SYNTHESIS OF ANNULATED 7-AZA-INDOLIZINES BY INTRAMOLECULAR [3+2]-CYCLOADDITION WITH PYRAZINIUM DICYANOMETHYLIDES

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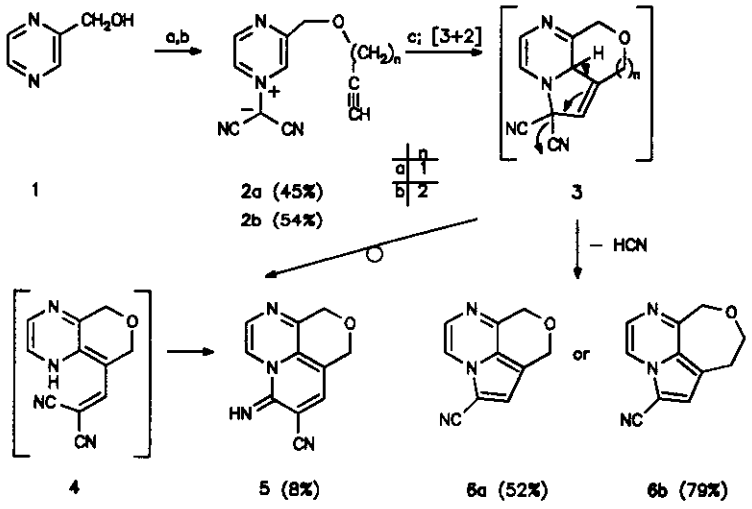
Abstract - Thermally induced intramolecular [3+2] cycloaddition reactions of the pyrazinium dicyanomethylides (**2**, **9**, and **15**), carrying different side chains with terminal alkynes as dipolarophiles, lead to the novel fused 7-aza-indolizines (**6**, **11**, **12**, and **18**) in high yields. In a combined inter/intramolecular cycloaddition the dicyanomethylide (**15b**) surprisingly furnishes the bimolecular adduct (**20**) besides the desired tricycle (**19**).

Since the general concept of the 1,3-dipolar cycloadditions was fully recognized by Huisgen in the early 1960s, the field of [3+2] cycloaddition chemistry has developed dramatically during the past 30 years.[1] According to this reaction principle, substituted indolizines and their aza analogs are easily obtainable[2] if one reacts pyridinium or diazinium dicyanomethylides

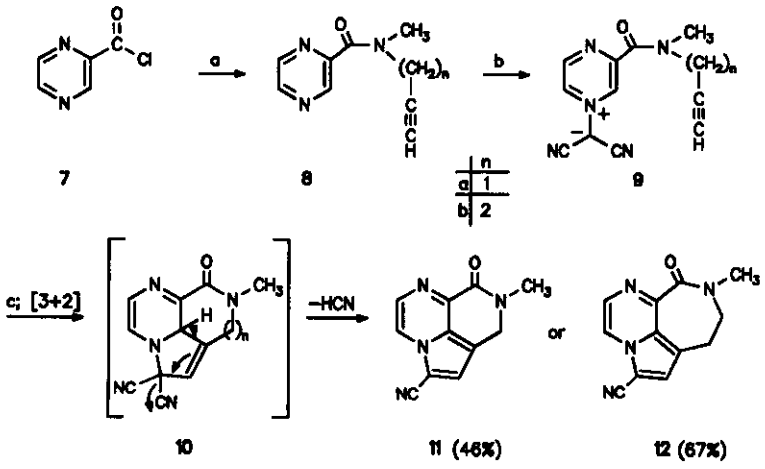


(a) NaH/THF/$BrCH_2$–C≡CH; (b) TCNEO, ether, 34°C; (c) toluene, 3 h, 110°C

as 1,3-dipoles with alkynes or alkenes as dipolarophiles. While inter- and intramolecular [3+2]cycloaddition reactions of pyridinium *N*-ylides are well documented,[3,4] transformations with pyrazinium dicyanomethylides have rarely been done.[5,6]

#Dedicated to Prof. R. Huisgen on the occasion of his 75th birthday.

