Monatshefte für Chemie 123, 247–250 (1992)

Monatshefte für Chemie
Chemical Monthly

Acetylenic Chemistry, Part 20 [1]: Ring Opening of 3-Azaisatoic Anhydride with Acetylenic Amines: Synthesis of Pyrido[2,3-d]pyrimidinones

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Summary. Ring opening of 3-azaisatoic anhydride with acetylenic amine gave the nicotinamides **3a–c**. The reaction of triphosgene with the nicotinamides **3a–c** yielded the pyrido[2,3-d]pyrimidinones **4a**, **5b**, **5c**, and **7b**.

Keywords. Acetylenic Amines; Pyrido[2,3-d]pyrimidinones.

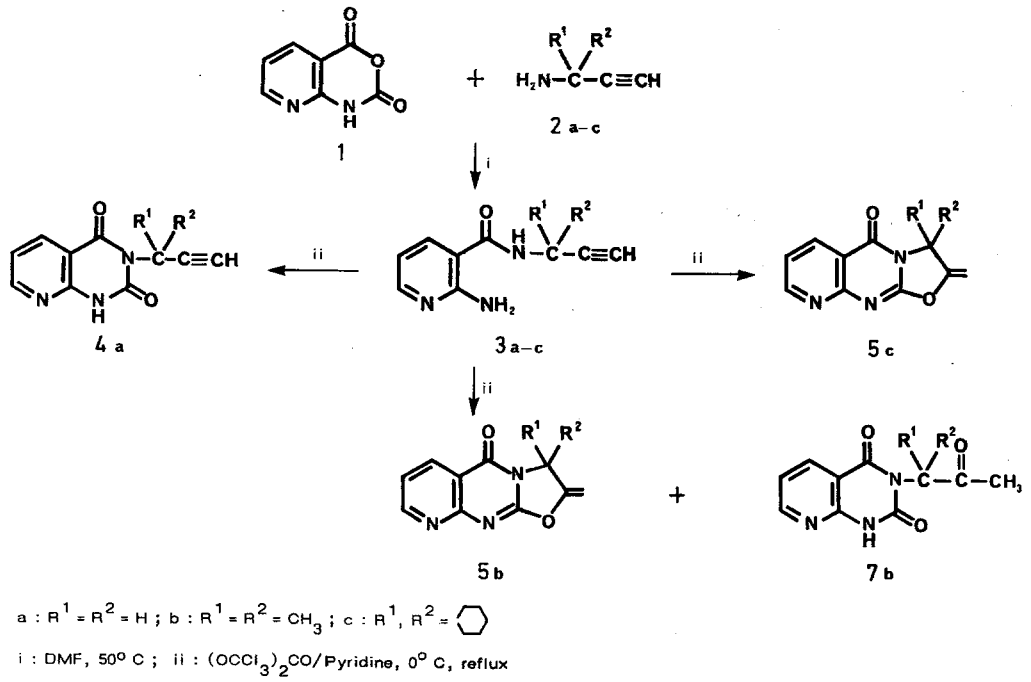
Acetylenchemie, 20. Mitt.: Ringöffnung von 3-Azaisatosäureanhydrid mit Acetylenaminen: Synthese von Pyrido[2,3-d]pyrimidinonen

Zusammenfassung. Bei Ringöffnung von 3-Azaisatosäureanhydrid mit Acetylenaminen entstehen die Nicotinamide **3a–c**. Die Reaktion von Triphosgen mit den Nicotinamiden **3a–c** führt zu den Pyrido[2,3-d]pyrimidinonen **4a**, **5b**, **5c** und **7b**.

The growing interest in the biological activities of condensed pyrimidine systems especially as diurectics [3], antitumor agents [4] as well as antagonists of heterocyclic constituents of nucleic acid and of folic-folinic acid family of vitamins [5] motivated the synthesis of some pyrido[2,3-d]pyrimidinones.

The reactions of isatoic anhydride with amines have received much attention in comparison to the 3-aza analog [6, 7]. This may be partially due to the non-availability of commercial 3-azaisatoic anhydride [8, 9].

The reaction of acetylenic amine in *DMF* with 3-azaisatoic anhydride yielded the corresponding nicotinamides **3a–c**. The reaction of the nicotinamides with triphosgene in pyridine gave different products depending on the type of substitution on the nicotinamide. When $R^1 = R^2 = H$, **4a** was obtained. The present synthetic method for **4a** is more convenient and the yield is also comparatively higher [7]. The tricyclic compounds **5b** and **5c** were obtained when $R^1 = R^2 = CH_3$ or R^1R^3 = cyclohexyl. This indicates that substitution influences the production of the desired tricyclic compounds. **7b** was also isolated in addition to **5b** which could have resulted from hydration of **5b** [7].



