Convenient and clean synthesis of imines from primary benzylamines†

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The current syntheses of imines from benzylamines are often performed in organic solvents or under harsh reaction conditions. Clean oxidation of primary benzylamines to imines has been successfully achieved using H_2O_2 in water at room temperature catalyzed by V_2O_5. Among the 10 imine products, 5 of them precipitated from the reaction and led pure products after simple filtration. No organic solvents are needed in the whole process. The yields are good to quantitative. This represents an efficient and green procedure of the synthesis of imines. A similar green oxidation of benzylamines to aromatic aldehydes is also reported. A benzylic anion-involved mechanism is proposed based on the experiments.

Introduction

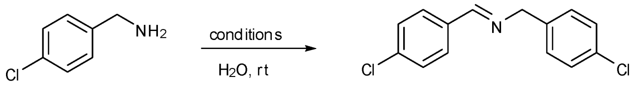
As imines are important intermediates in the synthesis of biologically active nitrogen-containing compounds,[1] their preparation attracts extensive attention. Considerable progress has been made in recent years in developing catalytic oxidation of secondary amines into imines.[2] However, comparatively little attention has been devoted to the oxidation of primary amines, probably because the corresponding imines usually constitute intermediate products that are rapidly dehydrogenated to nitriles[3] due to a second α-amino hydrogen. The oxidation of primary amines with IBX leads to the corresponding carbonyl species, even with the application of short reaction times, following hydrolysis of the initially formed imine product *in situ*.[4] As a result, extended efforts have been made to develop catalytic systems that utilize green oxidants for the synthesis of imines from primary amines; notable examples include 10% PVMo/C,[5] a series of uracil-annulated heteroazulene derivatives,[6] bulk gold powder and supported gold,[7] and tyrosine-derived quinone.[8] Most of the methods suffer from prolonged reaction times, or higher reaction temperatures. Furthermore, they all have to suffer from unfriendly organic solvents. Landge *et al.* have reported[9] the microwave-assisted oxidative coupling of amines to imines with a solid catalyst without the use of any solvent. However, the transformation is performed at 150 °C. We aim to find a green oxidation of amines under mild conditions.

Water as a reaction medium has attracted both academic and industrial interests because of its special properties such as safety, nontoxicity, inflammability, cheapness and environmental friendliness. Hydrogen peroxide along with oxygen is regarded as a green oxidant. We intend to develop an oxidation procedure using H_2O_2 in water catalyzed by V_2O_5. V_2O_5 is an inexpensive and stable chemical and has successfully catalyzed various oxidations.[10]

Results and discussion

In the present paper, we report our results relating to the oxidation of benzylamines to the corresponding imines using H_2O_2 catalyzed by V_2O_5 in water, at room temperature. Initially, the oxidation of 4-chlorobenzylamine (**1a**) was chosen as a model reaction and the reaction was carried out in water at room temperature. Control experiments (Table 1, entries 1 and 5) revealed that hydrogen peroxide and vanadium pentoxide are all required for this reaction. Without H_2O_2 no imine was detected (Table 1, entry 1). Without V_2O_5 very little of 4-chlorobenzaldehyde was obtained (Table 1, entry 5). We obtained the optimized reaction conditions, *viz*. 3 equiv. of H_2O_2 (30% solution in water) as an oxidant and 0.08 equiv. of V_2O_5 as a catalyst at room temperature (Table 1, entry 7).

Table 1 Optimization for the oxidation of *p*-chlorobenzylamine.[a]



1a **2a**

Entry	H_2O_2 (equiv.)	V_2O_5 (equiv.)	Time/h	Yield (%)[b]
1[c]	—	0.01	6	n.d
2	1	0.1	6	54
3	3	0.1	3.5	91
4	5	0.1	3.5	90
5	3	—	6	trace
6	3	0.05	3.5	63
7	3	0.08	3.5	90
8	3	0.15	3.5	89

[a] Reaction conditions: **1a** (200 mg, 1 equiv.), H_2O (5 mL), rt. [b] Isolated yields. [c] n.d = not detected.

