Synthesis of Mesoionic Triazolopyridine. I. *N*-Alkylation of 1,2,4-Triazolo[4,3-*a*]pyridin-3(2*H*)-one

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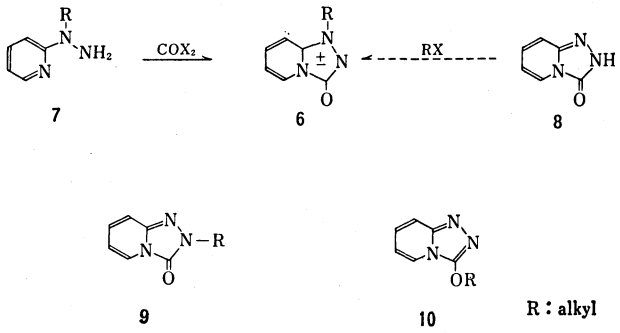
Mesoionic *anhydro*-1-alkyl-3-hydroxy-1,2,4-triazolo[4,3-*a*]pyridinium hydroxide (**6**) was synthesized by selective alkylation at the N^1-position of 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one (**8**). The selectively depends on the use of a mercuric salt catalyst in combination with the trimethylsilyl derivative of **8**, and its mechanistic features were also studied with reference to the benzylation of **8**.

During the course of an investigation on nucleoside and nucleotide synthesis we found that the mercuric salt catalyzed silyl procedure* is an excellent method for the glycosylation of purine and pyrimidine bases.[1] In this procedure, the reaction proceeds under mild conditions, the yield being satisfactory. The procedure has been widely applied[4] to the glycosylation of a variety of *N*-heterocycles.

In a series of studies on the application, we attempted the glycosylation of 2-trimethylsilyl-1,2,4-triazolo[4,3-*a*]-pyridin-3(2*H*)-one (**1**) with *O*-acyl-glycosyl halide (**2**) expecting to obtain N^2-glycosyltriazolopyridine (**4**). However, an unusual glycoside which showed strong fluorescence in an aprotic solvent in day light, exhibiting polar behavior as compared with **4** on TLC, was obtained as the main product along with a small amount of **4**. By comparison of its IR, UV, and NMR spectra with those of authentic samples of *anhydro*-1-benzyl-3-hydroxy-1,2,4-triazolo[4,3-*a*]pyridinium hydroxide (**6**, R=benzyl), the glycoside was found to have mesoionic structure (**3**), which was the first example of a mesoionic triazole glycoside.

Mesoionic 1,2,4-triazoles were prepared by cyclization of appropriate hydrazidine derivatives.[5] Mesoionic triazolopyridines (**6**, R=alkyl) have also been obtained[6] in this way from 1-alkyl-1-(2-pyridyl)hydrazine (**7**). It may be possible to obtain the mesoionic compound (**6**) if the reaction occurs exclusively at the N^1-position in the alkylation of 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one (**8**). In the alkylation of **8** an N^2-alkylated product (**9**) was known[7] to be obtained predominantly. Our findings in the glycosylation of **1** suggested the possibility of this approach. By applying the "mercuric salt catalyzed silyl procedure" to the alkylation, we found it possible to obtain the mesoionic compounds (**6**) from **8**.

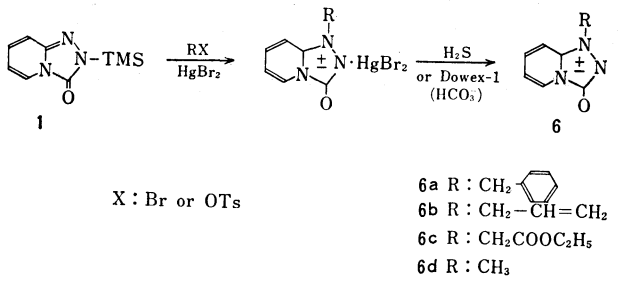


This report deals with a novel synthesis of mesoionic triazolopyridines (**6**). A detailed study of benzylation of **8** or **1** was also carried out under various conditions in order to clarify the procedure.