Experimental Part

M.p.: Kofler hot-stage apparatus. IR: Perkin-Elmer type 457 spectrometer; Kbr discs. ^{1}H NMR and ^{13}C NMR: Varian Gemini 200 MHz spectrometer; *TMS* as internal standard. Mass spectra: MAT 44S spectrometer. Column chromatography was carried out on Merck Kieselgel 60 (mesh 70–230, ASTM). Light petroleum refers to the fraction of boiling range 40–60°C.

General Synthetic Procedure of Nicotinamides **3 a–c** [10]

To a stirred solution of 3-azaisatoic anhydride (0.006 mol) in 15 ml DMF warmed to 50°C, acetylenic amine was added until TLC showed the absence of 3-azaisatoic anhydride (3–4 h). After cooling to room temperature, the reaction mixture was poured in to 100 ml of water, adjusted to *pH* 9 with 10% NaOH and extracted with dichloromethane. The organic phase was washed with 3 × 25 ml portions of water, dried over anhydrous Na_2SO_4, purified by column chromatography (dichloromethane) and recrystallised from appropriate solvent.

2-Amino-N-prop-2-inylnicotinamide (**3 a**)

Prop-2-inylamine (0.61 g, 0.01 mol) was added to 3-azaisatoic anhydride (1 g, 0.006 mol) in *DMF* and treated as above to give from $CHCl_3$ **3 a** as colourless needles (0.55 g, 57%), m.p. 137–138°C. IR: $\nu = 3390\,cm^{-1}$, 3300, 3180 (NH, NH_2), 2100 (C≡C), 1640 (C=O), 1620, 1600, 760. ^{1}H NMR (*DMSO-d*$_6$): δ (ppm) = 2.32 (t, 1 H, *J* = 2.5 Hz, 3′-H), 4.25 (dd, 2 H, *J* = 2.5, 5.4 Hz, 1-H), 6.50–6.71 (brs, 2 H, NH_2), 6.62 (dd, 1 H, *J* = 4.8, 7.8 Hz, 5-H), 7.88 (dd, 1 H, *J* = 1.8, 7.8 Hz, 6-H), 8.14 (dd, 1 H, *J* = 1.7, 4.8 Hz, 4-H). 8.28–8.42 (brs, 1 H, NH). ^{13}C NMR (*DMSO-d*$_6$): δ (ppm) = 28.4 (C-1′), 70.5 (C-3′), 80.2 (C-2′), 109.5 (C-3), 111.7 (C-5), 136.5 (C-4), 151.5 (C-6), 158.8 (C-2), 167.7 (C=O). MS (70 eV): *m/z* (%) = 175 (16) [M^+], 146 (17), 121 (100), 105 (30), 93 (92), 91 (68), 77 (5), 66 (24). $C_9H_9N_3O$ (175.2). Calcd. C 61.74, H 5.18, N 23.98; found C 61.63, H 5.19, N 24.18.

2-Amino-N-(1,1-dimethylprop-2-inyl)nicotinamide (**3b**)

1,1-Dimethylprop-2-inylamine (1.0 g, 0.01 mol) was added to 3-azaisatoic anhydride (1 g, 0.006 mol) in *DMF* and treated as in the general synthetic procedure to give from *Me*OH **3b** as colourless needles (0.8 g, 62%), m.p. 146–147°C. IR: ν = 3 180 cm^{-1}, 3 290, 3 400 (NH, NH_2), 2 100 (C ≡ C), 1 660 (C = O), 1 630, 1 600, 780. ^1H NMR ($CDCl_3$): δ (ppm) = 1.74 (s, 6 H, 2 × CH_3), 2.41 (s, 1 H, 3′-H), 6.16 (s, 1 H, NH), 6.40 (s, 2 H, NH_2), 6.58 (dd, 1 H, *J* = 4.8, 7.6 Hz, 5-H), 7.59 (dd, 1 H, *J* = 1.7, 7.7 Hz, 6-H), 8.14 (dd, 1 H, *J* = 1.6, 4.7 Hz, 4-H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 29.2 (C-2 × CH_3), 48.1 (C-1′), 69.7 (C-3′), 87.0 (C-2′), 110.9 (C-3), 112.5 (C-5), 135.9 (C-4), 152.1 (C-6), 159.2 (C-2), 167.6 (C = O). MS (70 eV) *m/z* (%) = 203 (12) [M^+], 181 (6), 161 (4), 146 (18), 121 (30), 93 (30), 69 (100). $C_{11}H_{13}N_3O$ (203.2). Calcd. C 65.01, H 6.45, N 20.67; found C 64.93, H 6.42, N 20.76.