Building upon this result, we treated a variety of substituted benzylamines with hydrogen peroxide in the presence of vanadium pentoxide at room temperature. The system gave the corresponding imines in good to quantitative yields and Table 2 summarizes the results. As some imines are solid and insoluble in water, 5 among 10 imine products (Table 2, entries 1, 4, 7, 8, 10) precipitated directly from the reaction mixtures. Products purer than 97% were collected by simple filtrations. No purification step was needed for any of the imine products. The yield of the oxidation of 2,3-dichlorobenzylamine into the corresponding imine was quantitative (Table 2, entry 7). However, in the literature, organic solvents were necessary either during the oxidation of the amines or in the work-up step. This represents an efficient and

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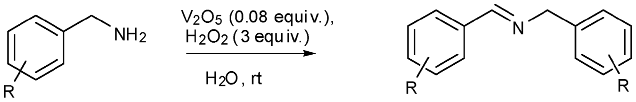
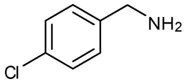
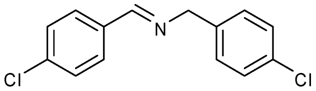
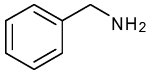
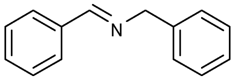
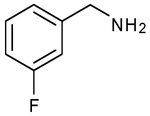
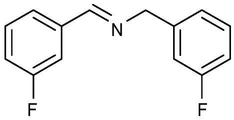
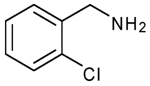
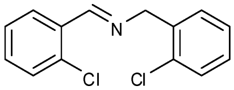
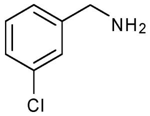
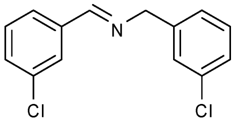
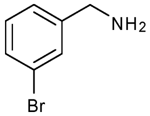
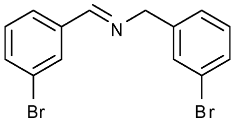
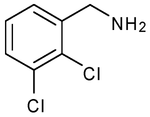
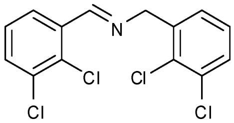
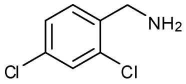
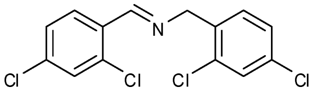
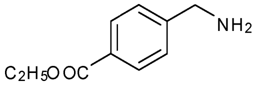
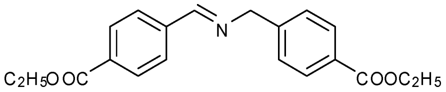
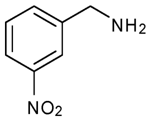
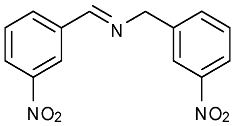
† Electronic supplementary information (ESI) available: Experimental procedures, ^1H NMR, ^{13}C NMR and MS spectral data for compounds. See DOI: 10.1039/c0ob00043d

Table 2 Oxidation of variously substituted benzylamines to imines.[a]



1 **2**

Entry	Substrate	Product		Time/h	Yield (%)[b]
1			**2a**	2.5	91
2			**2b**	10	64
3			**2c**	10	75
4			**2d**	4.5	80
5			**2e**	6	76
6			**2f**	6	87
7			**2g**	1	>99
8			**2h**	4	83
9			**2i**	8	66
10			**2j**	12	78[c]

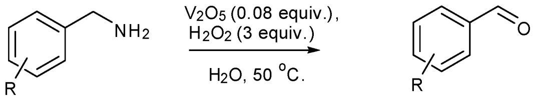
[a] Reaction conditions: substituted benzylamine (200 mg, 1 equiv.), H_2O_2 (30% solution in water) (3 equiv.), V_2O_5 (0.08 equiv), H_2O (5 mL), rt. All the conversions were 100% except for entry 10 (50%). [b] Isolated yields. [c] 50% of starting material was recovered.

green procedure for the synthesis of imines starting from primary benzylamines.

