Syntheses of Some Azinylhydroxylamines (1)

A. Tomažič, M. Tišler and B. Stanovnik

Department of Chemistry, University of Ljubljana, 61000 Ljubljana, Yugoslavia

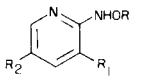
Received January 22, 1979

Syntheses of some hydroxylaminoazines and hydroxamic acids were investigated. For direct displacement with hydroxylamine a good leaving group, activated by other substituents, must be present.

J. Heterocyclic Chem., **16**, 861 (1979).

Hydroxylamines, *N*-substituted with heterocyclic radicals, are neither widely known nor easily accessible. In most cases they were obtained from the corresponding nitro compounds and various reducing agents. The disadvantage of this method is that it is difficult to stop the reduction at the hydroxylamine stage and usually other reduced compounds are formed as by-products. In the azine series, the reduction of nitro to hydroxylamino group was described in the pyridine (2-4), pyridazine (5,6), quinoline (7-9) or quinoxaline (10) series. In the biologically interesting pyrimidine and purine series, the former react directly with hydroxylamine by addition and substitution (11-15), whereas with purines displacement reactions of 6-halo-, 6-alkylthio- or 6-sulfonated purines were described (16-18).

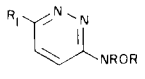
In view of these results, we were interested to investigate the synthesis of azinylhydroxylamines by displacement reactions of suitable leaving groups and to study the influence of other groups on these substitutions. In particular we were interested in such compounds where the hydroxylamino group is *ortho* to a ring nitrogen or to an amino group, as in *o*-aminoazinylhydroxamic acids.



1: R = R_2 = H, R_1 = NO_2

2: R = R_1 = H, R_2 = NO_2

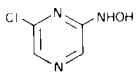
6: R = $CH_2C_6H_5$, R_1 = R_2 = NO_2



3: R = H, R_1 = Cl

4: R = H, R_1 = Me

7: R = COMe, R_1 = Cl



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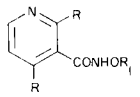
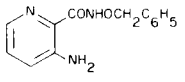


8: R = R_2 = H, R_1 = $CH_2C_6H_5$

9: R_2 = H, R_1 = $CH_2C_6H_5$, R = NH_2

10: R = R_1 = H, R_2 = NH_2



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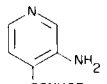
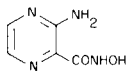


12: R = H

13: R = $CH_2C_6H_5$



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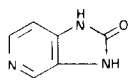

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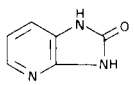

16

Since hydroxylamine can be alkylated with alkyl halides and only with some highly activated aryl halides (19) one could anticipate that also in the azine series the presence of activating groups should be necessary. Indeed, this could be observed since only compounds **1-3** and **5** could be obtained in reasonable yields from the chloroazines with a solution of free hydroxylamine in anhydrous ethanol. 3-Chloro-6-methylpyridazine failed to react in this manner, but compound **4** could be prepared from 3-methylthio-6-methylpyridazine by displacement of the methylthio group. This low reactivity towards hydroxylamine can be ascribed to the low nucleophilicity of hydroxylamine when compared to that of hydrazine or ammonia (if simply based on the pK_b values of these compounds: hydroxylamine, pK_b = 8.20; hydrazine, pK_b = 6.06; ammonia, pK_b = 4.90 (20). However, if we compare the experimental conditions for the synthesis of amino- and hydrazinopyridazines (21) and aminopyridines (22,23) with the experimental conditions under which the above mentioned hydroxylaminopyridines and -pyridazines were prepared, it becomes evident that a simple correlation of the basicity and nucleophilicity of the above nucleophiles is not appropriate.

Both, 3-nitro- and 5-nitro-2-chloropyridine yielded with hydroxylamine also the corresponding 2-pyridinones as by-products. Since the reaction was run under anhydrous conditions, hydrolytic displacement of the chlorine atom is not an acceptable explanation. Although the mechanism of pyridinone formation during this reaction is not known, it is most probable that they are formed thermally. By reducing the heating time the formation of pyridinones is eliminated.

It is theroretically possible that alternative structure of the above hydroxylamino compounds should be as *O*-substituted derivatives. Such structures seem to be very unlikely in view of the very low stability of few known representatives (24). Further support for a *N*-substitution follows from the synthesis of the corresponding *O*-benzyl derivative (**6**) from *O*-benzylhydroxylamine and 2-chloro-3,5-dinitropyridine. Moreover, acetylation of com-

0022-152X/79/050861-04$02.25

pound **3** afforded a diacetyl derivative. It ir spectrum revealed two different carbonyl groups at 1700 cm^{-1} (corresponding to an ester carbonyl) and 1805 cm^{-1} (corresponding to an amide carbonyl) and in the nmr spectrum two singlets for methyl groups appear at τ = 7.70 and 7.57. These data eliminate the alternative *N,N*-diacetyl structure and are in accord with structure **7**.

