batch



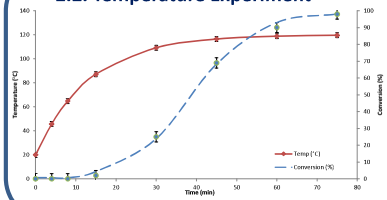
2.1. Optimisation

Optimisation was run on a 5 mmol (ca. 1 g) scale using methyl 4-chlorobenzoate **2** and pyrrolidine **3** as the model system. Modes of mixing were explored:

a). All reactants pre-mixed in flask and submitted to a pre-heated oil bath (120 °C)
b). Amine and ester pre-mixed and heated to reflux, DABAL added as a solid in one portion.
c). As in **b** but the DABAL was added over 20 min as a solution (in 9:1 toluene:pyridine)
•After 2 hours all three of these methods arrive at a similar conversion, however it is clear that the pre-mixed method operates the most efficiently.



2.2. Temperature Experiment

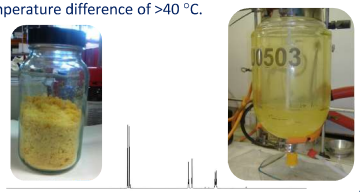


A temperature control experiment was run to monitor the conversion as temperature increased. It can be extrapolated that a minimum temperature for the reaction to take place exists at around 90 °C and perhaps inefficient heating is to blame for the previous stalls in reactivity.

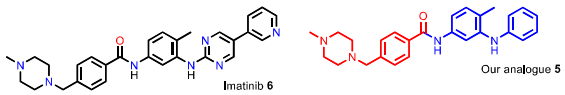
2.3. Scale-up

With the method optimised, the reaction was successfully scaled to **5**, **10** and **20** g obtaining high yields after just **1 h** of reaction time. (**>99%** conversion, **99%** isolated yield). The crude material was isolated very cleanly without the need for further purification.

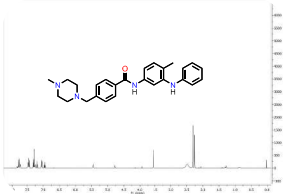
A successful **100 g** demonstration was run at **Aesica** using a jacketed reactor, the model amide was once again isolated in high purity and yield (**95%**). Interestingly, from a scale up perspective, when we quenched this larger scale reaction, it took significantly longer as we wanted to avoid any thermal stress on the jacketed reactor by avoiding having a internal and jacket temperature difference of >40 °C.

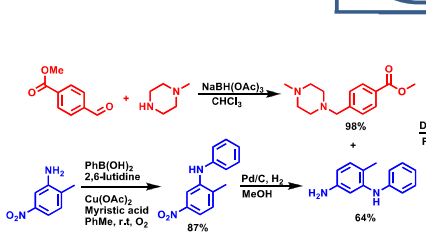


2.4. Synthesis and coupling of API Analogue fragments

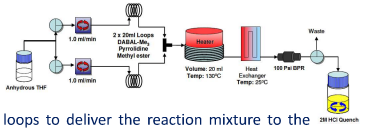


To reinforce the validity of DABAL-Me_3 as a viable amide coupling agent, we synthesised an analogue **5** of the potent anti-cancer drug Imatinib **6**. The starting fragments were obtained in three steps from commercially available materials and coupled in excellent yield. Again the isolated material was obtained in high purity.





3. Scale-up in Flow



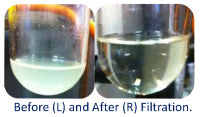
As DABAL couplings have been shown to work efficiently under microwave conditions[2] it stood to reason that the reaction could be carried out in a pressurised heated tube of a continuous flow set up.

We found initial success using a commercial FlowSyn unit using sample loops to deliver the reaction mixture to the heated coil (4.9 g).[3] However it was soon realised that the scale was limited by the volume of the sample loops available to us. Therefore we set out, in collaboration with the Dr Zac Amara of the Poliakoff group, to design a continuous flow system that would handle the air sensitive reaction mixture and process a lot of material in little time.

