Oxidation of primary amines to ketones.

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Abstract: A simple method for the oxidation of primary amines to the corresponding ketones that proceeds in the presence of both moisture and air is described. Treatment of an amine with benzoyl peroxide in the presence of caesium carbonate, followed by warming of the hydroxylamine product to 50–70 °C leads directly to the ketone. The method is shown to be effective for both benzylic and aliphatic substrates.

Key words: Amine, oxidation, hydroxylamine, benzoyl peroxide, ketone.

The ability of the chemist to manipulate the carbonyl group in a chemo-, stereo- and enantioselective manner has bestowed upon it a central role in synthetic chemistry.[1] New methods with which to prepare this functionality from readily available precursors are therefore of great use to the synthetic chemist.

Amines represent a significant class of available building blocks as well as fundamental synthetic intermediates which are readily accessible. There have been a number of reports describing the oxidation of amines to a wide variety of functional groups including imines, amides, nitriles, aldehydes and ketones. Early methods reported for this transformation include the use of stoichiometric transition metal reagents including nickel,[2] mercury,[3] lead,[4] manganese,[5] iron,[6] and zinc[7] derived species. More recently, catalytic methods have been described using palladium[8] as well as tungsten,[9] rhodium[10] ruthenium[11] and manganese[12] salts. Stoichiometric methods avoiding the use of transition metals have also been developed using iodosobenzene,[13] IBX,[14] sulfonyl peroxides,[15] and benzoquinones.[16] These methods represent important alternatives to perform the overall oxidation of primary amines, with varied levels of scope and limitations in substrate tolerance and reaction conditions. Of the transition-metal free methods each optimised method requires anhydrous reaction conditions and the use of an inert atmosphere. Circumventing these practical considerations would represent an advance in the methods available for the overall transformation. Within this letter we describe a simple method for the oxidation of primary amines to the corresponding ketones that proceeds under mild reaction conditions in the presence of both moisture and air, offering a practical alternative to existing methodology.

As part of our investigations into the chemistry of hydroxylamines[17,18,19,20,21] we reacted *N*-cyclohexyl-*O*-benzoyl hydroxylamine (**2**) with one equivalent of heptan-4-one (**1**) and were surprised to observe the α-functionalised cyclohexanone **7** as the major product. Rationalising that this could have arisen through decomposition of the reagent to give the imine **5** followed by condensation with a second molecule of hydroxylamine **2** to give the intermediate enamine **6**. Subsequent [3,3]-sigmatropic rearrangement followed by hydrolysis of the resulting imine then led to the observed product **7**. Intrigued that if we were able to stop this process at the intermediate imine **5** the transformation would represent a new method for amine oxidation we sought to examine this reaction further.
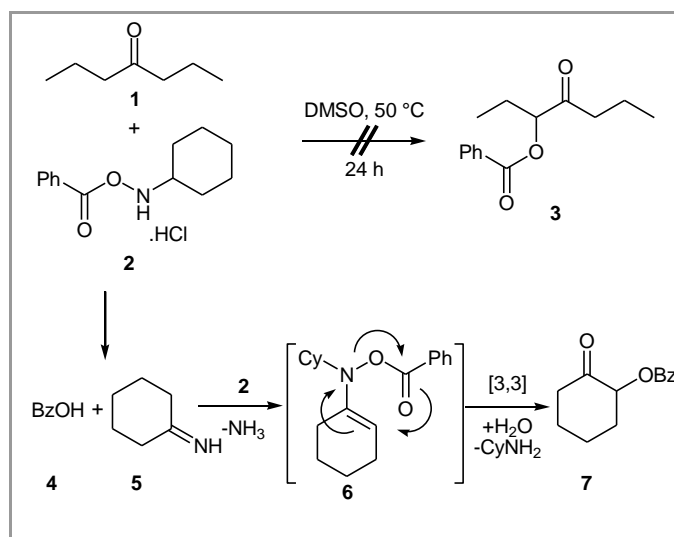
Scheme 1

Preparation of the substrates for the development of this transformation used a robust and convenient method reported by Phanstiel for the conversion of amines to *O*-benzoyl hydroxylamines.[22] Our key transformation was optimised with the phenethylamine derived hydroxylamine **8** (Table 1).[23] Use of **8**.HCl in chloroform at 50 °C proved to be inefficient (18%) and resulted in a number of unidentified by-products (entry 1). Heating of the free base **8** resulted in recovery of starting material after a 48 hour reaction period (entry 2). Addition of DBU (1 equivalent) significantly accelerated the reaction and provided the product in an encouraging 30% yield (entry 3). Examination of alternative solvents showed polar solvents to be more effective with DMF emerging as the optimal reaction medium (entries 3–5). Changing the base to caesium carbonate improved the yield further with acetophenone (**9**) being isolated in an excellent 84% yield (entry 7). It was also found that catalytic quantities of caesium carbonate could be used with 0.5 equivalents

(entry 8) and 0.1 equivalents (entry 9) giving the product in 76 and 71% isolated yield respectively.

