Solvent-free *N*-hydroxymethylation using formalin over basic alumina

Rajive Gupta*, Satya Paul and Puja Nanda

Department of Chemistry, University of Jammu, Jammu-180 006, India

E-mail : rajgupta@sancharnet.in Fax : 91-191-2505086

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A convenient and high yield method for *N*-hydroxymethylation of amines with formalin over basic alumina under solvent-free conditions with microwave heating is described.

N-Hydroxymethylation is among the important reactions finding applications in both laboratory as well as in industry. The most common and cheap reagent used for carrying out hydroxymethylation is formalin^{1a}. Formaldehyde in water^{1b}, 4% potassium carbonate and 40% formaldehyde solution², 50% aqueous ethanol, potassium carbonate and formaldehyde³, potassium hydroxide and 35% aqueous formaldehyde⁴ are other reagent systems used for carrying out hydroxymethylation. Recently, 38% formaldehyde solution and water under ultrasound⁵ has been used for carrying out *N*-hydroxymethylation.

Use of microwave irradiation for carrying out organic reactions is a well-established procedure since reactions are clean, fast and economical. Coupling of two techniques i.e. organic reactions using supported reagents under microwave irradiation has been a field which has shown excellent results leading to the development of many reaction procedures, which are environment friendly, falling in the domain of Green Chemistry. Work in this direction has been recently reviewed⁶.

Keeping in view our interest in devising solvent-free procedures⁷ and their coupling with microwave activation, we have successfully carried out *N*-hydroxymethylation of phthalimide, carbazole, benzamides and benzanilides using formalin (38% formaldehyde solution) over basic alumina.

Formalin (38% formaldehyde solution) over basic alumina is found to be the most efficient and adaptable reagent for carrying out *N*-hydroxymethylation. Further, the support, basic alumina can be reused several times without loss of activity after simple washing with diethyl ether and finally drying in an oven at 70°C.

In order to optimize the results, we carried out *N*-hydroxymethylation of phthalimide under different conditions by testing molar ratios and amounts of support as a

Table 1. *N*-Hydroxymethylation of phthalimide, carbazole, benzamides and benzanilides using formalin over basic alumina (power = 80 W)

		$\text{>N-H} \xrightarrow[\text{MW, power = 80 W}]{\text{HCHO/basic alumina}} \text{>N-CH}_2\text{OH}$			
Entry	Product	Reaction temp. ^a (°C)	Time (min)	Yield ^b (%)	Found m.p./lit.m.p. (°C)
1	<i>N</i> -Hydroxymethyl phthalimide	36–38	5	81	138–140/138 ⁵
2	<i>N</i> -Hydroxymethyl carbazole	42–45	10	70	126–129/128 ⁸
3	<i>N</i> -Hydroxymethyl benzamide	60–65	8	75	105–108/108 ⁹
4	<i>N</i> -Hydroxymethyl phenylacetamide	57–60	2	70	80/78 ³
5	<i>N</i> -Hydroxymethyl- <i>p</i> -chlorobenzamide	59–61	2	70	180–182/183 ¹⁰
6	<i>N</i> -Hydroxymethyl benzanilide	35–38	4	78	161–162 ^c
7	<i>N</i> -Hydroxymethyl- <i>p</i> -chlorobenzanilide	30–32	4	77	186–189 ^c
8	<i>N</i> -Hydroxymethyl- <i>o</i> -chlorobenzanilide	58–60	4	77	80–82 ^c
9	<i>N</i> -Hydroxymethyl- <i>p</i> -nitrobenzamide	48–50	2	71	138–141/140 ¹¹

^aTemperature noted at the end of exposure during microwave experiment by immersing glass thermometer into the reaction mixture and was approximate temperature range.

^bYield of isolated products.

^cSpectral data of entry 6–8 : entry 6 : ¹H NMR (CDCl₃) δ 5.56 (2H, s, CH₂), 6.5–7.06 (5H, m, H_{arom}), 7.5–7.9 (5H, m, H_{arom}), entry 7 : ¹H NMR (CDCl₃) δ 5.70 (2H, s, CH₂), 6.4–7.08 (5H, m, H_{arom}), 7.10–7.48 (2H, d, H_{arom}), 8.01–8.21 (2H, d, H_{arom}); entry 8 : ¹H NMR (CDCl₃) δ 5.68 (2H, s, CH₂), 6.8–7.0 (5H, m, H_{arom}), 7.61–7.82 (3H, m, H_{arom}), 8.21 (1H, s, H_{arom}).

test reaction. It was found that for 5 mmol of substrate, 34 mmol of formalin gave optimum results. The amount of support was also found to be crucial in order to carry out reaction in an environment friendly way and it was found that for 5 mmol of the substrate, 6 g of basic alumina was required. Further, reaction at different power levels from 80–800 W in case of phthalimide was carried out, in order to select the most appropriate power level. The power level of 80 W gave the best results as far as safety and efficiency was concerned.

Experimental

General remarks : Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a JNM-PMX 60 NMR spectrometer (60 MHz) in CDCl_3 using tetramethylsilane as internal standard. The IR spectra was recorded using KBr disc on Hitachi 270-30 spectrophotometer. The reactions were monitored by TLC. For the microwave irradiation experiments described below a conventional (unmodified) household microwave oven equipped with a turntable was used (BPL BMO 800, 800 W and operating at 2450 MHz).

General procedure for N-hydroxymethylation : To a mixture of phthalimide (5 mmol) and formalin (34 mmol), 6 g of basic alumina was added. This was grinded in a pestle and mortar till homogeneous powder was obtained, which was transferred into a 50 mL borosil beaker and irradiated in a microwave oven for an appropriate time (Table 1) at 80 W (monitored by TLC). On cooling at room temperature, the product was removed from the support on treatment with ether (3×15 mL). The combined ether extracts were washed with water and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave product which was crystallized from pet. ether : benzene (2 : 8). The support can be reused several times after simple washing with ether.

The structure of the products was confirmed by ^1H NMR, IR and mass spectra data and by comparison with authentic

samples.

Conclusion :

We have developed a rapid, solvent-free, inexpensive and environment friendly procedure for N-hydroxymethylation which can be a useful alternative to existing methods.

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