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Selective Alkylations of Tricyclic Pyrrolo- and Pyridazino-*as*-Triazines[1]. – A Novel Evidence of the Importance of the Lone-Pair Densities

Zsuzsanna Juhász-Riedl[a], György Hajós*[a], Eszter Gács-Baitz[a], Gert Kollenz[b] and András Messmer[a]

Central Research Institute for Chemistry[a],
P.O. Box 17, H-1525 Budapest, Hungary

Institute for Organic Chemistry, University of Graz[b],
Heinrichstraße 28a, A-8010 Graz, Austria

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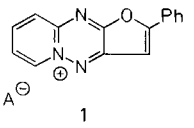
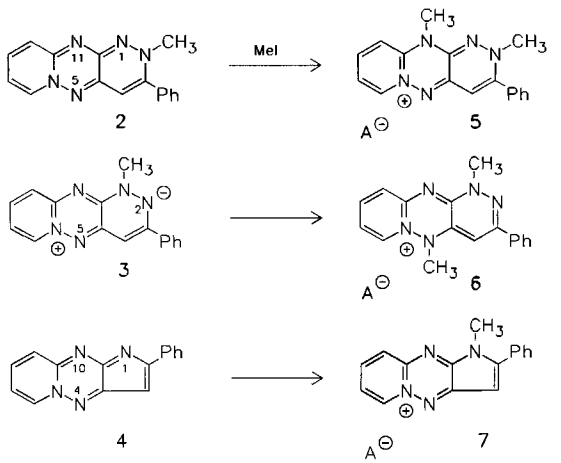
Methylation of **2**, **3**, and **4** obtained by ring transformations of **1** gives selectively **5**, **6**, and **7**, respectively. These regiospecific electrophilic attacks are interpreted by a modified application of the FMO theory involving consideration of the in-plane lone electron pairs of the ring nitrogens.

Recently, we have reported[2,3] that furo[2,3-*e*]pyrido[1,2-*b*]-*as*-triazinium salt **1** when treated with appropriate nucleophiles undergoes ring transformations resulting in the formation of new fused polyaza hetero rings.



1

We now describe the alkylation of three of these ring transformation products with methyl iodide. The three selected ring systems obtained by reaction of **1** with substituted hydrazines and ammonia represent three different electronic structures and are as follows: the deep blue 2-methyl-3-phenyl-2*H*-pyrido[1,2-*b*]pyridazino[3,4-*e*]-*as*-triazine (**2**) having a neutral quinonoide and antiaromatic (16-π) structure, the green 1-methyl-3-phenylpyrido[1,2-*b*]-pyridazino[3,4-*e*]-*as*-triazinium-2-ide (**3**) representing a zwitterionic and in part heteroaromatic structure, and the red 2-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*]-*as*-triazine (**4**) of an aromatic (14-π) system containing a bridgehead nitrogen. In all of these polycycles there are more (two or three) nitrogen atoms which may undergo alkylation[4].



2 **5** **3** **6** **4** **7**

We have found that all the three compounds react smoothly with methyl iodide under the same reaction conditions and every starting compound affords, interestingly enough, one product only in good yield (approximately 70%). Thus, **2** is methylated at N-11 to give the violet **5**. Compund **3** undergoes methylation at N-5 to furnish the red **6**, whereas methylation of **4** yields, also selectively, the deep yellow 1-methyl salt **7**. The visual observations of the color changes have been found to be accompanied by blue shifts in the UV.

The structures of the products have been verified by NMR spectroscopy using DNOE and INEPT long-range techniques. In the case of **5**, irradiation of the methyl protons at N-11 (δ = 3.01) results in an NOE of the 10-H proton. The structure is further corroborated by the INEPT long-range hetero correlation with the carbons C-10a and C-11a. The site of methylation in **6** is again deduced from the NOE difference experiment where irradiation of the N-5 methyl protons (δ = 3.45) produces NOE enhancements on 4-H and 7-H protons. Finally, the observed NOE on the *ortho* phenyl protons upon irradiation of the methyl protons has proved the N-1 location of the methyl substituent in **7**. The long-range connectivities observed between the methyl protons and C-2 and C-10a carbons in the INEPT long-range experiments in addition confirm the constitution of **7**.

