Heterocycles. CXLII. Synthesis of some Triazoloazine 3-Oxides

K. Babič, S. Molan, S. Polanc, B. Stanovnik, J. Stres-Bratoš, M. Tišler and B. Verček

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

Received January 26, 1976

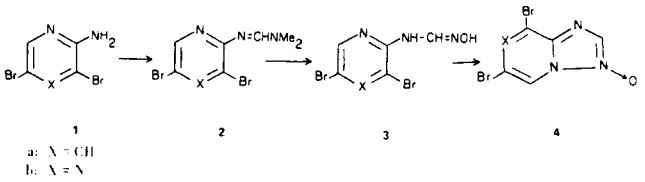
The formation of 3-oxides of triazolopyridine, triazolopyridazine and triazolopyrazine was investigated. The corresponding 3-oxides were obtained by oxidative cyclization of 2-hydroxyiminomethyleneaminoazines and some transformations are described.

J. Heterocyclic Chem., 13, 487 (1976).

Several years ago we have described (1) the first synthesis of azoloazine *N*-oxides with bridgehead nitrogen. Other synthetic approaches as well as their reactivity have been described in the following publications (2,3). All these compounds were the 5-oxides and since then only few examples of *N*-oxides at other positions of these bicyclic systems have been described (4,5). Representatives of azoloazine 3-oxides are known only in the *s*-triazolo[1,5-*a*]pyridine and *s*-triazolo[1,5-*a*]pyrimidine series (4,6). In addition, we have recently reported on a synthesis of *s*-triazolo[1,5-*b*]pyridazine 3-oxides (8) and we are now describing a general synthetic approach for at position 2 unsubstituted azoloazine 3-oxides.

In a similar manner as in the pyridazine series, we have attempted the synthesis of *s*-triazolo[1,5-*a*]pyridine 3-oxides. As starting material 2-hydroxyiminomethyleneaminopyridine was used and it was treated with bromine in acetic acid. However, the attempted cyclization failed, the side chain was degraded and 2-amino-3,5-dibromopyridine was formed. Therefore, the later compound (**1a**) was used as starting material and it was successively converted into the corresponding *N*,*N*-dimethylaminomethylene (**2a**) and hydroxyiminomethyleneamino derivative (**3a**), which upon treatment with bromine in acetic acid afforded the corresponding bicyclic 3-oxide (**4a**) in low yield. The 3-oxide was deoxygenated with phosphorus trichloride in the usual manner to give 6,8-dibromo-*s*-triazolo[1,5-*a*]pyridine. The bicyclic *N*-oxide is, however, not stable towards acid and was decomposed in hot 2*N* hydrochloric acid to give the starting 2-amino-3,5-dibromopyridine.

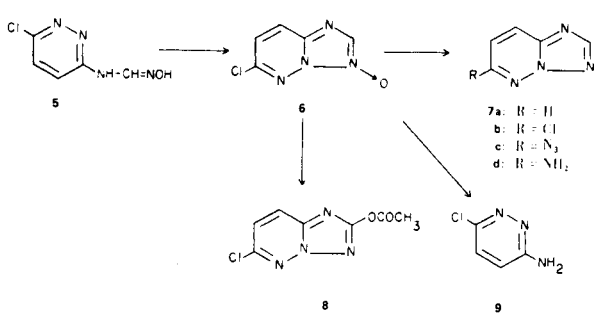
The failure to prepare the corresponding triazolopyridine from either 2-*N*,*N*-dimethylaminomethylene- or 2-hydroxyiminomethyleneaminopyridine is due to their instability in acetic acid as shown by separate experiments. Moreover, the corresponding derivatives of 2-amino-3,5-dibromopyridine (**2a** and **3a**) are unstable in the presence of 50% acetic acid or 10% aqueous potassium carbonate and are decomposed into the starting 2-amino-3,5-dibromopyridine.



