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ORIGINAL ARTICLE

One-pot sequential synthesis of *O*-(halo-substituted benzyl) hydroxylammonium salts

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Abstract In this study, we described a simple one-pot preparation of *O*-(halo-substituted benzyl) hydroxylamine derivatives by *O*-benzylation of *N*-hydroxyurethane, followed by basic *N*-deprotection. The advantages of the method were the chemo- and regio-selectivity in obtaining the desired *O*-benzyl hydroxylammonium salts in a high yield as well as the simplicity of the purification process.

1. Introduction

Hydroxylamine derivatives represent an important class of compounds due to their widespread use as synthetic intermediates and as structural components of numerous biological and pharmacological agents such as herbicides. Hydroxylamine derivatives have been reported to possess antibacterial (Foroumadi et al., 2006), antiviral (Okamoto et al., 1999), antifungal (Emami and Shafiee, 2001; Emami et al., 2002; Emami and Shafiee, 2005), herbicidal and antitumor activities (Rajabalian et al., 2007; Saban and Bujak, 2009) and to have anxiolytic, anticonvulsant, analgesic, CNS stimulating and enzyme inhibiting properties (Stanek et al., 1992; Guo et al., 1995; Conejo-Garcia and Schofield, 2005; Milovica et al., 2001). Among hydroxylamine derivatives, *O*-substituted hydroxylamines and their salts are of particular interest to the agrochemical field, mainly for the preparation of pesticides and crop protection agents. They are also used as intermediates for the production of various drugs, pharmaceutical compounds and fine chemicals (Schumann et al., 1964). Therefore, more efficient methods for the preparation of these substances in high yield and purity are of great interest.

Generally, methods for synthesizing *O*-substituted hydroxylamines rely on exploiting the nucleophilic power of oxygen and nitrogen in hydroxylamine motif toward an appropriate electrophilic component. It is known that substitution of a hydroxylamine leads to reaction at the amine nitrogen. In order to effect substitution at the hydroxyl group, it is generally necessary to block the amine function (Wild et al., 1992). There have been several strategies used to produce *O*-substituted hydroxylamines, but most follow the same general pathway: hydroxylamine nitrogen protection, substitution at the free oxygen and then removal of the protecting group. Substitution of *N*-pro-

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tected hydroxylamines at the oxygen does not present any problems. In contrast, elimination of the protective groups and isolation and purification of the *O*-substituted hydroxylamines are much more problematic (Wild et al., 1992). Several *N*-protected hydroxylamines (Scheme 1) are particularly used: ketoximes and aldoximes, especially acetoxime (Schumann et al., 1962; Balsamo et al., 1989); cyclic *N*-hydroximides, especially *N*-hydroxyphthalimide (Henmi et al., 1994; Kim et al., 1994; Motorina et al., 1996); hydroxamic acid derivatives (Cooley et al., 1960; Shatzmiller and Bercovici, 1992) for example *N*-hydroxyurethane (Ludwig et al., 1967); and *tert*-butyl *N*-hydroxycarbamate (BocHN–OH) (Albrecht et al., 2006). Another method for the preparation of *O*-substituted hydroxylamines is the reaction of hydroxylamine-*O*-sulfonic acid with alcohols (Endo et al., 1980) (Scheme 1).

In this report, we describe a simple one-pot preparation of *O*-benzyl hydroxylamine derivatives, which can used as intermediates for the production of various pharmaceutical compounds, pesticides, and fine chemicals.

2. Experimental

2.1. General

Chemical reagents and all solvents used in this study were purchased from Merck AG and Aldrich. *N*-Hydroxyurethane was prepared from hydroxylamine hydrochloride and ethyl chloroformate according to the literature method (Fuller and King, 1947). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a Bruker 80 or 500 MHz spectrometer and chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. The mass spectra were run on a Finigan TSQ-70 spectrometer (Finigan, USA) at 70 eV. Elemental analyses were carried out on CHN–O rapid elemental analyzer (GmbH-Germany) for C, H and N, and the results are within ±0.4% of the theoretical values. Merck silica gel F254 plates were used for analytical TLC.

