# Reactions between Azolium Salts and Nucleophilic Reagents

## IV. 1,3-Dimethyl-1,2,3-triazolium Salts and Sodium Methoxide

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1,3-Dimethyl-1,2,3-triazolium tosylate (III) and the dibromo-derivative (II), when treated with sodium methoxide, afford 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI) in high yield. The reaction proceeds by (II), brominating (III), giving (I), which in turn is converted into (VI) *via* the methoxy-triazolium salt (IV). The halogenation of (III) is much faster than the substitution of (II), which in turn is more rapid than the substitution of (I), which again is more rapid than the self-halogenation of (I), *i.e.* $k_{-A} > k_C = 4k_B > k_A$.

The reaction between 1,3-dimethyl-4-bromo-1,2,3-triazolium *p*-toluene-sulfonate (I) and aqueous sodium hydroxide was described previously.[1] It was found that the first step in this reaction is a rapid establishment of an equilibrium, leading to the formation of (II) and (III). This reaction was found to be base-catalyzed and is assumed to proceed *via* "ylide" anions.[1,2] Subsequently, the bromo-compounds (I) and (II) undergo nucleophilic substitution to give the products (VI) and (VII). The reactions are kinetically controlled, hence, the ratio of products is determined by the ratio between the velocity constants of the rate limiting substitution steps. Similar results were obtained with other 1,3-disubstituted 4-bromo-1,2,3-triazolium salts and sodium hydroxide.[2] The reactions of bromo-substituted 1,2,3-triazolium salts with methoxide ions have now been studied; the results are described in the present and subsequent papers.

Treatment of 1,3-dimethyl-4-bromo-1,2,3-triazolium tosylate (I) with 1 N sodium methoxide in methanol afforded 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI) in high yield. The bromo-triazolio-oxide (VII), the major product in the reaction of (I) with sodium hydroxide, was not formed in detectable amounts. Similarly, a 1:1 mixture of 1,3-dimethyl-1,2,3-triazolium tosylate (III) and 1,3-dimethyl-4,5-dibromo-1,2,3,-triazolium tosylate (II) gave the triazolio-oxide (VI) as the sole product in almost quantitative yield. This suggests that (II) halogenates (III), giving (I), which subsequently produces the triazolio-oxide (VI). As indicated by the NMR-spectra, the monobromo-compound (I), when treated with 1 N potassium hydroxide in methanol, undergoes rapid nucleophilic substitution by methoxide ion, giving the meth-

oxy-compound (IV), which in turn demethylates slowly, producing the tria-zolio-oxide (VI) (relative rates given in Tables 2 and 4). The salts (II) or (III) were not observed. Thus the substitution of (I) is so fast that the equilibrium acquires no importance.

The methoxy-compound (IV) was independently prepared from triazolio-oxide (VI) and methyl tosylate. The demethylation of (IV) was followed by NMR-spectroscopy. When the demethylation of the methoxy-compound (IV) was carried out in 1 N potassium hydroxide in tetradeuteriomethanol, the protons of the methoxy groups in (IV) were exchanged prior to demethylation (Table 3). The exchanged hydrogen appeared as methanol in the spectra. De-



