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Synthesis of Pyridinyl-4-pyrimidinamine Derivatives

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Summary. N-(1-Methyl-2-pyridin-3′(4′)-yl-vinyl)acetimidoyl chlorides (**5**, prepared by *Beckmann* rearrangement of the oximes of 3-methyl-4-pyridin-3′(4′)-yl-3-buten-2-ones (**4**)) react with cyanamide and N,N-dialkylcyanamides in the presence of titanium(IV) chloride to give 4-amino-2,6-dimethyl-5-pyridinyl-pyrimidine derivatives (**7**).

Keywords. Cyanamide; Imidoyl chlorides; Pyridinyl-4-pyrimidinamine.

Synthese von Pyridinyl-4-pyrimidinamin-Derivaten

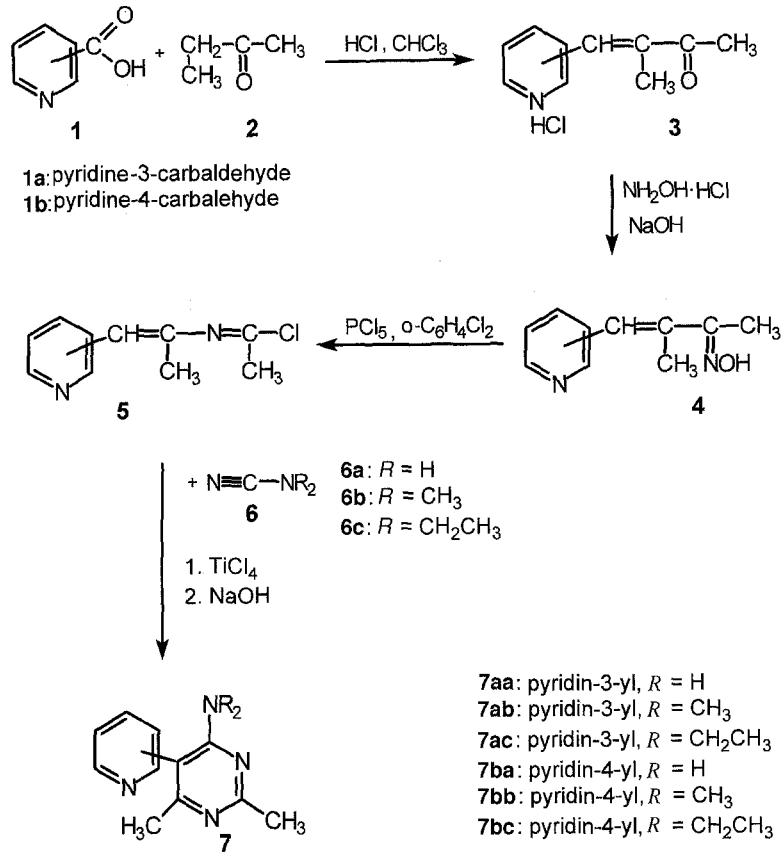
Zusammenfassung. N-(1-Methyl-2-pyridin-3′(4′)-yl-vinyl)acetimidoyl-chloride (**5**, dargestellt durch *Beckmann*-Umlagerung der Oxime von 3-Methyl-4-pyridin-3′(4′)-yl-3-buten-2-onen (**4**)) reagieren mit Cyanamid und N,N-Dialkylcyanamid in Gegenwart von Titan(IV)chlorid zu 4-Amino-2,6-dimethyl-5-pyridinyl-pyrimidin-Derivaten (**7**).

Introduction

Studies on the synthesis of pyridinylpyrimidine derivatives are of great interest owing to the proved pharmacological and fungicidal activity of numerous compounds of this group. Pyridinyl-2-pyrimidinamines, for example, exhibit cardiotionic activity [1], 2-pyridin-2′-yl-pyrimidines and 2-pyridin-4′-yl-pyrimidines are used as agrochemical fungicides [2–3]. We have prepared novel 4-amino-5-pyridin-3′(4′)-yl-pyrimidines (**7**) by reaction of N-(1-methyl-2-pyridin-3′(4′)-yl-vinyl)-acetimidoyl chlorides (**5**) with cyanamide **6a**, dimethylcyanamide **6b**, and diethylcyanamide **6c** in the presence of titanium(IV) chloride (Scheme 1).

