CROATICA CHEMICA ACTA CCACAA 47 (2) 153—157 (1975)

CCA-866

YU ISSN 0011-1643
547.852
Original Scientific Paper

Pyridazines. LXXV. Some Quaternary and Mesoionic *s*-Triazolo(4,3-*b*)pyridazines

I. Langof, B. Stanovnik, and M. Tišler

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

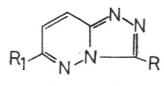
Received December 10, 1974

Quaternization of some *s*-triazolo(4,3-*b*)pyridazines, formation of a mesoionic derivative and some transformations of these compounds are described.

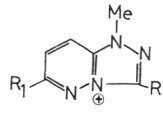
In the last years increasing attention has been directed towards the chemistry of mesoionic ring systems. Recently, we have described the preparation of some mesoionic derivatives of imidazo(1,2-*b*)pyridazine.[1,2] Since these were the first examples of mesoionic compounds in the azoloazine series, it seemed worthwhile to extend these investigations on other members of bicyclic heterocycles with bridgehead nitrogen.

6-Chloro-3-phenyl-*s*-triazolo(4,3-*b*)-pyridazine (*1a*) was used as starting material. Treatment with either methyl iodide or dimethyl sulfate yielded the quaternary derivative *2a* and *2b*. After short warming with an aqueous solution of potassium hydroxide the quaternary compound was transformed into the anhydro salt (*3*). Contrary to our observations in the imidazo(1,2-b)pyridazine series, the anhydro salt was stable and upon heating no formation of 1,5-dimethyl-3-phenyl-*s*-triazolo(4,3-*b*)-pyridazin-6(5H)one (*4*) could be observed. However, methylation of the anhydro salt afforded the 6-methoxy quaternary salt *2d*, obtainable also from the corresponding quaternized chloro derivative *2b* or from the unquaternized methoxy compound *1b*. Once again, no thermal group transposition to give the anticipated compound *4* could be observed. Treatment of the anhydro salt *3* with perchloric acid afforded the 6-hydroxy quaternary salt *2e*.

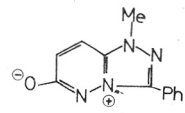
Quaternization similar to that of the 3-phenyl-6-methoxy derivative *1b* was less uniform when applied to 6-methoxy-s-triazolo(4,3-*b*)-pyridazine *1c*. The obtained product was found on hand of n. m. r. analysis to be an inseparable mixture of the 1-methyl-6-methoxy-*s*-triazolo(4,3-*b*)pyridazinium iodide (*2e*) and 2-methyl-6-methoxy-*s*-triazolo(4,3-*b*)pyridazinium iodide (*5*) in ratio of about 1 : 1. On the other hand, 6-chloro-*s*-triazolo(4,3-*b*)pyridazin-3(2H)one did not form a monomethyl quaternary salt, and a 1,2-dimethyl quaternary salt (*6*) could be isolated. Even with a sterically hindered compound, 3,6,7,8-tetrachloro-*s*-triazolo(4,3-*b*)pyridazine[3], quaternization took place under relatively mild reaction conditions to give compound 7. Apparently, *peri*-interaction does not prevent quaternization at the most basic nitrogen at position 1, although we have established previously[4] that the 8-methyl analog afforded a mixture



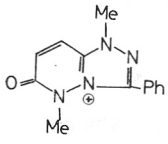
1



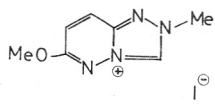
2



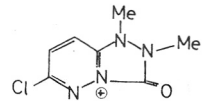
3



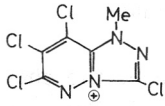
4



5



6



7

Compd.	R	R_1
1a	Ph	Cl
1b	Ph	OMe
1c	H	OMe
1d	Cl	H

Compd.	R	R_1	X
2a	Ph	Cl	I
2b	Ph	Cl	ClO_4
2c	Ph	OH	ClO_4
2d	Ph	OMe	ClO_4
2e	H	OMe	I
2f	Ph	H	ClO_4
2g	Cl	H	ClO_4

of the derivatives methylated at N_1 and N_2. It is anticipated that the chlorine atom at position *3* is also effective and assists the observed process of quaternization.