Table 1　Optimisation of key bond formation[a]

Entry	Reagent	Base	Solvent	Temp °C	% Yield[e]
1	**8**.HCl	None	CHCl$_3$	50	18
2	**8**	None	CHCl$_3$	50	0
3	**8**	DBU	CHCl$_3$	50	30
4	**8**	DBU	PhMe	50	34
5	**8**	DBU	DMF	50	66
6[b]	**8**	DBU	DMF	70	70
7	**8**	Cs$_2$CO$_3$	DMF	50	84
8[c]	**8**	Cs$_2$CO$_3$	DMF	50	76
9[d]	**8**	Cs$_2$CO$_3$	DMF	50	71

[a] All reactions performed at 0.5 M concentration in the presence of 1 equivalent of base for 24 hours unless stated.
[b] 2 equivalents of base added.
[c] 0.5 equivalents of base added.
[d] Reaction carried out for 48 hours with 0.1 equivalents of base.
[e] Isolated yield.

Having established efficient conditions for the conversion of **8** to acetophenone (**9**) we examined a series of alternative *O*-benzoyl hydroxylamines to determine some of the scope of this transformation (Table 2). The reaction worked efficiently for both benzylic (entries 1–7) and aliphatic (entries 8–12) amines. Both electron donating (entries 2 and 4) and withdrawing (entry 3) substituents were tolerated on the aromatic ring as well as increased steric crowding around the reactive nitrogen (entries 5 and 6). The conversion of *N*-benzyl-*O*-benzoyl hydroxylamine to benzaldehyde was particularly facile, the reaction proceeding at room temperature, however, this was accompanied by significant decomposition leading to a reduced isolated yield of the product (41%; entry 7). It was expected that enolisable aldehydes would be inherently unstable to the basic reaction conditions required for this transformation, therefore these substrates were not examined. The conditions are mild enough to be able to carry out the reaction on substrates that lead to enolisable ketones (entries 8–12) with all substrates examined effectively leading to the expected product, suggesting the reaction should have a reasonable scope.

Table 2　Scope of conversion

Entry	Hydroxylamine	Product	% Yield
1[a]			84
2[a]			72
3[a]			90
4[a]			90
5[a]			70
6[a]			75
7[b]			41
8[c]			53[d]
9[c]			29
10[c]			63
11[c]			68
12[c]			53

[a] Reaction performed at 50 °C.
[b] Reaction performed at 25 °C.
[c] Reaction performed at 70 °C.
[d] Product isolated as the 2,4-DNPH derivative.

Finally, having developed effective conditions for the conversion of *O*-benzoyl hydroxylamines to the corresponding ketone we sought to discover if a one-pot method for the direct conversion of primary amines to ketones could also be established. The synthesis of *O*-benzoyl hydroxylamines from primary amines has been shown to be most efficient under basic reaction conditions. Reported bases for this transformation include sodium carbonate,[22] sodium hydroxide,[24] *tert*-butylamine[25] and disodium hydrogen phosphate.[26] Pleasingly, caesium carbonate was found to be effective

in the reaction of primary amines with benzoyl peroxide allowing for the direct conversion of primary amines to ketones. Treatment of a cooled DMF solution of caesium carbonate (1.5 equivalents) and benzoyl peroxide (1 equivalent) with the primary amine (1.2 equivalents) followed by warming of the reaction mixture led directly to the corresponding ketone (Table 3). The reaction was effective for both benzylic (entries 1–4) and aliphatic (entry 5) primary amines and provides a convenient alternative for this overall transformation.

Table 3 One-pot transformation

Entry	Amine	Ketone	% Yield
1			59
2			66
3			57
4			69
5			59

In summary, we have shown that *O*-benzoyl hydroxylamines can efficiently be converted into the corresponding ketones by treatment with caesium carbonate. The reactions are simple to perform in the presence of both moisture and air and lead to the product in good to excellent yield. A direct method for the conversion of primary amines to ketones was also shown to be possible by reaction of a primary amine and benzoyl peroxide under basic reaction conditions. The reactions are effective for both benzylic and aliphatic primary amines and a variety of substitution patterns on the parent amine.

