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Vicarious nucleophilic substitution reactions in azolopyridazines controlled by methyl substituents

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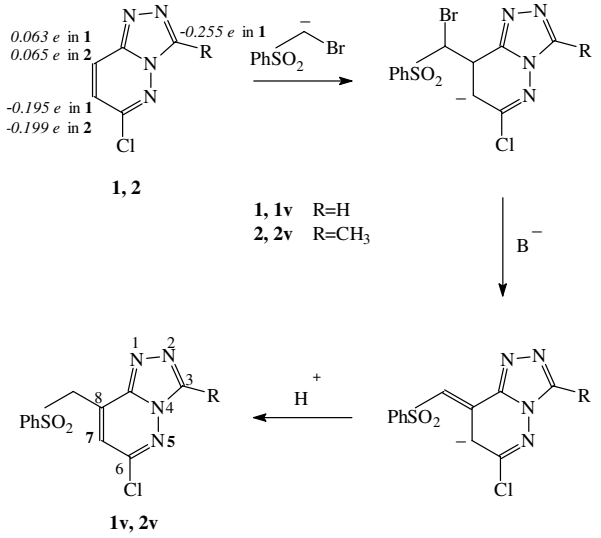
Abstract—Azolopyridazines, when treated with bromomethyl phenylsulfone in DMSO–*t*-BuOK at room temperature, yield mainly typical VNS reaction products, while 7-methylazolopyridazines under the same conditions undergo annulation with simultaneous conventional *ipso* nucleophilic substitution of the chlorine at C6. Consequently, methyl substitution offers a convenient means of controlling the course of VNS carbanion substitution. These competitive reactions illustrate the role of charge distribution and steric hindrance for the course of the nucleophilic substitution, and the methylated azolopyridazines appear to be convenient substrates for highly efficient propose annulation in fused azolopyridazine systems.

Azolopyridazines are applied mainly as pharmaceutical agents with hypotensive,[1] anticonvulsant,[2] and anxiolytic[3] activities. Due to the presence of four or five nitrogen atoms, azolopyridazines are electron-deficient and highly reactive in nucleophilic substitution (S_N).[4] Vicarious nucleophilic substitution (VNS) of hydrogen[5]—a convenient method for introducing carbon[6] and amine[7] substituents to nitroarenes or heteroaromatics, and a method for synthesising heterocyclic systems[8]—is a specific type of S_N.

The purpose of this study was to examine the VNS reactivity of azolopyridazines. We attempted the reaction between azolopyridazines and bromomethyl phenylsulfone,[9] which is a carbanion precursor under the typical reaction conditions.[10] In **1** there are three carbon atoms (C3, C7 and C8) prone to the nucleophilic attack, of which C3 is blocked by the methyl group in **2**. However, in the VNS reactions of compounds **1** and **2** only the hydrogen at C8 was substituted, giving products **1v** and **2v** in good yields (letter 'v' denotes the VNS product, Table 1). The reactions proceed according to the VNS mechanism via the σ-adduct and base-induced β-elimination (Scheme 1). In order to explain this substitution pattern, molecular orbital calculations have been carried out using the PM3 procedure, as implemented in the MOPAC program.[11] The calculations of charge distribution revealed negative magnitudes at C3 (−0.255 e) and C7 (−0.195 e) in compound **1** and at C7 (−0.199 e) in **2**, while positive charges are located at C8: 0.063 e in **1** and 0.065 e in **2**. Thus, exactly as expected, the substitution proceeds at the site with accumulated positive net-atomic charges.



Scheme 1.

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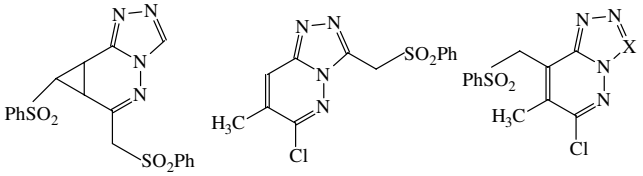
Surprisingly, the seemingly neutral modification of the molecular structures of **1** and **2** by methylation changes the course of these reactions. The C7-methylated compounds **3**–**5** react differently: instead of β-elimination, intramolecular nucleophilic substitution results in cyclopropane annulation. Such C7–C8 annulations in compounds **3a**–**5a** (letter 'a' denotes annulation product, Scheme 2), accompanied by the conventional *ipso* nucleophilic substitution of the chlorine atom at C6, proceed as the main processes in these reactions. The yields of products **3a**, **4a** and **5a** are quite high and exceed 70% (see Table 1). Moreover, an alternative reactivity has been observed for **1**, where it undergoes a competitive annulation reaction with a small yield of **1a** of about 3–4%. This trace VNS by-product (Scheme 3) has been successfully isolated and identified. The yields of the VNS and annulation reactions are compared in Table 1. Accordingly, the VNS and annulation reactions can be regarded as competitive with, nucleophilic substitution strongly controlled by the C7-methyl substituent. Only for the VNS reaction of **2** was no annulation product detected.

