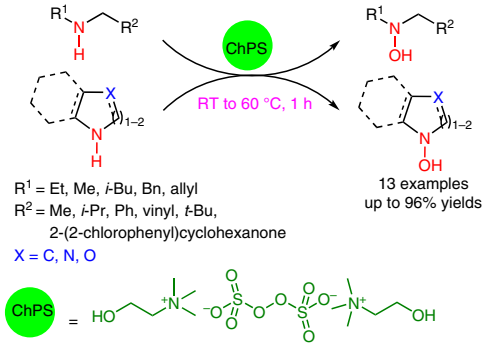
Synlett A. Banan et al. Letter

Selective Oxidation of Secondary Amines to N,N-Disubstituted Hydroxylamines by Choline Peroxydisulfate

Alireza Banan[a]
Hassan Valizadeh[a]
Akbar Heydari*[b]
Abolghasem Moghimi[c]

[a] Department of Chemistry, Faculty of Sciences, Azarbaijan Shahid Madani University, 53714-161 Tabriz, Iran
[b] Department of Chemistry, Tarbiat Modares University, 14155-4838 Tehran, Iran
heydar_a@modares.ac.ir
[c] Department of Chemistry, Faculty of Science, Islamic Azad University, North Tehran Branch, 191367-4711, Tehran, Iran



Received: 21.04.2017
Accepted after revision: 28.06.2017
Published online: 17.08.2017
DOI: 10.1055/s-0036-1589089; Art ID: st-2017-d0281-l

Abstract N,N-Disubstituted hydroxylamines were prepared directly from secondary amines by a reliable method using an oxidizing task-specific ionic liquid, choline peroxydisulfate. The operational simplicity, high selectivity, and green reaction conditions, make this method efficient and practical.

Key words hydroxylamines, ionic liquids, choline peroxydisulfate, oxidation, amines, green chemistry

Hydroxylamines are useful and highly valuable synthetic intermediates for the synthesis of nitrones,[1] hydroxamic acids,[2] nitroso compounds,[3] and natural products or pharmaceuticals such as alkaloids,[4] azanucleosides,[5] and other nitrogenated products.[6] Hydroxylamines have shown several important biological properties including antibacterial,[7] antifungal[8], anti-HIV,[9] antidiabetic,[10] and antitumor activities.[11] Moreover, hydroxylamines have relevant applications as antioxidants and spin-trap agents in age-related diseases.[12,13] Some examples of biologically active compounds containing hydroxylamine group are shown in Figure 1.

The preparation of N,N-disubstituted hydroxylamines through oxidation of an amino group is an attractive approach because a variety of secondary amines are commercially available, including compounds with high enantiomeric purities.[14] However, there have been few reports on the synthesis of N,N-disubstituted hydroxylamines directly from secondary amines. These oxidation reactions have serious limitations, such as reagent instability (e.g., dioxiranes),[15] competing overoxidation,[16] low yields,[17] limited chemoselectivity,[18] harsh reaction conditions,[19] formation of hazardous waste,[20] or the need for long reaction times.[21] Moreover, the reactions are often performed in commercial organic solvents that present inherent toxicity and have high volatility.[22]

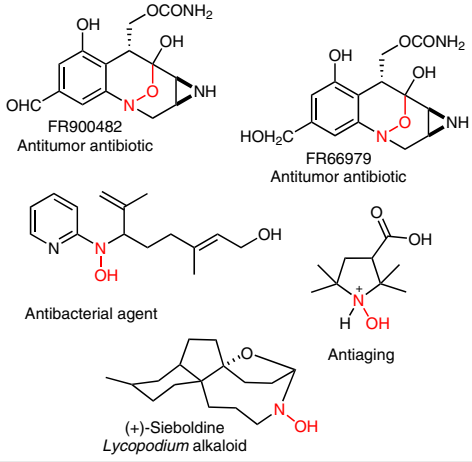


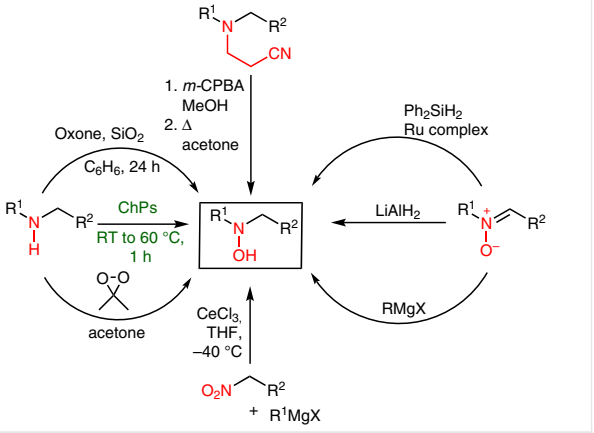
Figure 1 Selected biologically active compounds containing hydroxylamine groups