2-Amino-N-1-cyclohexylprop-2-inylnicotinamide (**3c**)

1-Cyclo-hexylprop-2-inylamine (1.5 g, 0.01 mol) was added to 3-azaisatoic anhydride (1.0 g, 0.001 mol) in *DMF* and gave from *Me*OH **3c** as colourless plates (0.96 g, 71%), m.p. 152–153°C. IR: ν = 3 180 cm^{-1}, 3 290, 3 460, (NH, NH_2), 2 100 (C ≡ C), 1 630 (C = O), 1 590, 780. ^1H NMR ($CDCl_3$): δ (ppm) = 1.20–2.35 (m, 10 H, cyclohexyl), 2.48 (s, 1 H, 3′-H), 6.06 (s, 1 H, NH), 6.39 (s, 1 H, NH_2), 6.58 (dd, 1 H, *J* = 4.8, 7.7 Hz, 5-H), 7.60 (dd, 1 H, *J* = 1.6, 7.7 Hz, 6-H), 8.26 (dd, 1 H, *J* = 1.6, 4.8 Hz, 4-H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.5 (C-3″, 5″), 25.3 (C-4″), 37.2 (C-2″, 6″), 52.2 (C-1′), 72.0 (C-3′), 85.5 (C-2′), 111.2 (C-3), 112.6 (C-5), 135.9 (C-4), 152.2 (C-6), 159.3 (C-2), 167.5 (C = O). MS (70 eV): *m/z* (%) = 243 (20) [M^+], 228 (6), 215 (44), 202 (12), 189 (32), 137 (8), 121 (100), 93 (50), 79 (8), 66 (24). $C_{14}H_{17}N_3O$ (243.3). Calcd. C 69.12, H 7.04, N 17.26; found C 68.70, H 7.00, N 17.24.

Reaction of Nicotinamides **3a–3c** *with Triphosgene* [10]

Triphosgene was added slowly to a stirred solution of nicotinamide (**3a–c**) in 10 ml pyridine cooled to 0°C. After reaching room temperature, the reaction mixture was slowly heated to reflux and maintained at reflux for 6 h. Excess pyridine was neutralised with 5% HCl, extracted with CH_2Cl_2 and the organic layer washed with 10% $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo. Subsequent column chromatography (CH_2Cl_2) gave the corresponding compounds.

3-Prop-2′-inylpyrido[2,3-d]pyrimidin-2,4-dione (**4a**)

Triphosgene (67 mg, 0.67 mmol) was added to compound **3a** (100 mg, 0.67 mmol) in pyridine and treated as above to give from *Et*O*Ac* as colourless needles **4a** (69 mg, 63%), m.p. 240–242°C (Ref. [7] 240–242°C). IR: ν = 3 280 cm^{-1} (C ≡ CH), 3 020 (NH), 2 100 (C ≡ C), 1 720, 1 670 (C = O), 1 440, 780. ^1H NMR (*DMSO-d*$_6$): δ (ppm) = 3.17 (t, 1 H, *J* = 2.5 Hz, 3′-H), 4.63 (d, 2 H, *J* = 2.4 Hz, 2′-H), 7.28–7.35 (dd, 1 H, *J* = 4.8, 7.8 Hz, 6-H), 8.35 (dd, 1 H, *J* = 1.8, 7.8 Hz, 7-H), 8.66 (dd, 1 H, *J* = 1.9, 4.8 Hz, 5-H), 12.15 (s, 1 H, NH). ^{13}C NMR (*DMSO-d*$_6$): δ (ppm) = 29.7 (C-1′), 73.2 (C-3′), 79.2 (C-2′), 109.4 (C-4a), 119.5 (C-6), 137.3 (C-5), 149.9 (C-8a), 151.3 (C-2), 155.4 (C-7), 161.3 (C-4). MS (70 eV): *m/z* (%) = 201 (58) [M^+], 172 (20), 159 (14), 147 (16), 130 (14), 119 (12), 103 (8), 93 (12), 84 (100), 72 (18), 65 (14), 58 (64).

