SHORT PAPER

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Solvent-free preparation of monoacylaminals assisted by microwave irradiation[†]

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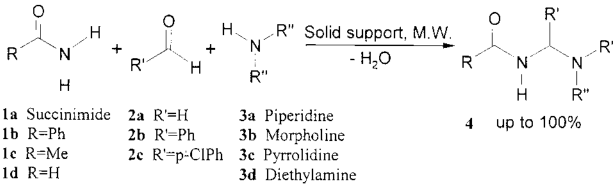
Reaction of amide **1**, aldehyde **2**, and amine **3** promoted by microwave irradiation produced monoacylaminals **4** up to 100% yield in a short time under solvent-free conditions.

The Mannich reaction is one of the most important C–C bond formation methods in organic synthesis.[1] A large variety of CH-acidic compounds have been previously used in Mannich reactions. Compounds containing acidic N–H are also used to give the corresponding Mannich bases. For example, Mannich reaction of amides gives monoacylaminals which are biologically active agents[2] and constituent units of retropeptides[3] or intermediates for the synthesis of heterocycles.[4] The reaction can also be used for the protection of amides[5] and amines.[6]

Many methods have been developed for the preparation of monoacylaminals including (i) the Mannich reaction of amines with formaldehyde and amines,[7] (ii) nucleophilic substitution of chloride in chloromethylamides or chloromethylamines with an appropriate nucleophile[8], (iii) reaction of imines with ketenes$_9$, (iv) amine or amide exchange in monoacylaminals[10], and (v) acetylation of cyclic aminals.[11] All of the above *wet* methods need solvents and long reaction times or are restricted to aminomethylation of amides. Recently Katrizky *et al*. have reported benzotriazole assisted aminoalkylation of amides,[12] in which an aldehyde, benzotriazole and an amide (or an amine) are linked together and subsequently reacted with an appropriate amine (or amide) to give the corresponding monoacylamines. Although this method among the others is the most general one, it needs *in situ* deprotonation of amides and relatively long reaction times.[12c]

In continuation of our research on Mannich reactions[13] and microwave assisted reactions,[14] we now report that solvent-free reaction of amide **1**, aldehyde **2**, and amine **3** over solid surfaces such as acidic alumina, KF-alumina and montmorillonite K-10, promoted by microwave irradiation, produces monoacylaminals **4** in a short time (Scheme 1).



Scheme 1

For instance succinimide **1a**, 40% aqueous solution of formaldehyde **2a**, and piperidine **3a** were mixed with acidic alumina and irradiated in a domestic microwave for 12 min, yielding 100% monoacylaminal **4a**.

The structures and the yields of the products are shown in Table 1.

When the reaction was carried out without using microwave irradiation, compound **4** was produced in very low yields (<30%) after mixing for 24 hours.

In order to investigate the role of supports on product yield, we have examined the yield of the reaction leading to the product **4j** with several solid supports (Table 2).

It is shown that basic supports like basic alumina or KF-alumina act better than acidic supports. This is presumably due to the activating amidic nitrogen of the amide in the presence of basic supports leading to higher yields.[12c]

In summary, we have reported a solvent-free method (environmentally friendly) for preparing monoacylaminals in good to excellent yields.

Experimental

M.p.s were determined on a hot stage or oil bath apparatus without correction. ^{1}H NMR (80 MHz or 300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 80 MHz or Bruker WP 300 MHz in $CDCl_3$ using TMS as internal standard. HRMS were obtained on a Finnigan MAT system MAT 212. Microwave induced reactions were carried out in a domestic microwave oven Moulinex MICRO-CHEF, 900 W at 2450 MHz in moderate power. All of the known products were being characterized with comparison of their melting points or NMR spectra with those in the literature.