Results and Discussion

Imidoyl chlorides **5a**–**5b** were obtained by *Beckmann* rearrangement of the oxime of 3-methyl-4-pyridin-3′-yl-3-buten-2-one (**4a**) and the oxime of 3-methyl-4-pyridin-4′-yl-3-buten-2-one (**4b**). 3-Methyl-4-pyridin-3′(4′)-yl-3-buten-2-ones **3a**–**b** were prepared by condensation of pyridine-3-carbaldehyde and pyridine-4-carbaldehyde with 2-butanone.



Scheme 1

The condensation reactions were carried out at 20–25 °C in chloroform in the presence of hydrogen chloride. Synthesis of 3-methyl-4-pyridin-2′-yl-3-buten-2-one by reaction of pyridine-2-carbaldehyde with 2-butanone was not successful under these conditions. 3-Methyl-4-pyridin-3′-yl-3-buten-2-one hydrochloride and 3-methyl-4-pyridin-4′-yl-3-buten-2-one hydrochloride were obtained in 80% and 86% yield, respectively. Oximation of ketones **3** gave oximes **4a** and **4b** in 70% and 74% yield. The structure of the prepared oximes was established by elemental analysis and spectroscopic data (see Experimental).

Beckmann rearrangement of **4** in *o*-dichlorobenzene in the presence of PCl_5 gave N-(1-methyl-2-pyridin-3′-yl-vinyl)-acetimidoyl chloride **5a** and N-(1-methyl-2-pyridin-4′-yl-vinyl)-acetimidoyl chloride **5b**. Similar rearrangements of oximes of 3-methyl-4-phenyl-3-buten-2-ones to N-(1-methyl-2-phenylvinyl)-acetimidoyl chloride derivatives have been described in Ref. [4–5]. For further reactions, the crude imidoyl chlorides were used after removal of most $POCl_3$ and HCl. Reaction of imidoyl chlorides **5a** and **5b** with cyanamide or dialkylcyanamides were carried out at 110 °C in *o*-dichlorobenzene in the presence of titanium(IV) chloride employing the reactants and titanium(IV) chloride in a 1:2:1 ratio. Equimolar amounts of the *Lewis* acid are required because the final products form 1:1 titanium complexes. From the titanium complexes, the free products are obtained by hydrolysis. 4-

Amino-2,6-dimethyl-5-pyridin-3′(4′)-yl-pyrimidines (**7**) were obtained in 85–96% yield (in relation to oximes **4**). The structures of the products were proved by elemental analysis and their MS, ^{1}H NMR, and UV spectra. No other structures than 4-amino-2,6-dimethyl-5-pyridinyl-pyrimidine derivatives (**7**) are in agreement with the spectroscopic data. In the absence of $TiCl_4$, the reaction of **5** with **6a**–**6c** does not lead to products **7**. Pyridinyl-4-pyrimidinamine derivatives are probably formed *via* 1-chloro-1-amino-3,5-dimethyl-6-pyridinyl-2,4-diaza-1,3,5-hexatriene intermediates which undergo cyclization to **7** in the presence of titanium(IV) chloride.

Experimental

UV spectra were measured using a SPECORD M-40 spectrophotometer; basic medium: 0.02 mol NaOH in 2% methanol, acidic medium: 0.02 mol HCl in 2% methanol. ^{1}H NMR spectra were recorded on a TESLA BS 587 NMR (80 MHz) spectrometer in $CDCl_3$ solution with *TMS* as internal standard. Mass spectra were obtained with a Shimadzu QP-2000 spectrometer. Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) thin layer chromatography plates using a benzene-ethyl acetate mixture (3:1 v/v) as the mobile phase. Melting points are uncorrected. The results from elemental analyses agree with the calculated values within experimental error.

4-Pyridin-3′-yl-3-methyl-3-buten-2-one (**3a**) *and 4-pyridin-4′-yl-3-methyl-3-buten-2-one* (**3b**); *general procedure*

A mixture of pyridine-3-carbaldehyde or pyridine-4-carbaldehyde (10.7 g, 0.1 mol) and methyl ethyl ketone (12 g, 0.2 mol) in chloroform (250 ml) was saturated with gaseous hydrogen chloride (0.1 mol). The reaction mixture was kept at 25 °C for 48 hours. Chloroform was evaporated, and the residue was washed with diethyl ether. The hydrochlorides of 4-pyridinyl-3-methyl-3-buten-2-ones were obtained as white powder.

