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Microwave acceleration in DABAL-Me$_3$-mediated amide formation

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ABSTRACT

Facile direct coupling of esters and secondary amines to afford tertiary amides proceeds under microwave irradiation using the air-stable trimethylaluminium source DABAL-Me$_3$ [(DABCO)(AlMe$_3$)$_2$]. Excellent yields (88–98%) are attained for cyclic secondary amines in reactions that are complete in 5–16 min. The process can be extended to the formation of Weinreb amides (upto 76% from commercial MeNHOMe·HCl) in a one-pot procedure using NaH to liberate the free methoxyamine.

The formation of amide bonds constitutes a widely used process for both synthetic organic chemists and biologists. Amide linkages are present in many biologically active molecules and key natural products. It has been noted recently that around 66% of all preliminary screening reactions in industrial medicinal chemistry laboratories involve amide formation.[1] Whilst many methods exist for amide formation,[2] a procedure for the direct coupling of secondary amines with simple esters would provide useful methodology for small molecule library formation and for key steps in total synthesis. We recently described direct preparation of primary amides from RCO$_2$Me using the air-stable trimethylaluminium source DABAL-Me$_3$ **1** under simple reflux conditions.[3] Inspired by recent developments in microwave-promoted chemistry,[4] we were encouraged to try such procedures for coupling of less reactive secondary amines with esters that gave unacceptable yields in our previous procedure (Scheme 1).

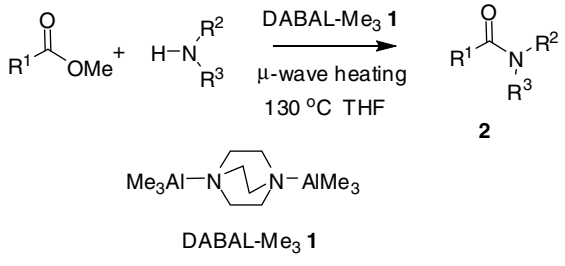
Preliminary optimization of the chemistry shown in Scheme 1 was carried out using the reaction of pyrrolidine and methyl benzoate (Table 1). Very significant rate accelerations are realized over the simple thermal procedure—complete conversion was attained within 8 min in tetrahydrofuran at 130 °C under microwave heating. Optimal amide coupling yields were attained through use of 0.8 equiv of DABAL-Me$_3$.

A variety of secondary amines **3a–d** were coupled to esters **4a–c** (Scheme 2, Table 2). Reactions were performed on a 1 mmol scale.[5] In the absence of DABAL **1** there was no reaction. In the case of

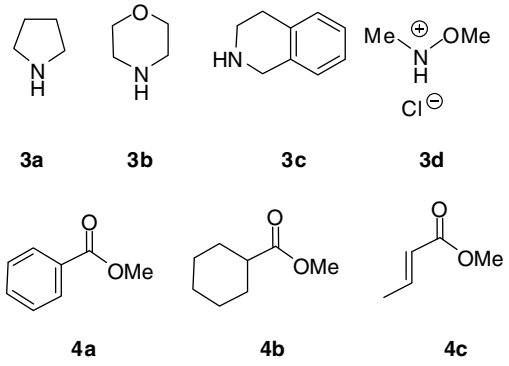
Table 1
Yield of secondary amine coupling realized from PhCO$_2$Me and various DABAL-Me$_3$ ratios

Run	DABAL-Me$_3$ equiv	Yield[a] (%)
1	0.4	55
2	0.6	74
3	0.8	92
4	1.0	74
5	1.2	58

[a] Isolated yield. Experimental procedure: Under an argon atmosphere PhCO$_2$Me (136 mg, 1.0 mmol) and pyrrolidine (72 mg, 1.0 mmol) were treated with DABAL-Me$_3$ (0.4–1.2 mmol) in THF (4 mL). Heating: 300 W at 130 °C for 8 min.



Scheme 1. Microwave-promoted formation of 3° amides.



Scheme 2. Esters and amines used in microwave coupling reactions.