Related experiments in the tetrazolo(1,5-*b*)pyridazine series were unsuccessful. This may be understandable if we take into consideration that protonation and quaternization of this ring system, although being observed,[5] is by far more difficult than in the analogous imidazo(1,2-*b*)- and *s*-triazolo(4,3-*b*)-pyridazine series. In addition, protonation and quaternization of tetrazolo(1,5-b)-pyridazine can destabilize the tetrazolo form[6] to generate the corresponding azidopyridazines.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. N. m. r. measurements were made on a JEOL JNM-C-60HL spectrometer (TMS as internal standard) and mass spectra were recorded on a Hitachi-Perkin Elmer RMU-6L instrument.

6-Methoxy-3-phenyl-s-*triazolo(4,3*-b*)pyridazine* (1b)

6-Chloro-3-phenyl-*s*-triazolo(4,3-b)pyridazine (*1a*)[7] (2.3 g) and a solution of methanolic sodium methoxide (prepared from 0.23 g of sodium and 20 ml methanol) were heated under reflux for 2 h. Upon filtration and evaporation of the solvent,

water (5 ml) was added and the product was filtered off. Upon crystallization from ethanol the product had m. p. 144—145 °C (yield 1.8 g, 80%). Mass spectrum: $M^+ = 226$.

Anal. $C_{12}H_{10}N_4O$ (226.23) calc'd.: C 63.70; H 4.46; N 24.77%
found: C 63.46; H 4.65; N 24.88%

6-Chloro-1-methyl-3-phenyl-s-triazolo(4,3-b)pyridazin-4-ium iodide (2a)

A suspension of 6-chloro-3-phenyl-s-triazolo(4,3-b)pyridazine (*1a*) (2.3 g) in methanol (50 ml) was treated with methyl iodide (2.86 g) and the reaction mixture was heated in a sealed vessel at 130 °C for 12 h. The solvent was evaporated *in vacuo* and the residue was crystallized several times from ethanol, m. p. 228—230 °C (yield 17%). Mass spectrum: $M^+ - \text{MeI} = 230$.

Anal. $C_{12}H_{10}ClIN_4$ (372.60) calc'd.: C 38.68; H 2.67; N 14.85%
found: C 38.96; H 3.16; N 15.15%

The perchlorate salt *2b* was obtained similarly. The chloro compound *1a* (0.57 g) and dimethyl sulfate (2 ml) were heated at 160 °C for 1 h. Upon cooling water (5 ml) was added and the mixture filtered. The filtrate was treated dropwise with perchloric acid (2 ml of 70%) and upon standing on ice for 1 h the product was filtered off and washed with water (15 ml) and ethanol (5 ml). The product was crystallized from ethanol and *N,N*-dimethylformamide (2 : 1), m. p. 245—248 °C (yeld 0.67 g, 77%). N. m. r. spectrum: DMSO-d_6: $\tau = 0.76$ (d, H_8), 1.50 (d, H_7), 1.70 and 2.20 (m, 3-Ph), 5.54 (s, 1-Me), $J_{7,8} = 9.5$ Hz.

Anal. $C_{12}H_{10}Cl_2N_4O_4$ (344.14) calc'd.: C 41.88; H 2.93; N 16.28%
found: C 41.64; H 3.15; N 15.92%

The following compounds were prepared in a similar manner:

1-Methyl-3-phenyl-s-triazolo(4,3-b)pyridazin-4-ium perchlorate (2f)

The compound was obtained in 79% yield, m. p. 238 °C (from ethanol and *N,N*-dimethylformamide, 2 : 1), Mass spectrum: $M - \text{HClO}_4 = 210$; n. m. r. spectrum: DMSO-d_6: $\tau = 0.73$ (dd, H_6), 1.80 (dd, H_7), 0.93 (dd, H_8), 5.58 (s, Me), 1.70 and 2.35 (m, Ph); $J_{6,7} = 4.5$, $J_{7,8} = 9.2$, $J_{6,8} = 1.5$ Hz.