1 2 3 4

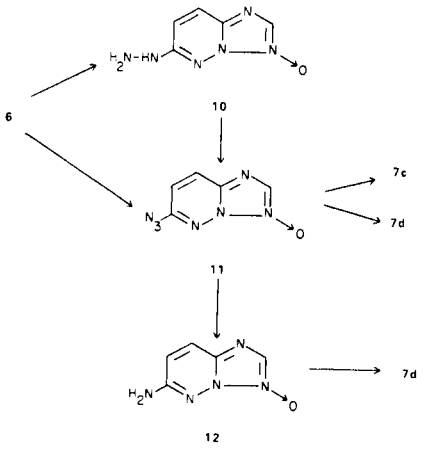
a: X = CH
b: X = N

In the *s*-triazolo[1,5-*a*]pyrazine series only the 7-oxide is known (5) and it was obtained by direct treatment of the bicycle with peroxyacetic acid. We have extended our synthetic approach to 2-hydroxyiminomethyleneaminopyrazine, but the compound when treated with bromine in acetic acid afforded only 2-formylaminopyrazine. The same result was observed when using lead tetraacetate for attempted cyclodehydration. Moreover, the corresponding 3,5-dibromo compound (**3b**), prepared from **1b** *via* **2b**, did not react in the anticipated manner with bromine in acetic acid and again only 2-formylamino-3,5-dibromopyrazine was obtained. The reaction was.



5 6 8 9

7a: R = H
b: R = Cl
c: R = N_3
d: R = NH_2



however, successful when *N*-bromosuccinimide in chloroform was used, although the corresponding 3-oxide (**4b**) was obtained in low yield.

In the pyridazine series oxidative cyclization of compound **5** with bromine in glacial acetic acid afforded the corresponding 3-oxide (**6**) in good yield. The compound, when stirred in an atmosphere of hydrogen and in the presence of palladized carbon, was deoxygenated and dehalogenated into *s*-triazole[1,5-*b*]pyridazine (**7a**). With phosphorus trichloride the *N*-oxide was deoxygenated to give **7b** and in the presence of hot dilute acid or base it was decomposed into 6-chloro-3-aminopyridazine (**9**). It is interesting to note that deoxygenation with phosphorus trichloride in the related benzimidazole system did not proceed in a comparable way and the corresponding benzimidazole and its 2-chloro derivative were obtained in almost equal quantities (9). Under the influence of hot acetic anhydride the *N*-oxide was transformed into the corresponding 2-acetoxy derivative (**8**).

It is well known that *N*-oxidation increases reactivity of the halogen atoms in the positions *ortho* or *para* to the ring nitrogen in π-deficient aromatic heterocycles towards nucleophilic substitution. However, the 3-oxide (**6**) was decomposed to **9** when heated with sodium thiophenolate. It appears that the nucleophile attacks preferentially the five-membered ring by cleaving the *N-N* bond and the postulated intermediate cyanoamino compound is then transformed into **9**. A still greater instability has been observed in the triazolopyridine and triazolopyrimidine series (4). Here, the corresponding 3-oxides are slowly deoxygenated when heated in xylene. Moreover, for a certain triazolopyrimidine *N*-oxide a temperature-dependent nmr spectrum was observed and the changes were attributed to a reversible isomerization to an open chain nitrosoimine.

With hydrazine hydrate, however, the chlorine atom at position 6 could be replaced by hydrazino group and compound **10** was isolated. Nucleophilic substitution with sodium azide was also successful and the 6-azido compound (**11**) could be obtained. On the other hand, this azide could be also prepared by nitrosation of the corresponding hydrazino derivative (**10**). In all these transformations the *N*-oxide group remained unaffected. Even when a methanolic solution of the azide (**11**) was stirred under hydrogen and in the presence of palladized carbon, the azide group was smoothly reduced to give the amino compound (**12**) and without affecting the *N*-oxide function. There are several examples of azine *N*-oxides where catalytic reduction over palladium-carbon catalyst in neutral solution results in deoxygenation (10-13). However, if some hydrochloric acid was added the *N*-oxide function was removed and 6-amino-*s*-triazolo[1,5-*b*]pyridazine (**7d**) was obtained.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. All nmr spectra were obtained on a JEOL JNM C60-HL spectrometer and mass spectra were recorded on an Hitachi-Perkin-Elmer RMU-6L instrument.