Result and Discussion

The synthesis of mesoionic compound (**6**) by an alkylation of **8** was conducted as follows.

The reaction of the trimethylsilyl derivative of **8** with an equimolar amount of alkyl halide or alkyl tosylate in the presence of mercury(II) bromide in nitrobenzene at 60—90 °C gave **6** as the $HgBr_2$-complex in moderate yield. The other alkylated products, **9** and **10**, were obtained in a negligible amount.



* The term "silyl solvent method" was proposed in a previous paper.[1b] It refers to an improved silyl procedure in which the glycosylation of trimethylsilylated purine or pyrimidine bases with *O*-acyl-glycosyl halide is conducted in the presence of a mercuric salt, *e.g.* mercury(II) chloride or mercury(II) bromide, in a solvent. An analogous procedure, in which the mercuric salt was used in combination with mercury(II) oxide, was reported independently by Wittenburg.[2] Several Lewis acids have been surveyed[3] as an alternative to the mercuric salt in this procedure, tin(IV) chloride being most widely employed.

Table 1. Yields and physical data of mesoionic triazolopyridines (**6**)

Compound	Mp °C	Yield[a] %	Found % C	Found % H	Found % N	Calcd % C	Calcd % H	Calcd % N	UV: λ_{max}^{MeOH} (nm)
6a	163—164	79	69.36	4.92	18.59	69.31	4.92	18.66	236,285,348
6b	108—109	74	61.71	5.36	23.89	61.70	5.17	23.98	235,282,341
6c	190	85	54.36	5.04	18.97	54.29	5.01	18.99	235,282,340
6d	220	78	56.34	4.73	28.16	56.55	4.71	27.93	235,281,342

a) Based on the products isolated.

The physical properties of the free mesoionic compounds (**6**) obtained by treating the complex with hydrogen sulfide or ion exchange resin (Dowex-1, HCO_3^-) are given in Table 1.

Detailed studies on the benzylation of **8** were carried out in order to elucidate the factor inducing the remarkable selectivity on alkylation.

Since **8** includes three active sites for alkylation N^1,N^2, and O), a number of products would be expected. In fact, three monoalkylated products, **6a**, **9a** (R=benzyl), and **10a** (R=benzyl) were obtained by the reaction of Ag-salt of **8** with benzyl bromide under mild conditions (80 °C, in nitrobenzene). The reaction of **8** with benzyl bromide at relatively high temperature gave **9a** predominantly with a small amount of **6a**. The reaction was accelerated by the addition of mercury(II) bromide, the main product being **6a**. Trimethylsilyl substitution at the N^2-position of **8** afforded a result similar to that obtained by the use of **8** itself on benzylation with regard to the distribution of the products. Sufficient selectivity to give **6a** on the benzylation was obtained by the use of **1** in combination with mercury(II) bromide. The results on the benzylation of **1** or **8** are given in Table 2.

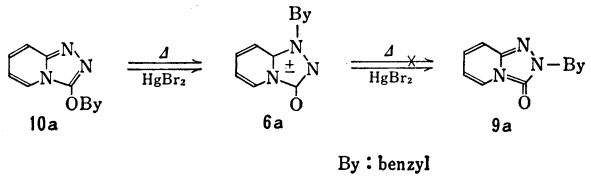
Table 2. Benzylation[a] of **1** or **8**: reaction conditions and products

Exp No.	Starting material	React temp (°C)	React time (h)	Cat ($HgBr_2$)	Yield[b] (%) of the product **10a**	**6a**	**9a**
1	Ag-salt of **8**	80	3	—	19	38	29
2	**8**	125	12	—	—	12	78
3	**8**	125	3	1-eq.	—	68	20
4	**1**	125	5	—	—	21	68
5	**1**	85	20	1-eq.	—	79	trace

a) Carried out using 1-eq. of benzyl bromide in nitrobenzene. b) Based on the product isolated.