Anal. $C_{12}H_{11}ClN_4O_4$ (310.70) calc'd.: C 46.39; H 3.57; N 18.04%
found: C 46.33; H 3.73; N 17.88%

3-Chloro-1-methyl-s-triazolo(4,3-b)pyridazin-4-ium perchlorate (2g)

was obtained from 3-chloro-*s*-triazolo(4,3-*b*)pyridazine (*1d*)[8] in 66% yield, m. p. 235 °C (from ethanol and *N,N*-dimethylformamide, 3 : 1). Mass spectrum: $M^+ - \text{HClO}_4 = 168$; n. m. r. spectrum: DMSO-d_6: $\tau = 0.66$ (dd, H_6), 1.68 (dd, H_7), 0.87 (dd, H_8), 5.57 (s, Me); $J_{6,7} = 4.5$, $J_{7,8} = 10.5$, $J_{6,8} = 1.5$ Hz.

Anal. $C_6H_6Cl_2N_4O_4$ (269.05) calc'd.: C 26.78; H 2.25; N 20.82%
found: C 26.67; H 2.50; N 20.78%

6-Methoxy-1-methyl-3-phenyl-s-triazolo(4,3-b)pyridazin-4-ium perchlorate (2d)

a) According to the above procedure it was obtained from *1b*, in 82% yield, m. p. 173 °C (from *N,N*-dimethylformamide and ethanol, 1 : 4). Mass spectrum: $M^+ - \text{HClO}_4 = 240$; n. m. r. spectrum: DMSO-d_6: $\tau = 2.03$ (d, H_7), 1.02 (d, H_8), 5.58 (s, 1-Me), 1.60 and 2.25 (m, Ph), 5.78 (s, 6-OMe), $J_{7,8} = 10.5$ Hz.

Anal. $C_{13}H_{13}ClN_4O_5$ (340.71) calc'd.: C 45.82; H 3.85; N 16.44%
found: C 45.67; H 3.81; N 16.21%

b) Alternatively, this compound could be prepared from 6-chloro-1-methyl-3-phenyl-*s*-triazolo(4,3-*b*)pyridazin-4-ium perchlorate (*2b*) (0.69 g) when suspended in methanol (10 ml) and treated with a methanolic solution of sodium methoxide

(prepared from 0.046 g sodium and 5 ml of methanol) and heated under reflux for 10 min. Upon cooling the separated product was filtered off and crystallized from *N,N*-dimethylformamide and ethanol, 1 : 4; m. p. 173 °C (yield 0.41 g, 60%). The compound was found identical with the product prepared as described under *a*).

c) The anhydro salt *3* (0.452 g) was treated with dimethyl sulfate (2 ml) and the mixture was heated under reflux for 5 min. Upon cooling and addition of water (5 ml), perchloric acid (1 ml of 70%) was added. Upon standing on ice overnight the crystals were separated and washed with iced water (yield 0.51 g, 75%). The compound was found to be identical with that prepared as described under *a)* or *b)*.

*6-Hydroxy-1-methyl-3-phenyl-*s*-triazolo(4,3-*b*)pyridazin-4-ium anhydro salt* (3)

Compound *2a* (3.73 g) and an aqueous solution of potassium hydroxide (30 ml of 10%) were heated under reflux for 5 min. Upon cooling the separated product was filtered off and washed with iced water. Upon recrystallization from ethanol the product had m. p. 265—266 °C (yield 1.65 g, 73%). Mass spectrum: $M^+ = 226$; n. m. r. spectrum: DMSO-d_6: $\tau = 3.20$ (d, H_7), 2.10 (d, H_8), 5.95 (s, Me), 1.70 and 2.50 (m, Ph), $J_{7,8} = 9.5$ Hz.