2.2. General procedure for the synthesis of O-benzyl hydroxylamine hydrochlorides (**2a**–**h**)

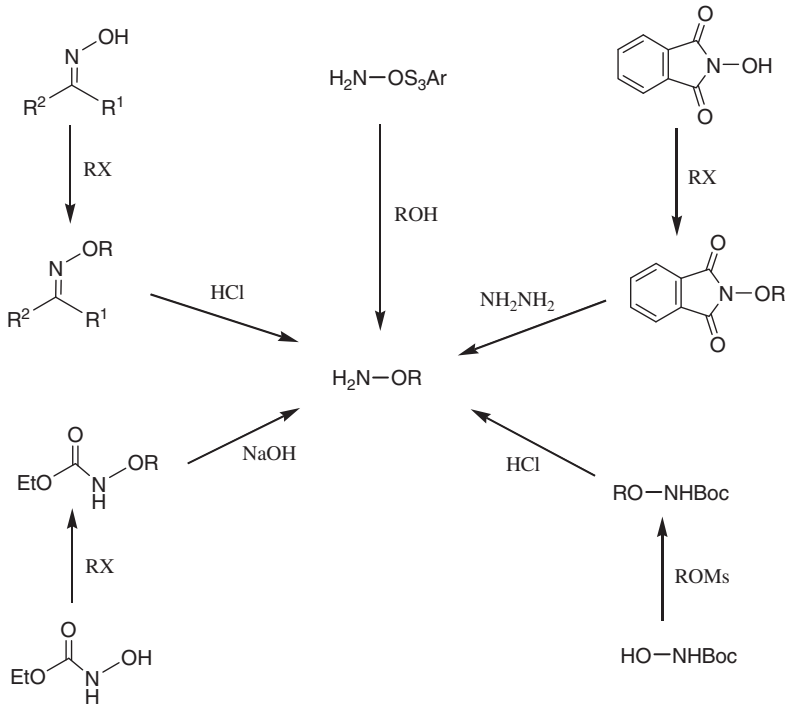
To a sodium ethoxide solution (prepared from 0.97 g sodium and 70 ml of absolute ethanol), *N*-hydroxyurethane (4.46 g) was added and stirred at room temperature. Appropriate benzyl halide **1a**–**h** (43 mmol) was added at such a rate that the temperature did not exceed 30 °C. The mixture was stirred for 8–10 h at room temperature. Then, a solution of NaOH in water (3.46 g in 70 ml) was added to the mixture and heated under reflux for 2 h. The ethanol was then removed by distillation and the cooled residue was extracted with ether (3 × 100 ml). The extract was dried (Na_2SO_4) and concentrated to 100 ml and then 8.5 ml of 5*N* ethanolic HCl was added carefully. The white precipitate which formed was separated and washed with cooled ether to give pure **2a**–**h** (Table 1).

2.2.1. O-Benzylhydroxylamine hydrochloride (**2a**)

IR (KBr, cm^{-1}) 3447, 2927, 2669, 1599, 1509, 1454, 1397, 1181, 1010, 896, 743, 693; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.06 (s, 2H, CH_2), 7.42 (br s, 5H, Ar), 11.2 (br s, 3H, H_3N^+). Anal. Calcd for $C_7H_{10}ClNO$: C, 52.67; H, 6.31; N, 8.78. Found: C, 52.80; H, 6.39; N, 8.66.

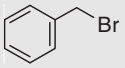
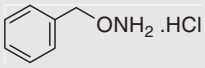
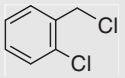
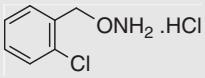
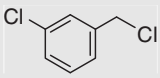
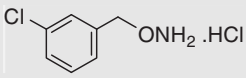
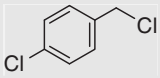
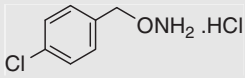
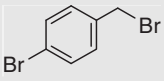
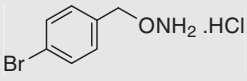
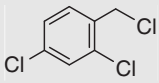
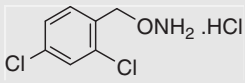
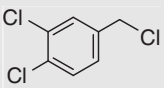
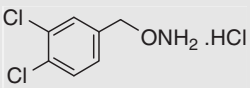
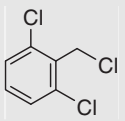
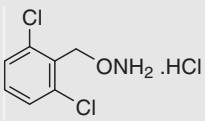
2.2.2. O-(2-Chlorobenzyl)hydroxylamine hydrochloride (**2b**)

^{1}H NMR (80 MHz, DMSO-d_6) δ: 5.19 (s, 2H, CH_2), 7.33–7.38 (m, 1H, Ar), 7.41–7.51 (m, 2H, Ar), 7.54 (t, 1H, J = 7.2 Hz,



Scheme 1 Strategies used to produce *O*-substituted hydroxylamines.