The results indicate that products can be selected by varying the reaction conditions appropriately. Previous studies[8] on the alkylation of purine bases revealed that alkyl migration plays an important role in determination of the reaction product. The following experiments suggest that the benzyl moiety attached to the triazolopyridine ring easily migrates under the same reaction conditions as described above, the migration proceeding successively in the order $O \rightarrow N^1 \rightarrow N^2$.

Heating of **10a** in nitrobenzene (100—110 °C, 23 h) gave **6a** exclusively. The conversion was accelerated by the addition of a mercuric salt catalyst, *e.g.* $HgBr_2$ or $Hg(CN)_2$. Conversion of **6a** into **9a** was observed in the presence of mercury(II) bromide, but not in the absence of the catalyst even at high temperature (150 °C).



By : benzyl

Benzyl bromide was found to act as a more efficient catalyst for these conversions. Treatment of **10a** with a catalytic amount of benzyl bromide in nitrobenzene at

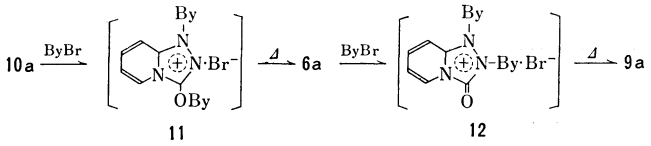
Table 3. Benzyl migration[a]: reaction conditions and products

Exp No.	Starting material	Cat	React temp (°C)	React time (h)	Yield (%) of the product **10a**	**6a**	**9a**	**11**	**12**
1	**10a**	—	100—110	23	15	76	—	—	—
2	**10a**	1-eq. $Hg(CN)_2$	100—110	15	17	73	—	—	—
3	**10a**	1-eq. ByBr	80	5.5	2	93	—	—	—
4	**10a**	0.1-eq. ByBr	80	25	33	63	—	—	—
5	**10a**	1-eq. ByBr +1-eq. $HgBr_2$	25	25					52[c]
6	**6a**	—	150	50	no reaction				
7	**6a**	1-eq. $HgBr_2$	150	50	—	8	55	trace	
8	**6a**	1-eq. ByBr	125	1	—	trace	90	—	—
9	**6a**	0.1-eq. ByBr	125	20	—	19	76	—	—
10	**6a**	1-eq. ByBr +1-eq. $HgBr_2$	125	3					37[c]

a) Conducted in nitrobenzene. b) Based on the product isolated. c) $HgBr_2$-complex.

80 °C for 5 h gave **6a** almost quantitatively. Conversion of **6a** into **9a** took place by a similar treatment of **6a** with benzyl bromide at 120 °C

Quaternary salts (**11**) and (**12**), assumed to be the intermediates of these conversions, could be isolated as $HgBr_2$-complexes. Detailed results are given in Table 3.



Demercuration of the complex of **12** gave a free quaternary salt which decomposed easily to give **9a** in nitrobenzene at 80 °C. On treatment with hydrogen sulfide, the $HgBr_2$-complex of **11** gave **6a** as a result of the instability of the free quaternary salt.

The results suggest that the primary factor determining the products of benzylation is the benzyl migration under the reaction conditions employed. Presumably, the initial product is either **6a** or **10a**. However, the formation of the latter is uncertain in the reaction of **8** with benzyl bromide since conversion of **10a** into **6a** is very rapid. When the reaction is carried out at high temperature, these compounds are transformed easily into thermodynamically more stable **9a** by benzyl migration. The migration seems to proceed mainly through intermediates **11** and **12**. In order to obtain the mesoionic compound (**6a**) by the benzylation of **8**, it is apparent that further benzylation of **6a** should be suppressed. The use of trimethylsilyl substituent with mercury(II) bromide for the benzylation makes the formation of **6a** under mild conditions possible, **6a** not undergoing further benzylation. The metal probably not only acts as a Friedel-Crafts catalyst but also suppresses the nucleophilic capability of the N^2-atom by the complex formation with **6a**.

By applying the mercuric salt catalyzed silyl procedure to the alkylation of **8**, the reaction was controlled sufficiently to give the mesoionic compound as a product. An analogous controlled acylation of **8** was found to give a new mesoionic *N*-acyltriazolopyridine (**6**, R= acyl).