The surprising findings that compounds **2**–**4** undergo alkylation in a regioselective manner and the targets of these electrophilic attacks have proved to be different in each case have raised the question of an interpretation of this selectivity.

In our recent study on other bridgehead nitrogen systems[5,6] we have found that the site of alkylation of poly-fused aza hetero aromatics can be correlated with the densities of the highest occupied in-plane orbitals (called n_{HOMO}) rather than the HOMO (of π-type) values or net charges. This approach is based on the high steric hindrance found experimentally in some cases[7] which suggests that the electrophilic attack at the heteroaromatic ring nitrogen occurs in the plane of the ring, from a direction where the so-called "lone pairs" are located. The HOMO electrons of π symmetry, in turn, have zero densities in this plane. The importance of the n_{HOMO}

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orbitals[5] in alkylations of heteroaromatics has also been discussed recently by a joint Israeli-Canadian work[8].

We have carried out an MO analysis for **2**, **3**, and **4**, by using the AM1[9] method, and calculated the c_{HOMO}, $c_{n\text{-}HOMO}$ (found to be the HOMO-2 in each case and differing from the HOMO's by 2.48, 2.38, and 1.59 eV, respectively) and q_{NET} values for those nitrogen atoms that can undergo alkylations. These data are listed in Table 1. Positions where the methylations have been found to take place are marked by asterisks.

Table 1. Electronic distribution of the highest occupied π (HOMO) and the highest *n* orbital of compounds **2**, **3**, and **4**

Standard geometry was assumed which was optimized on electronic energy. For simplification of these calculations, methyl groups were substituted by hydrogens. 200, 110, and 106 SCF iterations were carried out for **2**, **3**, and **4**, respectively.

		c^2_{HOMO}	$c^2_{n\text{-}HOMO}$	q_{NET}
2	N-1	0.11	0.13	−0.04
2	N-5	0.09	0.11	−0.08
2	N-11*	0.15	0.28	−0.20
3	N-2	0.12	0.05	−0.12
3	N-5*	0.27	0.24	−0.27
3	(N-11	0.11	0.24	−0.29)[24]
4	N-1*	0.22	0.25	−0.15
4	N-4	0.12	0.20	−0.13
4	N-10	0.04	0.11	−0.10

The data in Table 1 show that in the case of any compound one set of figures is superior to the others and thus N-11 in **2**, N-5 in **3**, and N-1 in **4** seem to be the preferred sites for an electrophilic attack. Although all three parameters calculated here show identical preference regarding the nucleophilicity of the various nitrogen atoms, the cases of compounds **2** and **3** indicate again the importance of the inclusion of both HOMO (π) and lone-pair densities in the FMO treatment: while the difference in HOMO values of **2** between atoms 1 and 11 is negligible, there is a significant difference between the $c^2_{n\text{-}HOMO}$ values of these two centers; similarly, the higher $c^2_{n\text{-}HOMO}$ value of N-5 compared to that of N-2 in **3** seems to support the higher nucleophilicity of N-5 more convincingly than the c^2_{HOMO} data. Interestingly, with the third model compound **4** the contribution of the n-HOMO's to the control of the reaction does not seem as significant as in cases of **2** and **3**; still these values are also in accordance with the experimental finding.

Furthermore, we would like to emphasize the site of alkylation (N-5) in **3**: a nitrogen atom adjacent to the bridgehead nitrogen. In the investigation of the methylation of different bridgehead nitrogen-containing systems we have generally found that the ring nitrogen adjacent to the bridgehead nitrogen is particularly unreactive toward electrophiles. To the best of our knowledge, no example has been described for an electrophilic attack on a nitrogen which is adjacent to a bridgehead nitrogen of a bicyclic 6 + 6 or 6 + 5 fused system[10]. In this respect the present finding with the tricyclic **3** can probably be interpreted by the conjugation of the negative charge formulated on N-2 in the pyridazine ring which strongly activates N-5.