Ionic liquids have been developed as green reaction media for the oxidation of organic compounds.[23] Nowadays, in functionalized (task-specific) ionic liquids, the roles of the ionic liquids go beyond their use merely as solvents.[24] Task-specific ionic liquids have particular applications in catalysis,[25] synthesis,[26] analysis,[27] and gas absorption,[28] and also as polarity-shifting additives[29] or as pharmaceuticals.[30]

Shankarling and co-workers recently synthesized choline peroxydisulfate hydrate (ChPS·H_2O) as a biodegradable task-specific ionic liquid for the oxidation of alcohols.[31] However, the use of task-specific ionic liquids for the synthesis of N,N-disubstituted hydroxylamines is unprecedented. The most convenient method for preparing N,N-disubstituted hydroxylamines is the direct oxidation of secondary amines. Here, we report the selective oxidation of

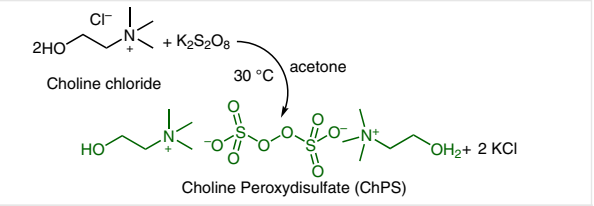
secondary amines with choline peroxydisulfate to give N,N-disubstituted hydroxylamines. ChPS proved to be an environmentally benign and biodegradable oxidant with a high catalytic activity that permits selective oxidation of a wide variety of secondary amines to the corresponding hydroxylamines in a rapid one-step reaction.

Generally there is no convenient method for the synthesis of N,N-disubstituted hydroxylamines. Among the various methods for preparing hydroxylamines, the direct oxidation of amines is the most convenient and cost-effective one. However, this method suffers from the problem of overoxidation to form nitrones. A brief overview of previously reported approaches is shown in Scheme 1. These methods include the oxidation of secondary amines with Oxone over silica gel, dilute solutions of dimethyldioxirane, or 2-(phenylsulfonyl)-3-aryloxaziridine (Davis's reagent);[21,32] the reduction or addition of an appropriate nucleophile (Grignard reagent, silylated compound, or organolithium reagent) to a nitrone;[33] the addition of an organometallic reagent to a nitroso or nitro compound,[34] or Cope elimination reactions of tertiary amine *N*-oxides.[35] However, overoxidation, generation of hazardous byproducts, and low yields are among the difficulties encountered in these methods.



Scheme 1 An overview of methods for the preparation of N,N-disubstituted hydroxylamines

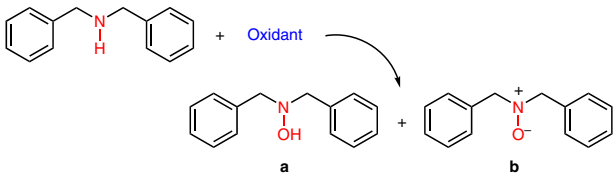
In this study, we synthesized ChPS by the reaction of choline chloride with potassium persulfate (Scheme 2),[36] and we then used it as catalyst for the synthesis of a series of hydroxylamines in a one-step process.[37]



Scheme 2 Synthesis of choline peroxydisulfate

Initially, we selected the reaction of dibenzylamine with ChPS as a model reaction (Table 1), and we examined the effects of the oxidant-to-amine ratio and the reaction time. When dibenzylamine was treated with an equimolar amount of ChPS, *N*,*N*-dibenzylhydroxylamine was obtained exclusively (Table 1, entry 1), whereas conventional oxidants such as hydrogen peroxide or molecular oxygen with a catalyst ($H_3PW_{12}O_{40}$ immobilized on SiO_2-coated Fe_3O_4 nanoparticles) in methanol failed to give the expected product, and gave the corresponding nitrone instead (entries 2 and 3). Oxidation of *N*,*N*-dibenzylhydroxylamine with various amounts of ChPS was evaluated, and the best oxidant/amine ratio was found to be 1.1 (entries 4 and 5). According to a previous report, nitrones and hydroxylamine compete to react with the oxidant.[38] However, in this study we observed that increasing the amount of oxidant to two equivalents did not have any significant effect on the yield of the hydroxylamine product. The effect of the reaction time on the yield of the desired product was also investigated, and it was observed that increasing the reaction time beyond one hour did not have much effect on the product yield (entries 5 and 7). Therefore, the optimal reaction conditions were found to be an oxidant-to-amine ratio of 1.1 and a reaction time of one hour at 60 °C in a single step.

