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Methylaluminoxane (MAO)-Assisted Direct Amidation of Esters

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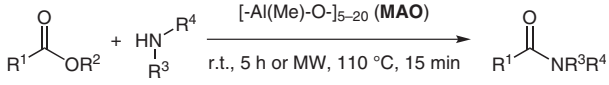

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Abstract Aliphatic and aromatic esters are efficiently transformed into amides in good to excellent yields, under mild conditions using methylaluminoxane (MAO). This reaction can be performed either at room temperature or by applying microwave irradiation.

Key words amidation, MAO, esters, amides, microwave

Amide-bond formation is a fundamental reaction in organic chemistry considering the frequent occurrence of amides in natural and pharmaceutical compounds.[1] Development of new and direct methods of amide synthesis is of great interest as existing ones may present some limitations due to the use of expensive reagents or the application of harsh conditions. Thus, in recent years, various complementary methods of direct amidation of esters or acids have been published in the literature.[2]

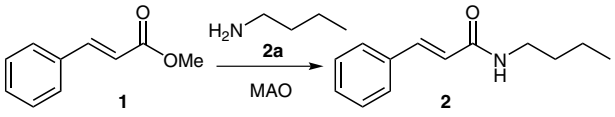
Aluminium-mediated amine activation, developed by Weinreb in the late 1970s,[3a] is one of the most general methods for direct amide-bond formation. A safer high-throughput version of this reaction has recently been developed using a microreactor system,[3b] and the scope of the reaction was extended to carboxylic acids.[3c] However, trimethylaluminium is highly pyrophoric and thus dangerous to handle on a large scale. In addition, the aluminium-amide intermediate is unstable at high temperatures and may lead to exothermic reaction even at room temperature. All these drawbacks have made this reaction inappropriate for many conversions despite its potential versatility.

We report herein the use of methylaluminoxane[4] (MAO) as a safe alternative to trimethylaluminium-mediated amide-bond formation. MAO is prepared by controlled hydrolysis of trimethylaluminium. Its structure is schematically represented as $[-Al(Me)O-]_{5-20}$ although, despite extensive research and many attempts to propose structural models, its exact composition remains unknown.[4a] Nevertheless, MAO is a very powerful cocatalyst used in combination with group 4 metallocenes for the polymerization of α-olefins on an industrial scale. However, its application in the laboratory is more limited, although Lipshutz recommended using it as a cocatalyst to improve the efficiency of carboalumination reactions.[5]

In order to validate the use of MAO as a safe substitute for trimethylaluminium, we studied the direct amidation of methyl cinnamate (**1**) with butylamine (**2a**). As expected, stirring compounds **1** and **2a** at room temperature for 18 hours only resulted in recovery of starting materials (Table 1, entry 1), while addition of MAO (10% in toluene) led to the formation of the desired amide **2**. The conversion rate was proportional to the amount of MAO added (from 0.2–2 equiv, Table 1, entries 2–5). With three equivalents of MAO, the conversion was almost complete in five hours (Table 1, entries 6 and 7). To reduce the amount of amine while keeping a good conversion rate, the reaction was performed at higher temperatures (Table 1, entries 8 and 9). Despite the stability of MAO under these conditions and the improvement of the conversion rate (Table 1, entries 4 and 8), the reaction was not complete. As we noticed an increase in the rate and speed of the conversion at higher temperatures, the reaction was carried out at 110 °C under microwave irradiation. Using three equivalents of MAO and two equivalents of *n*-butylamine, conversion was complete in a few minutes (Table 1, entries 11–14), whereas only the starting ester was recovered after 15 minutes when MAO was not used (Table 1, entry 10). Moreover, the reaction is chemoselective since the 1,4-addition product was never observed in the crude mixture. Finally, mixing the ester with two equivalents of amine, three equivalents of MAO either at room temperature for five hours or at 110 °C for 15 minutes under microwave irradiation gave the best results.

