Ambident Reactivity of a Thiazolo[3,2-*a*]pyridinium Salt With Nucleophiles [1]

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Reaction of thiazolo[3,2-*a*]pyridinium salt **1** with secondary amines, depending on the reaction condition, may result in both stable pseudo bases **2** as addition products and thiazolyl-dieneamines **4** as products of ring opening. The ambident reactivity of the title system is interpreted by frontier orbital theory.

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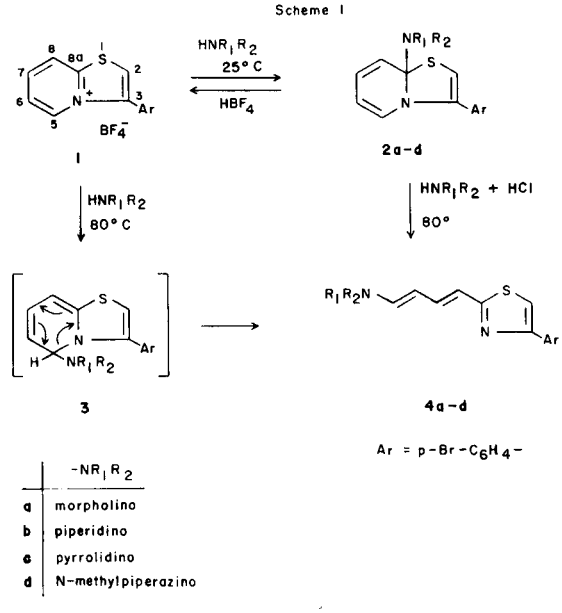
Up to now, only few examples of reactions of fused heteroaromatic azolium salts with nucleophiles has been described in the literature [2]. Recently we found [3,4,5,6] that tetrazolopyridinium salts, when reacted with different nucleophiles, undergo ring opening process leading to *inter alia* heteroaryl substituted diene derivatives under mild conditions.

This observation prompted us to investigate the nucleophilic reactivity of the thiazolo[3,2-*a*]pyridinium system. Because of the reduced number of hetero atoms compared to the tetrazolopyridinium system, a decreased reactivity was anticipated. As far as we know, nucleophilic reactions of only monocyclic thiazolium salts [7], partially reduced fused thiazolium systems [8] and few polyfused thiazolium compounds [9,10] have been published.

We found that, depending on the reaction conditions, the title system showed ambident behaviour and two different products could be isolated. Thus, reaction of 3-*p*-bromophenylthiazolo[3,2-*a*]pyridinium fluoroborate (**1**) with morpholine at room temperature afforded yellow crystals from which the starting quaternary salt **1** could be recovered by treatment with acid.

Scheme I



All spectroscopic data (ir and nmr) of the product were in agreement with a structure containing a morpholino group attached to the uncharged thiazolo[3,2-*a*]pyridine

Table I

Characteristics of Pseudo Bases **2a-d** and Dieneamines **4a-d** Obtained From **1** by Secondary Amines

Compound	Mp (°C)	Yield (%)	Formula	Analysis %, Calcd./Found C	H	N
2a	59-61	80	$C_{17}H_{17}BrN_2OS$	54.11	4.54	7.42
				53.95	4.68	7.25
2b	75-77	73	$C_{18}H_{19}BrN_2S$	57.60	5.10	7.46
				57.72	5.28	7.81
2c	90-92	71	$C_{17}H_{17}BrN_2S$	56.51	4.74	7.75
				56.83	4.42	7.60
2d	109-111	82	$C_{18}H_{20}BrN_3S$	55.38	5.16	10.77
				55.42	5.22	10.73
4a	158-159	55	$C_{17}H_{17}BrN_2OS$	54.11	4.54	7.42
				54.02	4.76	7.33
4b	126-128	52	$C_{18}H_{19}BrN_2S$	57.60	5.10	7.46
				57.42	4.83	7.12
4c	113-115	56	$C_{17}H_{17}BrN_2S$	56.51	4.74	7.75
				56.72	4.34	7.57
4d	129-131	54	$C_{18}H_{20}BrN_3S$	55.38	5.16	10.77
				55.62	5.41	10.50

ring **2a**. The position of the morpholino substituent in this pseudo base type product **2a** (three alternatives: 5-, 7- and 8a-substituted derivatives would be possible) was proved by ^{13}C-nmr spectroscopy (quaternary carbon peak at 85 ppm, assigned to C-8a).

A different reactivity of thiazolium salt **1** was, however, observed when it was reacted with morpholine in acetonitrile under reflux conditions. The pmr spectrum of the new yellow crystalline product showed that the pyridine ring had been opened to give 1-morpholino-4-(4'-bromophenylthiazolyl-2) dieneamine (**4a**). The possible route to **4** is an attack on C-5 resulting in intermediate **3** and a subsequent electrocyclic opening of the pyridine moiety shown by the bent arrows. The fully *trans* structure of **4a** is supported by the coupling constants ($J_{1,2}$ = 15 Hz, $J_{3,4}$ = 13 Hz) [11] in its ^{1}H-nmr spectrum.