$$A^- = p\text{-}CH_3C_6H_4SO_3^-$$
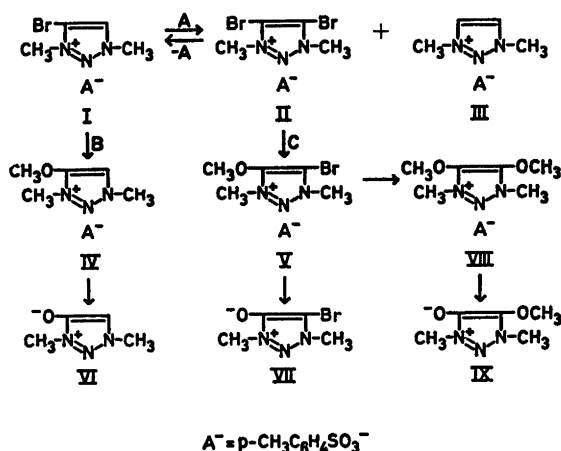
methylation of (IV) in methoxide leads to the formation of dimethyl ether. If no exchange took place, the demethylation reaction carried out in tetra-deuteriomethanol should give 100 % of 1,1,1-trideuterio-dimethyl ether. Due to the exchange reaction, however, the yield of the latter compound was only about 30 %, reflecting to the ratio between the rate of demethylation and ex-change (Tables 3 and 4). The methanol formed by the exchange appeared as a sharp singlet, and the methoxy group of (IV) was a sharp singlet throughout the exchange reaction. This excludes proton-deuterium coupling and indicates that the methyl group as such is exchanged, whereas a stepwise exchange of individual protons is excluded. This was confirmed by the fact that no exchange of the methoxy group of (IV) took place when mono-$O$-deuteriomethanol was used as the solvent. It seems unlikely, that the exchange is due to a realkyla-tion of the triazolio-oxide (VI), since methanol or dimethyl ether would hardly be alkylating agents under the prevailing conditions. More probably, the ex-change is caused by nucleophilic displacement of methoxy groups in (IV) with trideuteriomethoxide ions. When the methoxy-compound (IV) was treated with sodium thiomethoxide or with methylamine in trideuteriomethanol, demethylation took place with formation of dimethyl sulfide or di- and tri-methylamine. No exchange of the $-OCH_3$ group with $-SCH_3$ or $NHCH_3$

groups was observed, and the triazolio-oxide (VI) was the only triazole deriv-
ative formed.

1,3-Dimethyl-4,5-dibromo-1,2,3-triazolium tosylate (II), when treated
with 1 N sodium methoxide, afforded a mixture of 1,3-dimethyl-5-bromo-
1,2,3-triazolio-4-oxide (VII) (71 %), 1,3-dimethyl-5-methoxy-1,2,3-triazolio-
4-oxide (IX) (16 %), and 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI) (5 %).
NMR-spectra recorded during the reaction indicated that the dibromo-com-
pound (II) underwent rapid nucleophilic substitution to give the bromo-
methoxy-compound (V), which subsequently afforded demethylation to the
bromo-triazolio-oxide (VII). Concomitantly, (V) underwent further substi-
tution to give the dimethoxy-compound (VIII) and subsequently the methoxy-
triazolio-oxide (IX) (since the bromo-triazolio-oxide (VII) is stable under the
conditions of the reaction, the observed methoxy-triazolio-oxide (IX) does not
arise by substitution of the bromine atom in (VII)). The minor amount of the
triazolio-oxide (VI) observed in the spectra is probably formed by oxidation
of the methoxide ion *via* bromonium ion abstraction from the starting mate-
rial (II) or the intermediate bromo-methoxy-compound (V). In fact, traces
of formic acid could be detected after the reaction.

1,3-Dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate (V) was pre-
pared from the bromo-triazolio-oxide (VII) and methyl tosylate. (V), when
treated with 1 N aqueous sodium hydroxide, demethylated, forming the bromo-
triazolio-oxide (VII) in quantitative yield. Treatment of (V) with 1 N sodium
methoxide afforded a mixture of the triazolio-oxides (VI), (VII), and (IX).
When treated with 4 N sodium methoxide, (V) gave (VI) as the major product,
indicating that (V) is capable of oxidizing methoxide to formic acid (see above).