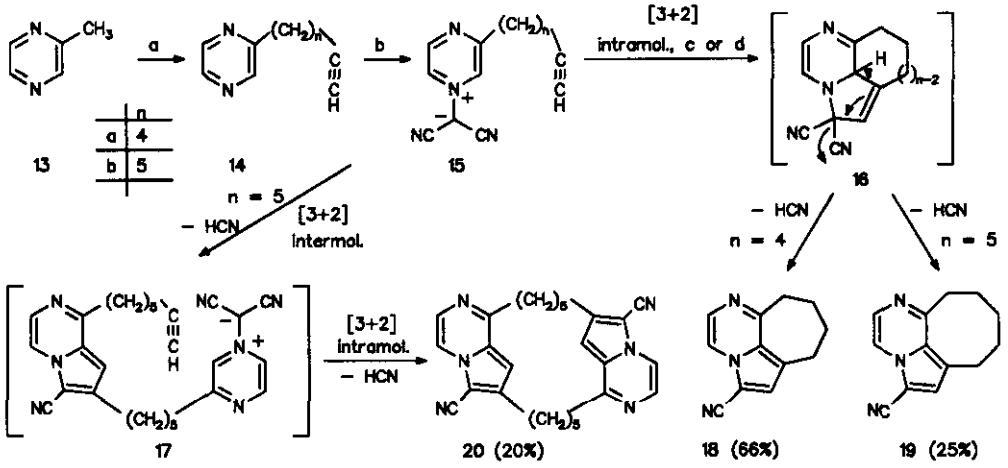
To our knowledge, the intramolecular variant has not been tried. In this communication, we disclose an effective method of preparing annulated [hi]azaindolizines by the intramolecular 1,3-dipolar addition reaction of pyrazinium dicyanomethylides.



(a) $CH_3NH-(CH_2)_n-C\equiv CH$; (b) TCNEO (c) 11: dioxane, 4.5 h, 100°C; 12: dioxane, 15 h, 100°C.

The pyrano[hi]azaindolizine (**6a**) and the oxepino[hi]azaindolizine (**6b**) were prepared in good yield from 2-hydroxymethylpyrazine (**1**).[7] First, the dipolarophile was introduced in the side chain. Tetracyanoethylene oxide (TCNEO)[8] then reacted regioselectively to give the dicyanomethylides (**2a**) or (**2b**). Heating in toluene for three hours converted the ylides (**2**) *via* **3** to the tricyclic products (**6a**) and (**6b**). With **2a** as educt the red azaquinolizine (**5**) was formed as by-product in small amount, probably through the intermediate (**4**). The analogous *N*-pyrazinium ylides (**9a,b**) were prepared from the carboxylic acid chloride (**7**) *via* (**8**). They reacted in the same fashion to give the novel fused pyrido- and azepinoazaindolizines (**11**) and (**12**).

When we started the reaction sequence with 3-methylpyrazine (**13**), we were able to obtain the first azaindolizines annulated with carbocycles, namely compounds (**18**) and (**19**). **13** was transformed into its anion with sodium amide;[9] this was reacted with ϖ-bromoalkynes to yield the pyrazines (**14a**) and (**14b**) with the terminal dipolarophile in the side chain. The pyrazines (**14a**) and (**14b**) gave the methylides (**15a**) and (**15b**) with TCNEO in refluxing ether in satisfactory yield. Subsequent heating induced the thermal intramolecular [3+2] cycloaddition reaction. The (non-isolable) intermediates (**16**) eliminated hydrogen cyanide, and the 10π-aromatic azaindolizines (**18**) and (**19**) were formed. **15b** showed a dichotomous reaction behaviour. Apart from the main product, the azaindolizine (**19**), we isolated a second fraction by column chromatography in 20% yield. The crystals from this fraction had a high melting point (273°C), and the analytical and spectroscopic data proved the constitution to be a dimeric azaindolizine (**20**). Obviously, the length of the connecting chain between dipolarophile and 1,3-dipole is crucial for the extent of entropic assistance towards the intramolecular cycloaddition reaction. A separation by a four- or five-atom tether, leading to fused systems such as **6**, **11** or **12**, is most effective towards the goal of an intramolecular reaction. By the time one reaches a six-atom tether as in the ylide (**15b**), the reaction rate approaches that of the (entropically non-assisted) intermolecular reaction. Therefore the heptyne (**15b**) reacts both



(a) 1. $NaNH_2/NH_3$; 2. $Br-(CH_2)_m-C\equiv CH$ (m=3,4); (b) TCNEO, ether, 34°C; (c) toluene, 24 h, 110°C; (d) toluene, 3 weeks, 110°C.

intramolecularly to give monomeric (**19**) *via* (**16b**) and intermolecularly to give dimeric (**20**) *via* **17**. The formation of the 8-membered ring in the tricycle (**19**) still seems to be slightly favoured over the intermolecular reaction, for of the 45% total isolated yield, 25% resulted from the intramolecular [3+2] cycloaddition reaction and 20% from the formation of the 18-membered ring. We did not find any oligomers, such as might be formed from the reaction of two primary adducts (**17**), or of **17** and the starting material **15**. The structures of all new compounds were deduced on the basis of their spectral data as well as elemental analyses.[10]

