HETEROCYCLES, Vol. 94, No. 1, 2017, pp. 140 - 146. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 11th November, 2016, Accepted, 13th December, 2016, Published online, 29th December, 2016
DOI: 10.3987/COM-16-13616

ONE-POT SYNTHESIS OF IMIDAZO[1,5-*c*]PYRIMIDINE DERIVATIVES FROM A 4,6-DICHLOROPYRIMIDINE DERIVATIVE AND BENZYL ISOCYANIDES

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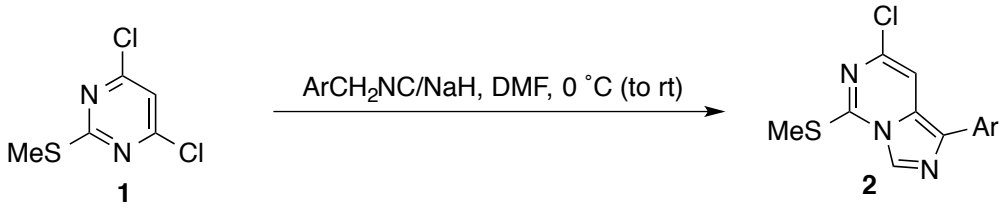
Abstract – A convenient method for the synthesis of imidazo[1,5-*c*]pyrimidine derivatives has been developed. Thus, benzyl isocyanides are treated with sodium hydride in DMF at 0 ˚C to generate the corresponding benzyl anions, which are allowed to react with 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) to afford 1-aryl-7-chloro-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidines in one pot in moderate yields.

Imidazo[1,5-*c*]pyrimidine derivatives have attract much attention of chemists, because some of these derivatives have been reported to exhibit biological activity.[1] The construction of the imidazo[1,5-*c*]pyrimidine structure[2] has been commonly achieved by acylation of 6-(aminomethyl)uracil followed by treatment with phosphoryl chloride.[2a] However, there have been no general methods for the preparation of this class of heterocycles so far. On the other hand, we recently reported syntheses of fused pyrimidine derivatives utilizing 4,6-dichloro-2-(methylsulfanyl)pyrimidine (DCSMP) (**1**) as a starting material.[3] We sought to demonstrate further its utility in heterocycle synthesis by reporting a one-pot preparation of 1-aryl-7-chloro-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidines (**2**) from **1** and benzyl isocyanides. It should be noted that after completion of the present work, we were aware of the report by Fleming *et al*., which described the synthesis of imidazo[1,5-*a*]pyridines by the reaction of 2-chloropyridines and benzyl isocyanides in the presence of potassium hexamethyldisilazide.[4]

Our one-pot synthesis of imidazopyrimidines (**2**) from DCSMP (**1**) and benzyl isocyanides was conducted by following the procedure illustrated in Scheme 1. Thus, after treatment of benzyl isocyanides with an equimolar amount of sodium hydride in DMF at 0 ˚C generating the corresponding carbanions stabilized by aryl and isocyano groups, DCSMP (**1**) was added at the same temperature and the mixture was stirred at the temperature for the times indicated in Table 1 to give, upon aqueous workup and subsequent purification by recrystallization or column chromatography on silica gel, the desired products **2** in moderate yields as compiled in Table 1. As can be seen from Table 1, room temperature and prolonged reaction times were required, when benzyl isocyanides carrying electron-donating group(s) on the benzene ring. It is noteworthy that ethyl isocyanoacetate and (*p*-toluenesulfonyl)methyl isocyanide (TOSMIC) did not perform well in the reaction and a considerably complicated mixture of products was obtained in each case.



Scheme 1

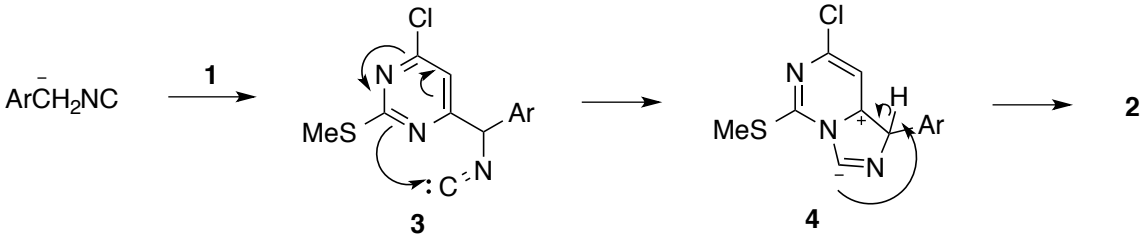
Table 1. Preparation of 1-arylimidazo[1,5-*c*]pyrimidine derivatives (**2**)