As in the previous case, demethylation of the bromo-methoxy-compound
(V) in trideuteriomethanol led to rapid exchange of the methoxy group (rates
given in Table 3). The ratio between the rates of nucleophilic substitutions
with methoxide in the monobromo- (I) and the dibromo-compound (II) was
0.25; the ratio was unchanged when hydroxide ions were employed. The for-
mation of the triazolio-oxide (VI) as the sole product, regardless whether the
monobromo-compound (I) or a 1:1 mixture of the dibromo-compound (II)
and the unsubstituted salt (III) are treated with sodium methoxide, may be
explained in terms of relative rates of the reactions involved. Thus, bromina-
tion of (III) with (II) is faster than the substitution of (II), since the product
resulting from substitution of (II) (see above) was not detected. Again, substi-
tution in (II) is faster than in (I), which again is faster than the selfhalogenation
of (I). The substitution rates of the bromo-compounds (I) and (II) by methoxide
are much higher than those observed with hydroxide ions and are in fact of
the same order of magnitude as the interhalogenation rates. In summary,
in sodium methoxide, $k_{-A} > k_C = 4k_B > k_A$, whereas in sodium hydroxide [1] $k_{-A}$
and $k_{-A} > k_C = 4k_B$.

A comparison of the demethylation rates of the methoxy-compound (IV)
and the bromoderivatives (V) indicates that the bromine atom increases the
demethylation rate of the adjacent methoxy group by a factor of 34 (Table
4). Analogously, bromine increases the exchange rate of the adjacent methoxy
group by a factor of 1890.

## EXPERIMENTAL

Thin layer and column chromatography were carried out as described previously.[3] NMR-spectra were obtained on a Varian A-60 instrument. Position of signals are given in ppm ($\delta$-values) relative to TMS. Deuteriochloroform was used as solvent, when not otherwise stated. Melting points are uncorrected.

## Preparative experiments

*1,3-Dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV).* 1,3-Dimethyl-1,2,3-triazolio-4-oxide (VI [3,4] (213 mg) and methyl tosylate (350 $\mu$l) were heated to 100° for 3 h. The mixture was washed with ether, recrystallized from methanol-ether, and washed with ethyl acetate, yielding 480 mg (93 %) of 1,3-dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) as colorless crystals, m.p. 121 — 125°. (Found: C 48.08; H 5.77; N 14.01; S 10.64. Calc. for $C_{12}H_{17}N_3O_4S$: C 48.15; H 5.73; N 14.04; S 10.71.)

*1,3-Dimethyl-4-methoxy-5-bromo-1,2,3-*triazolium tosylate *(V).* Similarly, 1,3-dimethyl-5-bromo-1,2,3-triazolio-4-oxide (VII) (467 mg) and methyl tosylate (0.50 ml), by heating to 100° for 3 h and washing with ether and ethyl acetate, gave 467 mg (51 %) of 1,3-dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate (V) as colorless crystals, m.p 109 — 111°. (Found: C 37.92; H 4.34; N 10.99; Br. 21.28; S 8.38. Calc. for $C_{12}H_{16}N_3O_4SBr$: C 38.10; H 4.27; N 11.11; Br 21.12; S 8.47.)

## Reactions with methoxide

*1,3-Dimethyl-4-bromo-1,2,3-triazolium tosylate (I)*[1] (192 mg) and 1 N sodium methoxide (1.77 ml) were heated to reflux for 3 h. The methanol was then removed and the residue extracted 5 times with boiling chloroform (10 ml). The chloroform was removed and the residue extracted with boiling ethyl acetate (4 × 5 ml). The ethyl acetate was removed and the residue boiled with ether (10 ml) for a few minutes. The volume was then reduced to 5 ml and the mixture cooled to — 30°. The precipitate was isolated and dried. Yield 61 mg (97 %) of 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI) as colorless crystals, m.p. 97 — 99°. Melting point, IR-, and NMR-spectra served to prove the identity with the material described previously.[3,4]