Experimental

Melting points were determined on a Yazawa hot-stage apparatus and are uncorrected. Infrared, UV and NMR spectra were recorded on Hitachi EPI-S2, Hitachi-124 and Varian T-60 spectrometers respectively.

Triazolopyridine (**8**) was prepared by the method of Potts and Burton.[9] An authentic sample of **6a** was prepared by ring closure of 1-benzyl-1-(2-pyridyl)hydrazine with urea and that of **10a** by the reaction of 3-bromo-1,2,4-triazolo[4,3-*a*]-pyridine with sodium benzyl alcoholate.

2-Trimethylsilyl-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one (1). To a mixture of **8** (13.6 g), trimethylchlorosilane (13.0 g) in dry benzene (200 ml) under stirring was added dropwise a solution of triethylamine (12.1 g) in dry benzene (50 ml). After being stirred at room temperature for 2 h, the reaction mixture was filtered, and the cake was washed with a small amount of dry benzene. The combined filtrate and washings were evaporated to give a solid product: yield 20.65 g (99.7%). UV: $\lambda_{max}^{Dioxane}$ 252, 268, 279, 345 nm. Found: C, 51.95; H, 6.45; N, 20.03%. Calcd for $C_{19}H_{13}N_3OSi$: C, 52.10; H, 6.31; N, 20.05%. (Owing to the instability of the product toward water, all the operation had to be performed under the conditions protected from atmospheric moisture.)

Anhydro-*1-(β-D-ribofranos-1-yl)-3-hydroxy-1,2,4-triazolo[4,3-a]pyridinium Hydroxide (5) and Its* N^2-*Isomer.* Acetic anhydride (0.05 ml) and acetic acid (5 ml) saturated with hydrogen bromide were added to a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-*D*-ribofranoside (2.52 g) in dry chloroform (5 ml). The resulting solution was allowed to stand at room temperature for 45 min, and then evaporated *in vacuo* to give a thick sirup at a temperature below 40 °C. Co-evaporation with dry toluene was repeated three times. The residual sirup was dissolved in dry benzene (10 ml), and mercury(II) bromide (1.80 g) and **1** (1.04 g) were added. The mixture was stirred at room temperature for 2 h, then evaporated *in vacuo*, and the residue was extracted with chloroform. The extract was washed successively with 25% potassium iodide (2 times) and with water, dried over anhydrous sodium sulfate, and evaporated to give an amorphous solid (3.169 g). The protected glycoside thus obtained was heated in methanol (70 ml) containing sodium methoxide (216 mg) under reflux for 60 min. The reaction solution was cooled, then evaporated *in vacuo* to dryness, and the residue was dissolved in water (10 ml). The aqueous solution was washed with ether, rendered neutral with 1M HCl, and applied to a column of 50 ml of Dowex-1×4 (OH^-, 100—200 mesh) anion exchange resin. The column was washed with water (200 ml) and eluted with 40% methanol. The eluate could be separated into two fractions. Evaporation of the first fraction gave **5**, which was recrystallized from aqueous ethanol. Yield 989 mg (74%); fine needles, mp 204—206 °C. UV λ_{max}^{MeOH} 236, 283, 339 nm. IR (Nujol): 1660 cm^{-1} (C=O). NMR (D_2O); δ: 8.18 (d, J=7 Hz, 1, H-5), 7.7—8.0 (m, 2, H-7 and H-8), 7.1—7.4 (m, 1, H-6), 6.12 (d, J=5 Hz, 1, H-1'), 3.8—4.9 ppm (m, 5, ribose ring protons). Found: C, 49.60; H, 5.07; N, 15.85%. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.47; H, 4.91; N, 15.73%. On evaporation, the second fraction yielded 2-(β-*D*-ribofranos-1-yl)-1,2,4-triazolo[4,3-*a*]-pyridin-3(2*H*)-one; 57 mg (4.3%) mp 172—173 °C. UV: λ_{max}^{MeOH} 220, 259(sh), 275, 328 nm. IR (Nujol); 1710 cm^{-1} (C=O). Found: C, 49.70; H, 4.92; N, 15.65%. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.47; H, 4.91; N, 15.73%.