Table 1 Optimization of the Reaction Conditions[a]

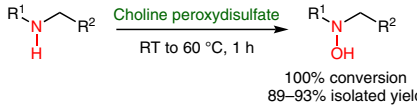


Entry	Oxidant	Oxidant /amine ratio	Time (h)	Yield[b] (%) of **a**	Yield[b] (%) of **b**
1	ChPS	1	1	78	0
2	H_2O_2/cat.[c]	1	2	0	86
3	O_2/cat.[c]	1	2	0	11
4	ChPS	2	1	89	0
5	ChPS	1.1	1	91	0
6	ChPS	1.1	0.5	76	0
7	ChPS	1.1	24	93	0

[a] Reaction conditions: 60 °C, N_2 atmosphere.
[b] Isolated yield.
[c] Nanoparticulate Fe_2O_3@SiO_2–$H_3PW_{12}O_{40}$.

As shown in Table 2, various aliphatic and heterocyclic hydroxylamines were then synthesized in moderate to good yields. All the products are known compounds except **1l** and **1m**, and they were characterized by comparison of their ^{1}H NMR and ^{13}C NMR spectroscopic data with the reported spectra.[15,17,39–44] Heydari and co-workers suggested that when a secondary amine that has a hydrogen atom attached to an α-carbon atom is oxidized, the resulting hy-

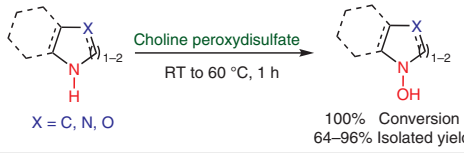
droxylamine tends to undergo further oxidation to the nitrone.[45] However, in our procedure, such aliphatic secondary amines were not oxidized to the nitrone, even in the presence of a stoichiometric excess of ChPS (Scheme 3).



Scheme 3 Synthesis of *N*,*N*-dialkyl hydroxylamines

Oxidation of dibenzylamine gave *N*,*N*-dibenzylhydroxylamine (Table 2, 1a) without any overoxidation to the nitrone. *N*-Benzyl-2-methylpropan-2-amine was oxidized to *N*-benzyl-*N*-(*tert*-butyl)hydroxylamine (**1b**). *N*,*N*-Diethylhydroxylamine (**1c**), an oxygen scavenger[46] and short stopping agent,[47] was readily prepared in good yield by oxidation of diethylamine, and *N*,*N*-diisobutylhydroxylamine (**1d**) was prepared by oxidation of diisobutylamine. Selective oxidation of diallylamine is known to be difficult, but surprisingly we observed that the allylic C–H bonds were not activated during the oxidation reaction in ChPS, and diallylamine was selectively oxidized to *N*,*N*-diallylhydroxylamine (**1e**), which has been used as a vinyl monomer in polymerizations.[48] Morpholine was oxidized to morpholin-4-ol (**1f**) in moderate yield. Piperidin-1-ol (**1g**) and pyrrolidin-1-ol (**1h**) were obtained by oxidation of piperidine and pyrrolidine, respectively.

The synthesis of 1*H*-imidazol-1-ol and its derivatives has recently received considerable attention due to their wide range of biological activities.[49] 1*H*-imidazol-1-ol (**1i**) was prepared by the mild oxidation of 1*H*-imidazole. Likewise, 1*H*-indol-1-ol (**1j**) was prepared by direct oxidation of indole[50] (Scheme 4).