In order to explain the role of the C7-methylation the net-atomic charges in compounds **1**–**5** have been investigated. The electron-donating character of the methyl group increases the nucleophilic properties of C7 in the σ-adducts of compounds **3**–**5**, which in turn favour the intermolecular nucleophilic substitution. Although the annulation process is a text-book reaction, generally it is connected with aziridine-ring formation,[12] whereas to our knowledge there are no descriptions of highly efficient cyclopropane-ring annulation reactions.

Despite the similar charge distributions in **1** and **2** and in methylated analogues **3**–**5,** their VNS reactions proceed differently, thus charge distribution only has a minor role in the course of the VNS reaction. When C7 is substituted by a methyl group, typical VNS products are obtained with low yields of about 1–2% from **3** and **4** and 20% from **5** (Table 1 and Scheme 3). The PM3 calculations have indicated that the negative charges in **3**, **4** and **5** are accumulated at C7: in **3** −0.153 e, in **4** −0.157 e and in **5** −0.111 e, while positive charges are located at C8: 0.044 e in **3**, 0.047 e in **4** and 0.015 e in **5**. The C8 substituted products **4v** and **5v** were obtained from substrates **4** and **5**. However, despite the negative charge located at C3 in compound **3**, a C3 substituted product **3v** (Scheme 3) was formed only in trace amounts. Thus, the negatively charged C3 (−0.257 e) in **3** is unlikely to be attacked by a nucleophilic reagent, whereas a C8-substituted product should be obtained according to the charge distribution. The formation of the C3-substituted derivative of this substrate can be explained by easier access by the carbanion to the triazole carbon than to the pyridazine carbon.

Table 1. The reaction yields of the unmethylated (**1**,**2**) and C7-methylated (**3**–**5**) azolopyridazines in the VNS reactions (Schemes 1 and 2)

Substrate product (%)	**1**	**2**	**3**	**4**	**5**
Typical VNS	86	84	1–2	1–2	20
Annulation	3–4	0	82	79	70

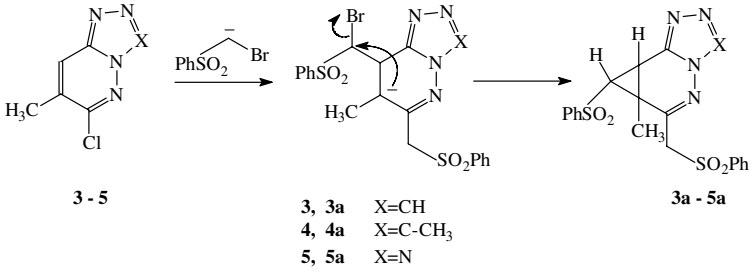


Scheme 3. Trace-yield products identified by ^{1}H NMR, ^{13}C NMR and MS and by elemental analyses.

All new compounds were identified by ^{1}H NMR, ^{13}C NMR and mass spectroscopy, elemental analyses and by X-ray diffraction.[13] The ^{1}H NMR spectra of annulation products **1a** and **3a**–**5a** show an interesting feature: the signal for the methylene protons at C6 forms separate doublets due to hindered rotation. When the methylene is located at C8 (compare **1v**, **2v,** **4v**, **5v**) or at C3 (**3v**), the signals for the methylene protons are represented by singlets. Analogous ^{1}H NMR peaks were also observed in the spectra of the VNS products of 9-nitroindole derivatives with chloromethyl sulfone.[14]

It can be concluded, that the VNS reaction pathway with carbanions can be controlled by the adjacent methyl substituent, which may lead either to VNS substitution or to annulation products. The change of reaction conditions does not alter the reaction course.[10]

General procedure: to a stirred solution of *t*-BuOK (6 mmol) in dry DMSO (5 ml), a solution of sulfone (2 mmol) and azolopyridazine (2 mmol) in dry DMSO



Scheme 2.

(10 ml) was added at room temperature.[10] The mixture was stirred for 1 h, poured into water containing glacial CH_3COOH, and extracted with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography with silica gel (acetone–hexane 3:2 or chloroform–acetone 15:1 as eluent).[15]

