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The *Semmler-Wolff* Aromatization and *Schmidt* Reaction Applied to Some Pyrido[2′,3′:3,4]pyrazolo[5,1-c][1,2,4]benzotriazines

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Pyrido[2′,3′:3,4]pyrazolo[5,1-c][1,2,4]benzotriazin-4(1*H*)ones were transformed via their oximes in a *Semmler-Wolff* aromatization process in the tetracyclic heteroaromatic amines **4** or by *Schmidt* reaction into a mixture of the same amine **4** and a ring enlarged lactam **3**. Syntheses of some halo pyrazolo[3,4-b]-pyridines and a photochemical transformation of 3-azidopyrazolo[3,4-b]pyridine are also described.

(Keywords: Rearrangement with aromatization and ring enlargement; Semmler-Wolff and Schmidt reaction; Substituted pyrazolo[3,4-b]pyridines; Substituted pyrido[2′,3′:3,4]pyrazolo[5,1-c][1,2,4]benzotriazines)

Über die Semmler-Wolff- und Schmidt-Reaktion einiger Pyrido[2′,3′:3,4]pyrazolo[5,1-c][1,2,4]benzotriazine

Pyrido[2′3′:3,4]pyrazolo[5,1-c][1,2,4]benzotriazin-4(1*H*)one werden über Oxime in einer *Semmler-Wolff*-Reaktion in die tetracyklischen aromatischen Amine **4** umgewandelt. In einer *Schmidt*-Reaktion wurden dieselben Ketone in ein Gemisch aus Amin **4** und Lactam **3** übergeführt. Synthesen von halogensubstituierten Pyrazolo[3,4-b]pyridinen und photochemische Umwandlung von 3-Azidopyrazolo[3,4-b]pyridin werden beschrieben.

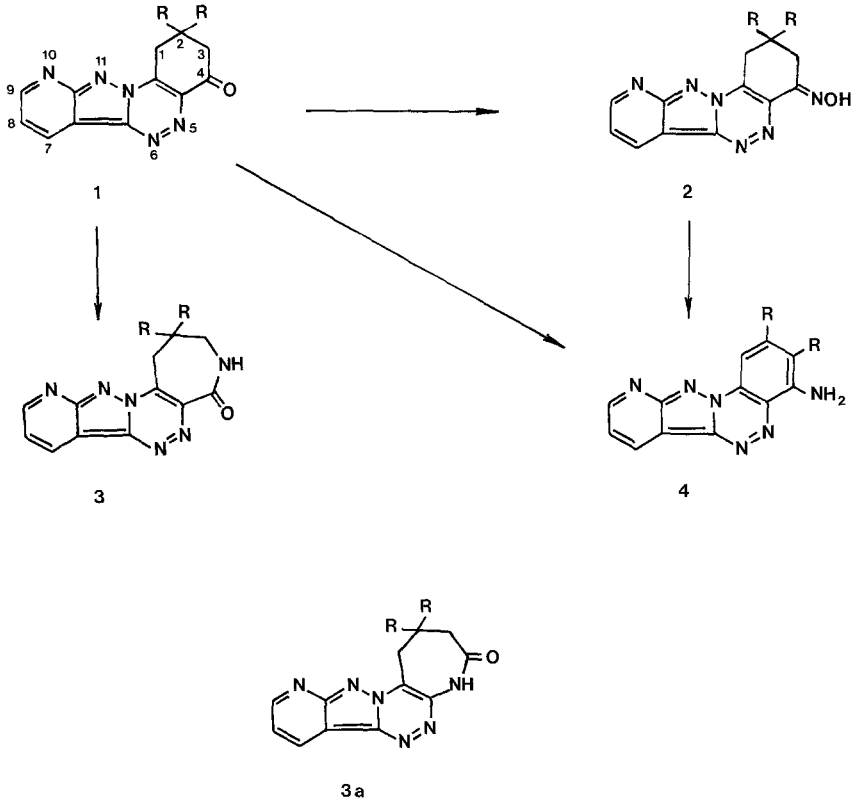
Introduction

Previously we have described 3-diazopyrazolo[3,4-b]pyridine as a versatile synthon for the preparation of new heterocyclic systems [1]. Among these, several pyrido[2′,3′:3,4]pyrazolo[5,1-c][1,2,4]benzotriazines [2] have been prepared from the mentioned diazo compound and 1,3-cyclohexanediones. We like to report now on some additional

transformations of 3-diazopyrazolo[3,4-b]pyridine and on aromatization and rearrangement of the above mentioned tetracyclic system.