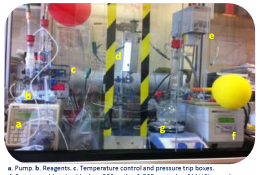
Uniqsis set-up.

3.1. Rig Set-up

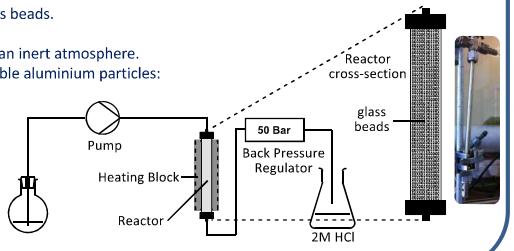
Pump: A Jasco PU2080i Inert pump with graphite seals and all internal parts made of PTFE & PEEK. Inlet parts were dried in a glove box prior to use.
Tubing: Stainless steel pipes with Swagelok fittings.
Reactor: 175 × 7 mm (4 mm ID) stainless steel tube, filled with 800 - 1000 µm glass beads.
Back Pressure Regulator: Automated with variable pressure settings.
Other: Rig is connected to a hi-vacuum and an argon inlet for drying and creating an inert atmosphere.
Reagents: Were pre-mixed and filtered through baked celite to remove any insoluble aluminium particles:



Before (L) and After (R) Filtration.



a. Pump. b. Reagents. c. Temperature control and pressure trip boxes.
d. Reactor and heating block. e. BPR outlet. f. BPR control. g. 2M HCl quench



3.2. Optimisation

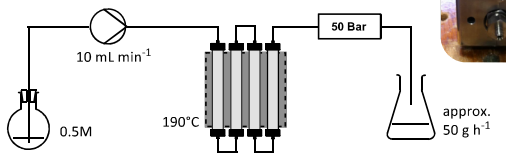
Changes in pressure had little effect, where as concentration has a small positive effect. Temperature appears to be the key to this reaction and at 190 °C the reaction operates very efficiently up to flow rates of 8 mL min^{-1} where the conversion begins to drop.

Entry	Concentration (M)	Flow Rate (mL min^{-1})	Temp. (°C)	Back Pressure (Bar)	Conversion (%)
1	0.25	1	130	n/a	7
2	0.25	1	130	50	10
3	0.5	1	130	50	25
4	0.5	1	130	75	22
5	0.5	1	130	100	20
6	0.5	1	150	100	40
7	0.5	1	170	100	97
8	0.5	1	170	50	99
9	0.5	1	190	50	98
10	0.5	2	190	50	100
11	0.5	4	190	50	100
12	0.75	8	190	50	86

Conversion determined by 1H NMR

3.3. High Throughput reactor

As outlined in **entry 12** at 8 mL min^{-1} the conversion begins to fall when using one reactor. To improve our throughput we employed 4 reactors in series, allowing us to obtain full conversion to the ester at a flow rate of 10 mL min^{-1}. This equates to approx. 50 g of ester per hour!



4. Conclusions

DABAL-Me_3 promoted couplings of amides on 1 - 100 g scales have been demonstrated in batch in both an laboratory and industrial setting. Several options for continuous flow processing have been developed . The potential for DABAL-Me_3 to be used in an API synthesis has been realised and demonstrated.

Acknowledgements

We are extremely grateful to Dr Zac Amara for building the flow rig and all his assistance with the flow project and to Mark Ladlow and Uniqsis for lending us the equipment for the initial trial. We thank Aesica for allowing us to run the large scale reaction in their development lab.

1. N. Dubois, D. Glynn, T. McInally, B. Rhodes, S. Woodward, D. J. Irvine, C. Dodds, *Tetrahedron* **2013, 69** 9890
2. D. Glynn, D. Bernier, S. Woodward, Tetrahedron Lett. **2008**, 49, 5687
3. 3. Uniqsis Application Note 28: Amide Bond Formation in Flow.