A Novel and Efficient Synthesis of Pyrido[1,2-*a*]-Fused 1,3-Diazaheterocyclic Compounds *via* a One-Pot Three-Component Reaction

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An efficient one-pot synthesis of pyrido[1,2-*a*]-fused 1,3-diazaheterocyclic compounds by three-component reaction of diamine, nitroketene dithioacetal (=1,1-bis(methylsulfanyl)-2-nitroethene), and electron-poor itaconic anhydride (=2-methylidenesuccinic anhydride=2-methylidenebutanedioic anhydride) in aqueous EtOH is reported. This protocol has the advantages of easiness, higher yields, and shorter reaction times. The structures were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this type of cyclization is proposed (*Scheme 2*).

Introduction. – Heterocyclic ketene aminals are versatile synthons for the synthesis of various types of heterocyclic compounds, and they have been receiving increasing attention. Considering the important biological properties of fused pyridines, we continued our efforts for design of new routes for the synthesis of a variety of biologically active fused polycyclic N-heterocycles *via* one-pot synthesis and the reaction of aminals [1]. Here, we describe an efficient synthesis of highly substituted pyrido[1,2-*a*]-fused 1,3-diazaheterocycles *via* a new and one-pot three-component reaction between nitroketene aminals, derived from the addition of various diamines to nitroketene dithioacetal (=1,1-bis(methylsulfanyl)-2-nitroethene) and itaconic anhydride (=2-methylidenebutanedioic anhydride).

Results and Discussion. – The new synthetic route is outlined in *Scheme 1*. The reaction of diamine **1**, 1,1-bis(methylsulfanyl)-2-nitroethene, and itaconic anhydride for 5 h in aqueous EtOH at room temperature afforded pyrido[1,2-*a*]-fused 1,3-diazaheterocycles **2** in excellent yields (*Table*).

Scheme 1. *Synthesis of Pyrido[1,2-*a*]-Fused 1,3-Diazaheterocycles*

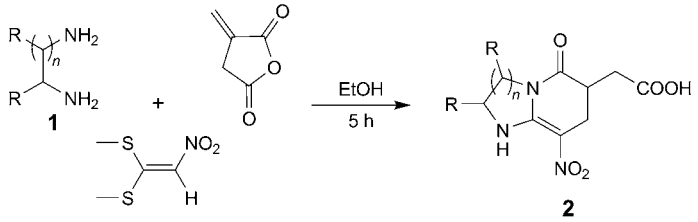
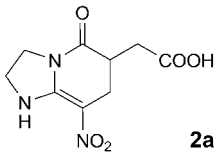
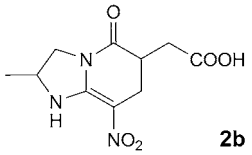
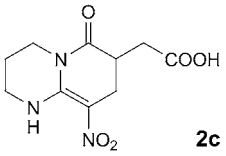
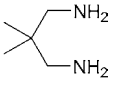
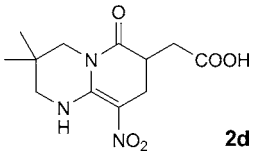
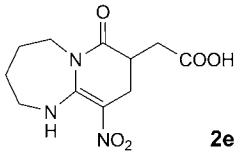
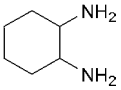
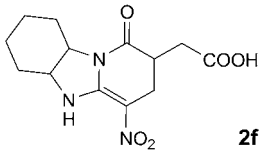
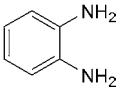
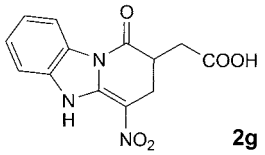


