Reaction of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione with α,ω-diamines as the first example of tandem nucleophilic substitution in neutral azines

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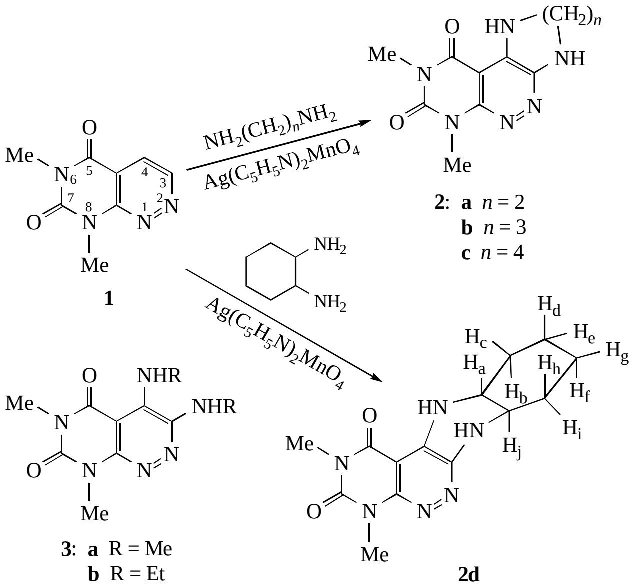
The title reaction proceeds in the presence of the oxidant $[Ag(C_5H_5N)_2MnO_4]$ to produce polycyclic compounds **2a–d**.

The tandem substitution of two good leaving groups (Hal, SO_2R, *etc.*) in azine molecules by bifunctional nucleophiles[1,2] and similar reactions of the $\mathrm{S_N^H} - \mathrm{S_N^{\mathit{ipso}}}$ type are well known.[3,4] However, to the best of our knowledge (*cf.* refs. 5 and 6), there are no data concerning tandem substitution of two hydrogen atoms, which are well known as very poor leaving groups ($\mathrm{S_N^H} - \mathrm{S_N^H}$ reaction). Here we report on the first azine substrate that exhibits such a type of reactivity.†

We found that 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7-(6*H*,8*H*)-dione **1**[8] reacts with an excess of 1,2-diaminoethane, 1,2-diaminocyclohexane, 1,3-diaminopropane or 1,4-diaminobutane in the presence of the oxidant $[Ag(C_5H_5N)_2MnO_4]$ to produce polycyclic compounds **2a**–**d** in 80, 70, 25 and 1% yields, respectively (Scheme 1).‡ The reaction of **1** with 1,2-diaminopropane proceeds in the same manner; however, the mixture of isomeric products could not be separated.

A remarkable property of the molecule of **1** consists in a considerable electron deficiency of the two adjacent C(3) and C(4) carbon atoms of a pyridazine ring, which is responsible for easy nucleophilic substitution at both of these centres. The effective positive π-charge at the 4-position (+0.100) is higher than that at the 3-position (+0.047).[9] As a consequence, compound **1** undergoes oxidative amination under the action of monofunctional primary alkylamines to afford corresponding 4-amino derivatives[9] along with a small amount (~10%) of 3,4-di(alkylamino)-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones **3**.§ These data suggest that a reaction of **1** with α,ω-diamines starts from the addition of a nucleophile to the 4-position with subsequent intramolecular attack at the 3-position by the second amino group. Evidently, the oxidative elimination of hydrogen atoms from both of the intermediate addition products accompanied the overall process. Judging from comparative yields of the final products, the second stage of the reaction is highly sensitive to an entropy factor (the yield of **2** decreases as the length of the α,ω-diamine alkylene chain increases).



Scheme 1

It was interesting to find other heterocyclic substrates that can enter into a similar tandem modification of the Chichibabin reaction. Cinnoline **4** and 1,3-dimethylpteridine-2,4(1*H*,3*H*)-dione (1,3-dimethyllumazine) **6** were tested as candidates. However, tandem amination was observed in none of the cases. Cinnoline was found to react with 1,2-diaminoethane in the presence of $Ag(C_5H_5N)_2MnO_4$ to produce dimer **5**[10] as a single product. Under the same conditions, 1,3-dimethyllumazine adds a nucleophile to the internuclear bond[11] to give derivative **7** in 9% yield (Scheme 2).¶

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† An analogy to the reaction reported appears to be the cycloaddition of bifunctional nucleophiles to azinium cations.[5,7] However, the latter is usually a multistep process. Note that in our case a neutral substrate participates in the one-pot procedure.

‡ *Typical procedure for the synthesis of* **2**: $Ag(C_5H_5N)_2MnO_4$ (1.4 g, 3.6 mmol) was added in portions to a solution of **1** (0.31 g, 1.6 mmol) in a correspoding diamine (10 ml) with stirring. After stirring at 20 °C for five days, the liquid phase was evaporated to dryness. The residue was extracted with $CHCl_3$ in a Soxhlet apparatus. Chromatography on Al_2O_3 ($CHCl_3$) followed by recrystallization from Pr^iOH gave **2** as yellow crystals.

All compounds **2a**–**d** gave analytical and spectral data consistent with their structure.

