One-Pot Synthesis of Pyrimidines *via* Cyclocondensation of β-Bromovinyl Aldehydes with Amidine Hydrochlorides

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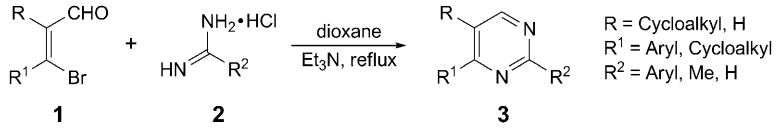
A series of pyrimidines were prepared by cyclocondensation of β-bromovinyl aldehydes with amidine hydrochlorides in the presence of Et_3N in excellent yields (74–95%).

Introduction. – As part of our interest in the development of simple and efficient procedures to synthesize various N-containing heterocycles with potential bioactivities [1], we report herein an efficient method, based on cyclocondensation of β-bromovinyl aldehydes **1** with amidine hydrochlorides **2**, for the rapid construction of a library of pyrimidines.

Results and Discussion. – Initially, an easily available starting material, β-bromovinyl aldehyde **1a**, was reacted with 0.83 equiv. of 4-(trifluoromethyl)benzamidine hydrochloride (**2a**) in 1,4-dioxane, catalyzed by Et_3N and at reflux for 8 h, successfully affording the pyrimidine **3a** in good yield (85%; *Scheme*; *Table*, *Entry 1*). The product was identified by spectroscopic data and high-resolution mass spectrometry.

Encouraged by this result, we explored the scope and limitations of cyclocondensation reactions involving various β-bromovinyl aldehydes **1** with a number of amidine hydrochlorides **2** (*Table*, *Entries 1–22*). The results revealed that β-bromovinyl aldehydes with various substituents were all good substrates for the cyclocondensation reaction (*Table*, *Entries 1–22*). The reactions usually only took 6–8 h at reflux in 1,4-dioxane in the presence of Et_3N and gave the target compounds in good yields.

Scheme. *Synthesis of Pyrimidines*



1 **2** **3**

The structures of the β-bromovinyl aldehydes **1** have modest influence on the reactivity and yields, so we cannot derive a general rule on the group effects of the

[1]) These authors contributed equally to this article.

Table. *Synthesis of Pyrimidines*

Entry	**1**	**2**	**3**	R	R^1	R^2	Yield [%][a]	M.p. [°] (lit. m.p.)
1	**1a**	**2a**	**3a**	H	Ph	4-CF_3–C_6H_4	85	208–210
2	**1a**	**2b**	**3b**	H	Ph	4-Cl–C_6H_4	92	116–120 (115–117) [2]
3	**1a**	**2c**	**3c**	H	Ph	Ph	93	71.5–73.5 (74–75) [2]
4	**1a**	**2d**	**3d**	H	Ph	4-Me–C_6H_4	92	86–87 (91–94) [3]
5	**1a**	**2e**	**3e**	H	Ph	H	74	58–61 (61–62) [4]
6	**1a**	**2f**	**3f**	H	Ph	Me	79	56 (54–54.5) [3]
7	**1b**	**2a**	**3g**	H	4-Cl–C_6H_4	4-CF_3–C_6H_4	84	217–221
8	**1b**	**2b**	**3h**	H	4-Cl–C_6H_4	4-Cl–C_6H_4	94	147–152
9	**1b**	**2c**	**3i**	H	4-Cl–C_6H_4	Ph	83	69–72
10	**1b**	**2d**	**3j**	H	4-Cl–C_6H_4	4-Me–C_6H_4	93	153–154.6
11	**1b**	**2e**	**3k**	H	4-Cl–C_6H_4	H	77	90–92 (80–90) [5]
12	**1b**	**2f**	**3l**	H	4-Cl–C_6H_4	Me	81	95–97 (91–93) [6]
13	**1c**	**2a**	**3m**	H	4-Me–C_6H_4	4-CF_3–C_6H_4	86	190–190.5
14	**1c**	**2b**	**3n**	H	4-Me–C_6H_4	4-Cl–C_6H_4	95	74–75.6
15	**1c**	**2c**	**3o**	H	4-Me–C_6H_4	Ph	88	102–104 (109.5–110) [3]
16	**1c**	**2d**	**3p**	H	4-Me–C_6H_4	4-Me–C_6H_4	91	114–116.5
17	**1c**	**2f**	**3q**	H	4-Me–C_6H_4	Me	80	70–72.5 (79–79.5) [3]
18	**1c**	**2g**	**3r**	H	4-Me–C_6H_4	Pyridin-4-yl	95	208–209.5
19	**1d**	**2b**	**3s**		–$(CH_2)_4$–	4-Cl–C_6H_4	93	159–163
20	**1d**	**2c**	**3t**		–$(CH_2)_4$–	Ph	89	50–52 (52–53) [7]
21	**1d**	**2d**	**3u**		–$(CH_2)_4$–	4-Me–C_6H_4	85	149–152
22	**1d**	**2g**	**3v**		–$(CH_2)_4$–	Pyridin-4-yl	91	95–96.5

