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Thermal and microwave-assisted N-formylation using solid-supported reagents

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Abstract—A rapid and easy route to formamides by microwave assisted *N*-formylation of primary and secondary amines is described. Using an insoluble polymer or an inorganic solid-supported reagent as a formylating agent, microwave irradiation furnished the corresponding formamides in high yields, with reduced reaction time and solvent volume over the conventional approach. © 2004 Elsevier Ltd. All rights reserved.

In the past few years, chemistry under microwave heating has been under intense study with significant benefits in the area of organic synthesis.¹ Reagents supported on organic polymers² and/or on the surface of inorganic matrices² have been instrumental in the development of automated parallel synthesis of chemical libraries, particularly in connection with microwave heating.³

During our previous studies, we reported on microwaveassisted transfer hydrogenation of electron-deficient alkenes in high yield, using Wilkinson's catalyst in connection with formate or formic acid supported either on an ion-exchange resin⁴ or on alumina,⁵ as a recyclable hydrogen source. A recent report⁶ extended the use of polymer-supported formate to the reduction of conjugated alkenes and an imine, under classical heating.

Herein we wish to report on the use of polymer (ion-exchange resin) and inorganic solid-supported reagents as a formylating agent to produce formamides starting from primary and secondary amines. Formamides are important precursors in the synthesis of pharmaceutically important compounds and also in general organic synthesis. The synthesis of formamides by the way of *N*-formylation of amines using known and new formylating agents is documented.^{7,8} However, most of them involve longer reaction times under classical reaction conditions and generally a non-recoverable formylating agent.

In continuation with our ongoing work, we investigated the use of a polymer-supported formate in studying microwave-induced catalytic transfer hydrogenation (CTH) for benzyl deprotection. The polymer supported formate utilised in this study was prepared using the procedure described previously.⁴ The formate loading was determined as 2.5 mmol/g resin by potentiometric titration.

Initially we attempted the N-debenzylation of N-benzylp-anisidine 1 under microwave irradiation. A mixture of the polymer-supported formate 2, 10 % Pd/C catalyst and N-benzyl-p-anisidine 1 in a minimum quantity of DMSO was microwave irradiated at 100 W for 30 s. Upon filtration, extraction and removal of the solvent, the isolated compound showed no evidence of the desired N-debenzylation product 3. Interestingly however, the isolated compound was characterised as N-benzyl-N-formyl-p-anisidine 4 resulting from the N-formylation of the starting amine (see Scheme 1). In view of this result and due to the fact that, to our knowledge, the use of inexpensive and recyclable polymer-supported formate as a formylating agent together with the advantages of microwave flash heating was never

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Scheme 1.

reported in the literature, our studies were directed into optimisation of the reaction conditions for *N*-formylation of primary and secondary amines.

In a typical reaction, benzylamine **5a** (0.049 g, 0.45 mmol) and solid-supported formate (1 g, corresponding to 2–2.5 mmol formate) were suspended in DMSO (0.5 mL) in a glass vial equipped with a screw cap. The reaction mixture was irradiated with microwaves (MW-10 Microwell microwave reactor) at 100 W for 30 s. On cooling, the mixture was diluted with dichloromethane (1 mL) and filtered under gravity. The filtrate was extracted with brine (2 × 5 mL), dried and evaporated under reduced pressure to give a colourless solid identified as *N*-benzylformamide **6a** (0.058 g, 95%) by comparison of its spectroscopic data (¹H NMR, ¹³C NMR, IR and MS) and melting point with those of an authentic sample.⁹

To further investigate the scope of the reaction, other primary and secondary amines were studied under similar reaction conditions (see Table 1). All amines con-

Table 1. Thermal and microwave assisted formylation of primary and secondary amines using a polymer-supported formate

N^+ 2 HCOO ⁻ 2. Recycling									
		R NH - R 5a-g	DMSO MW	R NCHO R [/] 6a-g					
Entry	Amine	R	R′	Product	Yield (%)				
					MW ^a	Thermal ^b			
1	5a	Ph	Н	6a	90	60			
2	5b	PhCH ₂	Н	6b	95	80			
3	5c	PhCH ₃ CH	Н	6c	95	85			
4	5d	$p-CH_3OC_6H_4$	Н	6d	80	60			
5	5e	PhCH ₂	PhCH ₂	6e	95	80			
6	5f	HN(CH ₂ CH ₂) ₂	-	6f	60	55			
7	5g	$O(CH_2CH_2)_2$		6g	60	50			

^a All microwave irradiations were performed at 100 W for 30 s.

^b All thermal reactions were carried out at 70-80 °C for 4 h in DMSO.

Table 2. Thermal and microwave assisted formylation of primary and secondary amines using alumina supported formic acid

		Al ₂ O ₃ /HC 7	COOH 1. Filtra 2. Recy	ation /cling		
		R NH R 5a-g	DMSO MW	R NCHO R 6a-g		
Entry	Amine	R	R′	Product	Yield (%)	
					MW ^a	Thermal ^b
1	5a	Ph	Н	6a	93	70
2	5b	PhCH ₂	Н	6b	95	85
3	5c	PhCH ₃ CH	Н	6c	85	80
4	5d	p-CH ₃ OC ₆ H ₄	Н	6d	80	55
5	5e	PhCH ₂	PhCH ₂	6e	95	80
6	5f	HN(CH ₂ CH ₂) ₂		6f	60	55
7	5g	O(CH ₂ CH ₂) ₂		6g	60	50

^a All microwave irradiations were performed at 100 W for 30 s.

^b All thermal reactions were carried out at 70 °C for 3-4 h in DMSO.

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verted readily into the corresponding formamides. Piperazine 5f was formylated at both secondary amine groups simultaneously to give piperazine dicarbalde-hyde 6f.

Formic acid supported on basic alumina, previously reported as a transfer hydrogenation source,⁵ could also be demonstrated to act as a formylating agent. Under microwave and conventional heating, the alumina supported formic acid 7, with a typical loading of 2 mmol/g, was now also applied to selected primary and secondary amines yielding the corresponding formamides (see Table 2). Overall, the polymer supported or alumina supported reagent both provided comparable results with respect to reaction rates and yields.

In all cases, it was noted that reactions conducted using microwave irradiation showed an improvement in yields in the range of 5-30% over the classical heating approach. Also, the reaction protocols under microwave heating utilise reduced solvent volume (0.5 mL). In general, using either of the formylating reagents, notable yield improvements for anilines (Tables 1 and 2, entries 1 and 4) were observed. Primary or secondary benzylamines (Tables 1 and 2, entries 2, 3 and 5) showed good to excellent yields within 30 s of microwave irradiation. However, the heterocyclic secondary amines (Tables 1 and 2, entries 6 and 7) maintained moderate yields with negligible difference under either heating conditions.

In summary, we have demonstrated that formate or formic acid immobilised on a solid support (polymer matrix or inorganic solid) can not only function as a transfer hydrogenation source but also as a formylating agent. The latter application allows for simplified synthesis of industrially important formamides with ease of purification and isolation, and in high to excellent yields. The use of recyclable solid supported reagents combined with microwave irradiation renders the reaction suitable for automated combinatorial and parallel synthesis protocols, or other contemporary synthetic chemistry techniques.

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