*1,3-Dimethyl-4,5-dibromo-1,2,3-triazolium tosylate (II)*[1] (502 mg) in 1 N sodium methoxide (3.90 ml) was heated to reflux for 3 h. The methanol was removed and the residue extracted with boiling chloroform (5 × 10 ml). The solvent was evaporated and the residue (201 mg) recrystallized 3 times from ethyl acetate-ether with cooling in dry ice, giving 128 mg (57 %) of 1,3-dimethyl-5-bromo-1,2,3-triazolio-4-oxide (VII) as colorless crystals, m.p. 139 — 141°. Melting point, IR, and NMR-spectra established the identity with the material described previously.[4] The combined mother liquors were chromatographed on silica gel (10 g). Elution with acetone-chloroform-hexane (12:3:5) gave 31 mg (14 %) of the bromo-triazolio-oxide (VII), m.p. 134 — 138°. (Total yield: 71 %.) Recrystallization as described above raised the melting point to 140 — 142°. The column was then eluted with ethyl acetate-methanol (1:1). The first fraction contained 27 mg (16 %) of 1,3-dimethyl-5-methoxy-1,2,3-triazolio-4-oxide (IX) as yellow, deliquescent crystals. Recrystallization from ethyl acetate-hexane with cooling in dry ice raised the melting point to 74 — 77°. The compound is very hygroscopic. (Found: C 41.78; H 6.29. Calc. for $C_5H_9N_3O_2$: C 41.49; H 6.33.) The second fraction contained 7.0 mg (5 %) of 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI). Melting point, IR-, and NMR-spectra proved the identity with the material described previously.[3,4]

*1,3-Dimethyl-4,5-dibromo-1,2,3-triazolium tosylate (II) and 1,3-dimethyl-1,2,3-triazolium tosylate (III).* A mixture of (II)[1] (149 mg) and (III)[1] (94 mg) in 1 N sodium methoxide (2.24 ml) was heated to reflux for 3 h. The methanol was removed and the residue extracted with chloroform (5 × 10 ml). Removal of the chloroform gave 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI) in quantitative yield as yellow crystals, m.p. 88 — 92°. Melting point, IR-, and NMR-spectra proved the identity with the material described previously.[3,4]

*1,3-Dimethoxy-5-bromo-1,2,3-triazolium tosylate (V)* (467 mg) and 1 N sodium methoxide (4.00 ml) were heated to reflux for 3 h. The methanol was removed and the residue extracted with chloroform (5 × 10 ml). The chloroform was evaporated and the residue (231 mg) recrystallized 3 times from ethyl acetate-ether with cooling in dry ice, giving 64 mg (27 %) of 1,3-dimethyl-5-bromo-1,2,3-triazolio-4-oxide (VII), m.p. 140 − 141°. The material was identified by its melting point, IR-, and NMR-spectra. The combined mother liquors were chromatographed on silica gel (10 g). Elution with acetone-chloroform-hexane (12:3:5) gave 153 mg of 1,3-dimethyl-5-bromo-1,2,3-triazolio-4-oxide (VII), m.p. 136 − 140°. Recrystallization from ethyl acetate-ether gave the pure product, 75 mg (32 %), m.p. 140 − 142° (total yield: 59 %). The column was then eluted with ethyl acetate-methanol (1:1). The first fraction contained 16 mg (9 %) of 1,3-dimethyl-5-methoxy-1,2,3-triazolio-4-oxide (IX). Recrystallization from ethyl acetate-ether with cooling in dry ice raised the melting point to 74 − 77°. The second fraction contained 4 mg (3 %) of 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI), identified through its spectra.

*1,3-Dimethyl-5-bromo-4-methoxy-1,2,3-triazolium tosylate (V) and 4 N sodium methoxide.* A mixture of (V) (381 mg) and 4 N sodium methoxide (0.77 ml) was heated to reflux for 3 h. The methanol was removed and the residue extracted with chloroform (5 × 10 ml). The chloroform was removed and the residue chromatographed on silica gel (15 g). Elution with acetone-chloroform-hexane (12:3:5) gave only minor amounts of unidentified products. The column was then eluted with ethyl acetate methanol (1:1). This gave 42 mg (37 %) of 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI) as a yellow crystalline mass m.p. 56 − 59°. The compound was identified by its IR- and NMR-spectra.