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10. Selected analytical data: **6a**: colorless crystals; mp 201 °C (decomp.); ir (KBr) 2210 cm^{-1} (CN); ^1H nmr ($CDCl_3$) δ 7.94 (d, 1H, ^3J = 5 Hz, pyraz.-H), 7.77 (d, 1H, ^3J = 5 Hz, pyraz.-H), 7.07 (s, 1H, pyrr.-H), 5.03 (s, 2H, OCH_2), 4.89 (s, 2H, OCH_2); ms m/z(%) 185 (100, $M^{+}\cdot$). **6b:** colorless crystals; mp 156 °C; ir (KBr) 2215 cm^{-1} (CN); ^1H nmr δ 8.0 (d, 1H, ^3J = 4.74 Hz, pyraz.-H), 7.73 (d, 1H, ^3J = 4.74 Hz, pyraz.-H), 7.17 (s, 1H, pyrr.-H), 5.03 (s, 2H, OCH_2), 4.14 (t, 2H, ^3J = 5.37 Hz, OCH_2), 3.19 (t, 2H, ^3J = 5.37 Hz, CH_2-pyrr.); ms m/z (%) =199 (89, $M^{+}\cdot$), 169 (100).

11: yellow crystals; mp 216 °C; ir (KBr) 2220 cm^{-1} (CN); ^1H nmr ($CDCl_3$) δ 8.02 (d, 1H, ^3J = 5,1 Hz, pyraz.-H), 7.99 (d, 1H, ^3J = 4.7 Hz, pyraz.-H), 7.20 (s, 1H, pyrr.-H), 4.95 (s, 2H, NCH_2), 3.31 (s, 3H, NCH_3); ms m/z (%) =212 (90, $M^{+}\cdot$), 211 (100).

12: yellow crystals; mp 230 °C; ir (KBr) 2210 cm^{-1} (CN); ^1H nmr ($CDCl_3$) δ 8.18 (d, 1H, ^3J = 4.6 Hz, pyraz.-H), 8.09 (d, 1H, ^3J = 4.6 Hz, pyraz.-H), 7.24 (s, 1H, pyrr.-H), 3.81 (m, 2H, NCH_2), 3.33 (s, 3H, NCH_3), 3.13 (m, 2H, CH_2-pyrr.); ms m/z (%) 226 (63, $M^{+}\cdot$), 155 (100).

18: colorless needles; mp 112 °C; ir (KBr) 2220 cm^{-1} (CN); ^1H nmr δ 7.95 (d, 1H, ^3J = 4.8 Hz, pyraz.-H), 7.68 (d, 1H, ^3J = 4.8 Hz, pyraz.-H), 7.10 (s, 1H, pyrr.-H), 3.22 (m, 2H, CH_2), 3.03 (m, 2H, CH_2), 2.02 (m, 4H, $(CH_2)_2$); ^{13}C nmr δ 158.6, 128.4, 127.9, 121.2, 120.3, 115.6, 112.4, 96.8, 39.5, 28.3, 27.6, 25.6; ms m/z (%) 197 (100, $M^{+}\cdot$).

19: colorless crystals; mp 123 °C; ir (KBr) 2220 cm^{-1} (CN); ^1H nmr ($CDCl_3$) δ 7.96 (d, 1H, ^3J = 4.7 Hz, pyraz.-H), 7.67 (d, 1H, ^3J = 4.7 Hz, pyraz.-H), 7.05 (s, 1H, pyrr.-H), 3.27 (t, 2H, ^3J = 7.1 Hz), 3.14 (t, 2H, ^3J = 7.1 Hz), 1.95 (m, 2H), 1.80 (m, 2H), 1.39 (m, 2H); ^{13}C nmr ($CDCl_3$) δ 157.6, 130.4, 129.4, 121.7, 118.6, 116.4, 112.6, 95.8, 35.5, 27.7, 26.9, 26.2, 22.6; ms m/z (%) 211 (100, $M^{+}\cdot$).

20: colorless crystals; mp 273 °C (decomp.); ir (KBr) 2220 cm^{-1} (CN); ^1H nmr (CF_3CO_2D) δ 8.57 (d, 2H, ^3J = 5.6 Hz, pyraz.-H), 7.82 (d, 2H, ^3J = 5.6 Hz, pyraz.-H), 7.52 (s, 2H, pyrr.-H), 3.43 (t, 4H, ^3J = 6.1 Hz), 3.10 (t, 4H, ^3J = 5.6 Hz), 2.13 (m, 4H), 2.02 (m, 4H), 1.38 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 156.8, 145.6, 129.9, 121.7, 119.3, 115.8, 109.6, 106.9, 32.3, 30.1, 29.3, 28.9, 27.5; ms m/z (%) 422 (100, $M^{+}\cdot$).

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