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Stereoelectronic Control in Ring Opening of Bridge-head Nitrogen Containing Fused Azolium Salts[1]

András Messmer*, György Hajós, and Géza Tímári
Central Research Institute for Chemistry, POB 17, H-1525, Budapest, Hungary

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Abstract: Reaction of tetrazolopyridinium salts **1** with nucleophiles proceeds through the neutral intermediate **2**. Ring opening of this leads to hetarylbutadienes (**3, 4, 5**) of different geometries. Experimental support has been provided for the theoretical supposition that **2** before opening up can undergo nitrogen inversion and the two invertomers of this intermediate (**2A** and **2B**) react via the two possible senses of disrotation, one of them (**2A**) under stereoelectronic control. By this mechanism unexpected stereoselectivities are explained and the degree of selectivity can be predicted.

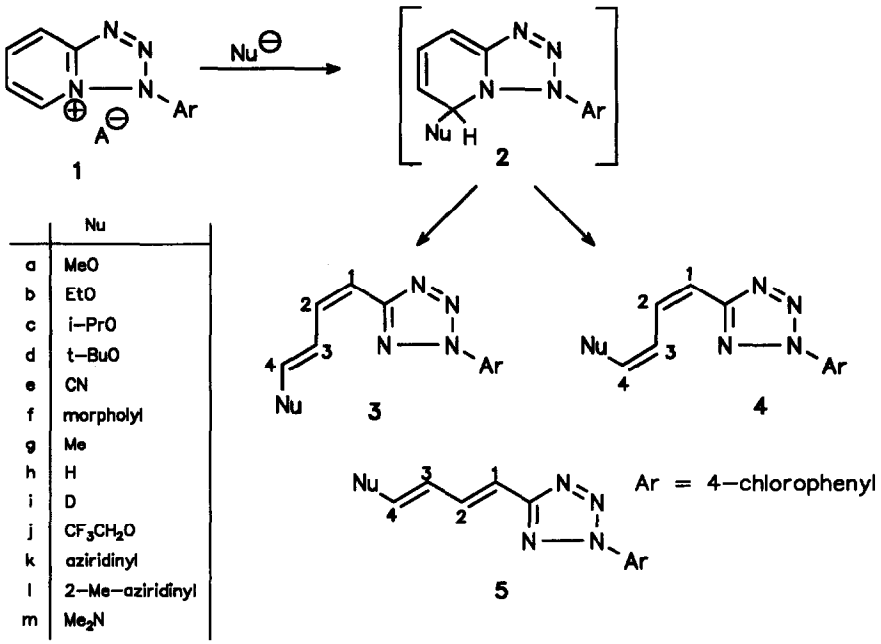
INTRODUCTION

In the course of our earlier investigations with bridge-head nitrogen containing fused azolium salts we found[2,11] that these systems (e.g. tetrazolopyridinium salt **1**) when reacted with nucleophiles easily undergo ring opening and afford azolyldiene derivatives (e.g. **3, 4**, and/or **5**). We also reported[2] that in those cases where different alcoholates were used as reagents, the double bond 1 (i.e.C1-C2 bond) attached to the heterocycle of the diene product retained its original cis geometry and the reactions afforded both 1-cis-3-trans (**3**) and cis-cis (i.e. all-cis) dieneethers (**4**). These products (**3** and **4**) proved to be stable and no change of their geometries was detected even under more forced conditions (e.g., in refluxing acetonitrile or in the presence of strong acid). We reported furthermore that, in contrast to the conversions with alcoholates, sodium salts of secondary amines (generated from the appropriate amine and sodium hydride) gave exclusively 1-cis-3-trans-dieneamines[3] (e.g. **3f**); however, in the presence of trace of acid, a facile isomerization occurred to give all-trans dieneamines **5**. The same all-trans compounds (**5**) were obtained directly from **1** with secondary amines themselves (protic conditions).

Because of these earlier results, according to which certain nucleophiles (e.g. alcoholates) afforded 1-cis-3-trans (**3**) or mixtures of 1-cis-3-trans (**3**) and 1-cis-3-cis (**4**) compounds, we decided now to clarify the chemical reason for formation of the different geometries. In order to do this, determination of the exact ratios of the isomers formed seemed necessary which could be appropriately accomplished by analysis of the crude reaction products by ^{1}H-NMR spectroscopy.

