Synthesis of 2-Oxopyridine-Fused 1,3-Diazaheterocyclic Compounds *via* a Three-Component Reaction

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An efficient and simple route for the preparation of 2-oxopyridine-fused 1,3-diazaheterocyclic compounds *via* a three component reaction is described. It involves the reaction between alkylenediamines **1**, 1,1-bis(methylsulfanyl)-2-nitroethene, and alkyl prop-2-ynoates **2** in refluxing THF (*Table*). The structures were corroborated by spectroscopic (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and elemental analyses. A plausible mechanism for this type of cyclization is proposed (*Scheme*).

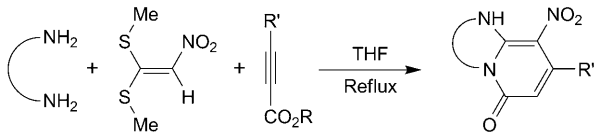
Introduction. – The development of new and simple methods for the efficient preparation of compounds containing 2-oxopyridine-fused 1,3-diazaheterocycle moieties is a beneficial and interesting challenge [1–6]. As a part of our research program, which is aimed at developing libraries of bioactive compounds, and in continuation of our interest in one-pot and multicomponent reactions (MCRs), a three-component reaction toward fused heterocycles is described herein.

Results and Discussion. – In this article, we report a simple method for the synthesis of 2-oxopyridine-fused 1,3-diazaheterocycles *via* a three-component reaction of alkylenediamines **1**, 1,1-bis(methylsulfanyl)-2-nitroethene, and alkyl prop-2-ynoates **2** (*cf.* the *Table*). The reactions were performed under one-pot condition in refluxing THF and led to compounds **3a**–**3g** in yields of 65–75%.

The structures of compounds **3a**–**3g** were deduced from their elemental analyses, and IR, ^{1}H- and ^{13}C-NMR, and mass spectra. The mass spectrum of **3a** displays the molecular-ion peak at *m*/*z* 195, which is in agreement with the proposed structure. The IR spectrum of **3a** shows four stretching frequencies at 3216, 1673, and 1579 and 1339 cm^{-1}, which correspond to an NH group, the CO group of an amide, and $\tilde{\nu}_{as}$ and $\tilde{\nu}_{s}$ of a NO_2 group, respectively. The ^{1}H-NMR spectra of **3a** exhibited a *singlet* at δ(H) 10.26 for NH, two *triplet*s for CH_2NH and CH_2N (δ(H) 3.63 ($J = 6.0$) and 4.07 ($J = 6.0$)), one *multiplet* for CH_2 (δ(H) 2.15–2.19), and two *doublet*s for a (*Z*)-configured CH=CH moiety (δ(H) 5.90 ($^3J = 10.1$), and 8.16 ($^3J = 10.1$)). The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed eight distinct resonances in agreement with the suggested structure. Partial assignments of these signals are given in the *Exper. Part.*

The proposed mechanism of the reaction is depicted in the *Scheme* and includes the nucleophilic attack of **1** at C(1) of 1,1-bis(methylsulfanyl)-2-nitroethene to yield intermediate **4** which cyclizes by a second nucleophilic attack to ketene aminal **5**. In the next step, the aza-ene reaction [7][8] between cyclic ene-1,1-diamine **5** and alkyl prop-

Table. *Reaction of Alkylenediamines* **1**, *1,1-Bis(methylsulfanyl)-2-nitroethene, and Alkyl Prop-2-ynoates* **2** *in Refluxing THF*

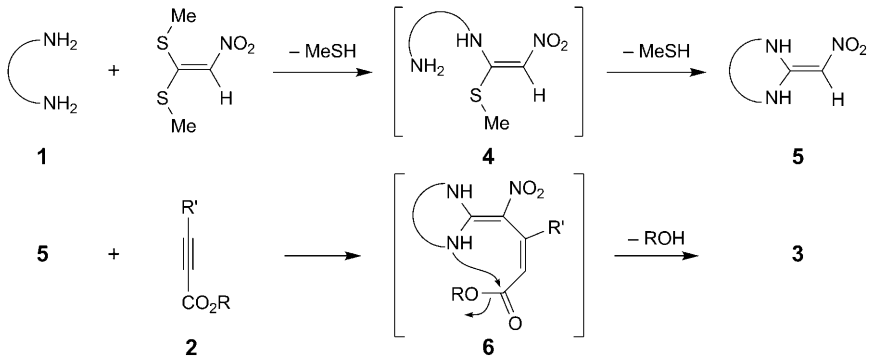


1 **2** **3**

Entry	**1**	R	R′	Product	Catalyst	Yield [%]
1	Propane-1,3-diamine	Me	H	**3a**	–	75
2	Propane-1,3-diamine	Et	Ph	**3b**	TsOH	65
3	2,2-Dimethylpropane-1,3-diamine	Me	H	**3c**	–	70
4	2,2-Dimethylpropane-1,3-diamine	Et	Ph	**3d**	TsOH	70
5	Butane-1,4-diamine	Me	H	**3e**	–	65
6	Butane-1,4-diamine	Et	Ph	**3f**	TsOH	70
7	Cyclohexane-1,2-diamine	Me	H	**3g**	–	70

2-ynoates **2** gives the intermediate **6**, which undergoes nucleophilic attack of the secondary amino group at the CO group of the ester function leading to adduct **3**. It should be mentioned that we applied TsOH for activating the CO group, when ethyl 3-phenylprop-2-ynoate was used as reagent **2**.