[a]) Yields of isolated products, based on amidine hydrochlorides **2**.

substrates **1** (*Table*, *Entries 1–6 vs. 7–12*, and *13–18 vs. 19–22*, resp.). On the contrary, the structures of the amidine hydrochlorides **2** can contribute to the reactivity and yields. Thus, the aryl-substituted amidine hydrochlorides always lead to good-to-excellent yields (83–95%; *Table*, *Entries 1–4*, *7–10*, *13–16*, and *18–22*), whereas the alkyl-substituted amidine hydrochlorides usually give good yields (74–81%; *Table*, *Entries 5*, *6*, *11*, *12*, and *17*).

Conclusions. – We have developed a procedure for simple synthesis of a variety of potentially bioactive pyrimidines. By this method, a diverse pyrimidine library was rapidly constructed with good-to-excellent yields by simply refluxing a reaction mixture of β-bromovinyl aldehydes and the amidine hydrochlorides, catalyzed by Et_3N. The one-pot conditions and the mild reaction conditions render this method an attractive alternative for the synthesis of this type of *N*-containing heterocycles.

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Experimental Part

General. Compounds **1a–1d** were synthesized according to [8], and **2a–2g** were purchased from *Aldrich*. All novel compounds were fully characterized by spectroscopic analysis. All chemicals and solvents were used as received without further purification unless otherwise stated. Column

chromatography (CC): silica gel (SiO_2; 200–300 mesh). The reactions were monitored by TLC using silica gel GF_{254}. M.p.: *XT-4A* melting-point apparatus; uncorrected. IR Spectra: *FT-IR Thermo Nicolet Avatar 360*; KBr pellets. NMR Spectra: *Bruker DRX500* (^{1}H: 500 MHz, ^{13}C: 125 MHz); chemical shifts (δ) in ppm, and J values in Hz; $CDCl_3$ as solvent. HR-MS: *Agilent LC/Msd* TOF instrument.

General Procedure for the Preparation of Pyrimidines **3a**–**3v**. A 25-ml round-bottom flask was charged with β-bromovinyl aldehyde **1** (1.2 mmol), 1,4-dioxane (6 ml), and Et_3N (1.5 ml), then, the soln. was added to the amidine hydrochloride **2** (1.0 mmol), and the mixture was heated at reflux. The resulting soln. was stirred for 6–8 h **1** was completely consumed. The reaction was quenched by the addition of H_2O (25 ml), and then AcOEt (25 ml) was added. The org. phase was washed with H_2O (3 × 8 ml), dried (Na_2SO_4), concentrated, and purified by CC (petroleum ether/AcOEt 10:1) to afford the final product.

4-Phenyl-2-[4-(trifluoromethyl)phenyl]pyrimidine (**3a**). M.p. 208–210°. IR: 3432, 2569, 2333, 1633, 1520, 1374, 1324, 1115, 1068, 873. ^{1}H-NMR: 7.26–7.28 (*m*, 1 arom. H); 7.47 (*d*, J = 7.3, 2 arom. H); 7.74–7.83 (*m*, 4 arom. H); 8.41–8.44 (*m*, 1 arom. H); 8.79–8.81 (*m*, 3 arom. H). ^{13}C-NMR: 126.0; 126.3; 128.7; 129.4; 129.6; 129.6; 129.9; 130.7; 139.6; 143.3; 170.9; 172.9. HR-MS (TOF-ES$^+$): 302.1040 ($[M+2\,H]^+$, $C_{17}H_{13}F_3N_2^+$; calc. 302.1020).

4-(4-Chlorophenyl)-2-[4-(trifluoromethyl)phenyl]pyrimidine (**3g**). M.p. 217–221°. IR: 3435, 2573, 2328, 2190, 1649, 1396, 825. ^{1}H-NMR: 7.21–7.82 (*m*, 7 arom. H); 8.31–8.77 (*m*, 3 arom. H). ^{13}C-NMR: 123.2; 125.4; 125.7; 126.0; 128.5; 130.3; 134.1; 135.0; 136.6; 139.5; 141.7; 170.9; 172.6. HR-MS (TOF-ES$^+$): 334.0491 (M^+, $C_{17}H_{10}ClF_3N_2^+$; calc. 334.0485).