RESULTS AND DISCUSSION

Table 1. lists both the earlier published ratios of isomers **3** and **4** as obtained after preparation[2] and those detected now by ^{1}H-NMR in the crude reaction mixtures. These latter data, which are independent from the isolation technique and show therefore the real ratios as formed in the reactions, also support the previously recognized clear trend[2] that with increasing size of the reagent the proportion of the all-cis isomer (**4**) decreases. Since these reactions are regarded to proceed through a retroelectrocyclic ring opening of the neutral intermediate **2** the preference for formation of the trans geometry at double bond 3 (**3**) with large size Nu substituents can obviously be due to a steric hindrance. Table 1, furthermore, also revealed that with the smallest nucleophiles (MeO and CN) unexpectedly the all-cis products (**4a** and **4e**, respectively) became predominant.



	Nu
a	MeO
b	EtO
c	i–PrO
d	t–BuO
e	CN
f	morpholyl
g	Me
h	H
i	D
j	CF_3CH_2O
k	aziridinyl
l	2–Me–aziridinyl
m	Me_2N

These two cases where the ratio of the all-cis products (**4a, 4e**) was found significantly higher than 50% (in these cases 62 and 92%, respectively,) called our attention and prompted us to reinvestigate thoroughly the above arguments concerning formation of dienes of 3-trans and 3-cis geometry. The observed stereoselectivity can not be simply interpreted by the steric hindrance because in these cases the all-cis isomers (**4a** and **4e**) are definitely preferred. This suggests that besides the steric effect another factor might also control, however in the opposite direction, the formation of the different geometries of the products.

Table 1. Comparison of yields of preparations of **3** and **4** with the ratios of these compounds in the crude products.

Nu	product	yields of preparation		ratio in the crude product	
		cis,trans	cis,cis	cis,trans	cis,cis
MeO	**3a, 4a**	12	38	38	62
EtO	**3b, 4b**	12	34	60	40
i-PrO	**3c, 4c**	75	5	95	5
t-BuO	**3d, 4d**	79	-	100	-
CN	**3e, 4e**	15	67	8	92
morpholyl	**3f, 4f**	69	-	100	-

Analysis of ratios of geometrical isomers **3** and **4** allows the following conclusions to be drawn. As shown in Fig. 1, the proposed intermediate **2A** having an axial Nu group can, before opening, undergo nitrogen inversion to give **2B**, where the introduced group Nu is now in the pseudo equatorial position.

It is known from the literature[4] that the energy barrier for such inversions is low enough to allow an equilibrium between **2A** and **2B** at room temperature.

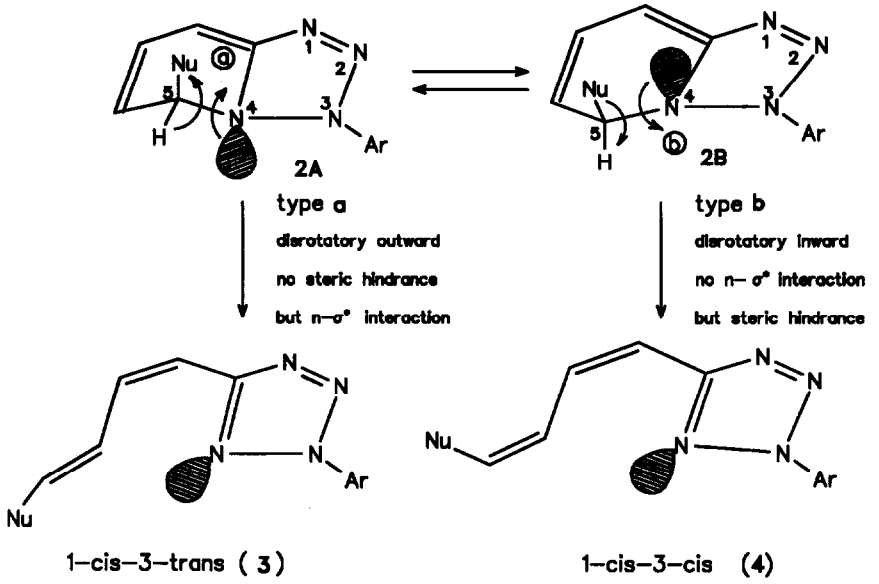


Fig. 1. Retroelectrocyclic ring openings of the two invertomers **2A** and **2B**.