Scheme. *Proposed Mechanism for the Formation of 2-Oxopyridine-Fused 1,3-Diazaheterocycles* **3**



In conclusion, we have developed a convenient one-pot procedure for the synthesis of 2-oxopyridine-fused 1,3-diazaheterocycles, which represent a class of potentially bioactive compounds. The starting materials are readily available.

Experimental Part

General. Reagents and solvents were obtained from *Fluka* (CH-Buchs) and used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: in KBr, *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: at 500 and 125 MHz, resp., *Bruker DRX 500-Avance* FT-NMR instrument, in $CDCl_3$ if not otherwise stated. MS: *Finnigan-MAT 8430* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer.

General Procedure (exemplified for **3a**). To a magnetically stirred soln. of 1,1-bis(methylsulfanyl)-2-nitroethene (0.166 g, 1 mmol) and propane-1,3-diamine (**1a**; 0.074 g, 1 mmol) in THF (5 ml) under reflux was slowly added methyl prop-2-ynoate (0.142 g, 1 mmol), and stiring was continued for 2–3 h. After completion of the reaction, the crude product was purified by CC (SiO_2; *Merck*, 230–240 mesh; hexane/AcOEt 5:1).

*1,2,3,4-Tetrahydro-9-nitro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one* (**3a**). Yield: 150 mg (75%). Yellow crystals. M.p. 222–226°. IR: 3216 (NH), 1673 (CON), 1579, 1339 (NO_2). ^{1}H-NMR: 2.15–2.19 (*m*, 2 H); 3.63 (*t*, *J* = 6.0, 2 H); 4.07 (*t*, *J* = 6.0, 2 H); 5.90 (*d*, *J* = 10.1, 1 H); 8.16 (*d*, *J* = 10.1, 1 H); 10.26 (*s*, 1 H). ^{13}C-NMR: 19.0; 39.0; 39.9; 106.6; 114.3; 135.7; 150.4; 161.2. EI-MS: 195 (100, M^+), 165 (81), 149 (13), 137 (35), 121 (89), 109 (17), 93 (26), 81 (22), 69 (37), 64 (40), 55 (39), 41 (50). Anal. calc. for $C_8H_9N_3O_3$ (195.18): C 49.23, H 4.65, N 21.53; found: C 49.20, H 4.69, N 21.57.

*1,2,3,4-Tetrahydro-9-nitro-8-phenyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one* (**3b**). Yield: 190 mg (65%). Yellow crystals. M.p. 210°. IR: 3211 (NH), 1683 (CON), 1587, 1368 (NO_2). ^{1}H-NMR: 2.13–2.18 (*m*, 2 H); 3.60–3.63 (*m*, 2 H); 4.12 (*t*, *J* = 5.9, 2 H); 5.83 (*s*, 1 H); 7.21–7.23 (*m*, 2 H); 7.36–7.40 (*m*, 3 H); 10.21 (*s*, 1 H). ^{13}C-NMR: 18.8; 39.1; 39.8; 109.5; 114.0; 125.9; 127.9; 128.1; 138.7; 150.1; 150.2; 159.7. EI-MS: 271 (100, M^+), 234 (57), 209 (26), 192 (26), 169 (17), 156 (16), 140 (23), 128 (30), 115 (28), 103 (57), 77 (74), 57 (63). Anal. calc. for $C_{14}H_{13}N_3O_3$ (271.27): C 61.99, H 4.83, N 15.49; found: C 61.94, H 4.87, N 15.53.

*1,2,3,4-Tetrahydro-3,3-dimethyl-9-nitro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one* (**3c**). Yield: 160 mg (70%). Yellow crystals. M.p. 202° (dec.). IR: 3229 (NH), 1675 (CON), 1601, 1347 (NO_2). ^{1}H-NMR: 1.14 (*s*, 6 H); 3.28 (*s*, 2 H); 3.75 (*s*, 2 H); 5.91 (*d*, *J* = 10.2, 1 H); 8.17 (*d*, *J* = 10.2, 1 H); 10.25 (*s*, 1 H). ^{13}C-NMR: 24.0; 26.4; 50.3; 50.6; 106.6; 106.7; 135.7; 149.5; 161.5. EI-MS: 223 (32, M^+), 211 (17), 149 (12), 117 (100), 112 (59), 100 (63), 91 (35), 83 (34), 71 (72), 57 (93), 41 (45). Anal. calc. for $C_{10}H_{13}N_3O_3$ (223.23): C 53.81, H 5.87, N 18.82; found: C 53.83, H 5.89, N 18.80.

