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Cite this: *Chem. Commun.*, 2012, **48**, 12237–12239

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COMMUNICATION

Lewis acid-catalyzed oxidation of benzylamines to benzamides†

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Received 1st October 2012, Accepted 3rd November 2012
DOI: 10.1039/c2cc37149a

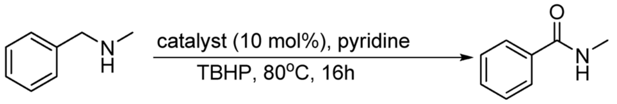
A novel Lewis acid-catalyzed oxidation of benzylamines to the corresponding amides has been developed. Using 10 mol% of $ZnBr_2$ or $FeCl_3$ as the catalyst and TBHP as the oxidant, amides were produced under mild conditions.

Oxidation reactions are one of the fundamental functional group transformation reactions in organic synthesis.[1] Especially the development of improved chemoselective oxidation methodologies is still eagerly needed in order to increase reaction efficiencies and to decrease the generation of waste. While the major interest has been on the oxidation of alcohols to the corresponding ketones and aldehydes,[2] the direct oxidation of benzylamines to the corresponding benzamides is rarely reported and much less developed.[3] One general problem in this transformation is the reaction selectivity.[4] Tuning of reaction conditions and selection of appropriate catalysts to produce one of the potential products selectively have been rarely reported. For example, recently Mizuno and co-workers demonstrated a $Ru(OH)_x/Al_2O_3$-catalyzed heterogeneous oxygenation of primary amines to primary amides in the presence of water and air (5 bar) at 130–160 °C.[3a] They found that manganese oxide octahedral molecular sieves (OMS-2) could also act as efficient and reusable heterogeneous catalysts for the transformation of various primary amines to the corresponding amides under air (6 bar) at 130–160 °C.[3b] More recently, Fu and co-workers reported a copper-catalyzed aerobic oxidation of benzyl amines.[3c] Amides were produced in moderate to good yields by using oxygen as an oxidant.

Considering the importance of amides[5] and the advantages of zinc and iron catalysts.[6] The replacement of noble metals with these cheap catalysts matches with the requests of sustainable development. Due to our continued interest in this area, here we wish to report a novel Lewis acid-catalyzed oxidation of benzylamines to amides under mild reaction conditions. Various amides were prepared in moderate to good isolated yields. To the best of our knowledge, this is the first example of zinc- and iron-catalyzed oxidations of benzylamines to amides under homogeneous conditions.

At the start of our work, we investigated the model oxidation of *N*-methyl benzylamine in the presence of various iron, copper, and zinc catalysts using *tert*-butyl hydroperoxide as the stoichiometric oxidant. As shown in Table 1, different simple zinc and iron salts gave good to excellent yields of the corresponding benzamide. The importance of both the solvent and the oxidant is exemplarily shown in Table 2 using $ZnBr_2$ as the pre-catalyst (Table 2). The yield of our desired amide significantly decreased when the reaction was carried out in NEt_3, DMF, NMP, MeCN, and water (Table 2, entries 1–5). The use of di-*tert*-butyl peroxide as an oxidant did not give any product with conversion of 3% of starting material and only 4% of amide was produced by using cumene hydroperoxide as the oxidant (Table 2, entries 6 and 7). The attempts to decrease the loading of oxidant, catalyst, and lower the reaction temperature resulted in a decrease in both conversion and yield (Table 2, entries 8–10). Interestingly, 75% of *N*-methyl

Table 1 Lewis acid-catalyzed oxidation of *N*-methyl benzylamine[a]



Entry	Catalyst [10 mol%]	Conversion[b] [%]	Yield[b] [%]
1	/	67	17
2	$ZnBr_2$	100	93
3	ZnF_2	100	77
4	$ZnCl_2$	100	60
5	$Zn(OAc)_2$	100	80
6	CuCl	100	34
7	Cu_2O	100	20
8	$Cu(OAc)_2$	100	22
9	$CuBr_2$	100	10
10	CuI	100	47
11	CuO	100	87
12	$FeCl_3$	100	95
13	$FeBr_2$	100	95
14	FeF_2	100	90
15	$Fe(acac)_3$	100	93
16	Fe_2O_3	100	60
17	Fe_3O_4	100	45

[a] *N*-Methyl benzylamine (1 mmol), catalyst (10 mol%), pyridine (2 mL), TBHP (*tert*-butyl hydroperoxide) (3 mmol), 80 °C, 16 h. [b] Conversion and yield were determined by GC using hexadecane as internal standard based on *N*-methyl benzylamine.

