Microwave-assisted direct transformation of amines to ketones using water as an oxygen source

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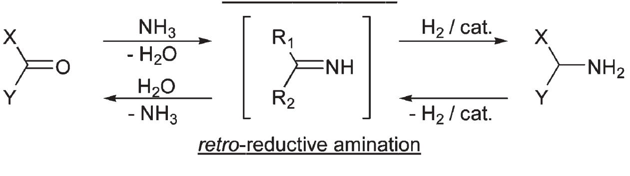
***Retro*-reductive aminations, direct transformations of amines to ketones, were catalyzed by Pd/C in water under microwave irradiation.**

Utilization of water as a chemical reagent and an alternative to organic solvents is an essential aspect of *Green Chemistry*.[1] We have found that some amines can be directly and rapidly converted to the corresponding ketones in good yields. This process is the first example of an efficient *retro*-reductive amination reaction[2] (Scheme 1).

Although the selective chemical transformation of an amine to a ketone is a relatively common biological process,[3] chemical conversions of amines to ketones are rather limited.[4] Some metal oxidizing reagents such as $KMnO_4$,[5] K_2FeO_4,[6] $Pb(OAc)_4$,[7] NiO_2,[8] and $HgO–I_2$[9] have been used to convert amines to ketones through imines. However these processes require stoichiometric or larger amounts of poisonous late transition metals. Using a strong base such as *n*-butyllithium[10] or DBU[11] to generate imines from amines and subsequent hydrolysis to obtain ketones has been reported. This two-step process needs dry conditions and the total yields of ketones from amines were fairly low.

In the last two decades, microwave-assisted organic synthesis has been an attractive tool for enhancing the selectivities and rates of chemical reactions.[12] Microwave irradiation has also been used in the selective regeneration of carbonyl compounds from amine derivatives such as oximes,[13] hydrazones[14] and semicarbazones[15] in good yields. Herein we report the direct transformation of amines to ketones with water, catalyzed by Pd/C, under microwave irradiation.

Table 1 lists the preliminary results with several types of butylamines. The reactions were conducted in the presence of Pd/C and water, under continuous microwave irradiation (2.45 GHz, 50 W), in a pressure resistant glass ampoule. Within 5 min of microwave irradiation, the temperature of the ampoule surface rose to 170 °C, measured by an infrared thermo detector, and the inside pressure of the ampoule was raised to 10.0 bar. Upon completion of the reactions, litmus paper indicated that the resulting aqueous solution was alkaline with a smell of ammonia.



Scheme 1

The reaction strongly depended on the structure of the butyl groups, especially the number of hydrogens on the carbon adjacent to the nitrogen. *sec*-Butylamine was completely converted to 2-butanone within 1 h (entry 4). The reactions of *n*-butyl and isobutylamines under the similar conditions were slower and afforded (butylidene)butylamines (**3**) and dibutylamines (**4**) along with a small amount of the desired aldehyde (entries 1–3). For *tert*-butylamine, the reaction did not proceed and the starting amine was quantitatively recovered (entry 8). Other heating methods were investigated. The reaction of *sec*-butylamine using a pre-heated oil bath at 170 °C for 1 h gave the desired 2-butanone in 29% yield without by-products (entry 5), but a longer reaction time increased the amount of di-*sec*-butylamine (entry 6), which was presumably formed by the reductive amination of 2-butanone with *sec*-butylamine. The reaction under reflux conditions with microwave irradiation (50 W for 2.5 h) is apparently too slow for practical purposes. Thus, microwave irradiation in a sealed vessel effectively enhances the selectivity and accelerates the reaction in the direct conversion of *sec*-butylamine to 2-butanone.

The reaction is generally applicable to other primary and secondary amines as summarized in Table 2. Thus, isopropylamine, diisopropylamine and di-*sec*-butylamine, *meso*–DL mixture, were directly converted to the corresponding ketones, acetone and 2-butanone (entries 1–3), within 1 h in excellent yields. When 1-amino-1-phenylethane and diphenylmethylamine were reacted under the same conditions, both amines were completely consumed within 10 min to afford the desired acetophenone and benzophenone in 69% and 56% yields, respectively, but the undesired hydrogenolysis products, ethylbenzene and diphenylmethane, were formed in 31% and 44% yields (entries 4–5).

Scheme 2 depicts a plausible reaction pathway. Oxidative removal of dihydrogen,[16] which is initially formed *in situ* in the reaction between the starting amine and Pd/C, produces an imine. The imine is hydrolyzed to give desired carbonyl compounds and ammonia. As for benzylic amines, the Pd/C–dihydrogen species causes hydrogenolysis as a side reaction, which increases the yield of hydrocarbon products (Table 2. entries 4–5). For alkylamines, the Pd/C–dihydrogen species releases dihydrogen to regenerate the starting Pd/C catalyst.

In summary, we have demonstrated the direct transformation of mono- or di-*sec*-alkylamines to the corresponding ketones with a catalytic amount of Pd/C in water under microwave irradiation conditions. The presently developed method should be very useful since the reaction proceeds smoothly without an oxidant based on

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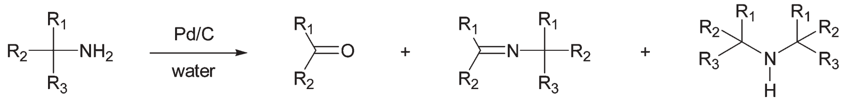
Table 1 Preliminary results of the direct conversion of butylamines into carbonyl compounds[a]

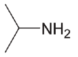
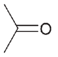
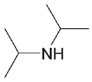
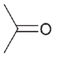
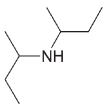
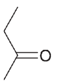
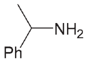
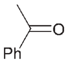
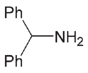
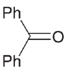
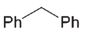