Both invertomers (**2A** and **2B**) can undergo ring openings, however, in different senses of disrotation possibilities[5], since the lone pair of the bridge-head nitrogen can turn only inward with respect to the bond-breaking because it should get into the plane of the five membered ring. This implies that **2A** can be opened only via route a leading to the 1-cis-3-trans compound **3**, whereas **2B** via the opposite sense (route b) affording the all-cis diene **4**.

Since the position of group Nu in **2A** is antiperiplanar related to the lone pair of the bridge-head-nitrogen, the σ^* orbital of the C-Nu bond can form a secondary overlap with the nitrogen lone pair. Thus, the bond order of N-C(5) will be relatively high and species **2A** will become less reactive than **2B** with respect to cleavage of this bond. As known from the literature[6], n-σ^*interaction (i.e. stereoelectronic effect) can be expected mainly with substituents of enhanced electronegativity. In other words, *Nu in 2A turns outward without steric hindrance but at the expense of the stereoelectronic stabilization, whereas Nu in 2B turns inward which motion is sterically hindered but indifferent for the n-σ^* interaction.*

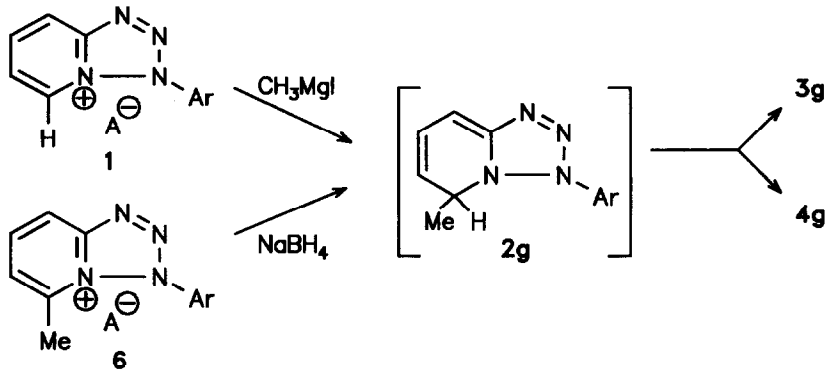
This hypothesis seems to be in accordance with the experimental results discussed above: formation of the all-cis products were observed with the electronegative methoxide and cyano groups, which are, in turn, also small enough to allow the sterically less favoured inward-turning of the Nu substituent. This mechanistic consideration implies, however, three assumptions which need to be checked thoroughly:

[a] pseudobase **2** is an existing intermediate in these reactions

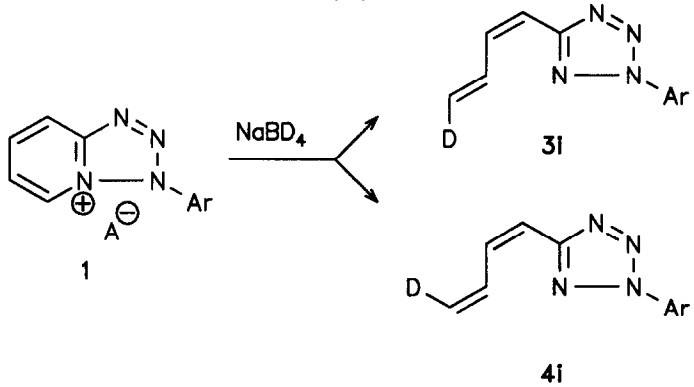
[b] with small and non-electronwithdrawing groups no preference exists either for 3-cis or 3-trans product.

[c] with two nucleophiles of equal steric demand but of different electronegativity, formation of the all-cis compound **4** is preferred in the more electronegative case.

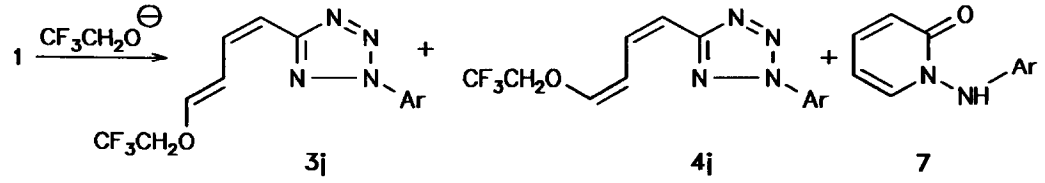
The existence of intermediate **2** (i.e. the fact that assumption [a] is correct) seems to be supported by the following finding. Tetrazolium salt **6** containing Me group in position 5 reacts with sodium boro-



