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A novel and simple transamidation of carboxamides in 1,4-dioxane without a catalyst

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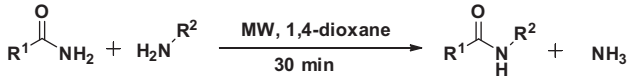
ABSTRACT

An easy acylation and formylation of amines has been achieved via transamidation using 1,4-dioxane. The investigation works efficiently without an added catalyst and completes within short time under microwave irradiation.

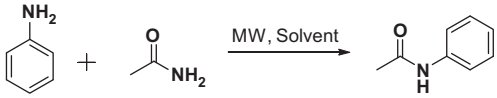
Development of novel and efficient methodologies for the synthesis of carboxamides is a vital task as they are prevalent in living systems and numerous biologically active compounds including pharmaceuticals, agrochemicals, and polymers.[1] The usual practice for the synthesis of amides involves the coupling of acid derivatives with amines,[2] although the lability of activated carboxylic acid derivatives remains a major drawback of this approach. To circumvent this problem, alternative methods for the synthesis of amides have been developed using amidation of aldehydes with amines,[3] aminocarbonylation of aryl halides[4] and alkynes,[5] direct amide synthesis from alcohols and amines,[6] direct amidation of alcohols with nitroarenes,[7] umpolung reaction of amines with α-halo nitro alkanes,[8] Beckmann rearrangement,[9] and cross coupling of formamides with alkyl/aryl halides.[10]

A significant current addition to amide synthesis is 'transamidation' which makes the use of cheap and abundant starting materials such as amines and amides. However, due to high inertness of amide bond, these reactions are generally catalyzed by activating agents or catalysts which are expensive and/or waste generating. Recent catalysts explored for transamidation include hydroxylamine hydrochloride, copper, cerium dioxide, boric acid, and borate esters.[11] Although, these methods have their own advantages, they all invariably suffer from long reaction times and elevated temperature profile of the reaction. Recently our group has reported a hypervalent iodine catalyzed mild and efficient transamidation reaction under microwave irradiation.[12]



Scheme 1. Catalyst-free transamidation using 1,4-dioxane.

Table 1
Effect of solvents on transamidation[a]



Entry	Solvent	Time (min)	Temp (°C)	Yield (%)
1	Toluene	30	120	20
2	Xylene	30	120	15
3	Chlorobenzene	30	120	0
4	DMSO	30	120	0
5	DMF	30	120	0
6	H_2O	30	100	10
7	Acetonitrile	30	80	0
8	1,4-Dioxane	30	100	0
9	1,4-Dioxane	30	120	73
10	1,4-Dioxane	40	120	73
11	1,4-Dioxane	30	130	73
12	PEG-600	30	120	0
13	Isopropanol	30	80	0
14	THF	30	70	0
15	DCE	30	80	0

[a] Reaction conditions: aniline (1 mmol), acetamide (1 mmol), solvent (2 ml), Anton Paar Monowave. Yield refers to separated yield after column chromatography.

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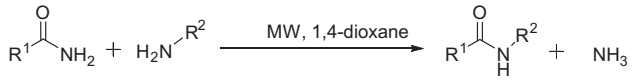
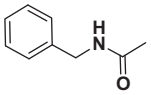
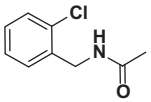
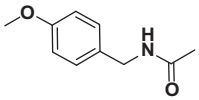
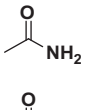
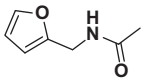
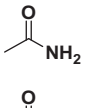
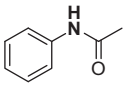
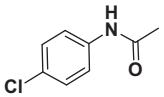
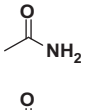
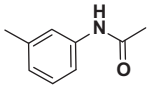
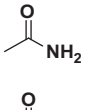
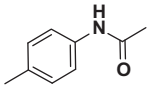
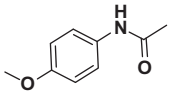
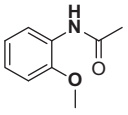
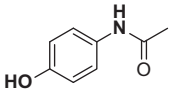
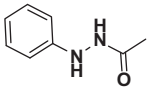
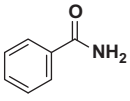
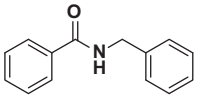
Table 2
1,4-Dioxane mediated transamidation[a]