The scope of this MAO-mediated direct amidation of ester was then studied by varying the amines **2a**–**14a**. The results of both method A (room temperature) and method B (microwave heating at 110 °C for 15 min) are detailed in Table 2.[6] Regardless of the conditions used, a complete conversion of ester **1** into the corresponding amide was observed for the less-hindered amines such as aniline (**3a**), benzylamine (**4a**), *N*-methylbenzylamine (**5a**), pyrrolidine (**6a**), morpholine (**7a**), *n*-butylamine (**2a**), and isopropylamine (**8a**; Table 2, entries 1–7). Despite these excellent conversions, the amide derived from pyrrolidine **6a** was ob-

Table 1 Optimization of the Amidation Reaction Conditions

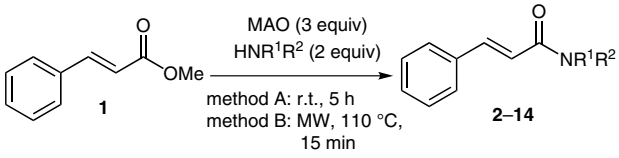


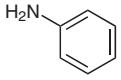
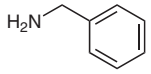
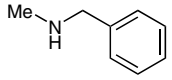
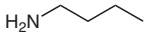
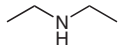
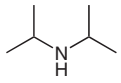
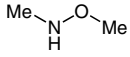
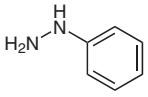
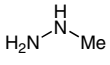
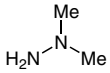
Entry	**2a** (equiv)	MAO (equiv)	Temp	Time	Conv. (%)[a]
1	1	0	r.t.	18 h	0
2	1	0.2	r.t.	18 h	24
3	1	0.5	r.t.	18 h	40
4	1	1	r.t.	18 h	66
5	1	2	r.t.	5 h	57
6	1	3	r.t.	5 h	94
7	2	3	r.t.	5 h	>95
8	1	1	80 °C	5 h	81
9	1	1	110 °C	5 h	82
10	2	0	110 °C (MW)	15 min	0
11	2	3	110 °C (MW)	5 min	85
12	2	3	110 °C (MW)	10 min	>95
13	2	3	110 °C (MW)	15 min	>95
14	2	3	110 °C (MW)	30 min	>95

[a] Conversion of **1** into **2** calculated from ^{1}H NMR spectrum of the crude mixture.

tained with only a moderate yield (Table 2, entry 4) due to difficulties in extraction. Furthermore, bulkier amines like *tert*-butylamine (**9a**), diethylamine (**10a**), and diisopropylamine (**11a**, Table 2, entries 8–10) led to the corresponding amides with lower yields due to incomplete conversion (close to zero for **11a**). The Weinreb amide **12** (Table 2, entry 11) could be obtained with a satisfactory yield but only at room temperature. Indeed, degradation was observed under microwave irradiation in the presence of *N*,*O*-dimethylhydroxylamine (**12a**). Hydrazines could also be used as substrates for direct amidation. The phenylhydrazine (**13a**) gave the expected *N*-phenylhydrazide (**13**) with a reasonable yield after purification (Table 2, entry 12) whereas the methylhydrazide (Table 2, entry 13) could not be isolated. Indeed an intramolecular Michael addition occurred leading to 5-phenylpyrazolidine-3-one in this case. The low yield observed in the amidation of the 1,1-dimethylhydrazine (Table 2, entry 14) suggests that the secondary amine of the hydrazines is more reactive than the terminal primary ones, thus leading to the branched N-substituted hydrazides.