2,4-Bis(4-chlorophenyl)pyrimidine (**3h**). M.p. 147–152°. IR: 3471, 2925, 2855, 2338, 1586, 1392, 1092, 789. ^{1}H-NMR: 7.11–7.22 (*m*, 6 arom. H); 7.36 (*d*, J = 5.2, 1 arom. H); 7.89 (*d*, J = 8.3, 2 arom. H); 8.30 (*d*, J = 8.3, 2 arom. H); 8.52 (*d*, J = 5.2, 1 arom. H). ^{13}C-NMR: 114.7; 128.8; 129.0; 129.8; 130.4; 135.4; 136.4; 137.0; 137.3; 158.4; 162.8; 163.6. HR-MS (TOF-ES$^+$): 301.0299 ($[M+H]^+$, $C_6H_{11}Cl_2N_2^+$; calc. 301.0294).

4-(4-Chlorophenyl)-2-phenylpyrimidine (**3i**): M.p. 69–72°. IR: 3434, 2924, 2571, 2348, 1636, 1546, 1393, 1089. ^{1}H-NMR: 7.54–7.57 (*m*, 6 arom. H); 8.20–8.23 (*m*, 2 arom. H); 8.86–8.89 (*m*, 2 arom. H); 9.24–9.27 (*m*, 1 arom. H). ^{13}C-NMR: 114.6; 128.7; 128.9; 129.6; 129.9; 131.2; 135.8; 137.6; 138.1; 158.4; 163.1; 165.1. HR-MS (TOF-ES$^+$): 267.0689 ($[M+H]^+$, $C_{16}H_{12}ClN_2^+$; calc. 267.0684).

4-(4-Chlorophenyl)-2-(4-methylphenyl)pyrimidine (**3j**). M.p. 153–154.6°. IR: 3434, 2578, 2312, 1553, 1489, 1435, 1374. ^{1}H-NMR: 2.45 (*s*, Me); 7.33 (*d*, J = 7.8, 2 arom. H); 7.49–7.52 (*m*, 3 arom. H); 8.16 (*d*, J = 8.0, 2 arom. H); 8.46 (*d*, J = 8.0, 2 arom. H); 8.81 (*d*, J = 5.1, 1 arom. H). ^{13}C-NMR: 21.9; 114.3; 128.7; 129.2; 129.6; 129.8; 135.4; 135.9; 137.5; 141.5; 158.4; 163.0; 165.2. HR-MS (TOF-ES$^+$): 281.0848 ($[M+H]^+$, $C_{17}H_{14}ClN_2^+$; calc. 281.0840).

4-(4-Methylphenyl)-2-[4-(trifluoromethyl)phenyl]pyrimidine (**3m**). M.p. 190–190.5°. IR: 3438, 2577, 2337, 1635, 1509, 1387, 1323, 820. ^{1}H-NMR: 2.42 (*s*, Me); 7.25–7.27 (*m*, 2 arom. H); 7.63 (*d*, J = 7.9, 1 arom. H); 7.77–7.81 (*m*, 3 arom. H); 8.34–8.38 (*m*, 1 arom. H); 8.74–8.77 (*m*, 3 arom. H). ^{13}C-NMR: 21.9; 125.2; 125.4; 126.0; 128.7; 129.6; 130.2; 132.9; 134.2; 139.6; 141.2; 143.3; 170.7; 173.0. HR-MS (TOF-ES$^+$): 353.0652 ($[M+K]^+$, $C_{18}H_{13}F_3KN_2^+$; calc. 353.0662).

2-(4-Chlorophenyl)-4-(4-methylphenyl)pyrimidine (**3n**). M.p. 74–75.6°. IR: 3426, 2573, 2345, 1604, 1488, 1398, 1328, 1271. ^{1}H-NMR: 2.34 (*s*, Me); 6.16–6.52 (*m*, 1 arom. H); 7.09–7.13 (*m*, 2 arom. H); 7.37–7.48 (*m*, 4 arom. H); 7.98–8.01 (*m*, 3 arom. H). ^{13}C-NMR: 21.6; 126.1; 127.0; 127.8; 128.1; 129.1; 129.5; 129.8; 133.9; 135.8; 138.2; 140.1; 160.5. HR-MS (TOF-ES$^+$): 281.0834 ($[M+H]^+$, $C_{17}H_{14}ClN_2^+$; calc. 281.0840).