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Table 2
Preparation of various tertiary amides under microwave heating in the presence of DABAL-Me_3

2	R^1	R^2	R^3	Time (min)	Yield[a] (%)
2aa	Ph	$-(CH_2)_4-$		5	92
2ba	Cy	$-(CH_2)_4-$		5	92
2cb	crotyl	$-(CH_2)_2O(CH_2)_2-$		16	52
2ab	Ph	$-(CH_2)_2O(CH_2)_2-$		5	98
2bb	Cy	$-(CH_2)_2O(CH_2)_2-$		5	92
2ac	Ph	$-(CH_2)_2C_6H_4(CH_2)-$		12	88
2bc	Cy	$-(CH_2)_2C_6H_4(CH_2)-$		12	82
2ad[b]	Ph	OMe	Me	10	76
2bd[b]	Cy	OMe	Me	16	62

[a] Isolated yield.
[b] Amine **3d** (THF solution) was treated with NaH (1.0 equiv., 22 °C, 25 min) and the resulting free amine NaCl mixture was treated directly with DABAL-Me_3 and the ester.

somewhat more hindered amine/ester pairs it was advantageous to extend the reaction time. However, all the reactions are technically trivial to carry out: all the components are simply combined and irradiated in a commercial apparatus.

In Table 2 the following nomenclature is used: the first letter refers to the parent ester in Scheme 2 and the second to the parent amine. Thus, **2aa** represents **2** with R^1 = Ph and R^2, R^3 = $(CH_2)_4$. Formation of both the morpholine analogues **2ab**, **2bb** and the quinoline analogues **2ac**, **2bc** occurred in excellent 98%, 92% 88%, and 82% yields, respectively (Table 2).

Direct use of the commercial Weinreb amide source **3d** led initially to very low yields, but this situation could be reversed by one-pot in situ deprotonation of **3d** with NaH followed by a microwave-promoted coupling. Unsaturated esters were not tolerated as well in the new process and gave only moderate yield transformations (**2cb**). Finally, the preparation using hindered acyclic 2° amines still proved highly challenging giving poor yields.

Overall, we have described a technically very simple procedure for the direct formation of tertiary amides from secondary amines and esters under microwave heating. Whilst high temperatures (130 °C) are required, few other direct procedures are currently available that are as convenient as those outlined here.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.090.

References and notes

1. Analysis of 128 drug candidate molecules prepared by AstraZeneca, GlaxoSmithKline and Pfizer: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, 2337–2447. For safety driven rationals in pharmaceutical route choice see: Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, *106*, 3002–3027.
2. (a) Sahasrabudhe, K.; Gracial, V.; Aube, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914–7922; (b) Sonntag, N. O. V. *Chem. Rev.* **1952**, *52*, 237–416; (c) El Kaim, L.; Grimau, L.; Oble, J. *Angew. Chem.* **2005**, *117*, 8175–8178; (d) Dineen, T. A.; Zajae, M. A.; Myers, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 16406–16409; (e) Azumaya, I.; Okamoto, T.; Imabeppu, F.; Takayanagi, H. *Tetrahedron* **2003**, *59*, 2325–2331.
3. Novak, A.; Humphreys, L. D.; Walker, M. D.; Woodward, S. *Tetrahedron Lett.* **2006**, *47*, 5767–5769.
4. (a) Katritzky, A. R.; Cai, C.; Singh, S. K. *J. Org. Chem.* **2006**, *71*, 3375–3380; (b) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233–236; (c) Khadilkar, B. M.; Madyer, V. R. *Synth. Commun.* **2005**, *32*, 1731–1734; (d) Hellal, M.; Bihel, F.; Mongeot, A.; Bourgignon, J.-J. *Org. Biomol. Chem.* **2006**, *4*, 3142–3146.
5. *Representative example:* A dry microwave vessel (4 ml) was charged with a magnetic stirrer bar and 1,2,3,4-tetrahydroisoquinoline (125 μl, 133 mg, 1.00 mmol). To this, THF (4 ml) was added along with DABAL-Me_3 (208 mg, 0.8 mmol) and methyl benzoate (136 mg, 125 μl, 1.00 mmol). The microwave vial was sealed with a plastic microwave cap and placed in a CEM discover microwave and irradiated (300 W) at 130 °C for 12 min. The reaction mixture was quenched with 1 M HCl (4 ml), and extracted with DCM (3 × 30 ml), the combined organics were dried over magnesium sulfate and evaporated to yield the crude product. The product was purified using column chromatography with 4:1 petrol/ethyl acetate as eluent.