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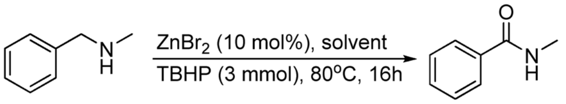
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR data. See DOI: 10.1039/c2cc37149a

Table 2 Zinc-catalyzed oxidation of *N*-methyl benzylamine[a]

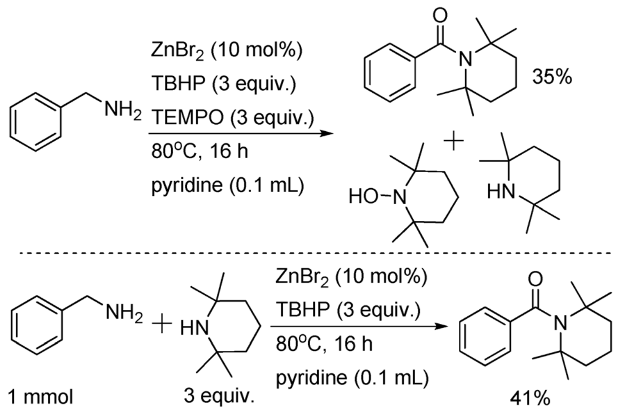


Entry	Solvent	Conversion[b] [%]	Yield[b] [%]
1	NEt_3 (2 mL)	15	8
2	DMF (2 mL)	100	29
3	NMP (2 mL)	100	18
4	MeCN (2 mL)	100	10
5	H_2O (2 mL)	100	0
6	Pyridine (2 mL)	3	0^c
7	Pyridine (2 mL)	12	4^d
8	Pyridine (2 mL)	60	18^e
9	Pyridine (2 mL)	66	37^f
10	Pyridine (2 mL)	58	0^g
11	Pyridine (0.1 mL)	100	75

[a] *N*-Methyl benzylamine (1 mmol), $ZnBr_2$ (10 mol%), solvent (2 mL), TBHP (*tert*-butyl hydroperoxide) (3 mmol), 80 °C, 16 h. [b] Conversion and yield were determined by GC using hexadecane as internal standard based on *N*-methyl benzylamine. [c] Di-*tert*-butyl peroxide (3 mmol). [d] Cumene hydroperoxide (3 mmol). [e] TBHP (2 mmol). [f] $ZnBr_2$ (5 mol%). [g] 40 °C.

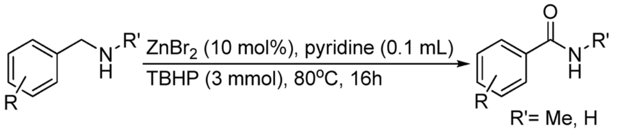
benzamide was successfully produced in 0.1 mL of pyridine while no amide was formed in the absence of pyridine (Table 2, entry 11).[7] Pyridine may coordinate to the Zn center and stabilize the real active species. It should be noted that in all the tested reactions, benzaldehyde and benzoic acid were formed when a significant difference between conversion and yield existed.

In order to shed some light on the mechanism of the reaction we added TEMPO (3 equiv.) to a standard oxidation of benzylamine under our best reaction conditions. Notably, the catalyst activity was totally inhibited and no benzamide was formed. Instead, phenyl-(2,2,6,6-tetramethylpiperidin-1-yl)methanone (35%), 2,2,6,6-tetramethylpiperidin-1-ol and a small amount of 2,2,6,6-tetramethylpiperidine were produced (Scheme 1). These results clearly indicate the radical nature of the reaction. We also carried out the reaction between benzylamine and 2,2,6,6-tetramethylpiperidine under our best conditions, as we expected, 41% of the amide was produced. We are now working on this zinc-catalyzed cross amidation of amines. No reaction was observed when we applied 3 equiv. of TEMPO as the oxidant instead of TBHP.



Scheme 1 Using TEMPO as additive for the oxidation of benzylamine.

Table 3 Lewis acid-catalyzed oxidation of benzylamines[a]