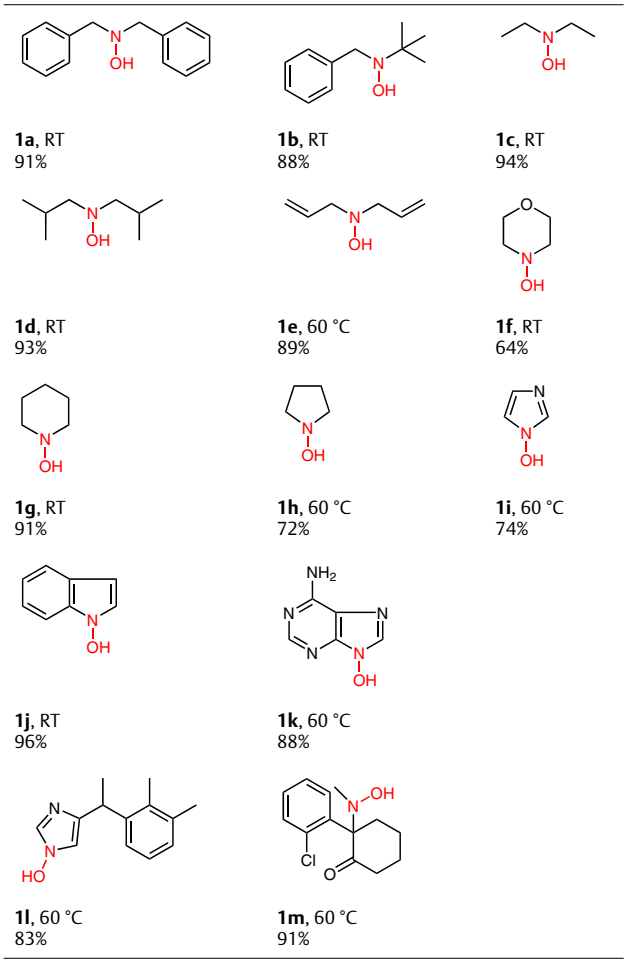


Scheme 4 Oxidation of heterocyclic amines

To the best of our knowledge, the direct oxidation of adenine to adenin-9-ol (**1k**) has not been previously reported, but **1k** was readily prepared by the oxidation of adenine. Medetomidine and ketamine, which are well known anesthetic agents,[51] were prepared as the free bases[52] and converted into their corresponding N-hydroxy derivatives **1l** and **1m**, respectively.

A plausible mechanistic pathway for the oxidation of secondary amines by ChPS hydrate is nucleophilic attack by the electron-rich secondary amine on the electron-deficient ChPS to give a transition state in which cleavage of O–O and O–S bonds gives the desired product (Scheme 5). It is

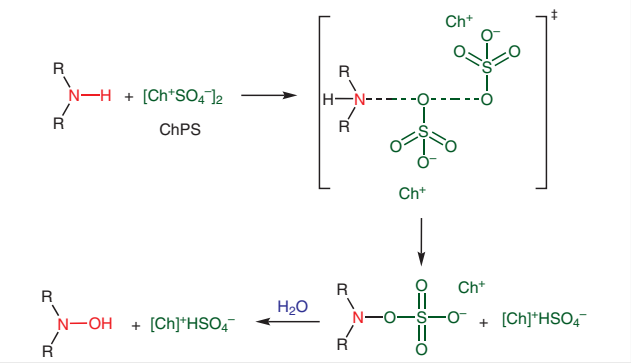
Table 2 Preparation of N,N-Disubstituted Hydroxylamines by ChPS[a, 51]



[a] *Reaction conditions*: secondary amine (5 mmol), Choline peroxydisulfate (5.5 mmol); time = 1 h.

well established that transesterification proceeds by addition of a hydroxide ion to the sulfate sulfur atom with subsequent expulsion of the appropriate anion, as suggested by Denney and Denney for the oxidation of secondary amines with benzoyl peroxide.[53]

The structures of the products were readily assigned by ^{1}H NMR spectroscopy. The structure of hydroxylamines was confirmed through the appearance in the ^{1}H NMR spectrum of a broad peak at δ ≈ 8–10 ppm with simultaneous disappearance of the NH peak. Moreover, the protons attached at the α-carbon atom in hydroxylamines were more deshielded than the equivalent protons in the corresponding amines. We also monitored the progress of the reaction by comparing the intensity in ^{1}H NMR of the peaks of the protons attached at the α-carbon atom. Monitoring the reaction in this way revealed that the amines were oxidized to



Scheme 5 Proposed reaction mechanism

hydroxylamines with a clear selectivity and quantitative conversions. The novel products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.[54]

In conclusion, a chemoselective and convenient method has been developed for the preparation of N,N-disubstituted hydroxylamines through the oxidation of secondary amines with ChPS. This method appears to be well suited to the oxidation of complex amines, such as medetomidine or ketamine. ChPS, as a versatile task-specific ionic liquid, has been shown to be a possible replacement for oxidants when mild oxidation conditions are required. Its unique properties include biodegradability, non-volatility, high thermal stability, high efficiency, and high chemoselectivity.