Entry	Ar	Temp	Time/h	**2**	Yield/%[a]
1	Ph	0 ˚C	2	**2a**	42
2	4-MeC_6H_4	rt	0.5	**2b**	52
3	2-ClC_6H_4	0 ˚C	2.5	**2c**	65
4	3-ClC_6H_4	0 ˚C	1	**2d**	66
5	4-ClC_6H_4	0 ˚C	1	**2e**	53
6	3,4-$Cl_2C_6H_3$	0 ˚C	2	**2f**	50
7	3-$MeOC_6H_4$	rt	5	**2g**	68
8	4-$MeOC_6H_4$	rt	24	**2h**	48
9	3,4-$(MeO)_2C_6H_3$	rt	12	**2i**	55
10	3,4,5-$(MeO)_3C_6H_2$	rt	4.5	**2j**	62

[a] Yields of isolated products.

The reaction leading to the formation of **2** from **1** is assumed to proceed as depicted in Scheme 2. Thus, 4-chloro substituent of **1** was replaced with the metallated isocyanide to generate the aryl(pyrimidin-4-yl)methyl isocyanides intermediate (**3**). Then, attack of 3-nitrogen of the pyrimidine ring on the isocyano carbon gives the betaine intermediate (**4**). Finally, 1,3-proton shift occurs to give rise to **2**. The use of two equivalents of sodium hydride caused decrease in the yields of the products. In these cases, some further by-products were observed by TLC analyses on silica gel. When THF was used as a solvent, the reaction

proceeded very reluctantly to give considerably lower yields of the products were obtained. DMSO did not work well to give rather complicate mixtures of products.



Scheme 2

In conclusion, we have developed a facile method for the preparation of 3-arylimidazo[1,5-*c*]pyrimidine derivatives. Although the yields of the products are only moderate, ready availability of the starting materials, DCSMP and benzyl isocyanides, the mild reaction conditions, and the easy experimental operations make the present method attractive.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded as KBr disks with a Perkin–Elmer Spectrum 65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a JEOL JMS-T100GCV spectrometer (EI, TOF; 70eV). Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. All chemicals used in this study are commercially available.

***N*-(Arylmethyl)formamides.** *N*-[(4-Methylphenyl)methyl]formamide[5] was prepared from (4-methylphenyl)methanamine and formic acid according to the reported procedure.[6] Other formamides, *N*-[(2-chlorophenyl)methyl]formamide,[7] *N*-[(3-chlorophenyl)methyl]formamide,[8] *N*-[(4-chlorophenyl)methyl]formamide,[9] *N*-[(3,4-dichlorophenyl)methyl]formamide,[10] *N*-[(3-methoxyphenyl)methyl]formamide,[11] *N*-[(4-methoxyphenyl)methyl]formamide,[12] *N*-[(3,4-dimethoxyphenyl)methyl]formamide[13] and *N*-[(3,4,5-trimethoxyphenyl)methyl]formamide,[14] were also prepared from the respective amines by the same procedure.

(Isocyanomethyl)benzenes 1. (Isocyanomethyl)benzene (**1a**) was commercially available. Other isocyanides, 1-(isocyanomethyl)-4-methylbenzene (**1b**),[15] 1-chloro-2-(isocyanomethyl)benzene (**1c**),[16]

1-chloro-3-(isocyanomethyl)benzene (**1d**),[17] 1-chloro-4-(isocyanomethyl)benzene (**1e**),[18] 1,2-dichloro-4-(isocyanomethyl)benzene (**1f**),[19] 1-(isocyanomethyl)-3-methoxybenzene (**1g**),[20] 1-(isocyanomethyl)-4-methoxybenzene (**1h**),[19] 1-(isocyanomethyl)-3,4-dimethoxybenzene (**1i**),[21] and 1-(isocyanomethyl)-3,4,5-trimethoxybenzene (**1j**)[22] were prepared by the treatment of the respective *N*-(arylmethyl)formamides with $POCl_3/Et_3N$ in THF under the conditions reported previously.[23]

General Procedure for the Preparation of 1-Arylimidazo[1,5-*c*]pyrimidine Derivatives (2). To a stirred suspension of NaH (60% in mineral oil; 80 mg, 2.0 mmol) in DMF (5 mL) at 0 ˚C was added one of $ArCH_2NC$ (2.0 mmol) dropwise. After evolution of H_2 gas had ceased, a solution of **1** (0.39 g, 2.0 mmol) in DMF (3 mL) was added dropwise and stirring was continued for the period at the temperature indicated in Table 1. Saturated aqueous NH_4Cl (20 mL) was added, and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by recrystallization or column chromatography on SiO_2 (CH_2Cl_2) to afford **2**.