General procedure for the preparation of monoacylaminals **4**: A mixture of amide (1 mmol), aldehyde (1 mmol and in the case of **2a**, 1.5 mmol as 40% solution in water) and amine (1.5 mmol) were mixed and ground with the solid support in a mortar. The mixture was transferred to a screw-cap Teflon container and irradiated in microwave oven for the required time.[19] The progress of reaction was monitored with TLC. After cooling, the mixture was extracted with ethylacetate and filtered off. Evaporation of the solvent and remaining amine under reduced pressure gives the crude product that if necessary can be purified by recrystallization or chromatography.[20]

N-(α-pyrrolidinobenzyl)benzamide (**4j**): m.p.: 92–94°C. ^{1}H NMR: $\delta = 1.7$ (s, 4H), 2.5 (br s, 2H), 2.6 (br s, 2H), 5.7 (d, 1H, $J = 9.5$ Hz), 6.8 (d, 1H, $J = 9.5$ Hz), 7.1–7.5 (m, 8H), 7.7 (d, 2H, $J = 7.5$ Hz). ^{13}C NMR: $\delta = 23.5$, 50.5, 71.7, 127.0, 128.0, 128.4, 128.5, 131.5, 134.3, 140.7, 166.5 HRMS (CI) Calcd. for $C_{18}H_{20}N_2O$ + H 281.1654, found 281.1653.

N-(α-pyrrolidino-p-chlorobenzyl)benzamide (**4k**): m.p.: 124–125°C. ^{1}H NMR $\delta = 1.7$ (s, 4H), 2.5 (br, s, 2H), 2.6 (br, s, 2H), 5.7 (d, 1H, $J = 9$ Hz), 6.7 (d, 1H, $J = 9$ Hz), 7.2–7.5 (m, 7H), 7.7 (d, 2H, $J = 7.2$ Hz). ^{13}C NMR: $\delta = 23.6$, 50.6, 71.1, 127.0, 128.5, 128.7, 128.8, 131.7, 133.8, 134.2, 139.4, 166.5 HRMS (CI) calcd. for $C_{18}H_{19}ClN_2O$ + H 315.1264, found 315.1213.

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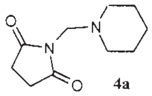
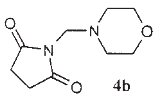
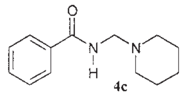
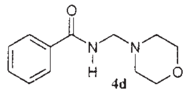
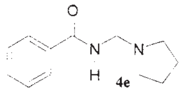
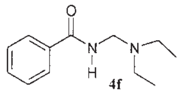
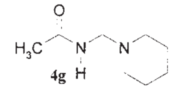
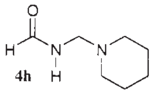
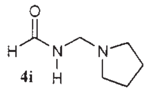
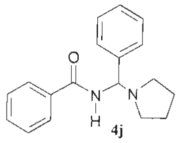
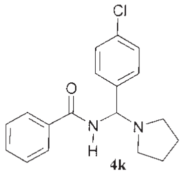
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Aminoalkylation of amides on solid supports promoted by microwave irradiation

Amide **1**	Aldehyde **2**	Amine **3**	Support[a]	Product **4**	Time (min)	Yield (%)	M.p (lit. m.p.)
1a	**2a**	**3a**	**A**	 4a	12	100	103 (104–105)[15]
1a	**2a**	**3b**	**A**	 4b	12	100	105–106 (108)[15]
1b	**2a**	**3a**	**A**	 4c	12	75	128 (127–128)[16]
1b	**2a**	**3b**	**A**	 4d	12	99	67–68 (68–69)[12c]
1b	**2a**	**3c**	**A**	 4e	12	95	Oil[17]
1b	**2a**	**3d**	**A**	 4f	12	80	Oil[18]
1c	**2a**	**3a**	**A**	 4g	12	100	Oil[12c]
1d	**2a**	**3a**	**A**	 4h	12	94	Oil[7f]
1d	**2a**	**3c**	**A**	 4i	12	95	Oil[7f]
1b	**2b**	**3c**	**B**	 4j	20	45	92–94
1b	**2c**	**3c**	**B**	 4k	20	40	124–125

[a]A= Acidic alumina; B= basic alumina.

Table 2 Effects of solid supports on the yield of the product **4j**

Support	Basic alumina	KF-alumina	Silica gel	Montmorillonite K-10	Acidic alumina
Yield	45%	42%	35%	<20%	<25%

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19 The times given in Table 1 are irradiation times. The intervals between irradiations must be considered and added.

20 **4c** was recrystallized from Benzene/petroleum ether and **4f, 4j** and **4k** were purified by chromatography on silica gel using Et_2O/pentane as eluent.