*1,3-Dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate and sodium hydroxide.* (V) (267 mg) and 1 N sodium hydroxide (1.70 ml) were heated to reflux for 3 h. The water was removed *in vacuo* and the residue was extracted 5 times with boiling chloroform

*Table 1.* NMR-data from spectroscopic experiments in 1 N solutions of potassium hydroxide in tetradeuteriomethanol with TMS as an internal standard.

| Compound | $OCH_3$ ppm | $NCH_3$ ppm | $NCH_3$ ppm | $SCH_3$ ppm |
|---|---|---|---|---|
| 1,3-Dimethyl-4-bromo-triazolium tosylate (I) | | 4.42 | 4.42 | |
| 1,3-Dimethyl-4,5-bromo-triazolium tosylate (II) | | 4.41 | 4.41 | |
| 1,3-Dimethyl-4-methoxy-triazolium tosylate (IV) | 4.25 | 4.32 | 4.08 | |
| 1,3-Dimethyl-5-bromo-4-methoxy-triazolium tosylate (V) | 4.44 | 4.28 | 4.13 | |
| 1,3-Dimethyl-4,5-dimethoxy-triazolium tosylate (VIII) | 4.45[a] 4.45 | 4.10 | 4.10 | |
| 1,3-Dimethyl-triazolio-4-oxide (VI) | | 4.00 | 3.69 | |
| 1,3-Dimethyl-5-bromo-triazolio-4-oxide (VII) | | 4.05 | 3.76 | |
| 1,3-Dimethyl-5-methoxy-triazolio-4-oxide (IX) | | 3.86 | 3.68 | |
| Methanol | 3.38 | | | |
| Dimethyl ether | 3.33 | | | |
| 1,1,1-Trideuteriodimethyl ether | 3.30 | | | |
| Dimethylsulfide | | | | 2.10 |
| Dimethylamine | | | 2.37 | |
| Trimethylamine | | | 2.24 | |

[a] Determined in 1 N potassium hydroxide in methanol.

(10 ml). Removal of the chloroform gave 1,3-dimethyl-5-bromo-1,2,3-triazolio-4-oxide (VII) in quantitative yield as colorless crystals, m.p. 140−142°. Melting point, IR-, and NMR-spectra were identical with those of the material described previously.[4]

## Spectroscopic experiments

The 1,2,3-triazolium salt ($4.0 \times 10^{-2}$ mM) was dissolved in a 1 N solution of potassium hydroxide in tetradeuteriomethanol (350 $\mu$l) at the appropriate temperature (see Tables 1−3), and NMR-spectra were obtained at intervals; the temperature inside the spectrom-

*Table 2.* Rates of substitution reactions.

| Starting material | Product | Rate min | Temp. °C | Relative rate |
|---|---|---|---|---|
| 1,3-Dimethyl-4-bromo-1,2,3-triazolium tosylate (I) | 1,3-Dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) | $T_{2/3} = 7.0$ | 0 | 1 |
| 1,3-Dimethyl-4,5-dibromo-1,2,3-triazolium tosylate (II) | 1,3-Dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate (V) | $T_{2/3} = 1.8$ | 0 | 3.9 |
| 1,3-Dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate (V) | 1,3-Dimethyl-4,5-dimethoxy-1,2,3-triazolium tosylate (VIII) | $T_{1/8} = 48$<br>$T_{1/8} = 12.5$ | 0<br>20 | |

*Table 3.* Rates of exchange of methoxy groups with trideuteriomethoxy groups.