7-Chloro-5-(methylsulfanyl)-1-phenylimidazo[1,5-*c*]pyrimidine (2a): a yellow solid; mp 144–146 ˚C (hexane/CH_2Cl_2); IR 3107, 1585, 1504 cm^{-1}; ^1H NMR δ 2.81 (s, 3H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.468 (s, 1H), 7.471 (t, *J* = 7.4 Hz, 2H), 7.82 (d, *J* = 7.4 Hz, 2H), 8.18 (s, 1H); ^{13}C NMR δ 13.49, 106.54, 125.61, 125.76, 126.38, 127.26, 128.88, 132.15, 133.52, 137.24, 148.73. HR-MS. Calcd for $C_{13}H_{10}ClN_3S$ (M): 275.0284. Found: *m/z* 275.0279. Anal. Calcd for $C_{13}H_{10}ClN_3S$: C, 56.62; H, 3.66; N, 15.24; S, 11.63. Found: C, 56.54; H, 3.73; N, 15.23; S, 11.88.

7-Chloro-1-(4-methylphenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2b): a yellow solid; mp 130–132 ˚C (hexane/CH_2Cl_2); IR 3110, 1586, 1506 cm^{-1}; ^1H NMR δ 2.40 (s, 3H), 2.79 (s, 3H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.43 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 8.15 (s, 1H); ^{13}C NMR δ 13.48, 21.24, 106.65, 125.42, 125.46, 126.28, 129.58, 130.66, 132.29, 136.89, 137.10, 148.62. HR-MS. Calcd for $C_{14}H_{12}ClN_3S$ (M): 289.0440. Found: *m/z* 289.0442. Anal. Calcd for $C_{14}H_{10}ClN_3S$: C, 58.03; H, 4.17; N, 14.50; S, 11.06. Found: C, 57.78; H, 4.14; N, 14.50; S, 11.25.

7-Chloro-1-(2-chlorophenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2c): a yellow solid; mp 145–147 ˚C (hexane/CH_2Cl_2); IR 3114, 1588, 1503 cm^{-1}; ^1H NMR δ 2.81 (s, 3H), 7.19 (s, 1H), 7.31–7.38 (m, 2H), 7.51 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.56 (dd, *J* = 7.4, 2.3 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR δ 13.55, 107.06, 125.57, 126.92, 127.28, 129.18, 129.81, 130.21 (2C), 132.08, 132.83, 137.06, 148.51. HR-MS. Calcd for $C_{13}H_9Cl_2N_3S$ (M): 308.9894. Found: *m/z* 308.9884. Anal. Calcd for $C_{13}H_9Cl_2N_3S$: C, 50.34; H, 2.92; N, 13.55. Found: C, 50.14; H, 3.15; N, 13.64.

7-Chloro-1-(3-chlorophenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2d): a yellow solid; mp 158–160 ˚C (hexane/CH_2Cl_2); IR 3121, 1588, 1505 cm^{-1}; ^1H NMR δ 2.80 (s, 3H), 7.28 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 8.15 (s, 1H); ^{13}C

NMR δ 13.55, 106.21, 124.26, 125.82, 126.23, 126.30, 127.17, 130.09, 130.64, 134.90, 135.36, 137.95, 149.00. HR-MS. Calcd for $C_{13}H_9Cl_2N_3S$ (M): 308.9894. Found: *m/z* 308.9893. Anal. Calcd for $C_{13}H_9Cl_2N_3S$: C, 50.34; H, 2.92; N, 13.55; S, 10.34. Found: C, 49.94; H, 3.04; N, 13.62; S, 13.06.

7-Chloro-1-(4-chlorophenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2e): a yellow solid; mp 151–153 °C (hexane/CH_2Cl_2); IR 3104, 1584, 1502 cm^{-1}; ^1H NMR δ 2.81 (s, 3H), 7.40 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 8.15 (s, 1H); ^{13}C NMR δ 13.54, 106.26, 125.73, 125.89, 127.47, 129.05, 130.97, 132.05, 132.95, 137.65, 148.92. HR-MS. Calcd for $C_{13}H_9Cl_2N_3S$ (M): 308.9894. Found: *m/z* 308.9893. Anal. Calcd for $C_{13}H_9Cl_2N_3S$: C, 50.34; H, 2.92; N, 13.55. Found: C, 50.41; H, 2.96; N, 13.62.