1 2 3 4

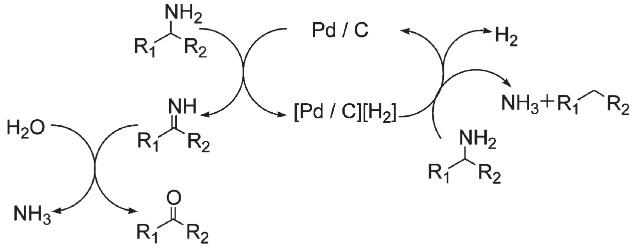
							Relative yield[b] (%)		
Entry	R_1	R_2	R_3	Method	Time (h)	Conversion[b] (%)	**2**	**3**	**4**
1	*n*-Pr	H	H	MW[c]	1	16	0	53	47
2	*i*-Pr	H	H	MW[c]	1	20	20	80	0
3	*i*-Pr	H	H	MW[c]	5	32	Trace	50	50
4	Me	Et	H	MW[c]	1	100	Quant.	0	0
5	Me	Et	H	170 °C[d]	1	29	Quant.	0	0
6	Me	Et	H	170 °C[d]	9	76	59	Trace	41
7	Me	Et	H	Reflux[e]	2.5	13	Quant.	0	0
8	Me	Me	Me	MW[c]	1	0	0	0	0

[a] Conditions; [amine]/[Pd/C] = 2 (mg/mg), 2 ml of water used. [b] Determined by GC and GC-MS. [c] Using pressure resistant glass ampoule with microwave irradiation (50 W). [d] Using a pre-heated oil bath. [e] Refluxing with microwave irradiation (50 W).

Table 2 Reaction of mono- and di-*sec*-alkylamines with Pd/C in water under microwave irradiation[a]

Entry	Compounds	Time (min)	Conversion[b] (%)	Products[b] (relative yield, %)
1		60	100	 (quant.)
2		60	100	 (quant.)
3		60	100	 (quant.)
4		5	100	 (69%), Ph—Et (31%)
5		10	100	 (56%),  (44%)

[a] Conditions; [amine]/[Pd/C] = 2 (mg/mg), 2 ml of water used. [b] Determined by GC and GC-MS.



Scheme 2

poisonous heavy metals and volatile organic solvents. Moreover, it has a high selectivity and a faster rate. Further investigations into detailed reaction mechanisms, and application of the methodology to other substrates are underway and will be published elsewhere.†

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Notes and references

† The typical experimental procedure was as follows (*i.e.* Table 1 entry 4): a mixture of 100 mg (1.4 mmol) of *sec*-butylamine, 50 mg of 5 wt% Pd/C (1.7 mol%) and 2 ml of water in a pressure resistant glass ampoule equipped with rubber septum and an aluminium cap, was introduced into the cavity of microwave apparatus (CEM Discover, 2.45 GHz, CEM Corporation, NC, USA). The reaction mixture was irradiated by microwave (50 W) continuously for 1 h. The reaction vessel was cooled in an ice–water bath and the organic products were extracted with ether. The ether fraction was analyzed by GC (FID detector) and GC-MS for identification and quantification of the products.

1 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.
2 W. S. Emerson, *Org. React.*, 1948, **4**, 174.
3 D. E. Metzler, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 1979, **50**, 1; L. Davis and D. E. Metzler, *The Enzymes*, Academic Press, New York, 3rd edn., 1972, vol. 7, pp. 33–65.
4 See reviews and references sited therein: A. R. Katrizky, O. Meth-Cohn and C. W. Rees, *Comprehensive Organic Functional Group Transformations*, Pergamon, London, 1995; I. T. Harrison and S. Harrison, *Compendium of Organic Synthetic Methods*, Wiley, New York, 1971, pp. 404–406.
5 S. S. Rawalay and H. Schechter, *J. Org. Chem.*, 1967, **32**, 3129–3131; N. A. Noureldin and J. W. Bellegarde, *Synthesis*, 1999, 939–942.
6 R. J. Audette, J. W. Quail and P. J. Smith, *Tetrahedron Lett.*, 1971, 279–282.
7 F. F. Stephens and J. D. Bower, *J. Chem. Soc.*, 1949, 2971–2972.
8 K. Nakagawa, H. Onoue and J. Sugita, *Chem. Pharm. Bull.*, 1964, **12**, 1135–1138.
9 K. Orito, T. Hatakeyama, M. Takeo, S. Uchiito, M. Tokuda and H. Suginhome, *Tetrahedron*, 1998, **54**, 8403–8410.
10 H. G. Chen and P. Knochel, *Tetrahedron Lett.*, 1988, **29**, 6701–6702.

11 T. F. Buckley and H. Rapoport, *J. Am. Chem. Soc.*, 1982, **104**, 4446–4450.

12 *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2002.

13 (*a*) R. S. Varma and H. M. Meshram, *Tetrahedron Lett.*, 1997, **38**, 5427–5428; (*b*) R. S. Varma, R. Dehiya and R. K. Saini, *Tetrahedron Lett.*, 1997, **38**, 8819–8820.

14 A. Boruah, B. Baruah, D. Prajapati and J. S. Sandhu, *Synlett*, 1997, 1251–1252.

15 (*a*) R. S. Varma and H. M. Meshram, *Tetrahedron Lett.*, 1997, **38**, 7973–7976; (*b*) M. Baruah, D. Prajapati and J. S. Sandhu, *Synth. Commun.*, 1998, **28**, 4157–4163.

16 S. Murahashi, N. Yoshimura, T. Tsumiyama and T. Kojima, *J. Am. Chem. Soc.*, 1983, **105**, 5002–5011.