2-Methylene-3-cyclohexyloxazolopyrido[2,3-d]pyrimidin-5-one (**5c**)

Triphosgene (40 mg, 0.4 mmol) was added to compound **3c** (100 mg, 0.4 mmol) in pyridine and treated as above to give **5c** as orange needles from *Me*OH (30 mg, 25%), m.p. 184–185°C. IR: ν = 1 720 cm^{-1} (C = O), 1 700 (C = CH_2), 1 640, 1600. ^1H NMR ($CDCl_3$): δ (ppm) = 1.64–2.12 (m, 8 H, cyclohexyl), 2.80–3.05 (m, 2 H, cyclohexyl), 4.84 (d, 1 H, *J* = 3.9 Hz, = CH_{trans}), 5.08 (d, 1-H, *J* = 3.9 Hz, = CH_{cis}), 7.34 (dd, 1 H, *J* = 4.8, 7.48 Hz, 7-H), 8.52 (dd, 1 H, *J* = 1.9, 7.8 Hz, 8-H), 8.80 (dd, 1 H, *J* = 1.9, 4.8 Hz, 6-H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.1 (C-3′, 5′), 23.6 (C-4′), 31.3 (C-2′, 6′), 67.4 (C-3), 90.8 (= CH_2),

115.4 (C-5a), 120.9 (C-7), 136.7 (C-6), 153.2 (C-9a), 156.5 (C-8), 158.6 (C-2), 159.1 (C-5), 160.2 (C-2b). MS (70 eV): *m/z* (%) = 269 (0.2) [M^+], 245 (9), 244 (11), 164 (100), 147 (11), 121 (19), 93 (11), 81 (11), 66 (11). $C_{15}H_{15}N_3O_2 \cdot H_2O$ (287.3). Calcd. C 62.71, H 5.96, N 14.62; found C 62.67, H 6.07, N 14.66.

2-Methylene-3,3-dimethyloxazolopyrido[2,3-d]pyrimidin-5-one (**5b**)

The reaction of triphosgene (98 mg, 0.98 mmol) and compound **3b** (200 mg, 0.98 mmol) in pyridine gave two products. Column chromatography (diethylether) of the solid afforded compound **5b** as the first eluate which from CH_2Cl_2/petroleum ether gave yellow plates (90 mg, 40%), m.p. 156–157°C. IR: $\nu = 1\,720\,cm^{-1}$ (C=O), 1 700 (C=CH_2), 1 640, 1 600. ^1H NMR ($CDCl_3$): δ (ppm) = 1.90 (s, 6 H, 2 × CH_3), 4.57 (d, 1 H, J = 4.1 Hz, =CH_{trans}), 5.02 (d, 1 H, J = 4.1 Hz, =CH_{cis}), 7.37 (dd, 1 H, J = 4.7, 7.8 Hz, 7-H), 8.56 (dd, 1 H, J = 2.1, 7.8 Hz, 8-H), 8.92 (dd, 1 H, J = 2.1, 4.7 Hz, 6-H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 26.5 (C-2 × CH_3), 64.4 (C-3), 87.4 (=CH_2), 115.3 (C-5a), 121.1 (C-7), 136.7 (C-6), 153.4 (C-9a), 156.6 (C-8), 159.2 (C-2), 160.8 (C-2b), 161.0 (C-5). MS (70 eV): *m/z* (%) = 229 (100) [M^+], 214 (79), 186 (6), 167 (12), 149 (20), 119 (9), 83 (16), 71 (28), 57 (32). $C_{12}H_{11}N_3O_2 \cdot \frac{1}{3}H_2O$ (235.2). Calcd. C 61.30, H 4.82, N 17.86; found C 61.03, H 4.62, N 17.61.

3-(1,1-Dimethylacetonyl)pyrido[2,3-d]pyrimidin-2,4-(1H,3H)-dione (**7b**)

The second eluate gave **7b** as colourless plates from CH_2Cl_2/petroleum ether (24 mg, 10%), m.p. 198–200°C. IR: $\nu = 1\,740\,cm^{-1}$, 1 720, 1 680 (C=O), 1 605. ^1H NMR ($CDCl_3$): δ (ppm) = 1.78 (s, 6 H, 2 × CH_3), 2.22 (s, 3 H, −$COCH_3$), 7.26 (dd, 1 H, J = 4.7, 7.8 Hz, 6-H), 8.42 (dd, 1-H, J = 1.9, 7.8 Hz, 7-H), 8.73 (dd, 1 H, J = 1.9, 4.7 Hz, 5-H), 11.12 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ (ppm) = 23.5 (C-2 × CH_3), 24.0 (C-3'), 68.3 (C-1'), 111.2 (C-4a), 119.7 (C-6), 138.7 (C-5), 143.0 (C-8a), 151.0 (C-2), 154.8 (C-7), 162.9 (C-4), 204.1 (C-2'). MS (70 eV): *m/z* (%) = 247 (21) [M^+], 205 (100), 190 (8), 164 (80), 147 (51), 121 (19), 93 (24), 71 (30), 57 (23). $C_{12}H_{13}N_3O_3$. Calcd. 247.0957; found 247.0953.

Acknowledgement

We thank the "Deutscher Akademischer Austauschdienst" (DAAD) for a fellowship to C. O. Usifoh.

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Received May 8, 1991. Accepted May 29, 1991