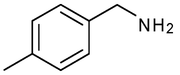
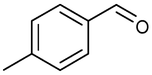
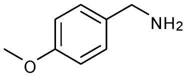
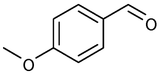
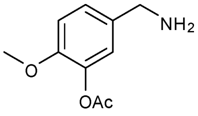
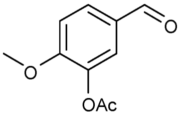
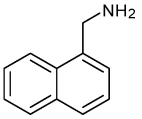
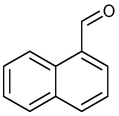
However, when benzylamines of Table 3 were treated with H_2O_2 and V_2O_5 at rt, no imines were obtained. When the systems were heated to 50 °C, they gave aromatic aldehydes in high yields (Table 3). In contrast to the benzylamines bearing electron-withdrawing groups in Table 2, the benzylamines in Table 3 bear electron-donating groups.

It has been reported[10a,11] that benzyl alcohols can be oxidated into aromatic aldehydes in water. However, in the literature[12] the

Table 3 Oxidation of benzylamines to aromatic aldehydes.[a]



1 **3**

Entry	Substrate	Product		Time/h	Yield (%)[b]
1			**3k**	10	76
2			**3l**	11	78
3			**3m**	12	66
4			**3n**	12	70[c]

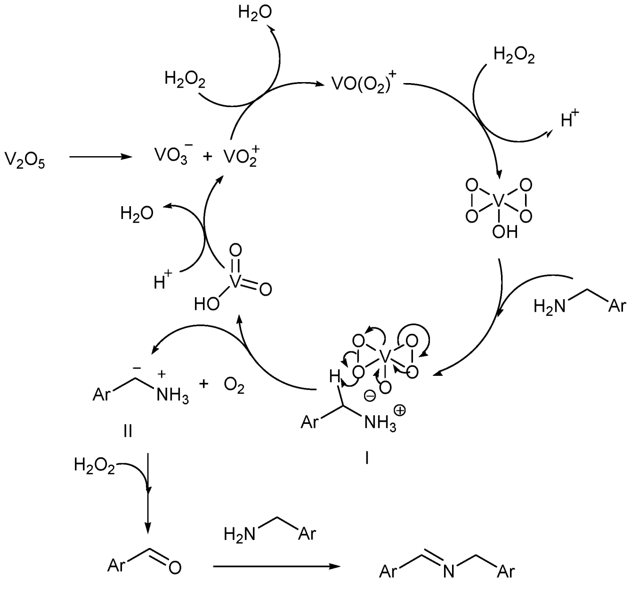
[a] Reaction conditions: substituted benzylamine (200 mg, 1 equiv.), H_2O_2 (30% solution in water) (3 equiv.), V_2O_5 (0.08 equiv) H_2O (5 mL), 50 °C. All the conversions were 100% except for entry 4 (70%). [b] Isolated yields. [c] 30% of starting material was recovered.

transformation of benzylamines into aromatic aldehydes often needs organic solvents. Only catalyzed by expensive enzymes[13] can the oxidations be performed in water. Our oxidation provides a greener synthesis of aromatic aldehydes from benzylamines in water catalyzed by inexpensive and stable catalyst (V_2O_5).

On the basis of the above experiments and previous researches,[10] a plausible mechanism is proposed (Scheme 1). After ionization V_2O_5 is oxidized by H_2O_2 into a yellow species $HOV(O_2)_2$. This is supported by the facts that the reaction solution is yellow and 3 equiv of H_2O_2 are needed for the completion of the reaction (Table 1). Acid $HOV(O_2)_2$ forms a salt (I) with benzylamine. One of the oxygens deprotonates the benzylic hydrogen leading to benzylic anion II. Electron-withdrawing groups on aromatic ring stabilize anion II; while electron-donating groups hamper the formation of benzylic anion II. Therefore, benzylamines of Table 2 were oxidized to the corresponding imines at room temperature and those of Table 3 had to be oxidized to aromatic aldehydes at elevated temperature (50 °C). Presumably, imines were also formed in the later process. However, they were hydrolyzed at higher temperature and the amines were then oxidized into the aromatic aldehydes.