Typical procedure for conversion of *N*-alkyl-*O*-benzoyl hydroxylamines to ketones

N-α-Methyl benzyl-*O*-benzoyl hydroxylamine (100 mg, 0.41 mmol) was dissolved in DMF (0.59 mL) at ambient temperature. Caesium carbonate (135 mg, 0.41 mmol) was added and the resulting reaction mixture was heated at 50 °C overnight. The resulting reaction mixture was allowed to cool and purified directly by column chromatography, eluting with 20% ethyl acetate/petrol, to give acetophenone (42 mg, 84%) as a clear colourless oil; IR (thin film): 1683, 1599, 1582, 1449, 1359, 1266, 1180, 1078, 1025, 955, 760, 690 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$): δ = 7.85 (d, *J* = 7.15 Hz, 2 H), 7.45 (t, *J* = 7.34 Hz, 1 H), 7.4–7.3 (m, 2 H), 2.5 (s, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 198.1, 137.1, 133.1, 128.6, 128.3, 26.6. MS (EI): *m/z* = 120.06 [M]$^{+}$.

Typical procedure for the one-pot conversion of primary amines to ketones:

Benzoyl peroxide (326 mg, 1.01 mmol, 75%) was dissolved in DMF (2.53 mL) and cooled to 0 °C. Caesium carbonate (493 mg, 1.51 mmol) was added with stirring followed by cyclohexyl ethylamine (0.18 mL, 1.21 mmol). The resulting reaction mixture was stirred at 0 °C for 2 hours before warming to r.t. Thin layer chromatography was used to confirm complete consumption of benzoyl peroxide before heating at 50 °C overnight. The resulting reaction mixture was purified directly by column chromatography, eluting with 20% ethyl acetate/petrol, to give cyclohexyl methyl ketone (75 mg, 59%) as a clear colourless oil; IR (thin film): 2931, 2854, 1706 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$): δ = 2.3–2.3 (m, 1 H), 2.05 (s, 3 H), 1.85–1.8 (m, 2 H), 1.75–1.7 (m, 2 H), 1.65–1.55 (m, 1 H), 1.3–1.05 (m, 5 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 212.2, 51.4, 28.4, 27.8, 25.8, 25.6. MS (EI): *m/z* = 126.22 [M]$^{+}$.

References

(1) *Modern Carbonyl Chemistry*, Otera, J. (Ed), Weinheim; Chichester: Wiley-VCH, 2000.
(2) Nakagawa, K.; Onoue, H.; Sugita, J. *Chem. Pharm. Bull.* **1964**, *12*, 1135–1138.
(3) Orito, K.; Hatakeyama, T.; Takeo, M.; Uchiito, S.; Tokuda, M.; Suginome, H. *Tetrahedron* **1998**, *54*, 8403–8410.
(4) Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971–2972.
(5) (a) Rawalay, S. S.; Shechter, H. *J. Org. Chem.* **1967**, *32*, 3129–3131. (b) Noureldin, N. A.; Bellegarde, J. W. *Synthesis* **1999**, 939–942.
(6) Audette, R. J.; Quail, J. W.; Smith, P. J. *Tetrahedron Lett.* **1971**, *12*, 279–282.
(7) Chen, H. G.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 6701–6702.
(8) Miyazawa, A.; Tanaka, K.; Sakakura, T.; Tashiro, M.; Tashiro, H.; Prakash, G. K. S.; Olah, G. A. *Chem. Commun.* **2005**, 2104–2106.
(9) Hamamoto, H.; Suzuki, Y.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2007**, *48*, 4239–4242.
(10) Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745–747.
(11) Murahashi, S.-I.; Komiya, N. In *Modern Oxidation Methods* Backvall J.-E. Ed.; Wiley-VCH: Weinheim, **2004**, 175–179.
(12) Larsen, J.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans II* **1992**, 1213–1217.
(13) Moriarty, R. M.; Vaid, R. K.; Duncan, M. P. *Tetrahedron Lett.* **1988**, *29*, 6913–6916.
(14) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.
(15) Hoffman, R. V. *J. Am. Chem. Soc.* **1976**, *98*, 6702–6704.

(16) Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429–1432.

(17) For the α-oxyacylation of carbonyl compounds see: (a) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729–5732. (b) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, T. C.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. *Chem. Commun.* **2005**, 1478–1480. (c) Jones, T. C.; Tomkinson, N. C. O. *Org. Synth.* **2007**, 233–241.

(18) For the formation of carbamates see: Hall, A.; Huguet, E. P.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Yau, S. C.; Tomkinson, N. C. O. *Synlett* **2007**, 293–297.