The following compounds were prepared with adherence to published techniques: 2-amino-3,5-dibromopyrazine (14) and 2-amino-3,5-dibromopyridine (15).

2-Dimethylaminomethyleneamino-3,5-dibromopyrazine (**2b**).

A mixture of 2-amino-3,5-dibromopyrazine (0.95 g.) and *N,N*-dimethylformamdie dimethyl acetal (0.7 ml.) was heated under reflux for 1 hour. Excess of the acetal was distilled off *in vacuo* and the remaining product was crystallized from ethanol, m.p. 121-123° (yield 37%); mass spectrum: M^+ = 306; nmr (DMSO-d_6): τ = 1.6 (s, N=CH), 1.78 (s, H_6), 6.89 (s, Me), 6.86 (s. Me).

Anal. Calcd. for $C_7H_8Br_2N_4$: C, 27.30; H, 2.62; N, 18.19. Found: C, 27.31; H, 2.79; N, 18.13.

In the same manner was prepared:

2-Dimethylaminomethyleneamino-3,5-dibromopyridine (**2a**):

The compound was obtained in 71% yield, m.p. 66-68° (from ethanol): mass spectrum: M^+ = 305; nmr (deuteriochloroform): τ = 2.10 (d, H_4), 1.86 (d, H_6), 1.63 (s, CH), 6.87 and 6.92 (s, NMe_2), $J_{4,6}$ = 2.0 Hz.

Anal. Calcd. for $C_8H_9Br_2N_3$: N, 13.69. Found: N, 14.03.

2-Hydroxyiminomethyleneamino-3,5-dibromopyrazine (**3b**).

Compound **2b** (0.4 g.) was dissolved in methanol (10 ml.), hydroxylamine hydrochloride (0.095 g.) was added and the mixture was heated under reflux for 20 minutes. The separated colorless crystals were filtered off, washed with water and crystallized from ethanol, m.p. 170° (yield 63%); mass spectrum: M^+ = 294; nmr (DMSO-d_6): τ = 1.66 (s, H_6), 2.31 (d, CH=), 1.84 (d, NH), 0.9 (broad, OH); J_{NHCH} = 9 Hz.

Anal. Calcd. for $C_5H_4Br_2N_4O$: C, 20.30; H, 1.36; N, 18.93. Found: C, 20.30; H, 1.54; N, 18.98.

In a similar manner was prepared:

2-Hydroxyiminomethyleneamino-3,5-dibromopyridine (**3a**).

It was obtained in 74% yield, m.p. 191-193° (from ethanol); mass spectrum: M^+ 293; nmr (DMSO-d_6); τ 2.16 (s, H_4), 1.75 (s, H_6), 1.78 (s, CH), 6.8 (broad, NH), 0.2 (broad, OH).

Anal. Calcd. for $C_6H_5Br_2N_3O$: C, 24.43; H, 1.71; N, 14.25. Found: C, 24.70; H, 2.01; N, 14.32.

6,8-Dibromo-*s*-triazolo[1,5-*a*]pyrazine 3-Oxide (**4b**).

A solution of compound **3b** (0.254 g.) in chloroform (5 ml.) was treated with *N*-bromosuccinimide (0.533 g.) and the mixture was heated under reflux for 5 hours. The cold reaction mixture was shaken with a saturated aqueous solution of sodium bicarbonate, the chloroform layer was separated, dried and the solvent evaporated to dryness. The residue was suspended in methanol and filtered. In the filtrate, the corresponding formylamino and aminopyrazine were detected by tlc. The 3-oxide was obtained in 8% yield, m.p. 160-162°; mass spectrum: M^+ = 292; nmr (deuteriochloroform): τ = 1.62 (s, H_2), 1.17 (s, H_5).

Anal. Calcd. for $C_5H_2Br_2N_4O$: C, 20.44; H, 0.68; N, 19.06. Found: C, 20.68; H, 1.12; N, 18.84.

6,8-Dibromo-*s*-triazolo[1,5-*a*]pyridine 3-Oxide (**4a**).