Our further interest was in *o*-amino heterocyclic hydroxamic acids. In general, azinylhydroxamic acids were prepared from the corresponding esters and hydroxylamine. In this manner, we have prepared the corresponding *o*-aminoazinylhydroxamic acids in the pyridine (**10,12**) and pyrazine (**14**) series. The nmr spectrum of compound **10** is of interest since a $J_{2,6}$ = 1.5 Hz could be observed. Such coupling constants are seldom observed in the pyridine series since the quadrupol effect of the ring nitrogen causes band broadening.

We have applied the same approach for the synthesis of the corresponding *O*-benzylhydroxamates. At room temperature no reaction took place, but at moderately elevated temperatures (70-120°) besides the starting compounds benzyl alcohol and *O*-benzylbenzaldoxime were isolated. The latter is formed evidently from *O*-benzylhydroxylamine, although it is stated that it is formed upon heating at 160° (25). For a successful transformation apparently a better leaving group should be present in the starting material and therefore we have introduced a new approach. The corresponding *o*-aminopyridinecarboxylic acid azides reacted smoothly with *O*-benzylhydroxylamine to give the substituted hydroxamates (**8, 9, 11** and **13**). The reaction takes place preferentially at room temperature. Upon heating lower yields of compounds **13** and **9** were obtained and as by-products the corresponding imidazopyridinones **15** and **16** were formed. The formation of these products may be explained as follows. The carbonylazide may undergo a Curtius rearrangement and the formed isocyanato group subsequently reacts with the *o*-amino group to form the imidazole ring. Alternatively, these may be formed from the products **13** and **9** by a Lossen type rearrangement (26) followed again by ring closure.

The stability of *O*-benzylhydroxamates was examined on *N*-benzoyl-*O*-benzylhydroxylamine as model compound. This is stable in hot 10% aqueous sodium hydroxide or in dilute hydrochloric acid (1:1) at room temperature. In hot hydrochloric acid (1:1) it is decomposed into benzoic acid and *O*-benzylhydroxylamine.

EXPERIMENTAL (27)

O-Benzyl-*N*-benzylhydroxylamine.

This compound was prepared according to the procedure as described by Beckmann (28) in 57% yield, m.p. 102-104°; ms: M^+ = 227 (22%); nmr (deuteriochloroform): τ = 2.5 (m, two C_6H_5), 5.0 (s, CH_2).

N-(6-Chloropyridazinyl-3)hydroxylamine (**3**).

A mixture of 3,6-dichloropyridazine (2.5 g.) in anhydrous ethanol (25 ml.) and ethanolic hydroxylamine (29) was heated under reflux for 6.5 hours. The reaction mixture was evaporated *in vacuo* to dryness and the residue was crystallized from 1,2-dimethoxyethane and *n*-hexane (3:1), m.p. 142-143° (yield 0.7 g., 28%); ms: M^+ = 145 (44 %); nmr (DMSO-d_6): τ = 2.85 and 3.10 (d, H_4 and H_5), $J_{4,5}$ = 10 Hz.

Anal. Calcd. for $C_4H_4ClN_3O$: C, 33.03; H, 2.77; N, 28.80. Found: C, 33.10; H, 3.11; N, 28.70.

In a similar manner the following compounds were prepared:

N-(3-Nitropyridyl-2)hydroxylamine (**1**).

This compound was obtained after 50 minutes of heating under reflux the reaction mixture in 52% yield, m.p. 133-136° (from ethanol and *n*-hexane, 4:1); ms: M^+ = 155 (75%); nmr (DMSO-d_6): τ = 1.5 (dd, H_6), 1.62 (dd, H_4), 3.22 (dd, H_5), $J_{4,5}$ = 9, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz.

Anal. Calcd. for $C_5H_5N_3O_3$: C, 38.72; H, 3.25; N, 27.09. Found: C, 38.90; H, 2.80; N, 27.02.

N-(5-Nitropyridyl-2)hydroxylamine (**2**).

This compound was obtained in 53% yield (45 minutes of reflux), m.p. 140-142° (from 1,2-dimethoxyethane and *n*-hexane, 4:1; ms: M^+ = 155 (100%); nmr (DMSO-d_6): τ 1.10 (d, H_6), 1.82 (dd, H_4), 3.30 (d, H_3), $J_{3,4}$ = 10, $J_{4,6}$ = 3 Hz.