hydride in a similar manner as found earlier for the unsubstituted case **1** (formation of **3h**)[10] and yields,consequently, 4-methyl substituted diene compounds **3g** and **4g**. Analysis of the NMR spectrum of this crude product showed a slight excess of the 1-cis-3-trans isomer **3g** related to the all-cis one **4g** (53:47). We found, however, that the same diene products can also be obtained by reacting the unsubstituted tetrazolium salt **1** with methyl magnesium iodide. On the basis of ^{1}H-NMR spectra, this reaction mixture proved to have exactly the same isomeric composition as above which is obviously accounted for formation of the same intermediate (**2g**).



In order to prove the second, [b] assumption we reacted tetrazolium compound **1** with sodium borodeuteride and determined the position of the introduced deuterium atom. 1H-NMR spectrum of the product showed that a mixture consisting of **3i** and **4i** in a ratio of exactly 1:1 was obtained. This result gave a direct evidence for the fact that the chances of the two senses of disrotation - with Nu's having a size and electronegativity similar to the hydrogen - are equal.



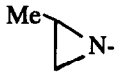
As a suitable reagent for verification of assumption [c], trifluoroethoxide anion was chosen and was compared with the reaction with ethoxide anion. As known, the size of the fluoro atom does not exceed essentially that of the hydrogen atom, nevertheless, its electronegativity differs significantly.

Reaction of **1** with sodium trifluoroethoxide was carried out under the same reaction conditions as with sodium ethoxide and the reaction mixtures were worked up analogously. Like with the ethoxide case[2], a certain amount of nitrogen-elimination[8] product: N-anilinopiridin-2(1H)-one (**7**) was also obtained. Analysis of the residue of the products showed that, compared to the ethoxide reaction, the cis-trans: all-cis ratio changed dramatically (from 60:40 to 20:80),i.e. with the trifluoro reagent the all-cis dieneether **4j** became the main product (table 2). This finding fits nicely to our prediction.

If this proposed mechanism is correct, it should also work with other different nucleophiles fulfilling the above mentioned requirements necessary for producing all-cis dienes: appropriately high electronegativity and small size of the Nu group. In the series of N-nucleophiles where only cis-trans and all-trans dienes (**3** and **5**, respectively) have been obtained up to now, formation of a full cis product (**4**, Nu = substituted amino group), however, would also be principally possible.

For this purpose three small N-nucleophiles: aziridine, 2-methylaziridine, and dimethylamine were now reacted with tetrazolium salt **1**. As table 2. shows, the results of each reaction are well supporting our theorem. With aziridine, a definite predominance (80%) of the all-cis product **4k** was observed whereas reaction with the sterically more crowded 2-methylaziridine afforded an opposite ratio of the isomers and, thus, the 1-cis-3-trans product **3l** was mainly formed (in 90%). Similar result was obtained with dimethylamine which also furnished the cis-trans isomer **3m** as main product (74%).

Table 2. Comparison of isomeric composition of ethyl and trifluoroethyl diene ethers (**3b**, **4b**, and **3j**, **4j**, respectively) and aziridinyl, 2-methylaziridinyl, and dimethyl dieneamines (**3k**, **4k**, **3l**, **4l**, and **3m**, **4m**, respectively)

Nu-	products		ratios of the crude products (3)	(4)
CF_3CH_2O-	**3j**	**4j**	20	80
CH_3CH_2O-	**3b**	**4b**	60	40
	**3k**	**4k**	20	80
	**3l**	**4l**	90	10
$(CH_3)_2N$-	**3m**	**4m**	74	26

The reaction with aziridine showed, furthermore, the particular feature that in spite of the related cases where generation of the sodium salt of the appropriate amine under water-free conditions was necessary to avoid the rapid isomerization to the more stable full trans compound **5** and hence to allow the detection of cis dienes **3** or **4**, the simple acetonitrile solution of aziridine led here to **3** and **4**, no full-trans isomer **5** was formed. This interesting exception is probably due to the fact that the lone pair of the aziridine - because of its rigid geometry - can not simply contribute to delocalization that would be necessary for such isomerizations[9].