References and notes

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15. Compound **1v**: $C_{12}H_9ClN_4O_2S$ (308.74); mp 208 °C (EtOH); δ_H (300 MHz; DMSO): 5.17 (s, 2H), 7.28 (s, 1H), 7.56–7.82 (m, 5H), 9.67 (s, 1H); δ_C (75 MHz; DMSO): 55.17; 123.78; 128.16; 129.03; 129.24; 134.37; 137.59; 139.38; 141.97; 148.25; MS (*m*/*z*, %): 308.7 (M^+, 16), 77 (100). Compound **1a**: $C_{19}H_{16}N_4O_4S_2$ (428.49); mp 215–217 °C (EtOH); δ_H (300 MHz; $CDCl_3$): 2.18–2.51 (m, 1H), 3.43–3.48 (m, 1H), 3.68–3.72 (m, 1H), 4.20, 4.23 (d, $J = 13.5$, 1H), 4.33, 4.38 (d, $J = 13.5$, 1H), 7.47–7.99 (m, 10H), 8.26 (s, 1H); δ_C (75 MHz; $CDCl_3$): 24.23; 44.32; 60.27; 128.91; 129.46; 30.22; 135.12; 140.04; 141.61; 154.01; MS (*m*/*z*, %): 428.0 (M^+, 10), 77 (100). Compound **2v**: $C_{13}H_{11}ClN_4O_2S$ (322.77); mp 198–200 °C (EtOH); δ_H (300 MHz; DMSO): 2.65 (s, 3H), 5.15 (s, 2H), 7.21 (s, 1H), 7.57–7.84 (m, 5H); δ_C (75 MHz; DMSO): 9.75; 55.18; 122.37; 128.37; 128.73; 129.43; 134.67; 137.93; 142.50; 147.82; 148.94; MS (*m*/*z*, %): 322.0 (M^+, 13), 257.1 (100), 77 (73.9). Compound **3v**: $C_{13}H_{11}ClN_4O_2S$ (322.77); mp 168–169 °C (EtOH); δ_H (300 MHz; $CDCl_3$): 1.57 (s, 3H), 5.37 (s, 2H), 6.25 (s, 1H), 7.54–8.10 (m, 5H); δ_C (75 MHz; $CDCl_3$): 15.12; 56.01; 122.42; 128.20; 128.63; 129.38; 134.67; 137.64; 140.01; 147.80; 148.61; MS (*m*/*z*, %): 322.0 (M^+, 19), 77 (100). Compound **3a**: $C_{20}H_{18}N_4O_4S_2$ (442.50); mp 156–157 °C (EtOH); δ_H (300 MHz; $CDCl_3$): 2.87 (s, 3H), 3.04–3.05 (d, $J = 5.4$, 1H), 3.61, 3.62 (d, $J = 5.4$, 1H), 4.43, 4.48 (d, $J = 14.5$, 1H), 4.81, 4.76 (d, $J = 14.5$, 1H), 7.62–8.07 (m, 10H), 8.40 (s, 1H); δ_C (75 MHz; $CDCl_3$): 15.39; 24.34; 44.29; 60.26; 128.89; 129.37; 130.22; 135.08; 140.04; 141.61; 154.01; MS (*m*/*z*, %): 442 (M^+, 24), 77 (100). Compound **4v**: $C_{14}H_{13}ClN_4O_2S$ (336.80); mp 239–240 °C (EtOH); δ_H (300 MHz; $CDCl_3$): 1.99 (s, 3H), 2.37 (s, 3H), 5.64 (s, 2H), 7.35–7.98 (m, 5H); δ_C (75 MHz; $CDCl_3$): 9.71; 15.40; 60.26; 123.71; 128.30; 128.53; 129.40; 134.56; 137.61; 142.38; 146.31; 148.23; MS (*m*/*z*, %): 336.2 (M^+, 4.3), 77 (100). Compound **4a**: $C_{21}H_{20}N_4O_4S_2$ (456.54); mp 248–249 °C (EtOH); δ_H (300 MHz; $CDCl_3$): 2.01 (s, 3H), 2.25 (s, 3H), 2.37, 2.44 (d, $J = 5.5$, 1H), 3.67, 3.68 (d, $J = 5.5$, 1H), 4.27, 4.31 (d, $J = 13.7$, 1H), 4.47, 4.52 (d, $J = 13.7$, 1H), 7.58–8.03 (m, 10H); δ_C (75 MHz; $CDCl_3$): 9.46; 15.39; 25.07; 43.87; 60.04; 127.82; 128.23; 129.41; 134.38; 139.33; 140.08; 149.40; 151.69; MS (*m*/*z*, %): 456.2 (M^+, 17), 77 (100). Compound **5v**: $C_{12}H_{10}ClN_5O_2S$ (323.76); mp 249 °C, subl. 218–220 °C (EtOH); δ_H (300 MHz; DMSO): 2.33 (s, 3H), 5.41 (s, 2H), 7.53–7.82 (m, 5H); δ_C (75 MHz; DMSO): 15.38; 59.87; 122.38; 128.23; 128.51; 129.42; 134.61; 138.92; 141.89; 148.92; MS (*m*/*z*, %): 323.8 (M^+, 13), 77 (100). Compound **5a**: $C_{19}H_{17}N_5O_4S_2$ (443.41); mp 78–80 °C (EtOH); δ_H (300 MHz; $CDCl_3$): 2.08 (s, 3H), 2.57, 2.59 (d, $J = 5.2$, 1H), 3.84, 3.83 (d, $J = 5.2$, 1H), 4.33, 4.38 (d, $J = 13.7$, 1H), 4.56, 4.60 (d, $J = 13.7$, 1H), 7.56–7.91 (m, 10H); δ_C (75 MHz; $CDCl_3$): 15.15; 23.51; 42.77; 60.71; 128.13; 128.45; 129.80; 134.85; 138.67; 140.60; 156.08; MS (*m*/*z*, %): 443.0 (M^+, 21), 77 (100). All new compounds gave correct microanalytical data.