To sum up, we can conclude that the present study obviously supports the importance of the lone pairs of ring nitrogen atoms for the orientation of the electrophilic reactions on polyfused azaheterocycles.

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Experimental

Melting points (uncorrected): Büchi apparatus. – IR: Nicolet 205 FT IR. – UV: HP 8452 A. – NMR: Varian XL-400; TMS as internal standard. ^{1}H assignments, if necessary, were performed with the aid of homonuclear spin decoupling experiments. Connectivities between identified protons and protonated carbons were obtained by two-dimensional (HETCOR) experiments. Assignment of quaternary carbon atoms was obtained by observing their correlations with identified protons (via long-range HETCOR and one- and two-dimensional INEPT long-range experiments).

General Procedure for Methylations of **2**, **3**, *and* **4**: A solution of the appropriate triazine compound (**2**, **3**, or **4**; 1 mmol) in absolute acetonitrile (2 ml) was heated at reflux with methyl iodide (4 ml) for 4 h. The precipitated crystals were removed by filtration and washed with ether to give the crude iodide salt. For analysis and identification, this product was converted into the tetrafluoroborate salt as follows: the suspension of the iodide salt in acetonitrile (3 ml) was mixed with 40% tetrafluoroboric acid (0.5 ml) and to the resulting solution ether (5 ml) was added. The obtained precipitate was filtered off to give the crude tetrafluoroborate salt which could be recrystallized from the appropriate solvent.

2,11-Dimethyl-3-phenylpyrido[1,2-b]pyridazino[3,4-e]-as-triazinium Tetrafluoroborate (**5**): The crude product obtained from the reaction of **2** was crystallized from acetonitrile: 0.29 g (77%) of red crystals; mp 236–241 °C. – IR (KBr): $\tilde{\nu}$ = 3065 cm^{-1}, 1630, 1560, 1480, 1470, 1455, 1380, 1340, 1330, 1170, 1150, 1055, 787, 760, 744. – UV (acetonitrile): λ_{max} (lg ε) = 222 nm (4.345), 238 (4.229), 288 (4.645), 330 (4.101), 358 (3.965), 376 (3.886), 516 (2.540). – ^{1}H NMR (CD_3CN): δ = 7.72 (m, 1H, 9-H, J_o = 8.6 and 7.5 Hz, J_m = 1.5 Hz), 7.55 (d, 1H, 7-H, J_o = 6.5 Hz, J_m = 1.5 Hz), 7.54 (m, 3H, 3′-, 4′-, 5′-H), 7.41 (m, 2H, 2′-, 6′-H), 6.95 (m, 1H, 8-H, J_o = 7.5 and 6.5 Hz, J_m = 1.5 Hz), 6.87 (d, 1H, 10-H, J_o = 8.6 Hz, J_m = 1.5 Hz), 5.32 (s, 1H, 4-H), 3.34 (s, 3H, 2-CH_3), 3.01 (s, 3H, 11-CH_3). – ^{13}C NMR (CD_3CN): δ = 157.49 (C-3), 150.99 (C-4a), 149.00 (C-10a), 144.23 (C-11a), 143.58 (C-9), 140.21 (C-7), 133.26 (C-1′), 131.69 (C-4′), 130.08 (C-3′, -5′), 128.88 (C-2′, -6′), 119.82 (C-8), 113.79 (C-10), 103.20 (C-4), 44.99 (2-CH_3), 30.57 (11-CH_3).