7-Chloro-1-(3,4-dichlorophenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2f): a yellow solid; mp 190–192 °C (hexane/CH_2Cl_2); IR 3097, 1583, 1501 cm^{-1}; ^1H NMR δ 2.81 (s, 3H), 7.38 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.91 (d, *J* = 1.7 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR δ 13.59, 106.01, 125.21, 125.92, 126.33, 127.86, 129.63, 130.76, 130.91, 133.10, 133.63, 138.28, 149.16. HR-MS. Calcd for $C_{13}H_8Cl_3N_3S$ (M): 342.9505. Found: *m/z* 342.9500. Anal. Calcd for $C_{13}H_8Cl_3N_3S$: C, 45.31; H, 2.34; N, 12.19. Found: C, 45.02; H, 2.53; N, 12.14.

7-Chloro-1-(3-methoxyphenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2g): a yellow solid, 153–155 °C (MeOH/CH_2Cl_2); IR 3091, 1567, 1506 cm^{-1}; ^1H NMR δ 2.80 (s, 3H), 3.89 (s, 3H), 6.86–6.90 (m, 1H), 7.35–7.39 (m, 3H), 7.49 (s, 1H), 8.18 (s, 1H); ^{13}C NMR δ 13.51, 55.35, 106.59, 111.75, 113.15, 118.73, 125.54, 125.94, 129.88, 131.99, 134.87, 137.36, 148.75, 160.08. HR-MS. Calcd for $C_{14}H_{12}ClN_3OS$ (M): 305.0390. Found: *m/z* 305.0387. Anal. Calcd for $C_{14}H_{12}ClN_3OS$: C, 54.99; H, 3.96; N, 13.74. Found: C, 54.74; H, 3.99; N, 13.78.

7-Chloro-1-(4-methoxyphenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2h): a yellow solid, 152–154 °C (hexane/CH_2Cl_2); IR 3118, 1615, 1588, 1505 cm^{-1}; ^1H NMR δ 2.79 (s, 3H), 3.86 (s, 3H), 7.00 (d, *J* = 9.2 Hz, 2H), 7.40 (d, *J* = 1.1 Hz, 2H), 7.74 (d, *J* = 9.2 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR δ 13.47, 55.34, 106.61, 114.35, 124.99, 125.35, 126.23, 127.64, 132.17, 136.64, 148.56, 158,97. HR-MS. Calcd for $C_{14}H_{12}ClN_3OS$ (M): 305.0390. Found: *m/z* 305.0400. Anal. Calcd for $C_{14}H_{12}ClN_3OS$: C, 54.99; H, 3.96; N, 13.74. Found: C, 54.99; H, 4.01; N, 14.02.

7-Chloro-1-(3,4-dimethoxyphenyl)-5-(methylsulfanyl)imidazo[1,5-*c*]pyrimidine (2i): a yellow solid; mp 176–178 °C (hexane/CH_2Cl_2); IR 3120, 1591, 1513 cm^{-1}; ^1H NMR δ 2.80 (s, 3H), 3.93 (s, 3H), 3.99 (s, 3H), 6.96 (d, *J* =8.6 Hz, 1H), 7.28 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.40 (s, 1H), 7.42 (d, *J* = 1.7 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR δ 13.48, 55.98, 56.01, 106.61, 109.92, 111.41, 118.55, 125.19, 125.30, 126.58, 132.19, 136.81, 148.56, 148.60, 149.48. HR-MS. Calcd for $C_{15}H_{14}ClN_3O_2S$ (M): 335.0495. Found: *m/z* 335.0504. Anal. Calcd for $C_{15}H_{14}ClN_3O_2S$: C, 53.65; H, 4.20; N, 12.51. Found: C, 53.43; H, 4.26; N, 12.18.

7-Chloro-5-(methylsulfanyl)-1-(3,4,5-trimethoxyphenyl)imidazo[1,5-*c*]pyrimidine (2j): a yellow solid; mp 146–148 °C (hexane/CH_2Cl_2); IR 3087, 1591, 1508 cm^{-1}; ^1H NMR δ 2.81 (s, 3H), 3.90 (s, 3H), 3.97 (s, 6H), 7.02 (s, 2H), 7.39 (s, 1H), 8.16 (s, 1H); ^{13}C NMR δ 13.52, 56.31, 60.97, 103.75, 106.38, 125.44, 125.53, 129.19, 132.13, 137.23, 137.63, 148.82, 153.69. HR-MS. Calcd for $C_{16}H_{16}ClN_3O_3S$ (M): 365.0601. Found: *m/z* 365.0600.Anal. Calcd for $C_{16}H_{16}ClN_3O_3S$: C, 52.53; H, 4.41; N, 11.49. Found: C, 52.55; H, 4.47; N, 11.40.

ACKNOWLEDGEMENTS

We thank Mrs. Miyuki Tanmatsu of our university for recording mass spectra and performing combustion analyses.

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