(19) For the formation of carbonates see: Hall, A.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Porzig, R.; Taylor, P. H.; Yau, S. C.; Tomkinson, N. C. O. *Synlett* **2006**, 3435–3438.

(20) For the α-oxysulfonylation of carbonyl compounds see: John, O. R. S.; Killeen, N. M.; Knowles, D. A.; Yau, S. C.; Tomkinson, N. C. O. *Org. Lett.* **2007**, *9*, 4009–4012.

(21) For the *N*-arylation of hydroxylamines see: Jones, K. L.; Porzelle, A.; Hall, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2008**, *10*, 797–800.

(22) Wang, Q. X.; King, J.; Phanstiel, O., IV. *J. Org. Chem.* **1997**, *62*, 8104–8108.

(23) All the known ketones prepared in this study were characterised by ^{1}H NMR, ^{13}C NMR, IR and LRMS.

(24) Roy, R. B.; Swan, G. A. *J. Chem. Soc. (C)* **1968**, 80–85 .

(25) Alewood, P .F.; Calder, I. C.; Richardson, R. L. *Synthesis* **1981**, 121–122.

(26) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681.

Graphical Abstract:

12 Examples 41-90%

R^1 = Alkyl, Aryl
R^2 = Alkyl, H
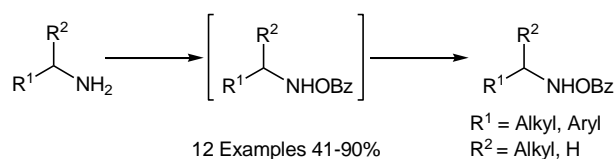
Short Title: Amine oxidation

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1 *Modern Carbonyl Chemistry*, Otera, J. (Ed), Weinheim; Chichester: Wiley-VCH, 2000.

2 Nakagawa, K.; Onoue, H.; Sugita, J. *Chem. Pharm. Bull.* **1964**, *12*, 1135–1138.

3 Orito, K.; Hatakeyama, T.; Takeo, M.; Uchiito, S.; Tokuda, M.; Suginome, H. *Tetrahedron* **1998**, *54*, 8403–8410.

4 Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971–2972.

5 (a) Rawalay, S. S.; Schechter, H. *J. Org. Chem.* **1967**, *32*, 3129–3131. (b) Noureldin, N. A.; Bellegarde, J. W. *Synthesis* **1999**, 939–942.

6 Audette, R. J.; Quail, J. W.; Smith, P. J. *Tetrahedron Lett.* **1971**, *12*, 279–282.

7 Chen, H. G.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 6701–6702.

8 Miyazawa, A.; Tanaka, K.; Sakakura, T.; Tashiro, M.; Tashiro, H.; Prakash, G. K. S.; Olah, G. A. *Chem. Commun.* **2005**, 2104–2106.

9 Hamamoto, H.; Suzuki, Y.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2007**, *48*, 4239–4242.

10 Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745–747.

11 Murahashi, S.-I.; Komiya, N. In *Modern Oxidation Methods* Backvall J.-E. Ed.; Wiley-VCH: Weinheim, **2004**, 175–179.

12 Larsen, J.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans II* **1992**, 1213–1217.

13 Moriarty, R. M.; Vaid, R. K.; Duncan, M. P. *Tetrahedron Lett.* **1988**, *29*, 6913–6916.

14 Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.

15 Hoffman, R. V. *J. Am. Chem. Soc.* **1976**, *98*, 6702–6704.

16 Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429–1432.

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18 For the formation of carbamates see: Hall, A.; Huguet, E. P.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Yau, S. C.; Tomkinson, N. C. O. *Synlett* **2007**, 293–297.

19 For the formation of carbonates see: Hall, A.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Porzig, R.; Taylor, P. H.; Yau, S. C.; Tomkinson, N. C. O. *Synlett* **2006**, 3435–3438.

20 For the α-oxysulfonylation of carbonyl compounds see: John, O. R. S.; Killeen, N. M.; Knowles, D. A.; Yau, S. C.; Tomkinson, N. C. O. *Org. Lett.* **2007**, *9*, 4009–4012.

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22 Wang, Q. X.; King, J.; Phanstiel, O., IV. *J. Org. Chem*. **1997**, *62*, 8104–8108.

23 All ketones prepared in this study were characterised by 1H NMR, 13C NMR, IR, LRMS and HRMS.

24 Roy, R. B.; Swan, G. A. *J. Chem. Soc. (C)* **1968**, 80–83.

25 Alewood, P .F.; Calder, I. C.; Richardson, R. L. *Synthesis* **1981**, 121–122.

26 Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681.