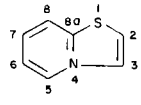
Compound **4** showed general behaviour of dieneamines. Thus, on reaction with *N*-phenylmaleinimide, **4a** resulted in a crystalline cycloadduct.

The ambident reactivity of **1** with morpholine could be generalized to several secondary amines. Thus, pseudo bases **2a-d** and dieneamines **4a-d** summarized in Table I were obtained in good yields.

For interpretation of the regiospecific behaviour of **1** with nucleophiles, the electronic distribution of cation **5** as model for compound **1** [12] was calculated by CNDO/2 method. According to frontier orbital theory [13] the attack on a cation like **1** by morpholine known as medium soft nucleophile [14,15] is expected to be governed by both the LUMO orbital of cation **1** and by the charge distribution [16]. Table II shows the calculated C_{LUMO} coefficients and the q net charges for all carbon atoms of model cation **5**.

Table II

Coefficients of the LUMO Orbital (C_{LUMO}) and Net Charges (q) Calculated for Carbon Atoms of the Model Cation **5** by the CNDO/2 Method



5

Atom	C_{LUMO}	q
C-2	0.29	+0.03
C-3	0.10	+0.04
C-5	0.41	+0.12
C-6	0.07	−0.01
C-7	0.51	+0.10
C-8	0.15	−0.02
C-8a	0.44	+0.16

Table II supports formation of C-8a substituted pseudo base **2** as C-8a has the highest positive charge and also a considerably high C_{LUMO} coefficient (kinetic control). Both values (C_{LUMO} and q) are, however, very similar for C-5, C-7 and C-8a, therefore at elevated temperatures nucleophilic attacks at all these carbon atoms are probable. The observed preference of attack at C-5 resulting in **3** may well be accounted for the structural pecularity of **3** allowing an easy retro-electrocyclization to yield the stable dieneamine **4** (thermodynamic control).

The supposition that formation of dieneamine **4** is due to thermodynamic control was convincingly proved experimentally as follows: the crystalline pseudo base **2** could be recovered from refluxing toluene even after a period of one hour. When **2**, however, was refluxed in acetonitrile in the presence of acid (allowing to establish the equilibrium between **2** and **1** and therefore formation of other pseudo bases, *e.g.* like **3**), the rather stable dieneamine **4** was isolated.

Our experimental results show that, in contrast to fused tetrazolium salts [3,4,5,6] reaction of thiazolo[3,2-*a*]pyridinium salt **1** with secondary amines can easily afford both pseudo base **2** and ring opened dieneamine **4**. This difference may be attributed to the smaller electronegativity of the sulfur atom as well as to the increased carbon-sulfur bond-length.

EXPERIMENTAL

The nmr spectra were obtained on Varian XL-100 equipment, the ir spectra on a Unicam SP-200 apparatus. Melting points are uncorrected. The CNDO/2 calculations [17] were carried out by IBM 3031 computer.

3-*p*-Bromophenylthiazolo[3,2-*a*]pyridinium Fluoroborate (**1**).

This compound was prepared according to the procedure of Bradsher *et al.* [18] described for the analogous perchlorate salt. The fluoroborate derivative was obtained from the reaction mixture by addition of 40 per cent fluoroboric acid, mp 216° (ethanol), yield 63%; ir (potassium bromide): 3050, 3000, 1620, 1540, 1190-1198 cm^{-1}.

Anal. Calcd. for $C_{13}H_9BBrF_4NS$ (378.03): C, 41.30; H, 2.40; N, 3.71; S, 8.48. Found: C, 41.22; H, 2.55; N, 3.48; S, 8.31.

3-*p*-Bromophenyl-4,8a-dihydro-8a-morpholinothiazolo[3,2-*a*]pyridine (**2a**).

A solution of 0.5 g (1.3 mmoles) of 3-*p*-bromophenylthiazolo[3,2-*a*]-pyridinium fluoroborate (**1**) in 5 ml of morpholine was stirred for 1.5 hours. Upon addition of water, a pale yellow precipitate was formed which was recrystallized from toluene to give 0.39 g (78%) of product, mp 160-162°; ir (potassium bromide): 3050, 2950, 2800, 1610, 1590 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.66 (AA'BB', *p*-bromophenyl), 7.31 (s, 1H, H thiazolyl), 6.60-6.34 (m, 3H, H_{5-7}), 6.10 (d, 1H, H_8).

Anal. Calcd. for $C_{17}H_{17}BrN_2OS$ (377.32): C, 54.11; H, 4.54; S, 8.50; Br, 21.18. Found: C, 53.95; H, 4.68; S, 8.25; Br, 20.80.

Derivatives **2b-d** were obtained by the same procedure, melting points, yields and analytical data are shown in Table I.

Compound **2b**.