Entry	Amide	Product	Time (min)	Yield (%)
1			30	76
2			30	68
3			30	79
4			30	80
5			30	73
6			30	78
7			30	74
8			30	78
9			30	80
10			35	70
11			30	76
12			30	78
13			35	0

[a] Reaction conditions: amine (1 mmol), amide (1 mmol), 1,4-dioxane (2 ml), Anton Paar Monowave. Yield refers to separated yield after column chromatography.

As a part of our ongoing program to develop efficient and green protocols,[13] we wish to describe herein an in-depth analysis of the effect of various solvents on the transamidation reaction. The findings led us to achieve a mild and effective 1,4-dioxane mediated transamidation approach without the use of any catalyst within short time under microwave (MW) irradiation (Scheme 1).

To begin with, we examined the effect of different solvents without the aid of a catalyst on the transamidation model reaction between aniline and acetamide and the results are described in Table 1. Out of different solvents tested during the course of optimization, the solvents such as DMSO, DMF, PEG-600, THF, isopropanol, dichloroethane, acetonitrile, and chlorobenzene were found to be completely ineffective (entries 3–5, 7, 12–15). Solvents such as toluene, xylene, and water could bring about only a little conversion (entries 1, 2, and 6). However, when the reaction was carried out in 1,4-dioxane, we were amazed and delighted to observe a single-handedly magical effect of 1,4-dioxane resulting in 73% isolated product yield at the temperature of 120 °C (entry 9). It is interesting to note that 1,4-dioxane could not afford any conversion at 100 °C (entry 8), hence implicating a crucial temperature effect on the reaction. A 20 °C rise in temperature caused a spectacular effect on the reaction.

In order to ensure the generality of this finding, the transamidation of amides with various amines was undertaken and the results are summarized in Table 2. Various amines having both electron donating and electron withdrawing groups underwent the reaction smoothly and gave rise to good to excellent product yields. Functional groups like hydroxyl, chloro, methyl, and methoxy were well tolerated in the reaction (entries 2, 3, 6–11). Low yield in the case of ortho substituted reactants is attributed to steric factors (entries 2 and 10). Interestingly the transamidation reaction with phenyl hydrazine gave excellent yield (entry 12). Transamidation reactions of benzamide, secondary and tertiary amides, however, could not succeed even at elevated temperatures.

From these results, it could be presumed that 1,4-dioxane strongly activates the amide linkage perhaps through the hydrogen bonding of amide group hydrogen atom with oxygen atom of the solvent,[14] thereby facilitating the reaction particularly in the case of aliphatic amides. Failure of transamidation in the case of benzamide, secondary and tertiary amides may be attributed to their high stability and also due to the failure of 1,4-dioxane to activate these amides to the desired extent. Thus, coordination or interaction of 1,4-dioxane with amide involving the formation of hydrogen bond (Fig. 1) is an underlying cause for the reaction to occur.

Further the applicability of the reaction[15,16] was extended to formamide. As regards the reaction with formamide, various amines reacted well and resulted in excellent product yields as listed in Table 3. Aliphatic amines as well as aromatic primary and secondary amines including *N*-methyl aniline reacted smoothly. The reaction was well tolerated by functional groups like hydroxyl, chloro, methyl, and methoxy, but a little lowering in the product yield was observed in the case of *o*-anisidine due to the steric factor. Heteroaromatic amines such as 2-amino pyridine and furfuryl amine also reacted smoothly.