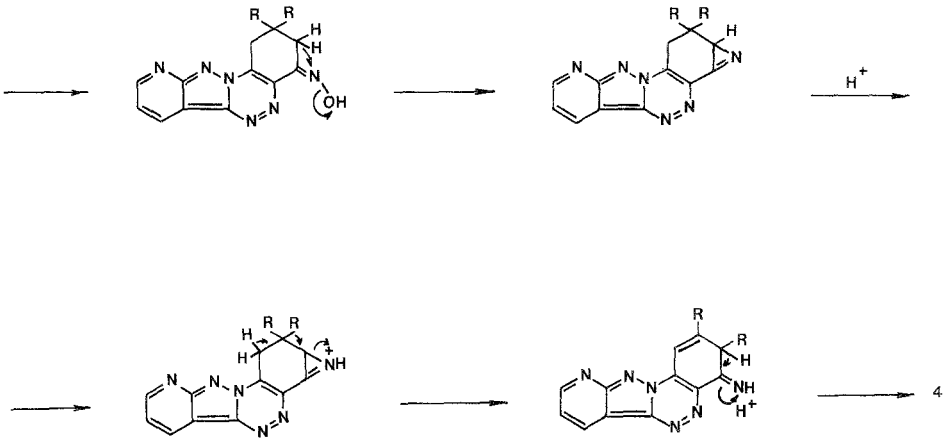
Results and Discussion

The tetracyclic ketone **1** (*R* = H or *Me*) was converted into the corresponding oxime **2** (*R* = H or *Me*). This, when heated in polyphosphoric acid at about 120 °C is transformed into the fully aromatic aminotetracycle **4** (*R* = H or *Me*) with simultaneous migration of the methyl group. These transformations represent the *Semmler-Wolff* aromatization which is regarded as an "abnormal" *Beckmann* rearrangement [3]. It is worthwhile to mention that this rearrangement has been described only for few heterocyclic systems like thiophenes [4], quinolines [5] and quinolizinium salts [6]. A plausible mechanistic interpretation of the *Semmler-Wolff* aromatization, applied to our tetracyclic system is presented in Scheme 1. It is noteworthy that an



examination of the reaction products resulting from treatment of tetralone-1-oxime with polyphosphoric acid revealed that in addition to the aromatization process also rearrangement with ring enlargement proceeded at a lower rate so that the corresponding lactam was formed to

Scheme 1



a small amount [3]. These results were interpreted in terms of both, *syn*- and *anti*-oximes being involved in the transformation. A careful examination of the reaction mixture from our experiments revealed the presence of no other products in addition to those resulting from the aromatization process. Moreover, it can be anticipated that the oxime hydrogen in **2** is participating in an intramolecular hydrogen bond formation, involving the neighbouring triazine ring nitrogen atom.

The ketones **1** (*R* = H or *Me*) were also submitted to the *Schmidt* reaction with hydrazoic acid. In the case of the dimethyl compound **1** (*R* = *Me*) the aromatic amine **4** (*R* = *Me*) and the lactam **3** (*R* = *Me*) were obtained in a ratio of about 3 : 1. The unsubstituted ketone afforded the analogous compounds in a ratio of about 1 : 1.2. Both aromatic amines were identical with those obtained by the *Semmler-Wolff* rearrangement. For the obtained lactams either structure **3** or **3a** is possible. Concerning this type of rearrangement there are usually two possibilities of group migration [7, 8]. The process is considered to be concerted and steric effects and migratory aptitudes influence the direction of migration. Although it was generally found that the largest group in the neighbourhood of the reaction centre will migrate preferentially, it was later found that also alkyl migration may prevail over aryl migration [9, 10].

As already mentioned, we could isolate only one type of heterocyclic lactam to which structure **3** was assigned by means of nmr data. For the

NH group a triplet was clearly discernible and the 3-CH_2 group was coupled ($J = 6$ Hz) with the amino group. This is only possible if structure **3** is present, whereas in the case of the alternative structure **3a** such coupling should be absent.

Finally, we like to describe a simple preparation of 3-halo substituted pyrazolo[3,4-b]pyridines **6** (X = F, Cl, Br or I) from the corresponding diazo compound **5** and HX or HBF_4 acids. In a more complex manner, the 3-azido compound **7** is decomposed photochemically into 3-cyanopyridine (**9**) and 3-cyano-2(1*H*)pyridone (**8**). This contrasts the previously reported photochemical decomposition of compound **5** in a clean transformation into 1*H*-pyrazolo[3,4-b]pyridine [2].

