First example of cine-substitution for halogens in azolopyrimidines

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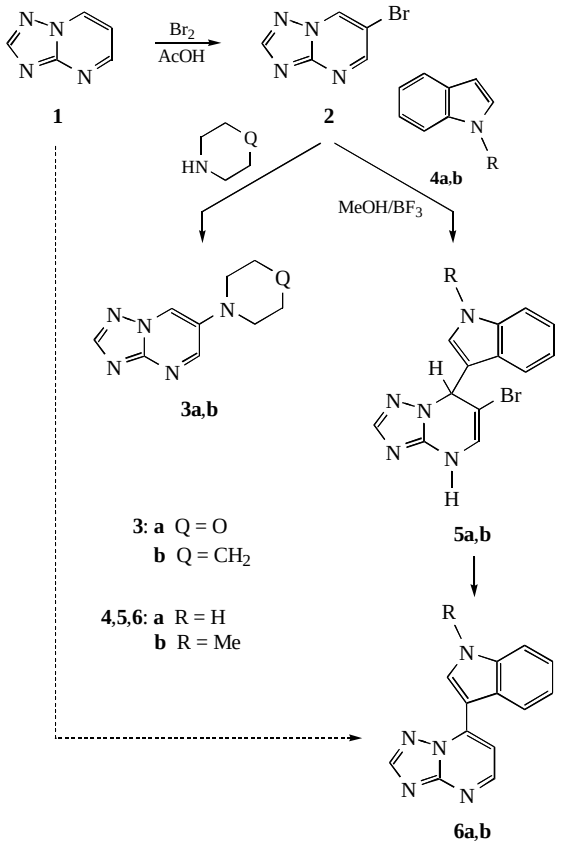
6-Bromo-1,2,4-triazolo[1,5-*a*]pyrimidine reacts with indoles in the presence of BF_3 to form σ^H-adducts, which undergo aromatization on treatment with triethylamine.

Nucleophilic substitution of hydrogen has currently become a successfully developed methodology for the introduction of electron-rich aromatic and heteroaromatic fragments into the pyrimidine ring. Usually, the S_N^H processes proceed through the formation of σ^H-adducts, which can be aromatised either by oxidation or *via* auto-aromatization facilitated by auxiliary groups (cine-, tele- and vicarious substitution).[1] These processes can successfully compete with the S_N^{ipso} substitution, because the primary kinetically controlled nucleophilic attack on heteroarenes is always directed at an unsubstituted carbon atom.



While studying the interaction of nucleophilic agents with 6-bromo-1,2,4-triazolo[1,5-*a*]pyrimidine **2** derived from direct bromination of **1**, it has been found that the bromine atom can be replaced by cycloalkylimine moieties, although Br in this position of the pyrimidine ring was previously considered as a bad nucleofugal group.[2] Thus, we have first succeeded to perform the synthesis of 6-morpholino- and 6-piperidino-1,2,4-triazolo[1,5-*a*]pyrimidines **3a**,**b**.† Compound **2** was expected to react with C-nucleophilic indoles **4a**,**b** to form 6-indolyl-substituted azolopyrimidines. However, we found that indoles attack the C-7 position of **2**, yielding corresponding 6-bromo-7-indolyl-substituted 4,7-dihydrotriazolopyrimidines **5a**,**b**.‡ The reaction proceeds smoothly at room temperature in the presence of catalytic amounts of BF_3. Final products **5a**,**b** are stable crystalline compounds. Compounds **5a**,**b** were found to undergo aromatization under basic conditions (triethylamine in boiling acetonitrile) to give 7-(indol-3-yl)triazolopyrimidine **6a** and 7-(1-methylindol-3-yl)triazolopyrimidine **6b**.§ The overall transformation of compound **2** into **6a**,**b** is an example of the cine-substitution which proceeds as a step-by-step reaction. It seems to be the first example of isolation of a key intermediate in the course of cine-substitution. Note that, contrary to the majority of the well-known cases of cine-substitution, an alternative aryne mechanism is completely excluded in the above examples.

In general, the mechanism suggested is similar to the classical cine-substitution in the 5-halopyrimidine series.[3] The aromatization of adducts **5a**,**b** is likely preceeded by their conversion into 6,7-dihydrotriazolopyrimidines **7a**,**b**. Some examples of similar tautomeric transformations in the 4,7-dihydropyrimidine series have been reported previously.[4] On the other hand, we have found this procedure to be useful for the introduction of

† The ^{1}H NMR spectra were recorded in [$^2H_6$]DMSO solutions using a Tesla BS 587A spectrometer at 80 MHz.

6-Morpholino-1,2,4-triazolo[1,5-a]pyrimidine **3a**. Compound **2** (0.5 mmol, 99 mg) was refluxed in morpholine (2.5 ml) for 3 h, the mixture was evaporated *in vacuo* and residue was recrystallised from toluene. Yield 90 mg (88%), mp 203–204 °C. ^{1}H NMR, δ: 8.98 (d, 1H, H^5, $J_{5,7}$ 2.8 Hz), 8.81 (d, 1H, H^7), 8.49 (s, 1H, H^2), 3.84–3.72 (m, 4H, H$^{3'}$,H$^{5'}$), 3.25–3.13 (m, 4H, H$^{2'}$,H$^{6'}$). Found (%): C, 52.35; H, 5.69; N, 33.95. Calc. for $C_9H_{11}N_5O$ (%): C, 52.69; H, 5.41; N, 34.14.