In summary, we have explored an effective 1,4-dioxane mediated transamidation of amides with different amine partners to afford diverse carboxamides in reasonably good to excellent yields. The reaction proceeds smoothly in the absence of a catalyst or activating agent and can tolerate a number of functionalities.

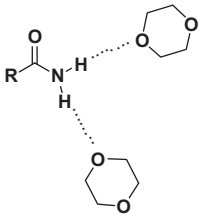
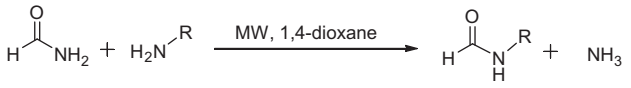
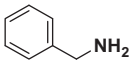
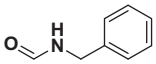
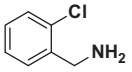
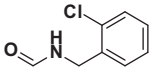
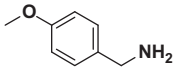
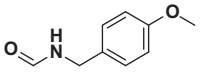
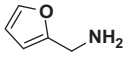
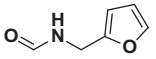
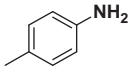
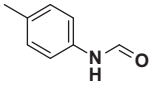
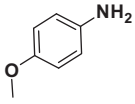
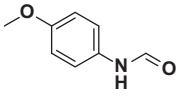
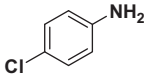
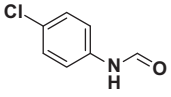
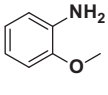
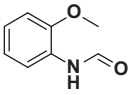
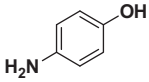
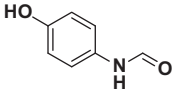
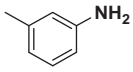
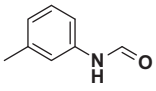
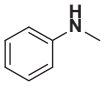
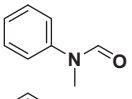
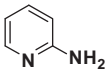
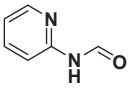


Figure 1. Proposed H-bond formation.

Table 3
1,4-Dioxane mediated formylation of amines[a]



Entry	Amine	Product	Time (min)	Yield (%)
1			30	85
2			30	70
3			30	87
4			30	86
5			30	80
6			30	82
7			30	81
8			30	69
9			30	79
10			30	74
11			30	70
12			30	78

[a] Reaction conditions: amine (1 mmol), formamide (1 mmol), 1,4-dioxane (2 ml), Anton Paar Monowave. Yield refers to separated yield after column chromatography.

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15. General experimental: Microwave reactions were performed using an Anton Paar Monowave 300 mono-mode microwave reactor with a sealed 10-mL vial containing teflon-coated magnetic stir bar. The microwave system contains a single magnetron that delivers up to 850 W installed microwave power in an unpulsed mode over the full power range. The sophisticated software prevents thermal overshoots and the design of the microwave applicator provides utmost field density, which allows efficient heating, even of low-absorbing solvents at any scale. A precisely adjusted IR sensor reflects the internal reaction temperature up to 300 °C. Pressure control up to 30 bars is provided by a non-invasive hydraulic piston embedded in the swiveling cover. For cooling, the cavity is flushed with compressed air automatically after the programed experiment has been processed.
16. General procedure for the 1,4-dioxane mediated transamidation of amides with an amine under microwave. An oven-dried 10-mL microwave reaction vial containing a Teflon-coated magnetic stir bar was charged with carboxamide (1 mmol), amine (1 mmol), and dioxane (2 ml) (undried). The vessel was sealed with a plastic microwave septum, stirred at room temperature for 5 min and then placed into the MW cavity for a specified temperature and time. After the completion of reaction (TLC), the mixture was cooled to room temperature; distilled water (10 mL) was added to it and then extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and then concentrated using a rotary vacuum evaporator. The crude product was purified by column chromatography using a mixture of ethyl acetate/n-hexane (10–20% of ethyl acetate depending upon the product) as an eluent.