The authors believe that these experimental results convincingly support the proposed mechanism implying the steric vs. stereoelectronic control of the two different senses of disrotatory ring opening in the course of the reactions of tetrazolopyridinium salt **1** with nucleophiles. In this context we wish to note that theoretical predictions and experimental support for selectivities in conrotatory ring openings of 3-substituted cyclobutene have been provided by Houk et al.[13]. Houk's thorough theorem and experimental findings reveal, interestingly, that the methoxy and cyano groups undergo an outward motion

in the *conrotation*. Our results, in turn, support that the same two groups of the cyclic intermediate with bridge-head nitrogen (**2**) turn preferably inward in a *disrotation* process, which contradiction is probably due to the marked differences in structures of the two types of model systems.

The study on reactivity of the hetaryldienes of various geometry (i.e. all-cis, cis-trans and all-trans) - a group of compounds found to be excellent synthons for numerous cycloaddition reactions[7,12] - is in progress.

EXPERIMENTAL

Melting points were measured on a Büchi apparatus and are not corrected. The IR spectra were recorded with a Nicolet 205 FT apparatus. The NMR spectra were registered on a Varian XL-400 equipment. TMS was used as internal standard.

General procedure for preparation of dieneethers 3a-d,j and 4a-d,j.

To a solution of 3-p-chlorophenyltetrazolo[1,5-a]pyridinium fluoroborate[8] (**1**, Ar=p-Cl-C_6H_4, A=BF_4; 0.95 g; 3 mmol) in acetonitrile (25 ml) at -40°C was added a solution of the reagent (15 mmol; prepared from the appropriate alcohol with an equivalent amount of sodium hydride in dry acetonitrile) and the mixture was stirred at this temperature for 4-5 hours. The reaction mixture was then poured onto ice and the precipitate was filtered. Characteristics of the products are shown in Table 3.

Reaction of tetrazolium salt 1 with sodium borodeuteride.

To a solution of 0.5 g (15.5 mmol) 3-p-chlorophenyltetrazolo[1,5-a] pyridinium bromide (**1**, Ar=p-Cl-C_6H_4, A=Br) in a mixture of acetonitrile (15 ml) and water (10 ml), sodium borodeuteride (0.25 g, 62 mmol) was added in portions with stirring at room temperature. The starting solution became turbid in 10 or 15 minutes, and then crystals formed. The product was separated by filtration and was then recrystallized from ethanol to give 4-deuterio-[2-(4-chlorophenyl) tetrazolyl]butadiene (0.23 g, 65%; a mixture of **3i** and **4i**).

Reaction of tetrazolium salt 1 with methyl magnesium iodide.

To a suspension of tetrazolium salt **1** (Ar=p-Cl-C_6H_4, A=BF_4; 0.5 g; 1.6 mmol) in abs. dichloromethane (20 ml), ethereal methyl magnesium iodide solution (1N, 5 ml) was added at 0°C, and the mixture was stirred at this temperature. The inorganic precipitate was filtered off and the solvent was evaporated. The yellow semi-solid residue was triturated with cold acetonitrile, and the resulting colourless crystals (0.21 g, 56%; TLC: Rf = 0.7 on silica with diethyl ether - petroleum ether 1:4 eluent) were collected and investigated by NMR. Physical data (^{1}H-NMR, mp) of this product proved to be identical with those obtained from **6** using sodium borohydride as described earlier[10].

Reaction of tetrazolium salt 1 with sodium trifluoroethylate.

To a solution of **1** (Ar=p-Cl-C_6H_4, A=BF_4; 5.0 mmol) in abs. acetonitrile (10 ml) at -40°C was added a solution of sodium trifluoroethoxide (20 mmol) in abs. tetrahydrofuran (20 ml) and the mixture was stirred at this temperature for 5 hours. During the reaction gas evolution was observed and the starting colourless solution became deep red. The reaction mixture was then evaporated and the residue was dissolved in water (30 ml) and extracted with dichloromethane (3x10 ml). After evaporation of the solvent the solid residue was crystallized from ethanol to give 0.27 g (26%) of N-(4-chlorophenyl amino)-pyridin- 2(1H)-one (**7**); mp. 203-204°C[8]. The mother liquor was evaporated and the residue was treated with petroleum ether to give 0.31 g (21%) of a mixture of dieneethers (**3j** and **4j**). Elution on preparative silica layer by a mixture of acetone petroleum ether (1:5) afforded pure 1-cis-3-cis-trifluoroethyltetrazolyldiene ether **4j**; mp.: 120-121°C. Anal. Calcd. for $C_{13}H_{10}ClF_3N_4O$ (314.5): C, 47.19; H, 3.02; N, 16.92. Found: C, 47.15; H, 3.20; N, 16.75.