Table 2 Scope of the Direct Amidation of Methyl Cinnamate (**1**)

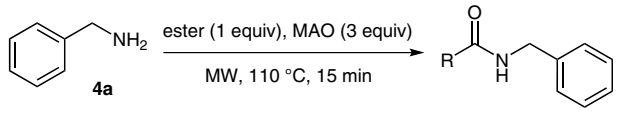


Entry	Amine		Method	Conv. (%)[a]	Yield (%)[b]
1	**3a**		A B	>95 >95	85
2	**4a**		A B	>95 >95	83
3	**5a**		A B	>95 >95	90
4	**6a**		A B	>95 >95	43
5	**7a**		A B	>95 >95	73
6	**2a**		A B	>95 >95	97
7	**8a**		A B	>95 >95	99
8	**9a**		A B	52 43	40
9	**10a**		A B	71 61	60
10	**11a**		A B	14 0	9 –
11	**12a**		A B	60 0	55 –
12	**13a**		A B	>95 >95	45[c]
13	**14a**		A B	>95 >95	42[c,d]
14	**15a**		A B	12 17	<10[c]

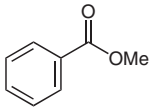
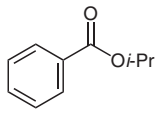
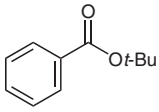
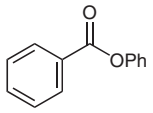
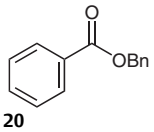
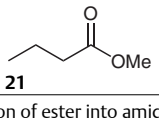
[a] Conversion of **1** into amide calculated from ^{1}H NMR spectrum of the crude mixture.
[b] Average yield obtained after aqueous HCl washing.
[c] Average yield obtained after flash chromatography on silica gel.
[d] The pyrazolidine-3-one was obtained.

Finally, the impact of the nature of the ester was studied (Table 3). For this purpose, benzylamine (**4a**) was stirred with different esters and MAO for 15 minutes with microwave heating. The reaction was found to be sensitive to the steric bulk of the aliphatic leaving groups. Indeed, a decrease in the conversion rate of the ester into the amide was observed between the methyl, isopropyl, and *tert*-butyl group (Table 3, entries 1–3). The phenyl and benzyl esters **19** and **20** led to the corresponding amide with very good yields (Table 3, entries 4 and 5). Moreover, despite the lower conversion rate, the aliphatic amide resulting from methyl butyrate **21** could be obtained in a moderate yield (Table 3, entry 6). This can probably be explained by ester volatility. Carboxylic acids were also tested under the same conditions but did not give the expected amides.

Table 3 Influence of the Nature of Ester in Direct Amidation



4a

Entry	Ester	Conv. (%)[a]	Yield (%)[b]
1	 **16**	>95	90
2	 **17**	90	75
3	 **18**	50	38
4	 **19**	>95	87
5	 **20**	>95	88
6	 **21**	80	54

[a] Conversion of ester into amide calculated from ^{1}H NMR spectrum of the crude mixture.
[b] Yield of isolated product obtained after flash column chromatography on silica gel.

In conclusion, a new and efficient method for the direct amidation of esters is disclosed using MAO as a safe alternative to trimethylaluminium. This easy-to-handle reaction can be performed either at room temperature or within a few minutes on exposure to microwave irradiation. Moreover, the conditions are well tolerated by a great range of amines and esters, despite the unfavorable influence of steric bulk of the reactants; although, this feature could be applied to develop selective amidation reactions in the presence of different esters.

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References and Notes

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(5) Lipshutz, B. H.; Butler, T.; Lower, A. *J. Am. Chem. Soc.* **2006**, *128*, 15396.

(6) **General Procedures**

Method A: To a mixture of ester (1 mmol) and amine (2 mmol) under an argon atmosphere was added a 10% solution of MAO in toluene (2 mL, 3 mmol). After 5 h at r.t., the solution was diluted with MTBE (3 mL) and quenched by addition of 10% aq NaOH (2 mL). The product was then extracted with MTBE (3×) and the combined organic layers were washed with a 1 M solution of HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give usually the pure product (purity >90%). Less pure products were purified by flash chromatography on silica gel using a mixture of heptane and EtOAc.

Method B: A mixture of ester (1 mmol) and amine (2 mmol) was placed in a MW vial under an argon atmosphere. A 10% solution of MAO in toluene (2 mL, 3 mmol) was then added, and the mixture was irradiated and stirred for 15 min at 110 °C. The solution was then cooled to r.t. and diluted with MTBE. The products were isolated in the same manner as in method A.