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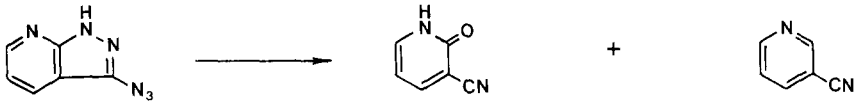

7 8 9

Experimental

Melting points were determined on a *Kofler* hot plate apparatus and are uncorrected. Nuclear magnetic resonance spectra (NMR) were obtained with a JEOL C-60 HL or JEOL JNM FX90Q spectrometer. Chemical shifts are reported in δ values relative to Me_4Si as the internal standard. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L spectrometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 240C. Most of the commercial chemicals were purified or dried by standard procedures.

2,2-Dimethyl-4-hydroxyimino-1,2,3,4-tetrahydropyrido[2',3' : 3,4]-pyrazolo[5,1-c][1,2,4]benzotriazine (**2**, $R = Me$)

A mixture of the ketone **1** ($R = Me$) (0.63 g), hydroxylamine hydrochloride (1.3 g), pyridine (15 ml) and anhydrous ethanol (15 ml) was heated under reflux for 4 h. The mixture was evaporated to dryness, the residue suspended in water (20 ml) and the undissolved product filtered. The compound was crystallized from N,N-dimethylformamide and from glacial acetic acid (yield 0.63 g, 95%), m.p. > 290 °C (dec.). Mass spectrum: m/e 282 (M^+), calcd. 282.3; ^{1}H NMR (*DMSO-d_6*, 150 °C) δ

8.50 (dd, H_9), 8.42 (dd, H_7), 7.08 (dd, H_8), 3.18 (s, 1-CH_2), 2.68 (s, 3-CH_2), 1.10 (s, 2 *Me*), 11.0 (broad s, OH); $J_{8,9} = 4.2$, $J_{7,8} = 7.8$, $J_{7,9} = 1.7$ Hz. Anal. calcd. for $C_{14}H_{14}N_6O$: C 59.56, H 5.00, N 29.77; found: C 59.48, H 5.36, N 29.62.

4-Amino-2,3-dimethylpyrido[2',3' : 3,4]pyrazolo[5,1-c][1,2,4]benzotriazine (**4**, *R = Me*)

The above oxime **2** (*R = Me*) (0.22 g) and polyphosphoric acid (2 g) were heated at 120–130 °C for 30 min. The resulting solution was diluted with water (15 ml), neutralized with solid $NaHCO_3$ to *pH* 6–7 and the separated product was filtered. It was crystallized from a mixture of dimethyl sulfoxide and methanol (yield 0.17 g, 82%), m.p. 286–289 °C. Mass spectrum: *m/e* 264 (M^+), calcd. 264.28; ^{1}H NMR (*DMSO-d*$_6$) δ 8.9 (m, H_7, H_9), 7.50 (dd, H_8), 7.36 (s, H_1), 6.80 (broad s, NH_2), 2.16 and 2.42 (s, 2- and 3-*Me*); $J_{8,9} = 4.0$, $J_{7,8} = 8.0$ Hz. Anal. calcd. for $C_{14}H_{12}N_6$: C 63.62, H 4.58, N 31.80; found: C 63.28, H 4.55, N 31.46.

Treatment of 2,2-dimethyl-2,3-dihydropyrido[2',3' : 3,4]pyrazolo[5,1-c][1,2,4]-benzotriazin-4(1H)one with hydrazoic acid. Formation of compounds **3** (*R = Me*) and **4** (*R = Me*)

To a mixture of the ketone **1** (*R = Me*) (0.3 g), chloroform (40 ml) and conc. sulfuric acid (1.5 ml) under stirring sodium azide (0.6 g) was added portionwise during 10 min at room temperature. The mixture was stirred for 3 h at room temperature and thereafter treated with ice and neutralized with solid sodium bicarbonate to *pH* 6. The two phases were separated and the aqueous layer was extracted twice with 40 ml of chloroform. The combined extracts were dried over anhydrous sodium sulfate and treated with charcoal. The residue, obtained after evaporation of the solvent was treated with ethanol (4 ml), cooled to − 5 °C, filtered and washed with some water. The product is a mixture of two compounds (0.2 g). They were separated in the following manner. To the mixture water (40 ml) was added and after heating to boil it was filtered. The insoluble part was washed again with some hot water, dried and crystallized from a mixture of *DMF* and some methanol. There were obtained 50 mg (17%) of the amino compound **4** (*R = Me*), identical in all respects with the compound prepared as described above.