The hydroxyiminomethyleneamino compound **3a** (0.7 g.) was suspended in glacial acetic acid (20 ml.) and sodium acetate (0.4 g.) was added. After excess of bromine in glacial acetic acid was added, a clear solution was obtained and it was neutralized with sodium bicarbonate. Upon filtration, the filtrate was extracted with chloroform and after evaporation of the solvent the residue was crystallized from ethanol (yield 7.5%), m.p. 173°; mass spectrum: M^+ = 291; nmr (deuteriochloroform): τ = 2.03 (s, H_2), 1.7 (s, H_5). 1.17 (s, H_7).

Anal. Calcd. for $C_6H_3Br_2N_3O$: N, 14.37. Found: N, 13.98.

If the above 3-oxide was heated in 2*N* hydrochloric acid for 1 hour, it was transformed into 2-amino-3,5-dibromopyridine.

In a similar manner was prepared:

2-Chloro-*s*-triazolo[1,5-*b*]pyridazine 3-Oxide (**6**).

This compound was obtained from 3-hydroxyiminomethyleneamino-6-chloropyridazine (**5**) (16) in 71% yield, m.p. 218° (from cyclohexane and 1,2-dimethoxyethane); mass spectrum: M^+ = 170; nmr (deuteriochloroform): τ = 1.57 (s, H_2), 2.56 (d, H_7), 1.98 (d, H_8), $J_{7,8}$ = 9.5 Hz.

Anal. Calcd. for $C_5H_3ClN_4O$: C, 35.22; H, 1.77; N, 32.85. Found: C, 35.34; H, 1.87; N, 32.88.

The compound, when stirred in an atmosphere of hydrogen at room temperature and in the presence of palladized carbon (5%), was transformed into *s*-triazolo[1,5-*b*]pyridazine (16). On the other hand, if treated with phosphorus trichloride, 6-chloro-*s*-triazolo[1,5-*b*]pyridazine (17) was obtained.

The above compound (**6**) when treated either with hot 2*N* hydrochloric acid, 2*N* sodium hydroxide, sodium ethylate or sodium thiophenolate was decomposed into 3-amino-6-chloropyridazine (18,19).

6-Hydrazine-*s*-triazolo[1,5-*b*]pyridazine 3-Oxide (**10**).

The chloro compound (**6**) (0.17 g.) was dissolved in ethanol (3 ml.), hydrazine hydrate (0.06 g. of 98%) was added and the mixture was heated under reflux for 15 minutes. The product was filtered off and washed with ethanol (yield 36%), m.p. 230-232°; mass spectrum: M^+ = 166; nmr (DMSO-d_6, 150°): τ = 1.78 (s, H_2), 3.00 (d, H_7), 2.25 (d, H_8), $J_{7,8}$ = 9.5 Hz.

Anal. Calcd. for $C_5H_4N_6O$: C, 36.14; H, 3.64; N, 50.59. Found: C, 36.44; H, 4.15; N, 51.26.

The compound formed a benzylidene derivative, m.p. 261-263°.

6-Azido-*s*-triazolo[1,5-*b*]pyridazine 3-Oxide (**11**).

A.

The above hydrazine compound (**10**) (0.14 g.) was dissolved in hydrochloric acid (1:1) and to an ice cold solution, an aqueous solution of sodium nitrite (0.065 g. in 3 ml.) was added dropwise. Upon neutralization with sodium bicarbonate, the reaction mixture was extracted with chloroform, the solvent evaporated and the residue crystallized from chloroform and petrol-ether (yield 83%), m.p. 134°; mass spectrum: M^+ = 177; nmr (deuteriochloroform): τ = 1.45 (s, H_2), 3.02 (d, H_7), 2.0 (d, H_8); $J_{7,8}$ = 9.5 Hz.

Anal. Calcd. for $C_5H_3N_7O$: C, 33.90; H, 1.70. Found: C, 33.81; H, 1.44.

B.