Table. *Prepared Pyrido[1,2-a]-Fused 1,3-Diazaheterocycles* **2**

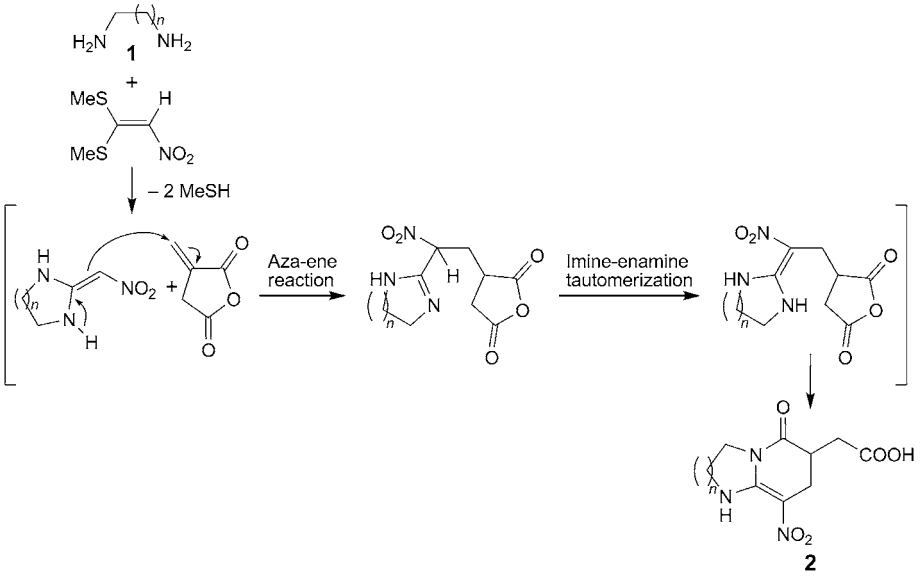
Entry	Diamine	Structure of **2**	Yield [%]
1		 **2a**	80
2		 **2b**	74
3		 **2c**	82
4		 **2d**	77
5		 **2e**	71
6		 **2f**	75
7		 **2g**	78

The structures of compounds **2a**–**2g** were deduced from their elemental analyses, and IR, high-field ^{1}H- and ^{13}C-NMR, and mass spectra. The mass spectrum of **2c** displayed the molecular-ion peak at *m*/*z* 255, which is in agreement with the proposed structure. The IR spectrum in KBr of **2c** showed absorption bands due to the OH and NH stretching at 3393 and 3050 cm^{-1}, respectively. Further absorption bands at 1705,

1621, and 1511 cm^{-1} are due to the CO_2H, C=O and NC=C groups, respectively. The ^{1}H-NMR spectrum of **2c** exhibited seven *multiplet*s for CH and CH_2 groups with diastereotopic H-atoms; (δ(H) 1.80–2.01, 2.41–2.49, 2.97–3.05, 3.38–3.46, 3.50–3.56, 3.57–3.59, and 3.77–3.80), two *doublet* of *doublet*s for the C–CH_2 group (δ(H) 2.68 (^2J = 11.2, ^3J = 5.7) and 3.21 (^2J = 11.2, ^3J = 5.7)), and two *singlet*s for NH and OH groups (δ(H) 11.53 and 12.27, resp.). The ^{1}H-decoupled ^{13}C-NMR spectrum of **2c** showed ten distinct resonances in agreement with the suggested structure.

A plausible mechanism of the ring-closure cascade reaction including nucleophilic substitution, aza-ene reaction, intramolecular imine–enamine tautomerization, followed by cyclization, is proposed (*Scheme 2*).

Scheme 2. *A Plausible Mechanism for the Formation of Products* **2a**–**2g**



In summary, we developed a concise approach to the synthesis of substituted pyrido[1,2-*a*]-fused 1,3-diazaheterocycles by one-pot reaction between diamines, 1,1-bis(methylsulfanyl)-2-nitroethene, and itaconic anhydride. Characteristics of this method are excellent yields of the products, fairly fast reaction times, mild reaction conditions, and use of simple and inexpensive starting materials. The present method has the advantage that the reaction is performed under neutral conditions without any further activation or modification. The simplicity of the present procedure renders it as an interesting alternative to complex multistep approaches.

Experimental Part

General. The diamines, 1,1-bis(methylsulfanyl)-2-nitroethene, and itaconic anhydride (=2-methylidenebutanedioic anhydride) were obtained from *Merck* (Germany) and *Fluka* (Switzerland) and were used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: in KBr on a *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: at 500 and 125 MHz, resp., with a *BRUKER*

DRX 500-AVANCE FT-NMR instrument, in $CDCl_3$, if not otherwise stated. MS: *Finnigan MAT 8430* mass spectrometer; at 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN–O–Rapid* analyzer.

General Procedure (exemplified for **2c**). A soln. of 1,1-bis(methylsulfanyl)-2-nitroethene (0.165 g, 1 mmol) and propane-1,3-diamine (0.074 g, 1 mmol) in EtOH (5 ml) was magnetically stirred for 4 h at reflux. Then, a soln. of itaconic anhydride (0.112 g, 1 mmol) in EtOH (2 ml) was added dropwise at r.t., and the mixture was stirred for 1 h. After completion, the mixture was filtered, and the precipitate was washed with cold EtOH to afford the pure product **2c**.