The aqueous filtrate was evaporated *in vacuo* to dryness and crystallized from ethanol to give 20 mg (6%) of pure lactam **3** (*R = Me*), m.p. > 275 °C (dec.). Mass spectrum: *m/e* 282 (M^+), calcd. 282.30; ^{1}H NMR (*DMSO-d*$_6$, 63 °C) δ 0.97 (m, H_8, H_{10}), 1.2 (t, NH), 2.40 (dd, H_9), 6.54 (s, 1-CH_2), 7.10 (d, 3-CH_2), 8.90 (s, 2 *Me*); $J_{9,10} = 4.4$, $J_{8,9} = 8.05$, $J_{NH,3\text{-}CH_2} = 6.35$ Hz. Anald. calcd. for $C_{14}H_{14}N_6O$: C 59.56, H 5.00, N 29.77; found: C 59.20, H 5.00, N 29.27.

4-Aminopyrido[2',3' : 3,4]pyrazolo[5,1-c][1,2,4]benzotriazine (**4**, *R* = H)

A mixture of the ketone **1** (*R* = H) (0.4 g), hydroxylamine hydrochloride (0.8 g), pyridine (10 ml) and anhydrous ethanol (10 ml) was heated under reflux for 9 h. After evaporation to dryness the residue was suspended in water (10 ml) and the *pH* adjusted to about 4. The product was filtered, washed with water, methanol and dried. The resulting product (0.39 g), the oxime, was suspended in polyphosphoric acid (4 g) and the mixture was heated at 120 °C for 40 min. The cooled solution was then treated with water (20 ml), neutralized with solid sodium bicarbonate and the separated product filtered. It was sublimed at 270 °C/266 Pa to give the amino compound (0.21 g, 53%), which was for analysis crystallized

from a mixture of dimethyl sulfoxide and ethanol, m.p. 293–295 °C. Mass spectrum: *m/e* 236 (M^+), calcd. 236.23; ^{1}H NMR (*DMSO-d*$_6$, 80 °C) δ 9.0 (m, H_7, H_9), 7.55–8.03 (m, H_1, H_2), 7.56 (dd, H_8), 7.12 (dd, H_3); $J_{8,9} = 4.2$, $J_{7,8} = J_{1,2} = J_{2,3} = 7.8$, $J_{1,3} = 1.8$ Hz. Anal. calcd. for $C_{12}H_8N_6$: C 61.00, H 3.41, N 35.58; found: C 60.99, H 3.51, N 35.31.

Reaction between 2,3-dihydropyrido[2',3' : 3,4]pyrazolo[5,1-c][1,2,4]-benzotriazin-4(1H)one and hydrazoic acid

The reaction was performed in essentially the same manner as described above for the 2,2-dimethyl analogue. 0.2 g of the starting ketone **1** (R = H) was used and sodium azide was added to a cold reaction mixture (0 °C). The mixture was then stirred at room temperature for 2 h and then treated in the described manner. Evaporation of the chloroform extract gave a crude mixture of two compounds (0.125 g). For separation, the mixture was dissolved in hot ethanol (15 ml) the undissolved material was filtered and crystallized from a mixture of *DMF* and ethanol to give the lactam **3** (R = H) (35 mg, 16%) as yellow crystals with m.p. > 280 °C (dec.). Mass spectrum: *m/e* 254 (M^+), calcd. 254.25; ^{1}H NMR (*DMSO-d*$_6$, 155 °C) δ 8.95 (m, H_8, H_{10}), 7.52 (dd, H_9), 3.76 (t, 1-CH_2), 3.2 (m, 3-CH_2), 2.3 (m, 2-CH_2), 8.0 (broad, NH); $J_{9,10} = 4.2$, $J_{8,9} = 8.0$, $J_{1,2} = 7.0$, $J_{2,3} = J_{NH,3\text{-}CH_2} = 6.3$ Hz. Anal. calcd. for $C_{12}H_{10}N_6O$: C 56.68, H 3.96, N 33.06; found: C 56.35, H 4.23, N 32.95.

The filtrate after the separation of lactam was evaporated to dryness and the residue was sublimed at 270 °C/266 Pa and thereafter crystallized from a mixture of *DMF* and methanol. The obtained amino compound **4** (R = H) (25 mg, 13% yield) was found to be identical in all respects with the product obtained from the oxime as described above.