*1,2,3,4-Tetrahydro-3,3-dimethyl-9-nitro-8-phenyl-6*H*-pyrido[1,2-*a*]pyrimidin-6-one* (**3d**). Yield: 210 mg (70%). Yellow crystals. M.p. 244–247°. IR: 3200 (NH), 1682 (CON), 1582, 1361 (NO_2). ^{1}H-NMR ((D_6)DMSO): 1.03 (*s*, 6 H); 3.31 (*s*, 2 H); 3.68 (*s*, 2 H); 5.61 (*s*, 1 H); 7.22 (*d*, *J* = 6.4, 2 H); 7.33–7.38 (*m*, 3 H); 10.08 (*s*, 1 H). ^{13}C-NMR ((D_6)DMSO): 23.6; 25.8; 50.2; 50.5; 108.5; 113.4; 126.3; 128.0; 128.4; 139.5; 149.4; 149.5; 159.7. EI-MS: 299 (100, M^+), 269 (43), 253 (8), 225 (7), 209 (5), 197 (6), 185 (6), 169 (9), 157 (6), 140 (15), 128 (11), 115 (15), 102 (10), 77 (9), 69 (7), 55 (11). Anal. calc. for $C_{16}H_{17}N_3O_3$ (299.33): C 64.20, H 5.72, N 14.04; found: C 64.24, H 5.75, N 14.08.

*2,3,4,5-Tetrahydro-10-nitropyrido[1,2-*a*][1,3]diazepin-7(1*H*)-one* (**3e**). Yield: 140 mg (65%). Yellow crystals. M.p. 157–160°. IR: 3229 (NH), 1688 (CON), 1579, 1371 (NO_2). ^{1}H-NMR: 2.01–2.10 (*m*, 4 H); 3.75 (*t*, *J* = 7.9, 2 H); 4.35 (*t*, *J* = 6.1, 2 H); 5.93 (*d*, *J* = 10.2, 1 H); 8.11 (*d*, *J* = 10.2, 1 H); 10.04 (*s*, 1 H). ^{13}C-NMR: 23.4; 24.2; 44.5; 44.9; 108.0; 116.5; 135.4; 155.0; 161.8. EI-MS: 209 (100, M^+), 192 (99), 179 (12), 162 (57), 134 (25), 106 (14), 80 (13), 55 (27). Anal. calc. for $C_9H_{11}N_3O_3$ (209.20): C 51.67, H 5.30, N 20.09; found: C 51.70, H 5.32, N 20.07.

*2,3,4,5-Tetrahydro-10-nitro-9-phenylpyrido[1,2-*a*][1,3]diazepin-7(1*H*)-one* (**3f**). Yield: 200 mg (70%). Yellow crystals. M.p. 202–206°. IR: 3303 (NH), 1665 (CON), 1549, 1333 (NO_2). ^{1}H-NMR: 1.98–2.10 (*m*, 4 H); 3.61 (*t*, *J* = 7.2, 2 H); 4.35 (*t*, *J* = 7.3, 2 H); 6.01 (*s*, 1 H); 7.23–7.27 (*m*, 2 H); 7.35–7.39 (*m*, 3 H); 9.11 (*s*, 1 H). ^{13}C-NMR: 23.6; 24.4; 45.4; 45.7; 112.3; 118.6; 125.7; 127.9; 128.0; 137.4; 149.1; 154.2; 160.8. EI-MS: 285 (100, M^+), 268 (34), 238 (30), 169 (16), 140 (20), 115 (21), 97 (27), 83 (27), 69 (39), 55 (67). Anal. calc. for $C_{15}H_{15}N_3O_3$ (285.30): C 63.15, H 5.30, N 14.73; found: C 63.18, H 5.33, N 14.74.

*5a,6,7,8,9,9a-Hexahydro-4-nitropyrido[1,2-*a*]benzimidazol-1(5*H*)-one* (**3g**). Yield: 160 mg (70%). Yellow crystals. M.p. 194–196° (dec.). IR: 3331 (NH), 1680 (CON), 1570, 1345 (NO_2). ^{1}H-NMR: 1.36–2.34 (*m*, 8 H); 3.49–3.55 (*m*, 1 H); 3.68–3.74 (*m*, 1 H); 5.85 (*d*, *J* = 10.1, 1 H); 7.96 (*d*, *J* = 10.1, 1 H); 8.07 (*s*, 1 H). ^{13}C-NMR: 23.2; 23.7; 28.7; 29.2; 63.3; 65.6; 109.7; 113.8; 134.5; 153.2; 162.0. EI-MS: 235 (100, M^+), 190 (21), 161 (21), 125 (12), 81 (34), 55 (11). Anal. calc. for $C_{11}H_{13}N_3O_3$ (235.24): C 56.16, H 5.57, N 17.86; found: C 56.13, H 5.60, N 17.83.

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