$C_{17}H_{16}N_5BF_4$ (377.2) Calcd. C 54.13 H 4.27 N 18.57
Found C 53.90 H 4.18 N 18.31

1,5-Dimethyl-3-phenylpyrido[1,2-b]pyridazino[3,4-e]-as-triazinium Tetrafluoroborate (**6**): The crude product derived from **3** was recrystallized from acetonitrile: 0.26 g (69%) of purple crystals; mp 241–242 °C. – IR (KBr): $\tilde{\nu}$ = 3110 cm^{-1}, 3070, 1630, 1550, 1510, 1500, 1350, 1270, 1250, 1040, 840, 780, 770, 690, 550, 530. – UV (acetonitrile): λ_{max} (lg ε) = 286 nm (4.658), 380 (4.036), 414 (3.847). – ^{1}H NMR (CD_3CN): δ = 7.83 (m, 2H, 2′-, 6′-H), 7.82 (m, 1H, 7-H), 7.66 (m, 1H, 9-H, J_o = 8.5 and 7.0 Hz, J_m = 1.5 Hz), 7.50 (m, 3H, 3′-, 4′-, 5′-H), 6.98 (m, 1H, 8-H, J_o = 7.0 and 7.0 Hz, J_m = 1.6 Hz), 6.85 (d, 1H, 10-H, J_o = 8.5 Hz, J_m = 1.5 Hz, J_p = 0.5 Hz), 6.5 (s, 1H, 4-H), 3.70 (s, 3H, 1-CH_3), 3.45 (s, 3H, 5-CH_3). – ^{13}C NMR (CD_3CN): δ = 154.68 (C-10a), 154.27 (C-3), 153.43 (C-11a), 143.63 (C-4a), 143.03 (C-9), 134.65 (C-2′), 133.70 (C-7), 131.80 (C-4′), 129.96 (C-3′, -5′), 127.10 (C-2′, -6′), 123.61 (C-10), 118.82 (C-8), 103.98 (C-4), 42.60 (1-CH_3), 42.40 (5-CH_3).

$C_{17}H_{16}N_5BF_4$ (377.2) Calcd. C 54.13 H 4.27 N 18.57
Found C 53.80 H 4.28 N 18.42

1-Methyl-2-phenylpyrrolo[2,3-e]pyrido[1,2-b]-as-triazinium Tetrafluoroborate (7): The crude product obtained from **3** was crystallized from ethanol: 0.23 g (66%) of yellow crystals; mp 222–224°C. – IR (KBr): $\tilde{\nu}$ = 3130 cm^{-1}, 3080, 1615, 1540, 1480, 1460, 1410, 1470, 1270, 1055, 1040, 767, 690. – UV (acetonitrile): λ_{max} (lg ε) = 248 nm (4.407), 306, (4.694), 422 (3.439). – ^{1}H NMR (CD_3CN): δ = 9.25 (d, 1H, 6-H, J_o = 7.0 Hz, J_m = 1.8 Hz, J_p = 0.8 Hz), 8.49 (m, 1H, 8-H, J_o = 8.6 and 7.0 Hz, J_m = 1.8 Hz), 8.41 (d, 1H, 9-H, J_o = 8.6 Hz, J_m = 1.6 Hz, J_p = 0.8 Hz), 8.01 (m, 1H, 7-H, J_o = 7.0 Hz, J_m = 1.8 Hz), 7.85 (m, 2H, 2′-, 6′-H), 7.71 (m, 3H, 3′-, 4′-, 5′-H), 7.20 (s, 1H, 3-H), 3.96 (s, 3H, 1-CH_3). – ^{13}C NMR (CD_3CN): δ = 163.66 (C-2), 146.17 (C-9a), 145.98 (C-3a), 145.45 (C-10a), 140.60 (C-8), 139.98 (C-6), 133.09 (C-4′), 130.63 (C-3′, -5′), 130.45 (C-2′, -6′), 129.34 (C-1′), 127.92 (C-9), 123.36 (C-7), 99.20 (C-3), 31.78 (1-CH_3).

$C_{16}H_{13}N_4BF_4$ (348.3) Calcd. C 55.20 H 3.76 N 16.09
Found C 55.01 H 3.83 N 15.96

CAS Registry Numbers

2: 126134-49-4 / **3**: 126134-46-1 / **4**: 121232-69-7 / **5**: 133497-24-2 / **6**: 133522-86-8 / **7**: 133522-88-0

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