Table 1 Structures and physicochemical properties of *O*-benzyl hydroxylammonium salts **2a**–**h**.

Compound	Substrate (**1a**–**h**)	Product (**2a**–**h**)	Yield[a] (%)	Mp (°C)
2a			82	236–237
2b			80	142–144
2c			82	204–208
2d			84	243–244
2e			88	215–217
2f			86	131–132
2g			83	191–192
2h			78	206–207

[a] Isolated yields.

Ar), 11.40 (s, 3H, H_3N^+). Anal. Calcd for $C_7H_9Cl_2NO$: C, 43.32; H, 4.67; N, 7.22. Found: C, 43.17; H, 4.76; N, 7.31.

*2.2.3. O-(3-Chlorobenzyl)hydroxylamine hydrochloride (**2c**)*

^{1}H NMR (80 MHz, DMSO-d_6) δ: 5.08 (s, 2H, CH_2), 7.22–7.60 (m, 3H, Ar), 7.62 (s, 1H, Ar), 11.21 (s, 1H, H_3N^+). Anal. Calcd for $C_7H_9Cl_2NO$: C, 43.32; H, 4.67; N, 7.22. Found: C, 43.30; H, 4.44; N, 7.49.

*2.2.4. O-(4-Chlorobenzyl)hydroxylamine hydrochloride (**2d**)*

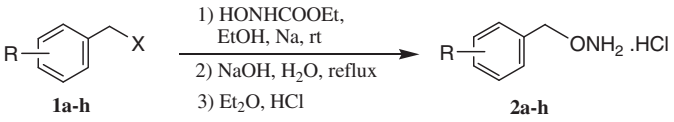
IR (KBr, cm^{-1}) 3444, 2947, 2651, 1600, 1492, 1095, 1016, 913, 814; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 4.79 (s, 2H, CH_2), 7.24 (d, 2H, J = 7.75 Hz, H-2 and H-6 Ar), 7.33 (d, 2H, J = 7.75 Hz, H-3 and H-5, Ar), 11.1 (br s, 3H, H_3N^+). MS (m/z, %) 157 (M^+, 5), 127 (80), 125 (100), 89 (43). Anal. Calcd for $C_7H_9Cl_2NO$: C, 43.32; H, 4.67; N, 7.22. Found: C, 43.19; H, 4.74; N, 7.40.

*2.2.5. O-(4-Bromobenzyl)hydroxylamine hydrochloride (**2e**)*

IR (KBr, cm^{-1}) 3437, 2923, 2649, 15934, 1486, 1408, 1075, 1013, 913, 810; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.03 (s, 2H, CH_2), 7.39 (d, 2H, J = 8.15 Hz, H-2 and H-6 Ar), 7.63 (d, 2H, J = 8.15 Hz, H-3 and H-5 Ar), 11.1 (br s, 3H, H_3N^+). Anal. Calcd for $C_7H_9BrClNO$: C, 35.25; H, 3.80; N, 5.87. Found: C, 34.98; H, 3.86; N, 6.11.

*2.2.6. O-(2,4-Dichlorobenzyl)hydroxylamine hydrochloride (**2f**)*

IR (KBr, cm^{-1}) 3401, 2923, 2667, 1593, 1563, 1476, 1382, 1106, 1057, 866, 815, 760; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 5.12 (s, 2H, CH_2), 7.37–7.56 (m, 2H, H-5 and H-6 Ar), 7.73 (d, 1H, J = 2.2 Hz, H-3 Ar), 10.9 (br s, 3H, H_3N^+). Anal. Calcd for $C_7H_8Cl_3NO$: C, 36.79; H, 3.53; N, 6.13. Found: C, 36.70; H, 3.44; N, 6.19.



Scheme 2 Synthetic route to desired *O*-benzyl hydroxylammonium salts.

*2.2.7. O-(3,4-Dichlorobenzyl)hydroxylamine hydrochloride (**2g**)*

IR (KBr, cm^{-1}) 3432, 2892, 2647, 1596, 1511, 1474, 1395, 1129, 1038, 875, 823; ^1H NMR (500 MHz, DMSO-d_6) δ: 5.06 (s, 2H, CH_2), 7.44 (dd, 1H, J = 8.2 and 1.7 Hz, H-6 Ar), 7.57 (d, 1H, J = 8.2 Hz, H-5 Ar), 7.71 (d, 1H, J = 1.6 Hz, H-2 Ar), 11.1 (br s, 3H, H_3N^+). Anal. Calcd for $C_7H_8Cl_3NO$: C, 36.79; H, 3.53; N, 6.13. Found: C, 37.03; H, 3.65; N, 6.10.