Conclusions

In conclusion, the methodology reported herein is expected to be a quite general route for oxidation a wide range of primary benzylamines in water, leading to imines or aromatic aldehydes. Its advantages are obvious from the perspective of green chemistry. Apart from being an environmentally benign reaction, the method benefits from the use of inexpensive and safe starting materials and produces imines or aromatic aldehydes in good to quantitative yields.



Scheme 1 A plausible mechanism for the oxidation of benzylamine

Experimental

General procedure for the preparation of imines in water

In a round bottom flask, benzylamine (200 mg, 1 equiv.), V_2O_5 (0.08 equiv) was suspended in water (5 ml) with vigorous stirring. Then, H_2O_2 (30% solution in water) (3 equiv.) was added to the reaction mixture. The reaction was slightly yellow. The solid imine was filtered to afford pure product when the reaction completed (monitored by TLC). The oily product was extracted with EtOAc

(2 × 5 mL). The extract was washed with water (2 × 3 mL), dried over anhydrous Na_2SO_4. The solvent was concentrated in vacuum to give pure imine without further purification.

N-(2-Chlorobenzyl) 2-chlorobenzaldimine (2d)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (s, 1H), 8.14 (d, J = 9.2 Hz, 1H), 7.46–7.23 (m, 7H), 4.97 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 136.8, 135.3, 133.4, 133.1, 131.7, 129.8, 129.7, 129.4, 128.5, 128.3, 127.0, 126.9, 62.2; MS (ESI): m/z (%) $[M + H]^+ = 264$ (100), 265 (18), 266 (60); Anal. Calcd. For $C_{14}H_{11}Cl_2N$: C, 63.66; H, 4.20; N, 5.30 Found: C, 63.74; H, 4.10; N, 5.22.

N-(2,3-Dichlorobenzyl) 2,3-dichlorobenzaldimine (2g)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.30–7.21 (m, 2H), 4.99 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 139.0, 135.1, 133.5, 133.4, 133.1, 132.4, 131.6, 129.1, 127.6, 127.4, 127.3, 126.7, 62.7; MS (ESI): m/z (%) $[M + H]^+ = 332$ (78), 334 (100), 336 (47); Anal. Calcd. For $C_{14}H_9Cl_4N$: C, 50.49; H, 2.72; N, 4.21 Found: C, 50.61; H, 2.67; N, 4.30.

General procedure for the preparation of aromatic aldehydes in water

In a round bottom flask, benzylamine (200 mg, 1 equiv.), V_2O_5 (0.08 equiv) was suspended in water (5 ml) with vigorous stirring. H_2O_2 (30% solution in water) (3 equiv.) was added to the reaction mixture. The system was heated to 50 °C and monitored by TLC to completion. The reaction mixture was extracted with EtOAc (2 × 5 mL). The extract was washed with water (2 × 3 mL), dried over anhydrous Na_2SO_4. The solvent was concentrated in a vacuum to give crude product, which was then filtered through a silica gel pad with petroleum ether to afford aromatic aldehyde.

Acknowledgements

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Notes and references

1 (*a*) S. I. Murahashi, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2443; (*b*) S. I. Murahashi and Y. Imada, in *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, 2nd edn, Wiley-VCH, Weinheim, Germany, 2004, vol. 2, p. 497.