4-Pyridin-3′-yl-3-methyl-3-buten-2-one hydrochloride (**3a**; $C_{10}H_{11}NO \cdot HCl$)

Yield: 80%; m.p.: 130 °C (dec.); ^{1}H NMR: $\delta = 2.05$ (3H, d, CH=C–CH_3, $J = 1.15$ Hz), 2.45 (3H, s, $COCH_3$), 7.40 (1H, q, CH=C), 7.81–9.10 ($4H_{arom}$) ppm; UV (methanol): λ_{max} ($\varepsilon \times 10^{-3}$) = 263 (8.6), 290 (6.3) nm; MS: *m/z* (%) = 161 (M^+, 5), 160 (15), 146 (10), 132 (5), 118 (22), 117 (17), 108 (10), 107 (76), 106 (47), 91 (13), 89 (6), 79 (13), 78 (85), 75 (5), 65 (9), 63 (12), 62 (6), 53 (14), 51 (100), 50 (61), 49 (13).

4-Pyridin-4′-yl-3-methyl-3-buten-2-one hydrochloride (**3b**; $C_{10}H_{11}NO \cdot HCl$)

Yield: 86%; m.p.: 104–106 °C; ^{1}H NMR: $\delta = 2.10$ (3H, d, CH=C–CH_3, $J = 1.15$ Hz), 2.50 (3H, s, $COCH_3$), 7.20 (1H, q, CH=C), 7.60–7.77 ($2H_{arom}$), 8.56–8.72 ($2H_{arom}$) ppm; UV (methanol): λ_{max} ($\varepsilon \times 10^{-3}$) = 261 (8.3) nm; MS: *m/z* (%) = 161 (M^+, 22), 160 (9), 146 (16), 136 (12), 118 (34), 117 (25), 108 (25), 107 (63), 106 (30), 103 (11), 91 (23), 89 (9), 80 (14), 79 (11), 78 (45), 75 (9), 65 (15), 63 (15), 62 (6), 53 (12), 51 (100), 50 (60), 49 (11).

Oximes of 4-pyridinyl-3-methyl-3-buten-2-ones (**4**); *general procedure*

An aqueous solution of ethanol containing 0.05 mol of 4-pyridinyl-3-methyl-3-buten-2-one hydrochlorides, 0.15 mol of hydroxylamine hydrochloride, and 0.10 mol of sodium hydroxide was refluxed for 1.5 h and then poured into a large quantity of water. The oxime formed was filtered off and crystallized from ethanol.

3-Methyl-4-pyridin-3'-yl-3-buten-2-one oxime (**4a**; $C_{10}H_{12}N_2O$)

Yield: 70%; m.p.: 131–132 °C; $R_f = 0.07$; ^{1}H NMR: $\delta = 2.10$ (3H, d, CH=C–CH_3, $J = 1.20$ Hz), 2.20 (3H, s, COCH_3), 6.80 (1H, q, CH=C, $J = 1.20$ Hz), 7.25–9.10 (5H, NOH and 4H$_{arom}$) ppm; UV (methanol): λ_{max} ($\varepsilon \times 10^{-3}$) = 212 (7.8), 273 (20.4) nm; MS: *m/z* (%) = 176 (M^+, 8), 175 (22), 158 (15), 144 (8), 131 (7), 130 (9), 118 (12), 117 (19), 106 (8), 91 (13), 89 (17), 80 (12), 79 (100), 78 (12), 77 (9), 65 (18), 63 (25), 51 (26).

3-Methyl-4-pyridin-4'-yl-3-buten-2-one oxime (**4b**; $C_{10}H_{12}N_2O$)

Yield: 74%; m.p.: 139–140 °C; $R_f = 0.08$; ^{1}H NMR: $\delta = 2.10$ (3H, d, CH=C–CH_3, $J = 1.18$ Hz), 2.17 (3H, s, COCH_3), 6.78 (1H, q, CH=C, $J = 1.18$ Hz), 7.14–7.26 (2H$_{arom}$), 8.52–8.65 (2H$_{arom}$), 9.50 (1H, broad s, NOH) ppm; UV (methanol): λ_{max} ($\varepsilon \times 10^{-3}$) = 222 (10.5), 282 (21.6) nm; MS: *m/z* (%) = 176 (M^+, 18), 175 (56), 158 (15), 144 (8), 131 (4), 118 (12), 117 (23), 106 (12), 91 (85), 77 (25), 72 (100), 65 (38), 51 (34).