Funding Information

Partial financial assistance from the Research Vice Chancellor of Azarbaijan Shahid Madani University is gratefully acknowledged

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589089.

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(36) **Choline Peroxydisulfate Hydrate**
A mixture of choline chloride (27 g, 193 mmol) and $K_2S_2O_8$ powder (30 g, 110 mmol) in acetone (100 mL) was stirred at 30 °C for 24 h and then filtered to remove the solid KCl. The filtrate was concentrated under reduced pressure to give a pale-yellow oily product; yield: 36.5 g (90%). The choline peroxydisulfate hydrate was stored at 0–5 °C.
(37) **N,N-Disubstituted Hydroxylamines 1a–m; General Procedure**
A round-bottomed flask was charged with the secondary amine (5 mmol) and ChPS (5.5 mmol) and the mixture was stirred for 1 h at 60 °C under N_2. The mixture was then dissolved in H_2O (5

mL) and the product was extracted with CH_2Cl_2 or EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

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(52) **Ketamine and Medetomidine Free Bases**
Ketamine or medetomidine hydrochloride (5 g) was neutralized with 1 M aq $NaHCO_3$ (25 mL), and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and vacuum filtered. The solvent was removed under reduced pressure to give a pale-yellow powder. The structure was confirmed by melting-point comparison and by ^{1}H NMR spectroscopy.
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(54) ***N,N*-Dibenzylhydroxylamine (1a)**
White powder; isolated yield: 970 mg (91%); mp 122–124 °C. ^{1}H NMR (DMSO-d_6): δ = 4.18 (s, 4 H, CH_2–), 7.47–7.63 (m, 10 H, C_6H_5–), 9.93 (br s, 1 H, N-OH). ^{13}C NMR (DMSO-d_6): δ = 50.07 (–CH_2–), 129.01 (C-4), 129.29 (C-3), 130.57 (C-2), 132.33 (C-1, C–CH_2–N–).
***N*-Benzyl-*N*-(*tert*-butyl)hydroxylamine (1b)**
White powder; isolated yield: 788 mg (88%); mp 70–72 °C. ^{1}H NMR (DMSO-d_6): δ = 1.46 (s, 9 H), 4.13 (s, 2 H), 9.29 (br s, 1 H, N-OH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6): δ = 25.30, 53.39, 56.95, 128.76, 129.94, 130.47, 133.10.
***N,N*-Diethylhydroxylamine (1c)**
Brown liquid; isolated yield: 418 mg (94%). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, *J* = 6.75 Hz, 6 H, CH_3), 3.04 (q, *J* = 6.75 Hz, 4 H, CH_2), 9.25 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 10.80 (CH_3), 41.93 (CH_2).
***N,N*-Diisobutylhydroxylamine (1d)**
Light-brown powder; isolated yield: 675 mg (93%); mp 57–59 °C. ^{1}H NMR ($CDCl_3$): δ = 1.10 (d, *J* = 6.75 Hz, 12 H, CH_3), 2.28 (m, 2 H, –CH–), 2.80 (q, ^1J = 12.25 Hz, ^2J = 6.50, 4 H, –CH_2–), 9.26 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 20.72 (CH_3), 25.24 (=CH–), 54.92 (–CH_2 –).
***N,N*-Diallylhydroxylamine (1e)**
Brown liquid; isolated yield: 503 mg (89%). ^{1}H NMR ($CDCl_3$): δ = 3.56 (d, *J* = 6.50 Hz, 4 H, –CH_2–N), 5.45 (t, ^1J = ^2J = 9.25 Hz, 4 H, =CH_2), 6.03 (m, 2 H, =CH–), 9.76 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 48.02 (–CH_2–), 123.98 (=CH_2), 128.75 (–CH=).