2 G. Jiang, J. Chen, J. S. Huang and C. M. Che, *Org. Lett.*, 2009, **11**, 4568, and references cited therein.

3 (*a*) K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, 2003, **42**, 1480; (*b*) K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani and K. Kaneda, *Chem. Commun.*, 2001, 461; (*c*) Y. Maeda, T. Nishimura and S. Uemura, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 2399; (*d*) K. Yamaguchi and N. Mizuno, *Chem.–Eur. J.*, 2003, **9**, 4353; (*e*) S. Kamiguchi, A. Nakamura, A. Suzuki, M. Kodomari, M. Nomura, Y. Iwasawa and T. Chihara, *J. Catal.*, 2005, **230**, 204, and references cited therein.

4 (*a*) K. C. Nicolaou, C. J. N. Mathison and T. Montagnon, *Angew. Chem., Int. Ed.*, 2003, **42**, 4077; (*b*) K. C. Nicolaou, C. J. N. Mathison and T. Montagnon, *J. Am. Chem. Soc.*, 2004, **126**, 5192.

5 (*a*) R. Neumann and M. Levin, *J. Org. Chem.*, 1991, **56**, 5707; (*b*) K. Nakayama, M. Hamamoto, Y. Nishiyama and Y. Ishii, *Chem. Lett.*, 1993, 1699.

6 (*a*) Y. Mitsumoto and M. Nitta, *J. Org. Chem.*, 2004, **69**, 1256; (*b*) S. I. Naya and M. Nitta, *Tetrahedron*, 2004, **60**, 9139; (*c*) M. Nitta, D. Ohtsuki, Y. Mitsumoto and S. I. Naya, *Tetrahedron*, 2005, **61**, 6073; (*d*) S. I. Naya, Y. Yamaguchi and M. Nitta, *Tetrahedron*, 2005, **61**, 7384.

7 (*a*) B. Zhu, M. Lazar, B. G. Trewyn and R. J. Angelici, *J. Catal.*, 2008, **260**, 1; (*b*) A. Grirrane, A. Corma and H. Garcia, *J. Catal.*, 2009, **264**, 138.

8 M. Mure, *Acc. Chem. Res.*, 2004, **37**, 131, and references therein.

9 S. M. Landge, V. Atanassova, M. Thimmaiah and B. Torok, *Tetrahedron Lett.*, 2007, **48**, 5161.

10 (*a*) C. Li, P. Zheng, J. Li, H. Zhang, Y. Cui, Q. Shao, X. Ji, J. Zhang, P. Zhao and Y. Xu, *Angew. Chem., Int. Ed.*, 2003, **42**, 5063; (*b*) D. Xu, W. Zhu, H. Li, J. Zhang, F. Zou, H. Shi and Y. Yan, *Energy Fuels*, 2009, **23**, 5929; (*c*) A. Butler, M. J. Clague and G. E. Meister, *Chem. Rev.*, 1994, **94**, 625, and references cited therein.

11 P. J. Figiel, A. Sibaouih, J. U. Ahmad, M. Nieger, M. T. Risnen, M. Leskel and T. Repo, *Adv. Synth. Catal.*, 2009, **351**, 2625.

12 (*a*) V. Rajalakshmi, V. R. Vijayaraghavan, B. Varghese and A. Raghavan, *Inorg. Chem.*, 2008, **47**, 5821; (*b*) S. Sharma, N. Barooah and J. B. Baruah, *J. Mol. Catal. A: Chem.*, 2005, **229**, 171; (*c*) H. Hamamoto, Y. Suzuki, H. Takahashi and S. Ikegami, *Tetrahedron Lett.*, 2007, **48**, 4239.

13 (*a*) A. Yoshida, Y. Takenaka, H. Tamaki, I. Frebort, O. Adachi and H. Kumagai, *J. Ferment. Bioeng.*, 1997, **84**, 603; (*b*) R. H. H. van den Heuvel, M. W. Fraaije, C. Laane and W. J. H. van Berkel, *J. Agric. Food Chem.*, 2001, **49**, 2954; (*c*) M. W. Fraaije, C. Veeger and W. J. H. van Berkel, *Eur. J. Biochem.*, 1995, **234**, 271.