Anhydro-*1-benzyl-3-hydroxy-1,2,4-triazolo[4,3-a]pyridinium Hydroxide (6a).* A mixture of **1** (2.08 g), benzyl bromide (1.75 g) and mercury(II) bromide (3.60 g) in nitrobenzene (10 ml) was stirred at 85 °C for 20 h. 2-Propanol was then added. The crystals deposited were collected by filtration to give $HgBr_2$-complex of **6a**: yield 4.878 g (83.5%); mp 116—117 °C. The complex was suspended in methanol (300 ml), and then treated with hydrogen sulfide stream until the starting white crystals disappeared. The resulting precipitate of mercury sulfide was filtered off. The filtrate was evaporated to give a yellow powder, which was crystallized from 2-propanol. Yield 1.79 g (79.5%, based on **1**); yellow needles; mp 163—164 °C. UV; λ_{max}^{MeOH} 236, 285, 348 nm. IR (Nujol); 1660 cm^{-1} (C=O). NMR (DMSO-d_6); δ: 8.21 (m, 1, H-5), 7.5—7.9 (m, 2, H-7 and H-8), 7.02 (m, 1, H-6), 5.41 ppm (s, 2, $C\underline{H}_2$-Ph). Found: C, 69.36; H, 4.92; N, 18.59%. Calcd for $C_{13}H_{11}N_3O$: C, 69.31; H, 4.93; N, 18.66%.

General Procedure for the Preparation of 6. A mixture of **1** (10 mmol), alkyl halide (or alkyl tosylate) (10—11 mmol) and mercury(II) bromide in nitrobenzene (10 ml) was stirred at 60—90 °C under monitoring with TLC until the starting material disappeared, and then evaporated *in vacuo*. The residue was dissolved in methanol. The resulting solution

was neutralized with Dowex-1 (HCO_3^-), and the resin was filtered off. The filtrate was evaporated *in vacuo* to give a yellow powder, which was crystallized from appropriate solvent. Yields and physical constants of the products are given in Table 2.

Reaction of the Ag-salt of 8 with Benzyl Bromide. A suspension of the Ag-salt of **8** (121 mg) in nitrobenzene (1 ml) containing benzyl bromide (81 mg) was stirred at 80 °C for 3 h, and then evaporated *in vacuo* to give sirupy residue which was extracted with chloroform. Chromatographic separation of the extract on a silica gel plate yielded three isolated products: **9a** (31.1 mg), **10a** (20.3 mg) and **6a** (40.5 mg). Physical constants of **9a**: mp 114—115 °C. UV λ_{max}^{MeOH} 222, 260 (sh), 268, 278, 331 nm. IR (Nujol); 1720 cm^{-1} (C=O). NMR (DMSO-d_6); δ: 7.89 (m, 1, H-5), 7.36 (s, 5, C_6H_5), 7.15—7.3 (m, 2, H-7 and H-8), 6.63 (m, 1, H-6), 5.15 ppm (s, 2, $C\underline{H}_2$-Ph). Found: C, 69.22; H, 5.02; N, 18.69%. Calcd for $C_{13}H_{11}N_3O$: C, 69.31; H, 4.93; N, 18.66%. Physical constant of **10a**: oil. UV λ_{max}^{MeOH} 227, 256 (sh), 260, 271, 301 nm. NMR (DMSO-d_6); δ: 8.08 (m, 1, H-5), 7.2—7.7 (m, 2, H-7 and H-8), 7.43 (s, 5, C_6H_5), 6.85 (m, 1, H-6), 5.70 ppm (s, 2, $C\underline{H}_2$-Ph).