The corresponding chloro compound (**6**) (1.70 g.) was dissolved in ethanol (6 ml.), sodium azide (0.065 g.) was added and the mixture was heated under reflux for 3 hours. The separated product was filtered off, dissolved in water and extracted with chloroform. The obtained product was found to be identical in all respects with the compound prepared as described under A.

The obtained compound, when treated with phosphorus trichloride, was deoxygenated to give 6-azido-*s*-triazolo[1,5-*b*]pyridazine (16).

6-Amino-*s*-triazolo[1,5-*b*]pyridazine 3-Oxide (**12**).

A solution of the azide compound **11** (0.109 g.) in methanol (30 ml.) was treated with palladized carbon (0.016 g. of 5%) and stirred in an atmosphere of hydrogen for 6 hours. The reaction mixture was heated to boiling and filtered. The filtrate was evaporated to dryness and the residue was crystallized from methanol and *N*,*N*-dimethylformamide (5:1) (yield 65%), m.p. 263°; mass spectrum: M^+ = 151.

Anal. Calcd. for $C_5H_5N_5O$: C, 39.73; H, 3.33. Found: C, 39.61; H, 3.68.

If the same reaction was performed in the presence of some concentrated hydrochloric acid, 6-amino-*s*-triazolo[1,5-*b*]pyridazine (16) (**7d**) was obtained and identified. The same compound was also obtained if the above 6-amino-*s*-triazolo[1,5-*b*]pyridazine 3-oxide (**12**) was stirred in an atmosphere of hydrogen in the presence of palladized carbon and hydrochloric acid.

2-Acetoxy-6-chloro-*s*-triazolo[1,5-*b*]pyridazine (**8**).

Compound **6** (0.3 g.) was heated with excess of acetic anhydride under reflux for 1 hour. The solvent was evaporated to dryness and from the residual oil the product was separated after addition of ethanol (yield 4%), m.p. 230° dec., (from ethanol and cyclohexane); mass spectrum: M^+ = 212.

Anal. Calcd. for $C_7H_5ClN_4O_2$: C, 39.56; H, 2.37; N, 26.36. Found: C, 39.66; H, 2.67; N, 26.68.

REFERENCES AND NOTES

(1) A. Pollak, B. Stanovnik, and M. Tišler, *J. Heterocyclic Chem.*, 5, 513 (1968).

(2) A. Pollak, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, 35, 2478 (1970).

(3) A. Pollak, S. Polanc, B. Stanovnik, and M. Tišler, *Monatsh. Chem.*, 103, 1591 (1972).

(4) T. L. Gilchrist, C. J. Harris, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 486 (1974).

(5) T. Okamoto, Y. Torigoe, M. Sato, and Y. Isogai, *Chem. Pharm. Bull.*, **16**, 1154 (1968).

(6) According to the Ring Index orientation and numbering, the correct name for these compounds would be *s*-triazolo[1,5-*a*]-pyrimidine 1-oxides. An alternative name for this system is *s*-triazolo[2,3-*a*]pyrimidine (7).

(7) W.L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Pt. II., Interscience Publishers, New York, 1961, p. 878.

(8) J. Bratoš-Stres, S. Polanc, B. Stanovnik, and M. Tišler, *Tetrahedron Letters*, 4429 (1975).

(9) S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, 12, 783 (1964).

(10) H. Yamanaka, *ibid.*, 7, 158 (1959).

(11) T. Wieland and H. Biener, *Chem. Ber.*, 95, 277 (1962).

(12) T. Higashino, *Yakugaku Zasshi*, 79, 831 (1959).

(13) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, 82, 475 (1960).

(14) B. Camerino and G. Palamidessi, British patent, 928,152 (1963); *Chem. Abstr.*, 60, 2971 (1964).

(15) J. P. Wibaut and G. M. Kraay, *Rec. Trav. Chim.*, 42, 1084 (1923).

(16) S. Polanc, B. Verček, B. Šek, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, 39, 2143 (1974).

(17) S. Polanc, B. Verček, B. Stanovnik, and M. Tišler, *Tetrahedron Letters*, 1677 (1973).

(18) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 37, 121 (1954).

(19) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, 76, 3225 (1954).