*2.2.8. O-(2,6-Dichlorobenzyl)hydroxylamine hydrochloride (**2h**)*

IR (KBr, cm^{-1}) 3436, 2596, 1561, 1437, 1192, 1090, 1010, 982, 866, 780, 766, 723; ^1H NMR (500 MHz, DMSO-d_6) δ: 5.38 (s, 2H, CH_2), 7.39–7.57 (m, 3H, Ar), 11.2 (br s, 3H, H_3N^+). Anal. Calcd for $C_7H_8Cl_3NO$: C, 36.79; H, 3.53; N, 6.13. Found: C, 36.87; H, 3.37; N, 6.34.

3. Results and discussion

For the preparation of *O*-benzyl hydroxylamines, *N*-hydroxyurethane, an *N*-protected, directing synthetic equivalent of hydroxylamine can be utilized in cases where regiospecificity under basic conditions is required. Thus, the *O*-benzylation of *N*-hydroxyurethane with appropriate benzyl halides **1a**–**h** in ethanolic solution of sodium ethoxide at room temperature afforded *O*-benzyl carbethoxyhydroxamates, which on subsequent hydrolysis with aqueous solution of alkali produced corresponding *O*-benzyl hydroxylamines. The concentrated reaction mixture was extracted with diethyl ether and the hydrochloride salts of target compounds (**2a**–**h**) were readily crystallizable from diethyl ether by the addition of ethanolic HCl (Scheme 2). The overall yield was over 78% (Table 1).

Behrend et al. prepared *O*-benzyl hydroxylamine hydrochloride by the hydrolysis of acetone oxime *O*-benzyl ether in 50% yield (for final step) (Behrend and Leuchs, 1890). Bonaccorsi et al. prepared *O*-benzyl hydroxylamine in large scale by the reaction of *N*-hydroxyphthalimide and benzyl chloride in the phase transfer conditions, followed by acidic hydrolysis of *N*-benzyloxyphthalimide, with an overall yield of 65% (Bonaccorsi and Giorgi, 1997).

Production pathways via oximes and *N*-hydroxyphthalimides represent the conventional method. However, in these methods the elimination of the ketone and phthalic acid moiety, respectively after introducing the *O*-substituent is not quantitative. In addition the purification process is difficult and expensive. For example, in the production pathways via *N*-hydroxyphthalimide, the hydrazinolysis of phthalimidoethers is a frequently used laboratory method. But in this method, in addition to the precipitated phthalic hydrazide, the basic compound *N*-aminophthalimide is also formed; separation of the latter compounds from the *O*-substituted hydroxylamine, which is likewise basic, presents very considerable problems (Wild et al., 1992). Thus, the disadvantages of the conventional methods were the difficulty in obtaining the desired *O*-substituted hydroxylamines in a high yield as well as the expenses of the purification process.

The advantage of our process over the conventional methods of the preparation of *O*-substituted hydroxylamines is that the cleavage of *O*-benzyl carbethoxyhydroxamates takes place readily and without side reactions. In addition, the respective alcoholic and aqueous processes allow the formation of the *O*-benzyl hydroxylamines in one pot with no need to isolate the *O*-benzyl carbethoxyhydroxamates. The *O*-benzyl hydroxylamines are particularly readily separated from the aqueous cleavage products by ethereal extraction and hydrochloride salt formation. It is advisable in this case to isolate the *O*-benzyl hydroxylammonium salts in place of the *O*-benzyl hydroxylamines because the unreacted components are then present in the filtrate together with the inert additive after the removal of the hydroxylammonium salt.

4. Conclusion

In this study, we described a simple one-pot preparation of halo-substituted *O*-benzyl hydroxylamine derivatives by *O*-benzylation of *N*-hydroxyurethane, followed by basic *N*-deprotection. The representative process makes it possible to prepare, in good yields, halogenated *O*-benzyl hydroxylammonium salts, which could not be obtained by conventional methods in high yield with several steps. The advantages of the method were the chemo- and regio-selectivity in obtaining the desired *O*-benzyl hydroxylammonium salts as well as the simplicity of the purification process.

Acknowledgments

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