For **2a**: mp 295–297 °C (decomp.). ^1H NMR (250 MHz, $CDCl_3$) δ: 3.37 [s, 3H, Me–N(8)], 3.51 (m, 2H, CH_2), 3.62 (m, 2H, CH_2), 3.64 [s, 3H, Me–N(6)], 5.13 [s, 1H, NH(3)], 8.85 [s, 1H, NH(4)]. IR (KBr, ν/cm^{-1}): 1649, 1688 (CO), 3203, 3328 (NH). MS, *m*/*z*: 248 (M^+).

For **2b**: mp 289–290 °C (decomp.). ^1H NMR (250 MHz, $CDCl_3$) δ: 2.06 (m, 2H, CH_2), 3.36 [s, 3H, Me–N(8)], 3.51 (m, 2H, CH_2), 3.62 [s, 3H, Me–N(6)], 3.73 (m, 2H, CH_2), 5.32 [m, 1H, NH(3)], 9.63 [m, 1H, NH(4)]. IR (KBr, ν/cm^{-1}): 1641, 1701 (CO), 3213, 3294 (NH). MS, *m*/*z*: 262 (M^+).

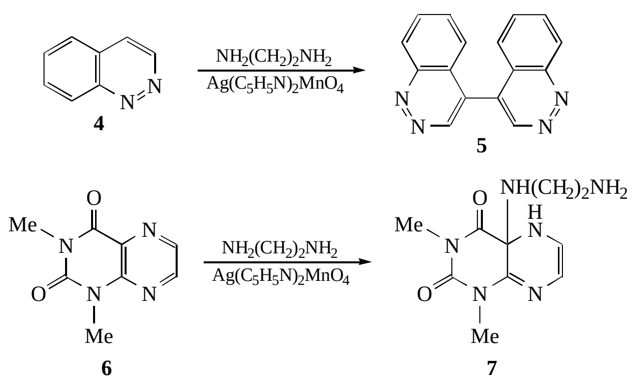
For **2c**: mp 285–287 °C (decomp.). ^1H NMR (250 MHz, $[^2H_6]$DMSO) δ: 1.84 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 3.28 [s, 3H, Me–N(8)], 3.35 (m, 2H, CH_2), 3.51 (m, 2H, CH_2), 3.56 [s, 1H, NH(3)], 3.64 [s, 3H, Me–N(6)], 4.46 (m, 2H, CH_2), 8.04 [t, 1H, NH(4), *J* 4.13 Hz]. IR (KBr, ν/cm^{-1}): 1672, 1707 (CO), 3200–3468 (br., NH). MS, *m*/*z*: 276 (M^+).

For **2d**: mp 329–331 °C (decomp.). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.4 [m, 4H, H_b, H_d, H_f and H_h], 1.86 [m, 2H, H_e and H_g], 2.06 [m, 2H, H_c and H_i], 2.94 [td, 1H, H_a, J_{aj} 8.64 Hz, J_{ab} 10.62 Hz, J_{ac} 3.66 Hz], 3.19 [td, 1H, H_j, J_{ja} 8.64 Hz, J_{jh} 10.69 Hz, J_{ji} 3.89 Hz], 3.37 [s, 3H, Me–N(8)], 3.63 [s, 3H, Me–N(6)], 5.27 [s, 1H, NH(3)], 8.68 [s, 1H, NH(4)]. IR (KBr, ν/cm^{-1}): 1647, 1701 (CO), 3170, 3299 (NH). MS, *m*/*z*: 302 (M^+).

§ For **3a**: mp 222–223 °C. ^1H NMR (250 MHz, $CDCl_3$) δ: 3.05 [d, 3H, Me–N(3), *J* 3.93 Hz], 3.30 [d, 3H, Me–N(4), *J* 5.59 Hz], 3.36 [s, 3H, Me–N(8)], 3.64 [s, 3H, Me–N(6)], 4.73 [m, 1H, NH(3)], 9.54 [m, 1H, NH(4)]. IR (Nujol, ν/cm^{-1}): 1660, 1690 (CO), 3160, 3445 (NH).

For **3b**: mp 100–102 °C. ^1H NMR (250 MHz, $[^2H_6]$DMSO) δ: 1.17 [t, 3H, Me, *J* 7.14 Hz], 1.19 [t, 3H, Me, *J* 7.14 Hz], 3.20 [s, 3H, Me–N(8)], 3.33 (m, 2H, CH_2), 3.45 [s, 3H, Me–N(6)], 3.70 (m, 2H, CH_2), 5.77 [pseudosinglet, 1H, NH(3)], 9.04 [pseudosinglet, 1H, NH(4)]. IR (Nujol, ν/cm^{-1}): 1655, 1715 (CO), 3245, 3375 (NH).

¶ For **7**: ^1H NMR (300 MHz, $CDCl_3$) δ: 2.73 [s, 3H, Me–N(1)], 3.00 [s, 3H, Me–N(3)], 3.35 (m, 2H, CH_2), 3.50 (m, 2H, CH_2), 7.62 [d, 1H, H(6), *J* 6.2 Hz], 8.15 [d, 1H, H(7), *J* 6.2 Hz], 8.26 (m, 2H, NH_2), 8.46 [m, 2H, NH and H(5)]. IR (KBr, ν/cm^{-1}): 1624, 1663 (CO), 3327, 3408 (NH). MS, *m*/*z*: 252 (M^+).



Scheme 2

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