Anal. Calcd. for $C_5H_5N_3O_3$: C, 38.72; H, 3.25; N, 27.09. Found: C, 38.49; H, 3.55; N, 27.35.

N(6-Chloropyrazinyl-2)hydroxylamine (**5**).

This compound was obtained in 35% yield (2 hours under reflux), m.p. 135-137° (from 1,2-dimethoxyethane and *n*-hexane, 3:1); ms: M^+ = 145 (100%); nmr (DMSO-d_6): τ = 1.88 and 2.05 (s, H_3 and H_5).

Anal. Calcd. for $C_4H_4ClN_3O$: C, 33.01; H, 2.77; N, 28.87. Found: C, 33.15; H, 3.0; N, 29.03.

N-(6-Chloropyridazinyl-3)-*N,O*-diacetylhydroxylamine (**7**).

A solution of the hydroxylamine (**3**) (0.5 g.) in 1,2-dimethoxyethane (12 ml.) was treated with acetic anhydride (0.7 ml.) and the reaction mixture was heated under reflux for 2 hours. The mixture was evaporated in vacuo to dryness and the residue was crystallized from 1,2-dimethoxyethane (5 ml.), m.p. 119-121° (0.4 g., 51% yield); ms: M^+ = 229 (10%); nmr (DMSO-d_6): τ = 1.7 and 2.0 (d, H_4 and H_5), 7.57 and 7.70 (s, two Me groups), $J_{4,5}$ = 10 Hz.

Anal. Calcd. for $C_8H_8ClN_3O_3$: C, 41.85; H, 3.51; N, 18.30. Found: C, 41.97; H, 3.57; N, 18.61.

N-(6-Methylpyridazinyl-3)hydroxylamine (**4**).

A solution of 3-methylthio-6-methylpyridazine (31) (2.0 g.) in anhydrous ethanol (10 ml.) was treated with ethanolic hydroxylamine (29) (125 ml.) and dry hydroxylamine hydrochloride (0.2 g.). The reaction mixture was heated under reflux for 9 hours, it was evaporated in vacuo to dryness and the residue was dissolved in cold water (20 ml.). The solution was extracted with chloroform (5 times of 70 ml.), the extracts were dried, filtered and the solution evaporated to dryness. The residue was repeatedly crystallized from benzene and petroleum ether (2:1), m.p. 133-137° (0.45 g., 25% yield); mass spectrum: M^+ = 125 (39%); nmr (DMSO-d_6): τ = 3.25 (s, H_4 and H_5), 7.85 (s, Me).

Anal. Calcd. for $C_5H_7N_3O$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.71; H, 5.89; N, 33.19.

N-(3,5-Dinitropyridyl-2)-O-Benzylhydroxylamine (**6**).

To a stirred solution of 2-chloro-3,5-dinitropyridine (1.5 g.) in diethyl ether (25 ml.) was added dropwise a solution of *O*-benzylhydroxylamine (32) (1.8 g.) in diethyl ether (20 ml.) at room temperature. After the addition was complete the precipitated *O*-benzylhydroxylamine hydrochloride was filtered off and the filtrate was evaporated to dryness. The crude product was crystallized first from diethyl ether and thereafter from 1,2-dimethoxyethane and n-hexane (6:1), m.p. 125-126° (0.90 g., 42% yield); ms: M^+ = 290 (1%); nmr (DMSO-d_6): τ = 0.95 (d, H_6), 1.25 (d, H_4), 2.57 (m, C_6H_5), 4.92 (s, CH_2), $J_{4,6}$ = 3 Hz.

Anal. Calcd. for $C_{12}H_{10}N_4O_5$: C, 49.66; H, 3.47; N, 19.30. Found: C, 49.89; H, 3.71; N, 19.08.

O-Benzyl Pyridine-3-carbohydroxamic Acid (**8**).

A solution of nicotinyl azide (33) (0.87 g.) in chloroform (25 ml.) was treated with a solution of *O*-benzylhydroxylamine (0.72 g.) in chloroform (10 ml.). The reaction mixture was left at room temperature for 43 hours and then evaporated to dryness. The residual oil crystallized upon standing in a refrigerator for 24 hours. The crude product was crystallized from carbon tetrachloride and *n*-hexane (3:1), m.p. 74-77° (0.83 g., 61% yield); mass spectrum: M^+ = 228 (100%); nmr (deuteriochloroform): τ = 1.15 (d, H_2), 1.45 (dd, H_6), 1.85 (ddd, H_4), 2.65 (dd, H_5), 2.65 (m, C_6H_5), 4.95 (s, CH_2).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.34; H, 5.49; N, 12.10.

Following the above procedure the following compounds were prepared:

O-Benzyl 3-Aminopyridine-2-carbohydroxamic Acid (**11**).