*2-(1,2,3,5,6,7-Hexahydro-8-nitro-5-oxoimidazo[1,2-*a*]pyridin-6-yl)acetic Acid* (**2a**). Yield: 193 mg (80%). Brown powder. M.p. 150–160° (dec.). IR: 3393 (OH), 3050 (NH), 1705 (CO_2H), 1621 (CO), 1511 (NCC), 1251 (C–N), 1142 (C–O). ^{1}H-NMR: 2.44–2.56 (*m*, 2 H); 2.68 (*dd*, $^2J = 11.2$, $^3J = 5.3$, 1 H); 2.95–3.99 (*m*, 1 H); 3.11 (*dd*, $^2J = 11.2$, $^3J = 5.3$, 1 H); 3.72–3.91 (*m*, 4 H); 10.01 (*s*, 1 H); 10.57 (*s*, 1 H). ^{13}C-NMR: 26.56; 34.59; 37.42; 43.22; 43.84; 111.34; 152.86; 170.05; 173.17. EI-MS (70 eV): 239 (1), 218 (1), 178 (3), 149 (23), 121 (31), 93 (30), 55 (100). Anal. calc. for $C_9H_{11}N_3O_5$ (241.20): C 44.82, H 4.60, N 17.42; found: C 44.54, H 4.52, N 17.45.

*2-(1,2,3,5,6,7-Hexahydro-2-methyl-8-nitro-5-oxoimidazo[1,2-*a*]pyridin-6-yl)acetic Acid* (**2b**). Yield: 189 mg (74%). White powder. M.p. 150–160° (dec.). IR: 3298 (OH), 3070 (NH), 1703 (CO_2H), 1637 (CO), 1522 (NCC), 1278 (C–N), 1154 (C–O). ^{1}H-NMR: 1.29 (*s*, 3 H); 2.16–2.52 (*m*, 1 H); 3.04–3.14 (*m*, 2 H); 3.35–3.46 (*m*, 1 H); 3.88–4.15 (*m*, 2 H); 4.43–4.49 (*m*, 1 H); 9.67 (*s*, 1 H); 12.28 (*s*, 1 H). ^{13}C-NMR: 20.46; 26.13; 34.03; 36.89; 49.64; 51.82; 102.38; 151.81; 169.69; 172.55. EI-MS (70 eV): 255 (1, M^+), 239 (1), 192 (7), 163 (20), 135 (16), 93 (30), 68 (59), 55 (100). Anal. calc. for $C_{10}H_{13}N_3O_5$ (255.23): C 47.06, H 5.13, N 16.46; found: C 47.02, H 5.10, N 16.48.

*2-(1,3,4,6,7,8-Hexahydro-9-nitro-6-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)acetic Acid* (**2c**). Yield: 209 mg (82%). White powder. M.p. 150–160° (dec.). IR: 3298 (OH), 3150 (NH), 1704 (CO_2H), 1642 (CO), 1510 (NCC), 1287 (C–N), 1156 (C–O). ^{1}H-NMR: 1.80–2.01 (*m*, 2 H); 2.41–2.49 (*m*, 2 H); 2.68 (*dd*, $^2J = 11.1$, $^3J = 5.6$,1 H); 2.97–3.05 (*m*, 1 H); 3.21 (*dd*, $^2J = 11.2$, $^3J = 5.7$, 1 H); 3.38–3.46 (*m*, 1 H); 3.50–3.56 (*m*, 1 H); 3.57–3.59 (*m*, 1 H); 3.77–3.80 (*m*, 1 H); 11.53 (*s*, 1 H); 12.27 (*s*, 1 H). ^{13}C-NMR: 19.17; 25.35; 34.14; 36.23; 38.77; 39.09; 105.49; 137.71; 170.81; 172.60. EI-MS (70 eV): 255 (1, M^+), 163 (13), 135 (14), 107 (14), 80 (22), 66 (24), 55 (100). Anal. calc. for $C_{10}H_{13}N_3O_5$ (255.23): C 47.06, H 5.13, N 16.46; found: C 67.11, H 5.12, N 16.45.

*2-(1,3,4,6,7,8-Hexahydro-3,3-dimethyl-9-nitro-6-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-7-yl)acetic Acid* (**2d**). Yield: 218 mg (77%). White powder. M.p. 150–160° (dec.). IR: 3387 (OH), 3017 (NH), 1705 (CO_2H), 1620 (CO), 1509 (NCC), 1248 (C–N), 1140 (C–O). ^{1}H-NMR: 0.97 (*s*, 6 H); 2.43–2.55 (*m*, 2 H); 2.70 (*dd*, $^2J = 11.1$, $^3J = 5.9$, 1 H); 3.03–3.09 (*m*, 1 H); 3.18–3.25 (*m*, 1 H); 3.22–3.60 (*m*, 2 H); 3.30–3.33 (*m*, 1 H); 3.58–3.61 (*m*, 1 H); 11.50 (*s*, 1 H); 12.29 (*s*, 1 H). ^{13}C-NMR: 23.18; 23.42; 23.42; 34.11; 36.19; 49.81; 49.87; 105.28; 151.22; 170.99; 172.47. EI-MS (70 eV): 283 (1, M^+), 237 (9), 220 (7), 191 (13), 137 (12), 106 (9), 80 (16), 68 (24), 55 (100). Anal. calc. for $C_{12}H_{17}N_3O_5$ (283.28): C 50.88, H 6.05, N 14.83; found: C 50.86, H 6.07, N 14.82.