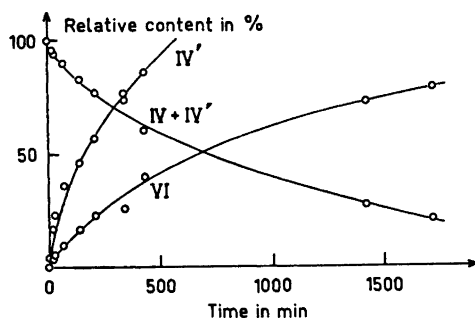| Compound | Rate min | Temp. °C | Relative rate |
|---|---|---|---|
| 1,3-Dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) | $T_{1/2} = 3400$<br>$T_{1/2} = 163$ | 0<br>20 | 1 |
| 1,3-Dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate (V) | $T_{1/2} = 1.8$ | 0 | 1890 |



*Fig. 1.* The reaction of 1,3-dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) with 1 N potassium hydroxide in tetradeuteriomethanol with formation of the trideuterio-methoxy-derivative (IV′) and 1,3-dimethyl-1,2,3-triazolio-4-oxide (VI).
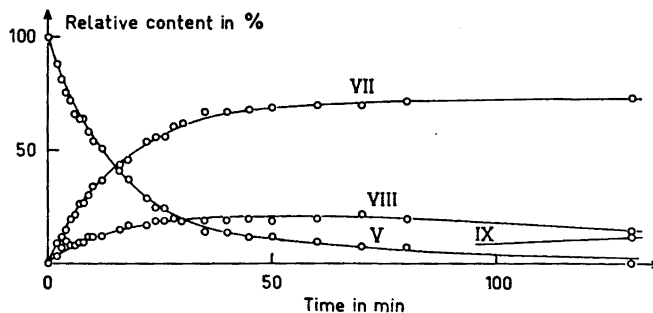
*Fig. 2.* The reaction of 1,3-dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate (V) with 1 N potassium hydroxide in tetradeuteriomethanol, showing the formation of 1,3-dimethyl-5-bromo-1,2,3-triazolio-4-oxide (VII), and 1,3-dimethyl-4,5-dimethoxy-1,2,3-triazolium tosylate (VIII). The latter subsequently forms 1,3-dimethyl-5-methoxy-1,2,3-triazolio-4-oxide (IX).

*Table 4.* Rates of demethylations.

| Starting material | Nucleophilic reagent | Product | Rate min | Temp. °C | Relative rate |
|---|---|---|---|---|---|
| 1,3-Dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) | KOH in CD$_3$OD | 1,3-Dimethyl-1,2,3-triazolio-4-oxide (VI) | $T_{1/2} = 670$ | 20 | 1 |
| 1,3-Dimethyl-4-methoxy-5-bromo-1,2,3-triazolium tosylate (V) | KOH in CD$_3$OD | 1,3-Dimethyl-5-bromo-1,2,3-triazolio-4-oxide (VII) | $T_{1/2} = 20$ | 20 | 34 |
| 1,3-Dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) | NaSCH$_3$ in CD$_3$OD | 1,3-Dimethyl-1,2,3-triazolio-4-oxide (VI) (and dimethylsulfide) | | | |
| 1,3-Dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) | CH$_3$NH$_2$ in CD$_3$OD | 1,3-Dimethyl-1,2,3-triazolio-4-oxide (VI) (and dimethylamine and trimethylamine) | | | |

eter was maintained using the Varian V-6040 temperature controller. The same procedure and the same concentrations were used when 1,3-dimethyl-4-methoxy-1,2,3-triazolium tosylate was treated with sodium thiomethoxide or methylamine. All products, with the exception of 1,1,1-trideuterio-dimethyl ether, were identified spectroscopically by adding the pure substances to the solutions. The 1,1,1-trideuterio-dimethyl ether was identified by adding a minute amount of methyl iodide to the solution and allowing it to react with the deuteriomethoxide. δ-Values of the compounds are given in Table 1. As representative examples, the reaction of 1,3-dimethyl-4-methoxy-1,2,3-triazolium tosylate (IV) and the bromo-derivative (V) with potassium hydroxide in tetradeuteriomethanol are shown in Figs. 1 and 2, respectively.

The relative rates given as the time in which 1/n conversion has taken place according to the NMR-spectra are presented in Tables 2 – 4.

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