4-Amino-2,6-dimethyl-5-pyridinyl-pyrimidines (**7**), *general procedure*

A solution of 0.005 mol of oxime **4** in 40 ml of *o*-dichlorobenzene was added dropwise with stirring to a cooled (5–10 °C) suspension of PCl_5 (0.01 mol) in 20 ml of dry benzene. The reaction mixture was stirred at room temperature until the oxime could not be detected by thin layer chromatography (5–20 min). The crude imidoyl chlorides were used for further reaction after the removal of benzene with almost all of $POCl_3$ and HCl under vacuum at 20–25 °C. To the crude imidoyl chloride in *o*-dichlorobenzene, dialkylcyanamide (0.01 mol) or cyanamide (0.01 mol) in 5 ml of diethyl ether was added. The solution was allowed to stand for 1 h at room temperature. Then a solution of $TiCl_4$ (0.005 mol) in 10 ml of benzene was added dropwise to the well stirred reaction mixture. The mixture was stirred at room temperature for 30 min, heated to 110 °C for 2 h, cooled, and 30 ml of 10% HCl were added. The acidic water layer was separated, washed with diethyl ether, alkalized with concentrated NaOH, and extracted with chloroform. The crude product was purified by distillation or crystallization from *n*-hexane.

4-Amino-2,6-dimethyl-5-pyridin-3'-yl-pyrimidine (**7aa**; $C_{11}H_{12}N_4$)

Yield: 85%; m.p.: 180–182 °C (dec.); $R_f = 0.08$; ^{1}H NMR: $\delta = 2.14$ (3H, s, 6-CH_3), 2.54 (3H, s, 2-CH_3), 4.62 (1H, broad s, NH_2), 7.32–8.72 (4H$_{arom}$) ppm; UV: basic: λ_{max} ($\varepsilon \times 10^{-3}$) = 215 (14.4), 237 (8.4), 270 (7.4) nm; acidic: λ_{max} ($\varepsilon \times 10^{-3}$) = 205 (17.9), 255 (14.4) nm; MS: *m/z* (%) = 200 (M^+, 77), 199 (100), 158 (11), 118 (11), 117 (11), 90 (14), 89 (12), 64 (11), 63 (20), 42 (20).

4-Dimethylamino-2,6-dimethyl-5-pyridin-3'-yl-pyrimidine (**7ab**; $C_{13}H_{16}N_4$)

Yield: 92%; m.p.: 49–50 °C; $R_f = 0.12$; ^{1}H NMR: $\delta = 2.13$ (3H, s, 6-CH_3), 2.54 (3H, s, 2-CH_3), 2.71 (6H, s, N(CH_3)$_2$), 7.28–8.63 (4H$_{arom}$) ppm; UV: basic: λ_{max} ($\varepsilon \times 10^{-3}$) = 214 (7.5), 262 (9.6), 281 (7.1) nm; acidic: λ_{max}($\varepsilon \times 10^{-3}$) = 267 (12.9), 281 (10.6) nm; MS: *m/z* (%) = 228 (M^+, 29), 227 (100), 213 (11), 198 (9), 184 (14), 143 (12), 117 (11), 116 (19), 90 (11), 89 (16), 63 (17), 51 (22), 44 (26).