Table 3. ^{1}H-NMR chemical shifts and coupling constants of tetrazolyldiene products **3** and **4**

No	mp (°C)	H-1	H-2	H-3	H-4	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
			δ ppm				Hz	
3a	96-97	6.20	6.61	6.91	7.13	11.5	11.0	11.5
4a	163-164	6.29	6.55	7.02	6.46	11.2	10.5	6.0
3b	53-54	6.21	6.48	7.30	6.91	11.3	10.5	11.8
4b	66-67	6.21	6.58	7.05	6.76	11.2	10.6	6.0
3c	76-77	6.21	6.49	6.84	6.44	11.2	10.8	10.8
4c	83-84	6.18	6.52	6.94	6.81	11.4	10.5	6.0
3d	105-106	6.18	6.39	7.78	6.82	10.8	11.1	11.6
4d	-	-	-	-	-	-	-	-
3e	140-142	6.54	6.42	8.11	4.92	11.9	11.2	15.8
4e	158-160	6.40	6.78	8.08	4.75	11.6	10.9	11.2
3f	93-94	6.22	6.81	7.27	6.65	10.1	10.8	12.9
4f	-	-	-	-	-	-	-	-
3g	-	6.35	6.58	7.46	6.11	11.6	11.8	16.5
4g	-	6.52	6.76	7.41	5.95	11.6	11.8	10.7
3j	-	6.86	7.17	6.49	6.35	12.5	11.5	11.5
4j	120-121	6.41	7.05	6.71	6.25	11.5	13.0	6.0
3k	79-81*	6.23	6.55	7.19	6.73	11.5	11.5	13.5
4k		6.41	7.20	6.85	6.18	11.5	12.5	8.0
3l	100-103*	6.23	6.54	7.12	6.75	11.2	11.5	14.3
4l	-	6.40	7.11	6.84	6.27	11.5	12.5	8.2
3m	-	6.24	6.67	7.23	6.71	11.1	11.8	12.8
4m	-	6.38	7.15	6.91	6.23	11.3	13.1	9.4

*M.p. of the obtained mixture; efforts to separate the pairs **3k, 4k**, as well as **3l, 4l** were unsuccessful.

Reaction of tetrazolium salt 1 with dimethylamine.

To a solution of tetrazolium salt **1** (Ar=p-Cl-C_6H_4, A=BF_4; 30 mg; 0.1 mmol) in hexadeuteriodimethyl sulfoxide (0.5 ml) excess of dimethylamine solution in the same solvent was added at 20°C in an NMR tube and the spectra of the solution was immediately recorded. This spectrum showed the

presence of a mixture of **3m** and **4m** (Table 3.). Either on prolonged standing at room temperature or treatment of the solution with water resulted in isomerization to the all trans diene **5m**[8]. Also **5m** was obtained when the reaction was performed in acetonitrile.

Reaction of tetrazolium salt 1 with aziridine

A solution of **1** (Ar=p-Cl-C_6H_4, A=BF_4; 1.5 g, 5 mmol) in acetonitrile (15 ml) was treated with aziridine (50 mmol) with stirring at 0°C. The mixture was allowed to stand overnight at this temperature and was then poured onto ice-water. The resulting precipitate was filtered off and dried to give 1.1 g (82%) of product (a mixture of **3k** and **4k**) as yellow crystals. Anal. Calcd. for $C_{13}H_{12}ClN_5$ (273.68): C, 57.03; H, 4.42; N, 25.59. Found: C, 57.01; H, 4.59; N, 25.68.

Reaction of tetrazolium salt 1 with 2-methylaziridine

A mixture of a solution of **1** (Ar=p-Cl-C_6H_4, A=BF_4; 1.5 g, 5 mmol) in acetonitrile (15 ml) and potassium carbonate (1 g) was treated with 90% 2-methylaziridine (Aldrich product, 3.0 g; 50 mmole) was stirred at room temperature for 5 hours. The yellow solution was poured onto ice-water and the resulting precipitate was filtered off and dried to give 0.9 g (63%) of crude product: a mixture of **3l** and **4l**. Anal. Calcd. for $C_{14}H_{14}ClN_5$ (287.68): C, 58.45; H, 4.90; N, 24.33. Found: C, 58.37; H, 4.93; N, 24.28.

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