Morpholin-4-ol (1f)
Brown oily liquid; isolated yield: 329 mg (64%). ^{1}H NMR (DMSO-d_6): δ = 3.19 (t, *J* = 4.75 Hz, 4 H, –CH_2–N), 3.66 (t, *J* = 4.75 Hz, 4 H, –CH_2–O), 10.11 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 58.7 (–CH_2–N), 65.9 (–CH_2–O).
Piperidin-1-ol (1g)
Brown solid; isolated yield: 460 mg (91%); mp 32–34 °C. ^{1}H NMR ($CDCl_3$): δ = 1.66 (br s, 2 H, CH_2), 1.88 (br s, 4 H, CH_2), 3.16 (br s, 4 H, CH_2–N), 9.33 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 22.34, 22.37, 44.37.
Pyrrolidin-1-ol (1h)
Brown oily liquid; isolated yield: 313 mg (72%). ^{1}H NMR ($CDCl_3$): δ = 2.01 (br s, 4 H, CH_2), 3.31 (br s, 4 H, CH_2–N), 9.58 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 24.31 (–CH_2–), 44.96 (–CH_2–N).
1*H*-Imidazol-1-ol (1i)
Light-yellow liquid; isolated yield: 310 mg (74%). ^{1}H NMR ($CDCl_3$): δ = 7.13 (br s, 2 H, CH–N), 7.27 (br s, 1 H, N–CH–N), 7.76 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 121.62, 135.02.
1*H*-Indol-1-ol (1j)
Brown oily liquid; isolated yield: 638 mg (96%). ^{1}H NMR ($CDCl_3$): δ = 6.54 (br s, 1 H, CH-3), 7.12 (t, *J* = 6.75 Hz, 1 H, CH-5), 7.15 (br s, 1 H, CH-2), 7.19 (t, *J* = 6.75 Hz, 1 H, CH-6), 7.37 (d, *J* = 7.75 Hz, 1 H, CH-7), 7.65 (d, *J* = 7.75 Hz, 1 H, CH-4), 8.18 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 102.4 (C-3), 111.0 (C-7), 119.7 (C-6), 120.7 (C-4), 121.9 (C-5), 124.2 (C-2), 127.7 (C-9) 135.7 (C-8).
6-Amino-9*H*-purin-9-ol (1k)
Plum powder; isolated yield: 664 mg (88%); mp 210–212 °C. ^{1}H NMR (DMSO-d_6): δ = 7.88 (br s, 2 H, NH_2), 8.25 (s, 2 H, –CH–) 4.55 (br s, 1 H, –OH). ^{13}C NMR ($CDCl_3$): δ = 112.56 (C-5), 140.96 (C-8), 149.87 (C-4), 150.72 (C-2), 153.80 (C-6).
4-[1-(2,3-Dimethylphenyl)ethyl]-1*H*-imidazol-1-ol (1l)
Yellow solid; isolated yield: 897 mg (83%); mp 188–190 °C. ^{1}H NMR ($CDCl_3$): δ = 1.68 (d, *J* = 7.00 Hz, 3 H, CH_3), 2.22 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 4.58 (q, *J* = 7.00 Hz, 1 H, CH), 6.70 (s, 1 H, CH), 7.01–7.08 (m, 3 H), 8.77 (s, 1 H), 14.41 (br s, 1 H, NOH). ^{13}C NMR ($CDCl_3$): δ = 14.9 (CH_3), 20.52 (CH_3), 20.94 (CH_3), 32.18 (CH), 115.14 (CH), 123.91 (CH), 125.89 (CH), 128.94 (CH), 132.90 (quat C), 134.21 (quat C), 137.31 (CH), 138.57 (quat C), 139.49 (quat C).
2-(2-Chlorophenyl)-2-[hydroxy(methyl)amino]cyclohexanone (1m)
Light-yellow powder; isolated yield: 1176 mg (91%); mp 206–208 °C. ^{1}H NMR ($CDCl_3$): δ = 1.55–2.00 (m, 6 H), 2.44–2.63 (m, 5 H), 7.46–7.52 (m, 3 H), 8.14 (d, *J* = 0.75 Hz, 1 H), 9.53 (br s, 1 H, –OH), 10.57 (br s, 1 H, –OH). ^{13}C NMR ($CDCl_3$): δ = 21.60 (CH_2), 28.29 (CH_2), 29.41 (CH_3), 38.26 (CH_2), 40.19 (CH_2), 72.60 (quat C), 128.50 (CH), 128.67 (CH), 131.76 (CH), 131.89 (CH), 131.96 (quat C), 135.27 (quat C), 205.28 (quat C, C=O).