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Formylation of Amines through Catalyst- and Solvent-free Transamidation Reaction

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ABSTRACT

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The formyl moiety (-CHO) is one of the simplest group that can be used to protect an amine function,¹ and the resulting formamides may serve as isocyanate precursors.² Among all the methods available for this purpose, reaction between amines and the inexpensive formamide $HC(O)NH_2$ offers, in theory, a very interesting way since ammonia is the only effluent produced. Unfortunately in practice transamidation processes remained unattractive for a long time due to the harsh conditions systematically required.^{3,4} However, some friendlier protocols have recently emerged to promote these reactions by mean of catalysts under heating (30-150 °C) for several hours (5-36 h): Cp₂ZrCl₂,⁵ L-proline,⁶ B(OCH₂CF₃)₃,⁷ boric acid with water⁸ and hydroxylamine hydrochloride.^{9,10} In these two latter cases, authors suggested that an hydrogen bonding activation of the starting amide by the catalysts B(OH)3 and HO-NH2·HCl was a key point of the reaction success.^{8,9} In this line, water is a molecule that exhibits both excellent H-bonding donation and acceptance ability, and could thus be used as solvent to promote formyl transfer from formamide (1.3 eq) to benzylamine (Table 1). At room temperature, the reaction proceeded very slowly to afford, after 4 days, 1a as single product in only 37% yield (entry 1). Encouraged by this result and by previous works on the beneficial effects of hyperbaric conditions on the kinetics of organic reactions in water,^{11,12} this transamidation reaction was assessed under ultra-high pressure conditions. Thus, by increasing the pressure to 5 kbars, the reaction was significantly accelerated and 1a was obtained in 66% yield within only 24 h, still at room temperature (entry 2). However, when the same reaction was performed in ethanol (20 °C, 5 kbars), which also

The transamidation between formamide and various amines proceeds under heating, without any catalyst nor solvent, providing thus green and neutral conditions for the formylation of primary and secondary amines. The resulting amide product can be directly transformed, in a one pot sequence, into monomethylamine.

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1

exhibits interesting H-bonding properties, the yield in transamidation product dropped to 30% (entry 3). Surprisingly, performing the reaction in water at 80 °C under ambient atmosphere gave a very good 82% yield (entry 4), while the conversion was still low under the same conditions in ethanol (30%, entry 5), showing thus the unique role of water in this reaction. However, the best result was obtained by performing the reaction without any solvent at 80 °C, allowing thus almost full conversion into the target product (97%, entry 6).

Table 1

Transamidation between benzylamine and formamide^a

$H \stackrel{O}{\longrightarrow} H_{2} $					
Entry	Solvent	P (bars)	T (°C)	t (h)	Yield (%) ^b
1	H ₂ O	1	20	96	37
2		5000	20	24	66
3	EtOH	5000	20	24	30
4	H_2O	1	80	24	82
5	EtOH	1	80	24	33
6	neat	1	80	24	97

^a Conditions: benzylamine (1 mmol), formamide (1.3 mmol), solvent (0.7 mL).

^{b 1}H NMR yield

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These preliminary experiments show that water is a very good solvent for the formylation of benzylamine with a slight excess of $HC(O)NH_2$ (1.3 eq) under pressure or thermal activation, but best results were obtained just by performing this transformation neat at 80 °C. The scope of the reaction was then studied with various amines at 80 °C, without any solvent, and with an improved amount of formamide (1.0 eq). Results are presented in Table 2.

Under these conditions, N-formyl benzylamine 1a was isolated in 82% yield after 24 h (entry 1).¹³ The reaction was also performed under microwave irradiation in a shorter reaction time (3 h), but **1a** was afforded in a lower yield (68%, entry 2). The transformation was also successfully extended to 2-(aminomethyl)-naphthalene (62% yield for 1b; entry 3) and 2-(aminomethyl)-pyridine (96% yield for 1c; entry 4). The formylation of \pm - α -methylbenzylamine was more difficult with 72 h at 120 °C (66% yield for 1d; entry 5). Moreover, aliphatic amines cyclohexylamine and dodecylamine also underwent effective formyl transfer (80% for 1e and 70% yield for 1f; entries 6 and 7). The reaction of secondary amines is also effective: morpholine and N-methylbenzylamine yielded the desired products in good yields (72% for both 1g and 1h, entries 8 and 9). However, when starting from the bulky dibenzylamine, several days were required to obtain 1i in 60% yield (entry 10). Aromatic amine indoline was also successfuly transformed after 48 h at 80 °C (71% yield for 1j). Interestingly, with tryptamine as substrate, the formyl moiety was exclusively transferred onto the -NH₂ without any formylation of the -NH (87% for 1k). As last example, enantiopure L-valine ethyl ester gave the corresponding *N*-formyl valinate **11** in excellent 92% yield with full preservation of the optical purity (entry 13).¹⁴

Besides protection purpose, the transfer of a formyl moiety onto an amine is also one of the surest way to selectively access to the corresponding monomethylamine, since the secondary formamide product can be fully reduced into monomethylamine by mean of a hydride reactant.¹⁵ Since we have been able to perform transamidation between simple formamide and amine in stoichiometric amounts without solvent, we imagined that the corresponding monomethylamine could be obtained in a one-pot fashion without isolating the intermediate amide product. Thus, benzylamine was reacted with formamide as reported in Table 1 (80 °C, 24 h), and the crude product **1a** was dissolved in THF at 0 °C and LiAlH₄ was added to afford the expected monomethylamine **2a** in 81% yield (Scheme 1).



Scheme 1. One pot monomethylation of benzylamine

In conclusion, we have been able to implement simple conditions for uncatalyzed transamidation reaction between inexpensive formamide and amines: whereas a good conversion was obtained with water as solvent under 5 kbars, best results were attained under thermal heating without any solvent. By this mean various primary and secondary amines (aliphatic, benzylic, aromatic) have been succesfully formylated. Moreover, these neutral conditions offers a convenient access to monomethylamines in a one-pot fashion. Table 2

Formylation of amines under solvent-free conditions^a

1 01111	fution of unines unde	i sorrer	n nee	conditions		
	R ¹ NH + H ₂ N	√Цн		neat, Δ	R ¹ NH	
	R ²				R ²	
Entry	RR'NH	T (°C)	t (h)	Product		Yield (%) ^b
1		80	24	0		82
2°	BnNH ₂	80	3		1a	68
3	2-(C ₁₀ H ₇)CH ₂ NH ₂	80	24	()	~_N,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	62
4	3-(C ₅ H ₄ N)CH ₂ NH ₂	80	24		⊖ H 1¢	96
5	PhCH(Me)NH ₂	120	72		1 1d	66
6	$C_6H_{11}NH_2$	80	36	₩ v	H 1e	80
7	<i>n</i> -C ₁₂ H ₂₅ NH ₂	80	31	M ₁₀ NH	H 1f	70
8	Morpholine	80	24		1g	72
9	BnNHMe	80	24	Ph N H		72
10	Bn ₂ NH	120	263		+ 1i	60
11	Indoline	80	48		^H 1j	71
12	Tryptamine	80	24			87
13	L-Valine ethyl ester	80	24	EtO ₂ C N	0 ↓ H 11	91

^a Starting from amine (3 mmol) and formamide (3 mmol).

^b Isolated yields.

^c Performed under microwave irradiation (200 W).

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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