Reaction of 8 with Benzyl Bromide. a) A mixture of **8** (1.35 g) and benzyl bromide (1.80 g) in nitrobenzene (10 ml) was stirred at 125 °C for 12 h, and then evaporated *in vacuo*. The residue was dissolved in methanol, neutralized with Dowex-1 (HCO_3^-), and the resin was filtered off. The filtrate was concentrated *in vacuo* giving a crystalline mass, which was recrystallized from 2-propanol to give pure **9a**: yield 1.482 g (66%); mp 114—115 °C. A further crop of **9a** (280 mg, 12.4%) and **6a** were isolated from the mother liquor by column chromatography on silica gel.

b) In the Presence of $HgBr_2$. A mixture of **8** (1.35 g), benzyl bromide (1.80 g) and mercury(II) bromide (3.60 g) in nitrobenzene (10 ml) was stirred at 125 °C for 3 h, then evaporated *in vacuo*, and the residue was dissolved in methanol. The solution was neutralized with Dowex-1 (HCO_3^-), filtered, and the filtrate was evaporated to give a sirupy residue. Chromatographic separation of the residue on silica gel (40 g, 1% methanol in chloroform was used as eluent) yielded two isolated product: **6a** (1.537 g, 68.3%) and **9a** (450 mg, 20%).

1-Benzyl-3-benzyloxy-1,2,4-triazolo[4,3-a]pyridinium Bromide (11). A solution of **10a** (678 mg), benzyl bromide (513 mg) and mercury(II) bromide (1.08 g) in nitrobenzene (3 ml) was stirred at room temperature for 20 h, and then poured into a large amount of ethanol. The precipitate formed was crystallized from methanol to give $HgBr_2$-complex of **11**: yield 1.175 g (51.7%); mp 78—80 °C. UV λ_{max}^{MeOH} 218, 260 (sh), 299 nm. NMR (DMSO-d_6); δ: 7.4—8.8 (m, 14, pyridine and phenyl ring H), 5.83 and 5.74 ppm (two s, 4, $C\underline{H}_2$-Ph). Found: C, 31.75; H, 2.40; N, 5.55; Br, 10.56%. Calcd for $C_{20}H_{18}N_3OBr \cdot HgBr_2$: C, 31.90; H, 2.70; N, 5.49; Br, 10.72%.

1,2-Di-benzyl-3-oxo-1,2,4-triazolo[4,3-a]pyridinium Bromide (12). A solution of **6a** (1.13 g), benzyl bromide (90 mg) and mercury(II) bromide (1.80 g) in nitrobenzene (5 ml) was stirred at 125 °C for 3 h. Methanol was added to the reaction solution giving a crystalline solid. On filtration, the pure $HgBr_2$-complex of **12** was obtained: yield 1.39 g (36.8%); mp 157—158 °C. Found: C, 41.77; H, 3.31; N, 7.16; Br, 14.08%. Calcd for $C_{20}H_{18}N_3OBr \cdot 1/2HgBr_2$: C, 41.73; H, 3.49; N, 7.77; Br, 13.82%.

The complex (577 mg) was dissolved in methanol. Hydrogen sulfide was bubbled through the solution until the precipitation of mercury sulfide was complete. The precipitate was then filtered off. Evaporation of the filtrate gave white powder which was crystallized from ethanol–ether to give pure **12**: yield 376 mg (95%); mp 157—158 °C. UV λ_{max}^{MeOH} 212, 230 (sh), 260 (sh), 328 nm. IR (Nujol); 1770 cm^{-1} (C=O). NMR (DMSO-d_6); δ: 8.79 (m, 1, H-5), 8.2—8.5 (m, 2, H-7 and H-8), 7.56 (m, 1, H-6), 5.85 and 5.41 ppm (two s, 4, $C\underline{H}_2$-Ph). Found: C, 60.41;H, 4.60; N, 10.55; Br, 20.05%. Calcd for $C_{20}H_{18}N_3OBr$: C, 61.60; H, 4.58; N, 10.60; Br, 20.16%.

Benzyl Migration. A solution of the starting material (**10a** or **6a**, 10 mmol) in nitrobenzene (10 ml) was heated with (or without) a catalyst ($HgBr_2$ or benzyl bromide) in the desired temperature range. The reaction mixture was worked up in the manner described above.

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