6-Piperidino-1,2,4-triazolo[1,5-a]pyrimidine **3b**. Prepared in a manner similar to that described for **3a** from compound **2** and piperidine. Yield 25%, mp 110–112 °C. ^{1}H NMR, δ: 8.95 (d, 1H, H^5, $J_{5,7}$ 2.8 Hz), 8.75 (d, 1H, H^7), 8.46 (s, 1H, H^2), 3.17 (m, 4H, H$^{2'}$, H$^{6'}$), 1.59 (m, 6H, H$^{3'}$, H$^{4'}$,H$^{5'}$). Found (%): C, 59.21; H, 6.66; N, 34.40. Calc. for $C_{10}H_{13}N_5$ (%): C, 59.10; H, 6.45; N, 34.46.

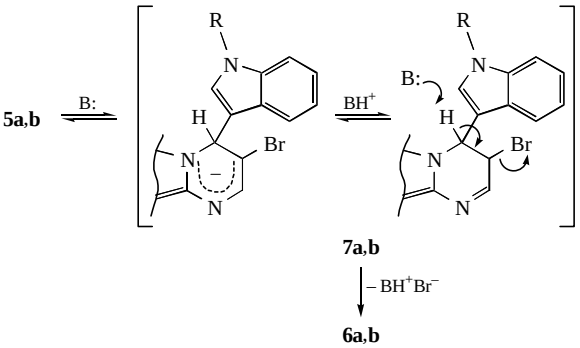
‡ *6-Bromo-7-(indol-3-yl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine* **5a**. Indole **4a** (1.5 mmol, 175.5 mg) and 6-bromotriazolopyrimidine **2** (1.5 mmol, 299 mg) was dissolved in methanol (7 ml), several drops of $BF_3{\cdot}OEt_2$ were added and the mixture was kept for 5 h at room temperature. The precipitate formed was filtered off, washed with 95% ethanol and dried to yield 290 mg (61%) of **5a**. Mp 169–172 °C (from methanol). ^{1}H NMR, δ: 11.12 (br. s, 1H, NH), 10.12 (d, 1H, NH, $J_{4,5}$ 3.6 Hz), 7.50 (s, 1H, H^2), 7.49 (d, 1H, H$^{2'}$), 7.37 (d, 1H, H$^{7'}$), 7.21 (d, 1H, H$^{4'}$), 7.1–6.9 (m, 3H, H$^{5'}$, H$^{6'}$, H^5), 6.37 (s, 1H, H^7). Found (%): C, 49.25; H, 3.05; N, 22.11. Calc. for $C_{13}H_{10}N_5Br$ (%): C, 49.37; H, 3.16; N, 22.15.

6-Bromo-7-(1-methylindol-3-yl)-4,7-dihydro-1,2,4-triazolo[1,5-a]-pyrimidine **5b**. Prepared in a manner similar to that described for **5a** from compounds **2** and **4b**. Yield 71%, mp 154–156 °C. ^{1}H NMR, δ: 10.12 (d, 1H, NH, $J_{4,5}$ 4.2 Hz), 7.48 (s, 2H, H^2, H$^{2'}$), 7.41 (d, 1H, H$^{7'}$), 7.22 (d, 1H, H$^{4'}$), 7.2–6.9 (m, 3H, H$^{5'}$, H$^{6'}$, H^5), 6.34 (s, 1H, H^7), 3.78 (s, 3H, N–Me). Found (%): C, 51.13; H, 3.62; N, 21.17. Calc. for $C_{14}H_{12}N_5Br$ (%): C, 50.93; H, 3.66; N, 21.21.

§ *7-(Indol-3-yl)-1,2,4-triazolo[1,5-a]pyrimidine* **6a**. Compound **5a** (0.3 mmol, 95 mg) was refluxed in a mixture of acetonitrile (3 ml) and triethylamine (0.7 mmol) for 0.5 h. The mixture was cooled and diluted with water (10 ml), the precipitate was collected by filtration, washed with water and dried. Yield 55 mg (78%), mp 263–265 °C. ^{1}H NMR, δ: 12.23 (br. s., 1H, NH), 9.12 (s, 1H, H^2), 8.83 (d, 1H, H^5, $J_{5,6}$ 5.0 Hz), 8.75 (s, 1H, H$^{2'}$), 7.87 (d, 1H, H^6), 8.23–7.27 (m, 4H, H$^{4'-7'}$). Found (%): C, 66.36; H, 3.70; N, 29.90. Calc. for $C_{13}H_9N_5$ (%): C, 66.38; H, 3.83; N, 29.79.

7-(1-Methylindol-3-yl)-1,2,4-triazolo[1,5-a]pyrimidine **6b**. Prepared in a manner similar to that described for **6a** from compound **5b**. Yield 77%, mp 191 °C. ^{1}H NMR, δ: 9.11 (s, 1H, H^2), 8.81 (d, 1H, H^5, $J_{5,6}$ 5.0 Hz), 8.76 (s, 1H, H$^{2'}$), 7.85 (d, 1H, H^6), 8.28–7.32 (m, 4H, H$^{4'-7'}$), 4.01 (s, 3H, N–Me). Found (%): C, 67.56; H, 4.42; N, 28.30. Calc. for $C_{14}H_{11}N_5$ (%): C, 67.46; H, 4.45; N, 28.09.

indole substituents into the 7-position of the *s*-triazolo[1,5-*a*]-pyrimidine system.



The conversion of compound **1** into **6a**,**b** can formally be considered as nucleophilic substitution for hydrogen *via* the following steps: (i) introduction of an auxiliary leaving group (Br) in the position adjacent to the reaction centre; (ii) addition of a nucleophile to form a σ^H-adduct and (iii) elimination of HBr under basic conditions. The procedure suggested does not include an oxidation step, which is undesirable in S_N^H reactions because it restricts the range of nucleophiles in use and requires a suitable oxidising agent.

References

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