Anal. $C_{12}H_{10}N_4O$ (226.23) calc'd.: N 24.77%
found: N 24.52%

The same treatment, but using the perchlorate salt *2b*, afforded the anhydro salt in 78% yield.

If the anhydro salt was suspended in water and treated with perchloric acid, the perchlorate salt *(2c)* separated upon cooling, m. p. 210—212 °C. Mass spectrum: $M^+ - HClO_4 = 226$.

Anal. $C_{12}H_{11}ClN_4O_5$ calc'd.: C 44.15; H 3.39; N 17.15%
found: C 44.37; H 3.60; N 17.47%

*6-Chloro-1,2-dimethyl-3-oxo-*s*-triazolo(4,3-*b*)pyridazin-4-ium perchlorate* (6)

A mixture of 6-chloro-*s*-triazolo(4,3-*b*)pyridazin-3(2H)one[8] (0.85 g) and dimethyl sulfate (3 ml) was heated at 160 °C for 30 min. Upon cooling, water (5 ml) was added and upon filtration the filtrate was treated dropwise with perchloric acid (2 ml of 70%). Upon standing on ice for 30 min the product was filtered off, washed with water (10 ml) and crystallized from ethanol and *N,N*-dimethylformamide, 2 : 1, m. p. 225 °C (yield 1.19 g, 73%). N. m. r. spectrum: DMSO-d_6: $\tau = 1.65$ (d, H_7), 1.17 (d, H_8), 5.85 (s, 1-Me), 6.20 (s, 2-Me), $J_{7,8} = 9.5$ Hz.

Anal. $C_7H_8Cl_2N_4O_5$ calc'd.: C 28.11; H 2.70; N 18.69%
found: C 28.17; H 3.06; N 18.61%

*1-Methyl-3,6,7,8-tetrachloro-*s*-triazolo(4,3-*b*)pyridazin-4-ium perchlorate* (7)

A mixture of perchloro-*s*-triazolo(4,3-*b*)pyridazine[3] (0.492 g) and dimethyl sulfate (2 ml) was heated under reflux for 30 min. Upon cooling, water (5 ml) was added and the solution was treated with perchloric acid (2 ml of 70%). Upon standing on ice the separated product was filtered off and crystallized from ethanol and *N,N*-dimethylformamide, 2 : 1, m. p. 310—313 °C (yield 0.57 g, 76%). Mass spectrum: $M^+ - ClO_4 = 271$.

Anal. $C_6H_3Cl_5N_4O_4$ (372.40) calc'd.: N 15.05%
found: N 15.13%

Acknowledgement. The authors acknowledge the financial support of this work by the Boris Kidrič Fund.

REFERENCES

1. M. Furlan, B. Stanovnik, and M. Tišler, *J. Org. Chem.* **37** (1972) 2689.
2. S. Ostroveršnik, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta* **41** (1969) 135.
3. B. Stanovnik, M. Tišler, and V. Žigon, *Monatsh. Chem.* **103** (1972) 1624.
4. M. Japelj, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **6** (1969) 559.
5. M. Tišler and B. Stanovnik, in: R. N. Castle, Ed., »*Condensed Pyridazines Including Cinnolines and Phthalazines*« J. Wiley, New York 1973, p. 896.
6. V. Pirc, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta* **45** (1973) 547.
7. A. Pollak and M. Tišler, *Tetrahedron* **22** (1966) 2073.
8. P. Francavilla and F. Lauria, *J. Heterocycl. Chem* **8** (1971) 415.

IZVLEČEK

Piridazini. LXXV. O nekaterih kvarternih in mezoionskih *s*-triazolo(4,3-*b*) piridazinih

I. Langof, B. Stanovnik in M. Tišler

Opisane so kvaternizacije nekaterih *s*-triazolo(4,3-*b*)piridazinov, tvorba mezoionskega derivata in nekatere pretvorbe teh spojin.

FAKULTETA ZA NARAVOSLOVJE IN TEHNOLOGIJO
61000 LJUBLJANA

Prispjelo 10. prosinca 1974.