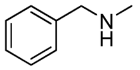
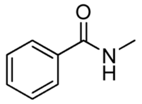
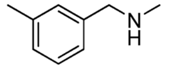
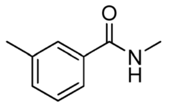
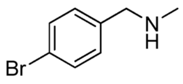
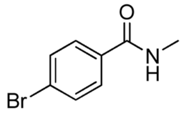
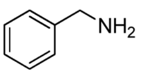
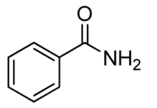
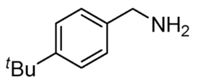
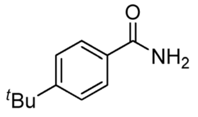
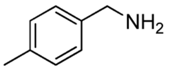
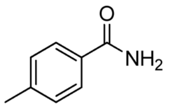
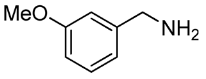
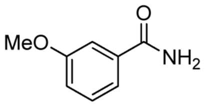
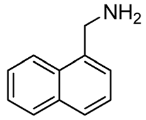
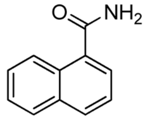
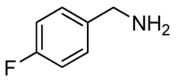
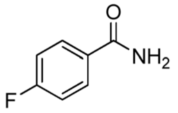
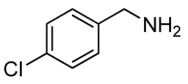
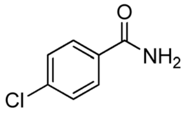
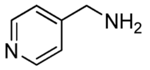
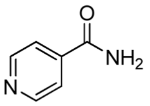
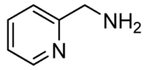
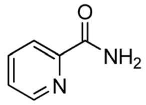
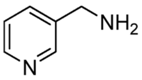
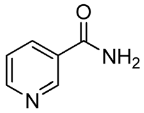
Entry	Benzylamine	Product	Yield[b] [%]
1			59
2			39 59^c
3			48
4			38 50^c 85^d 61^e
5			59 70^c 77^d
6			61
7			51
8			72
9			66
10			66
11			65
12			61

Table 3 (*continued*)

Entry	Benzylamine	Product	Yield[b] [%]
13			81

[a] Benzylamines (1 mmol), $ZnBr_2$ (10 mol%), pyridine (0.1 mL), TBHP (*tert*-butyl hydroperoxide) (3 mmol), 80 °C, 16 h. [b] Isolated yield. [c] Pyridine (2 mL). [d] $FeCl_3$ (10 mol%), yield was determined by GC using hexadecane as internal standard based on benzylamines. [e] $FeCl_3$ (5 mol%) was used.

With convenient reaction conditions in our hands, we started the evaluation of the generality and efficiency of the reaction using different substrates (Table 3). 59% of *N*-methyl benzamide was isolated under our standard conditions (Table 3, entry 1). 3-Methyl-substituted *N*-methyl benzamide was formed in 39% yield, which increased to 59% when carrying out the reaction in 2 mL of pyridine (Table 3, entry 2). 4-Bromo-substituted *N*-methyl benzamide was produced in 48% yield as well (Table 3, entry 3). Again, in these cases the corresponding benzaldehydes and benzoic acids were also detected. *N*,*N*-Dimethyl benzylamine could be applied as a substrate as well, 10% of *N*,*N*-dimethyl benzamide was isolated together with certain amounts of benzaldehyde. In addition to the secondary benzylamines, primary benzylamines were successfully applied as substrates under our standard conditions.

In comparison with secondary amines, primary amines that are more easily available led to higher yields of useful primary amides. Hence, 38% of benzamide was produced from benzylamine in 0.1 mL of pyridine, which was improved to 50% when using 2 mL of pyridine and to 85% when using 10 mol% of $FeCl_3$ as the pre-catalyst (Table 3, entry 4). *tert*-Butyl-, methyl-, and methoxy-substituted benzamides were isolated in moderate yields, which are all potentially possible to be improved by carrying out the reactions in 2 mL of pyridine or using $FeCl_3$ as catalyst (Table 3, entries 4 and 5). Naphthalen-1-ylmethanamine can also be applied as a substrate and gave the corresponding primary amide in 72% yield (Table 3, entry 8). Additionally, 66% of 4-fluoro- or 4-chloro-decorated benzylamides were isolated by the oxidation of their corresponding benzylamines (Table 3, entries 9 and 10). Remarkably, picolylamine derivatives were successfully oxidized to the corresponding primary amides in good isolated yields without further optimizations (Table 3, entries 11–13). Finally, 2-phenylethanamine and butylamine were tested under our standard reaction conditions as well. Here, 15–20% of the desired primary amides were isolated with significant amounts of aldehydes, acids, and nitriles being formed, too.

In conclusion, a novel Lewis acid-catalyzed oxidation of benzylamines to the corresponding amides using TBHP as the terminal oxidant has been developed. In the presence of 10 mol% of $ZnBr_2$ or $FeCl_3$, in 0.1 mL of pyridine at 80 °C, not only secondary amines, but also useful primary benzylamines can be applied as substrates. Both electron-donating and electron-withdrawing aryl groups such as aryl halides and picolines are tolerated. With respect to the reaction mechanism, it is under investigation in our laboratory.

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