This compound was obtained in 66% yield (after 92 hours at room temperature), m.p. 109-111° (from chloroform and carbon tetrachloride, 1:2); ms: M^+ = 243 (35%); nmr (deuteriochloroform): τ = 2.27 (dd, H_6), 2.65 (m, C_6H_5), 2.92 (dd, H_5), 3.10 (dd, H_4), 5.0 (s, CH_2), $J_{4,5}$ = 8.5, $J_{4,6}$ = 2 Hz.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 63.99; H, 5.61; N, 17.40.

O-Benzyl 3-Aminopyridine-4-carbohydroxamic Acid (**13**).

This compound was obtained in 51% yield (after 336 hours at room temperature), m.p. 154-156° (from chloroform); ms: M^+ = 243 (99%); nmr (DMSO-d_6): τ = 1.8 (s, H_2); 2.25 (d, H_6); 2.55 (m, C_6H_5); 2.80 (d, H_5, 5.05 (s, CH_2), $J_{5,6}$ = 5.5 Hz.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.35; H, 5.69; N, 17.17.

By heating the above reaction mixture under reflux for 5 hours, only 22% of the chloroform insoluble by-product, imidazo [4,5-*c*]pyridin-2-one (**15**) (34) (0.085 g. from 0.24 g. of starting azide) was obtained.

O-Benzyl 2-Aminopyridine-3-carbohydroxamic Acid (**9**).

This compound was obtained in 71% yield (after 336 hours at room temperature), m.p. 147-150° (from chloroform and carbon tetrachloride, 1:1, and thereafter from ethyl acetate); ms: M^+ = 243 (69%); nmr (DMSO-d_6): τ = 1.92 (dd, H_6), 2.30 (dd, H_4), 2.6 (m, C_6H_5), 3.45 (dd, H_5), 5.05 (s, CH_2), $J_{4,5}$ = 8, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.21; H, 5.40; N, 17.31.

By heating the above reaction mixture under reflux for 1.5 hours, a 10% yield of the chloroform insoluble by-product imidazo[4,5-*b*]pyridin-2one (**16**) (34) (0.15 g. from 0.92 g. of the starting azide) was obtained.

3-Aminopyridine-4-carbohydroxamic Acid (**12**).

A solution of hydroxylamine hydrochloride (1.39 g.) in water (2 ml.) was added to cold aqueous sodium hydroxide (8 ml. of 20%). The obtained solution (9 ml.) was added to a solution of methyl 3-aminopyridine-4-carboxylate (1.2 g.) in methanol (8 ml.). After standing at room temperature for 7 days methanol was distilled off *in vacuo* and the solution was treated with water (5 ml.). The hydroxamic acid was precipitated by dropwise addition of acetic acid (about 1.5 ml.). The collected product was crystallized from water and thereafter from *N,N*-dimethylformamide and chloroform (1:1), m.p. 170-174° (yield 33%); ms: M^+ = 153 (9%); nmr (DMSO-d_6): τ = 1.8 (s, H_2), 2.25 (d, H_6), 2.77 (d, H_5), $J_{5,6}$ = 5 Hz.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 46.63; H, 4.89; N, 27.27.

In a similar manner **10** was prepared.

4-Aminopyridine-3-carbohydroxamic Acid (**10**).

This compound was obtained in 72% yield, m.p. 260-262° (recrystallized from water); mass spectrum: M^+ = 153 (30%); nmr (deuterium oxide): τ = 1.60 (d, H_2), 1.92 (dd, H_6), 2.95 (d, H_5), $J_{2,6}$ = 1.5, $J_{5,6}$ = 7 Hz.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; H, 27.44. Found: C, 47.01; H, 4.73; N, 27.30.

2-Aminopyrazine-3-carbohydroxamic Acid (**14**).

A solution of methyl 2-aminopyrazine-3-carboxylate (0.5 g.) in anhydrous ethanol (15 ml.) was treated with ethanolic hydroxylamine (29) (28 ml.). The mixture was heated under reflux for 5 hours, evaporated to dryness and the residue was crystallized from a mixture of 1,2-dimethoxyethane and *n*-hexane, 1:1, and thereafter again from the same solvents in a ratio of 4:1, m.p. 199-201° (yield 0.12 g., 24%) (lit. (35) gives m.p. 196°) (yield 0.12 g., 24%); ms: M^+ = 154 (83%); nmr (DMSO-d_6): τ = 1.8 and 2.2 (d, H_5 and H_6), $J_{5,6}$ = 3 Hz.

Anal. Calcd. for $C_5H_6N_4O_2$: C, 38.97; H, 3.93; N, 36.35. Found: C, 39.46; H, 4.30; N, 36.23.

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