3-Fluoro-1H-pyrazolo[3,4-b]pyridine (**6**, X = F)

A solution of 3-diazopyrazolo[3,4-b]pyridine [2] (**5**) (0.35 g) in tetrafluoroboric acid (11 ml of 50%) was irradiated (λ = 254 nm) for 48 h. The reaction mixture was diluted with water (15 ml), neutralized with solid sodium bicarbonate to *pH* 6 and extracted with diethyl ether (4 times with 50 ml). The combined extracts were evaporated and the residue crystallized from water (yield 60 mg, 17%), m.p. 158–160 °C. Mass spectrum: *m/e* 137 (M^+), calcd. 137.12; ^{1}H NMR (*DMSO-d*$_6$) δ 8.6 (dd, H_6), 8.21 (ddd, H_4), 7.24 (dd, H_5); $J_{4,5} = 8.0$, $J_{4,6} = 1.6$, $J_{5,6} = 4.4$, $J_{H_4,F} = 1.6$ Hz. Anal. calcd. for $C_6H_4FN_3$: C 52.55, H 2.94, N 30.65; found: C 52.36, H 2.94, N 30.38.

3-Chloro-1H-pyrazolo[3,4-b]pyridinine (**6**, X = Cl)

A mixture of the diazo compound **5** (0.145 mg) and conc. hydrochloric acid (2.5 ml) was heated under reflux for 35 min. Water (7 ml) was added and the mixture neutralized with solid sodium bicarbonate. The separated product was collected and crystallized from water (yield 0.142 g, 93%), m.p. 174.5–176.5 °C. Mass spectrum: *m/e* 153 (M^+), calcd. 153.57; ^{1}H NMR (*DMSO-d*$_6$) δ 8.72 (dd, H_6), 8.28 (dd, H_4), 7.36 (dd, H_5), 13.9 (broad s, NH); $J_{4,5} = 8.0$, $J_{4,6} = 1.6$, $J_{5,6} = 4.4$ Hz. Anal. calcd. for $C_6H_4ClN_3$: C 46.93, H 2.63, N 27.36; found: C 47.09, H 2.72, N 27.16.

In the filtrate after neutralization and extraction with chloroform a small amount of 1*H*-pyrazolo[3,4-b]pyridine has been detected by TLC (R_f = 0.64, on DC-Fertigplatten Merck, Kieselgel 60 F-254, 0.25 mm thickness, methanol and chloroform, 1 : 10, as the mobile phase).

3-Bromo-1H-pyrazolo[3,4-b]pyridine (**6**, X = Br)

6 (X = Br) was prepared in a similar manner in 90% yield using 48% hydrobromic acid. M.p. 170–171 °C (from water). Lit. [2] gives m.p. 170–171 °C for the product, obtained by decomposition of a triazene with hydrobromic acid. Mass spectrum: *m/e* 198 (M^+), calcd. 198.03; ^{1}H NMR (*DMSO-d*$_6$) δ 8.70 (dd, H_6), 8.15 (dd, H_4), 7.32 (dd, H_5), 14.2 (broad s, NH); $J_{4,5}$ = 8.4, $J_{4,6}$ = 1.6, $J_{5,6}$ = 4.6 Hz. Anal. calcd. for $C_6H_4BrN_3$: C 36.39, H 2.04, N 21.22; found: C 36.36, H 2.36, N 20.96.

3-Iodo-1H-pyrazolo[3,4-b]pyridine (**6**, X = I)

6 (X = I) was prepared similarly with 47% hydroiodic acid at 105 °C for 15 min in 68% yield, m.p. 188–190 °C (from aqueous ethanol). Mass spectrum: *m/e* 245 (M^+), calcd. (245.02); ^{1}H NMR (*DMSO-d*$_6$) δ 8.72 (dd, H_6), 8.04 (dd, H_4), 7.35 (dd, H_5), 14.2 (broad s, NH); $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.6, $J_{5,6}$ = 4.4 Hz. Anal. calcd. for $C_6H_4IN_3$: C 29.41, H 1.65, N 17.15; found: C 29.66, H 1.41, N 17.27.

Photochemical transformation of 3-azido-1H-pyrazolo[3,4-b]pyridine

A solution of the azido compound **7** [2] (0.6 g) in methanol (15 ml) was iradiated (λ = 254 nm) for 7 days. The solution was evaporated and the residue was sublimed at 100 °C/1 333 Pa to give 3-cyanopyridine (**9**) (0.1 g, 26%). At higher temperature, 180–190 °C/1 333 Pa 3-cyano-2(1*H*)pyridone (**8**) (70 mg) was obtained and for analysis it was crystallized from methanol (yield 40 mg, 9%), identical in all respects with an authentic specimen [11].

Acknowledgements

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