2,4-Bis(4-methylphenyl)pyrimidine (**3p**). M.p. 114–116.5°. IR: 3432, 2565, 2310, 1555, 1408, 817, 779. ^{1}H-NMR: 2.42 (*s*, 2 Me); 7.29–7.32 (*m*, 4 arom. H); 7.51 (*d*, J = 5.0, 1 arom. H); 8.11 (*d*, J = 7.7, 2 arom. H); 8.46 (*d*, J = 7.7, 2 arom. H); 8.76 (*d*, J = 5.0, 1 arom. H). ^{13}C-NMR: 21.9; 22.2; 114.3; 127.5; 128.7; 129.7; 130.1; 134.7; 135.7; 141.3; 141.7; 158.1; 164.2; 165.0. HR-MS (TOF-ES$^+$): 261.1390 ($[M+H]^+$, $C_{18}H_{17}N_2^+$; calc. 261.1386).

4-(4-Methylphenyl)-2-(pyridin-4-yl)pyrimidine (**3r**). M.p. 208–209.5°. IR: 3438, 3034, 2916, 2351, 2202, 1627, 1509, 1372. ^{1}H-NMR: 2.40 (*s*, Me); 7.1–7.9 (*m*, 4 arom. H); 8.18–8.85 (*m*, 6 arom. H). ^{13}C-NMR: 22.0; 122.6; 128.8; 129.2; 129.8; 130.8; 141.5; 143.4; 144.0; 151.3; 170.6; 173.4. HR-MS (TOF-ES$^+$): 248.1190 ($[M+H]^+$, $C_{16}H_{14}N_3^+$; calc. 248.1182).

2-(4-Chlorophenyl)-5,6,7,8-tetrahydroquinazoline (**3s**). M.p. 159–163°. IR: 3448, 2932, 2850, 1607, 1494, 1335, 1273, 1175, 1086. ^{1}H-NMR: 1.60–1.70 (*m*, 2 CH_2); 2.20–2.68 (*m*, 2 CH_2); 6.33 (*s*, 1 arom. H); 7.34 (br. *s*, 2 arom. H); 7.96 (br. *s*, 2 arom. H). ^{13}C-NMR: 22.5; 25.0; 25.4; 26.4; 121.7; 128.8; 129.0; 129.2; 134.0; 137.4; 138.1; 160.0. HR-MS (TOF-ES$^+$): 245.0835 ($[M+H]^+$, $C_{14}H_{14}ClN_2^+$; calc. 245.0840).

5,6,7,8-Tetrahydro-2-(4-methylphenyl)quinazoline (**3u**). M.p. 149–152°. IR: 3426, 2935, 2850, 2569, 1683, 1626, 1540, 1419, 1084. ^{1}H-NMR: 1.85–1.86 (*m*, CH_2); 1.91–1.93 (*m*, CH_2); 2.41 (*s*, Me); 2.71–2.76 (*m*, CH_2); 2.91–2.94 (*m*, CH_2); 7.27 (*d*, $J=7.8$, 2 arom. H); 8.26 (*d*, $J=7.8$, 2 arom. H); 8.43 (*s*, 1 arom. H). ^{13}C-NMR: 21.7; 22.8; 26.0; 32.6; 39.1; 127.9; 128.2; 129.6; 135.7; 140.6; 157.4; 162.5; 166.5. HR-MS (TOF-ES$^+$): 225.1396 ($[M+H]^+$, $C_{15}H_{17}N_2^+$; calc. 225.1386).

5,6,7,8-Tetrahydro-2-(pyridin-4-yl)quinazoline (**3v**). M.p. 95–6.5°. IR: 3315, 2935, 1642, 1537, 1420, 1087, 922, 771. ^{1}H-NMR: 1.86–1.89 (*m*, CH_2); 1.92–1.97 (*m*, CH_2); 2.78–2.90 (*m*, CH_2); 2.93–2.96 (*m*, CH_2); 8.24 (*d*, $J=5.4$, 2 arom. H); 8.48 (*s*, 1 arom. H); 8.73 (*d*, $J=5.4$, 2 arom. H). ^{13}C-NMR: 22.5; 22.6; 26.0; 32.4; 122.2; 130.0; 145.8; 150.7; 157.7; 160.3; 167.0. HR-MS (TOF-ES$^+$): 212.1191 ($[M+H]^+$, $C_{13}H_{14}N_3^+$; calc. 212.1182).

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