*2-(1,2,3,4,5,7,8,9-Octahydro-10-nitro-7-oxopyrido[1,2-*a*][1,3]diazepin-8-yl)acetic Acid* (**2e**). Yield: 191 mg (71%). White powder. M.p. 155–165° (dec.). IR: 3384 (OH), 3090 (NH), 1705 (CO_2H), 1610 (CO), 1523 (NCC), 1275 (C–N), 1137 (C–O). ^{1}H-NMR: 1.60–1.85 (*m*, 4 H); 2.30–2.48 (*m*, 2 H); 2.59–2.68 (*m*, 1 H); 2.87–3.26 (*m*, 2 H); 3.24–4.27 (*m*, 4 H); 11.11 (*s*, 1 H); 12.26 (*s*, 1 H). ^{13}C-NMR: 24.26; 24.41; 25.02; 33.67; 37.13; 44.95; 45.24; 109.68; 157.25; 171.92; 172.60. EI-MS (70 eV): 269 (30, M^+), 252 (12), 206 (87), 192 (31), 177 (73), 123 (26), 95 (16), 70 (35), 55 (100). Anal. calc. for $C_{11}H_{15}N_3O_5$ (269.25): C 49.07, H 5.62, N 15.61; found: C 49.10, H 5.60, N 15.59.

*2-(1,2,3,5,5a,6,7,8,9,9a-Decahydro-4-nitro-1-oxopyrido[1,2-*a*]benzimidazol-2-yl)acetic Acid* (**2f**). Yield: 225 mg (78%). White powder. M.p. 175–180° (dec.). IR: 3307 (NH), 3062 (OH), 1705 (CO_2H), 1629 (CO), 1522 (NCC), 1255 (C–N), 1176 (C–O). ^{1}H-NMR: 1.29–1.53 (*m*, 4 H); 1.60–1.83 (*m*, 4 H); 2.51–2.74 (*m*, 3 H); 3.07–3.33 (*m*, 2 H); 4.00–4.10 (*m*, 1 H); 4.27–4.36 (*m*, 1 H); 9.68 (*s*, 1 H); 12.27 (*s*, 1 H). ^{13}C-NMR: 23.38; 23.65; 26.92; 27.83; 28.31; 33.76; 36.64; 62.36; 63.66; 103.93; 153.79; 170.03; 172.65. EI-MS (70 eV): 295 (2, M^+), 232 (17), 203 (17), 175 (7), 147 (16), 119 (16), 93 (2), 81 (65), 55 (100). Anal. calc. for $C_{13}H_{17}N_3O_5$ (295.29): C 52.88, H 5.80, N 14.23; found: C 52.85, H 5.79, N 14.24.

2-(1,2,3,5-Tetrahydro-4-nitro-1-oxopyrido[1,2-a]benzimidazol-2-yl)acetic Acid (**2g**). Yield: 225 mg (78%). Brown powder. M.p. 175–180° (dec.). IR: 1405 (OH), 3196 (NH), 1716 (CO_2H), 1620 (CO), 1406 (NCC), 1270 (C–N), 1150 (C–O). ^{1}H-NMR: 2.62–2.66 (*m*, 1 H); 2.76–2.88 (*m*, 2 H); 3.28–3.48 (*m*, 2 H); 7.27 (*t*, ^3J = 7.7, 1 H); 7.35 (*t*, ^3J = 7.7, 1 H); 7.52 (*d*, ^3J = 7.7, 1 H); 8.02 (*d*, ^3J = 7.7, 1 H); 11.44 (*s*, 1 H); 12.92 (*s*, 1 H). ^{13}C-NMR: 25.95; 30.62; 33.61; 103.31; 112.55; 114.37; 124.20; 125.87; 128.80; 131.65; 146.26; 169.81; 172.47. EI-MS (70 eV): 285 (1), 225 (4), 169 (36), 144 (30), 118 (30), 90 (85), 63 (100). Anal. calc. for $C_{13}H_{11}N_3O_5$ (289.24): C 53.98, H 3.83, N 14.53; found: C 53.99, H 3.81, N 14.52.

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Received June 30, 2011