4-Diethylamino-2,6-dimethyl-5-pyridin-3'-yl-pyrimidine (**7ac**; $C_{15}H_{20}N_4$)

Yield: 90%; b.p.: 170–172 °C/3.5 torr; $R_f = 0.29$; ^{1}H NMR: $\delta = 0.90$ (6H, t, 2 × NCH$_2$CH_3, $J = 7$ Hz), 2.08 (3H, s, 6-CH_3), 2.52 (3H, s, 2-CH_3), 3.17 (4H, q, 2 × NCH_2CH$_3$), 7.30–8.65 (4H$_{arom}$) ppm; UV basic: λ_{max} ($\varepsilon \times 10^{-3}$) = 263 (10.7), 286 (8.7) nm; acidic: λ_{max} ($\varepsilon \times 10^{-3}$) = 266 (15.0), 286 (12.3) nm; MS: *m/z* (%) = 256 (M^+, 12), 255 (18), 227 (34), 117 (14), 116 (16), 105 (11), 104 (100), 93 (35), 92 (11), 89 (10), 78 (12), 77 (71), 76 (33), 72 (19), 65 (14), 64 (12), 63 (20), 58 (27), 55 (26), 53 (10), 52 (19), 51 (47), 44 (26), 43 (41).

4-Amino-2,6-dimethyl-5-pyridin-4'-yl-pyrimidine (**7ba**; $C_{11}H_{12}N_4$)

Yield: 87%; m.p.: 178–180 °C (dec.); $R_f = 0.05$; ^{1}H NMR: $\delta = 2.15$ (3H, s, 6-CH_3), 2.52 (3H, s, 2-CH_3), 4.60 (1H, broad s, NH_2), 7.15–7.27 (2H_{arom}), 8.68–8.80 (2H_{arom}) ppm; UV: basic: λ_{max} ($\varepsilon \times 10^{-3}$) = 215 (13.0), 230 (7.8), 263 (6.2), 285 (4.6) nm; acidic: λ_{max} ($\varepsilon \times 10^{-3}$) = 205 (13.6), 260 (11.4), 305 (2.2) nm; MS: *m/z* (%) = 200 (M^+, 87), 199 (100), 182 (11), 158 (19), 131 (11), 118 (12), 117 (11), 91 (10), 89 (17), 65 (12), 64 (15), 63 (32), 62 (9), 52 (10), 51 (17).

4-Dimethylamino-2,6-dimethyl-5-pyridin-4'-yl-pyrimidine (**7bb**; $C_{13}H_{16}N_4$)

Yield: 96%; m.p.: 65–67 °C; $R_f = 0.15$; ^{1}H NMR: $\delta = 2.12$ (3H, s, 6-CH_3), 2.52 (3H, s, 2-CH_3), 2.72 (6H, s, $N(CH_3)_2$), 7.06–7.20 (2H_{arom}), 8.52–8.64 (2H_{arom}) ppm; UV: basic: λ_{max} ($\varepsilon \times 10^{-3}$) = 218 (10.1), 249 (8.7), 282 (7.2) nm; acidic: λ_{max} ($\varepsilon \times 10^{-3}$) = 218 (10.4), 264 (11.1), 282 (9.2) nm; MS: *m/z* (%) = 228 (M^+, 44), 227 (100), 213 (26), 198 (17), 184 (22), 144 (10), 143 (12), 117 (17), 116 (17), 90 (17), 89 (23), 72 (12), 63 (23), 64 (15), 51 (22), 44 (26), 43 (12).

4-Diethylamino-2,6-dimethyl-5-pyridin-4'-yl-pyrimidine (**7bc**; $C_{15}H_{20}N_4$)

Yield: 94%; b.p.: 141–142 °C/1.5 torr; $R_f = 0.25$; ^{1}H NMR: $\delta = 0.92$ (3H, t, NCH_2CH_3), 1.25 (3H, t, NCH_2CH_3), 2.08 (3H, s, 6-CH_3), 2.51 (3H, s, 2-CH_3), 3.05 (2H, q, NCH_2CH_3), 3.18 (2H, q, NCH_2CH_3), 7.02–7.25 (2H_{arom}), 8.50–8.72 (2H_{arom}) ppm; UV: basic: λ_{max} ($\varepsilon \times 10^{-3}$) = 250 (8.2), 286 (5.5) nm; acidic: λ_{max} ($\varepsilon \times 10^{-3}$) = 262 (11.0), 286 (7.7) nm; MS: *m/z* (%) = 256 (M^+, 30), 255 (25), 241 (15), 228 (16), 227 (100), 213 (14), 184 (11), 161 (13), 143 (11), 118 (15), 117 (16), 116 (13), 104 (10), 93 (97), 92 (14), 85 (23), 83 (33), 72 (15), 43 (17).

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