This compound had ^{1}H-nmr (deuteriochloroform): δ 7.66 (AA'BB', *p*-bromophenyl), 7.22 (s, 1H, H thiazolyl), 6.64-6.28 (m, 3H, H_{5-7}), 6.02 (d, 1H, H_8), 3.18 (m, 6H, $-CH_2-$), 1.60 (m, 4H, $-CH_2-$).

Compound **2c**.

This compound had ^{1}H-nmr (deuteriochloroform): δ 7.66 (AA'BB', *p*-bromophenyl), 7.25 (s, 1H, H thiazolyl), 6.52-6.20 (m, 3H, H_{5-7}), 6.00 (d, 1H, H_8), 3.32 (m, 4H, $-CH_2-$), 1.94 (m, 4H, $-CH_2-$).

Compound **2d**.

This compound had ^{1}H-nmr (deuteriochloroform): δ 7.66 (AA'BB', *p*-bromophenyl), 7.25 (s, 1H, H thiazolyl), 6.60-6.25 (m, 3H, H_{5-7}), 6.04 (d, 1H, H_8), 3.23 (m, 4H, $-CH_2-$), 2.43 (m, 4H, $-CH_2-$), 2.28 (s, 3H, CH_3).

1-(*p*-Bromophenylthiazolyl-2)-4-morpholinobutadiene (**4a**).

A mixture of 0.5 g (1.3 mmoles) 3-*p*-bromophenylthiazolo[3,2-*a*]pyridinium fluoroborate (**1**), 1 ml of morpholine and 8 ml of acetonitrile was refluxed for 40 minutes. The yellow solution was poured onto ice whereas an oil separated which slowly crystallized. In one hour it was filtered, dried and recrystallized from ethyl acetate to give 0.28 g (56%) of product, mp 158-159°; ir (potassium bromide): 3050, 2950, 1620 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.68 (m, AA'BB', *p*-bromophenyl), 7.20 (s, 1H, H thiazolyl), 7.11 (q, 1H, H_2), 6.45 (d, 2H, H_1), 5.37 (q, 1H, H_3), J_{12} = 15 Hz, J_{23} = 11 Hz, J_{34} = 13 Hz.

Anal. Calcd. for $C_{17}H_{17}BrN_2OS$ (377.32): C, 54.11; H, 4.54; S, 8.50; N, 7.42; Br, 21.18. Found: C, 54.02; H, 4.76; S, 8.68; N, 7.33; Br, 20.90.

Dieneamines **4b-d** were obtained by the same procedure, see data in Table I.

Compound **4b**.

This compound had ^{1}H-nmr (deuteriochloroform): δ 7.63 (AA'BB', *p*-bromophenyl), 7.13 (s, 1H, H thiazolyl), 7.11 (q, 1H, H_2), 6.48 (d, 1H, H_4), 6.35 (q, 1H, H_1), 5.28 (q, 1H, H_3), J_{12} = 15 Hz, J_{23} = 10.5 Hz, J_{34} = 13 Hz.

Compound **4c**.

This compound had ^{1}H-nmr (deuteriochloroform): δ 7.66 (AA'BB', *p*-bromophenyl), 7.11 (s, 1H, H thiazolyl), 7.12 (q, 1H, H_2), 6.79 (d, 1H, H_4), 6.36 (d, 1H, H_1), 5.12 (q, 1H, H_3), J_{12} = 15 Hz, J_{23} = 11 Hz, J_{34} = 13 Hz.

Compound **4d**.

This compound had ^{1}H-nmr (deuteriochloroform): δ 7.62 (AA'BB', *p*-bromophenyl), 7.13 (s, 1H, H thiazolyl), 7.08 (q, 1H, H_2), 6.42 (d, 1H, H_4), 6.36 (d, 1H, H_1), 5.12 (q, 1H, H_3), J_{12} = 15 Hz, J_{23} = 11 Hz, J_{34} = 13 Hz.

Dieneamine **4a**, when refluxed with *N*-phenylmaleinimide in acetonitrile solution for one hour gave cycloadduct in 64% yield, mp 160-162°.

Anal. Calcd. for $C_{27}H_{24}BrN_3O_3S$ (550.50): C, 58.91; H, 4.39; N, 7.67. Found: C, 58.60; H, 4.52; N, 7.38.

Reaction of **2a** With Morpholine in the Presence of Acid.

A mixture of pseudo base **2a** (100 mg, 0.26 mmole), 3 ml of morpholine and 0.5 ml of concentrated hydrochloric acid was refluxed for two hours. The reaction mixture was worked up as with compound **4a**. The product, 68 mg, 68%, proved to be fully identical (tlc, mp, ir spectrum) with the authentic sample of dieneamine **4a**.

Acknowledgement.

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[12] In model cation **5**, the *p*-bromophenyl group in **1** was replaced by hydrogen to achieve an essential simplification of the calculation. The geometry of **1** has recently been established by X-ray: L. Párkányi, K. Sasvári, Gy. Hajós, H. Hess and W. Schwartz, *Acta Cryst.*, **B 36**, 1229 (1980).

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