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# Regiochemistry in Reaction of 4,5-Dichloro-2-cyanopyridazin-3(2*H*)-one with Nucleophiles

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Pyridazin-3(2*H*)-ones are stable, inexpensive, and easily prepared heterocycles whose utility as synthetic auxiliaries was recently demonstrated by Yoon *et al*.[1] Since pyridazin-3(2*H*)-ones readily form stable anions[2] and can act as good leaving groups.[1,3] The reactivity of C-4, C-5 and C-6 on the pyridazin-3(2*H*)-one is affected by the substituent at N-2 position.[4] Therefore, reaction of 2-substituted-di(or mono)halopyridazin-3(2*H*)-ones with nucleophiles may be give mixed products such as 5-monosubstituted- and/or 4,5-disubstituted-pyridazin-3(2*H*)-ones due to halogens on the ring of pyridazin-3(2*H*)-one. Actually, 5-alkyl (or aryl)aminopyridazin-3(2*H*)-ones is the by-product in the reaction of 2-substituted-pyridazin-3(2*H*)-ones such as 2-cyano-, 2-nitro- and 2-benzenesulfonyl derivatives with nucleophiles such as amines in the organic solvents.[1j,1q,1u,1t] According to the literature[1j,1q,1u,1t] and our preliminary experiments, the reactivity of C-4 and C-5 carbons depends upon the substituent of N-2 and the solvent polarity. Based upon the atomic charges of compound **1**,[4] the C-5 position is more active slightly than the C-α and C-4 positions about the nucleophiles (Fig. 1). Therefore, we investigated the regiochemistry in the reaction of compound **1** with phenol, 2-mercaptopyrimidine, aniline, and sodium azide in eight solvents. In this paper, we report the dependence of nucleophile and solvent polarity for these reactions.

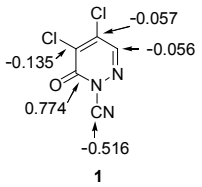

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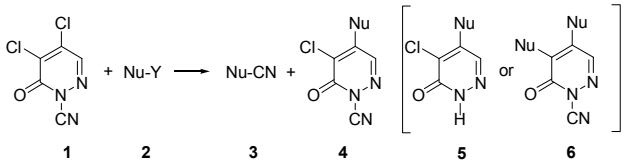
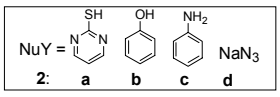
**Figure 1.** Atomic charge of carbons at the MP2/6-311+G** for compound **1**.[4]




**Scheme 1**

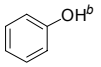
First we examined the solvent effect in the reaction of **1** with 2-mercaptopyrimidine (**2a**) in eight solvents. Compound **1** was reacted with **2a** in refluxing eight solvents with different polarity to give selectively cyanation product **3a** in good to excellent yields except for acetonitrile, DMF and water (entries 1-8, Table 1). When acetonitrile was used, we obtained **3a** (19%) and **4a** (66%). Conversely, the reaction was carried out in DMF to give only **4a** in 89% yield, whereas the reaction in water gave **3a** (61%) and **6a** (17%). The reaction of **1** with phenol (**2b**) under neutral condition do not progress. Therefore, the product distribution in the reaction of **1** with phenol (**2b**) is determined in the presence of potassium carbonate. The results show in Table 1 (entries 9-10).

Although the reaction did not occur in *n*-hexane and cyclohexane, the isocyanate **3b** is main product in toluene, THF and DMF (entries 11, 13 and 14 in Table 1). Using ethyl acetate and acetonitrile solvents, we obtained the compound **4b** as the main product in low yields due to the decomposition during silica gel column. Compound **1** was also reacted with aniline (**2c**) in six solvents at refluxing temperature except for cyclohexane and toluene under neutral condition to give only the compound **4c** (entries 17, 20-24 in Table 1), whereas the reactions were carried out in cyclohexane and toluene to give **3c** and **4c** as the main product (entries 18 and 19 in Table 1).

On the other hand, we examined the reaction of compound **1** with sodium azide (**2d**). Reaction of compound **1** with sodium azide (**2d**) in ethyl acetate, THF, DMF and acetonitrile to afford only **4d** in 34 - 72% yields, however the reactions did not occur in *n*-hexane, cyclohexane and toluene used. The structures of the products were established by IR, NMR and elemental analyses.

In conclusion, the regiochemstry was investigated for the reaction of compound **1** with four nucleophiles in seven organic solvents with the different polarity. In the case of 2-mercaptopyrimidine, the low polarity solvents such as *n*-hexane, cyclohexane, toluene, ethyl acetate and tetrahydrofuran gave selectively thiocyanatopyrimidine (**3a**) in good to excellent yields, whereas DMF, acetonitrile and water afforded two products such as **3a** and **4a**. In the case of phenol, aniline and sodium

**Table 1.** Reaction of 2-cyano-4,5-dichloropyridazin-3(2*H*)-one (**1**) with nucleophiles **2** in various solvents

| Entry | Nucleophile **2** | Solvent (polarity)[5] | Time (h) | Isolated yield (%)[a] | |
|---|---|---|---|---|---|
| | | | | **3** | **4** |
| 1 | **a**  | *n*-hexane (0.0) | 4.5 | **3a** (89) | - |
| 2 | | cyclohexane (0.0) | 1.5 | **3a** (82) | - |
| 3 | | toluene (2.4) | 0.2 | **3a** (94) | - |
| 4 | | ethyl acetate (3.7) | 2.5 | **3a** (86) | - |
| 5 | | tetrahydrofuran (4.2) | 1.5 | **3a** (80) | - |
| 6 | | *N*,*N*-dimethylformamide (6.0) | 0.5 | - | **4a** (89) |
| 7 | | acetonitrile (6.2) | 3 | **3a** (19) | **4a** (66) |
| 8 | | water (9.0) | 0.2 | **3a** (61) | **4a** (17) |
| 9 | **b**  | *n*-hexane (0.0) | 120 | - | - |
| 10 | | cyclohexane (0.0) | 120 | - | - |
| 11 | | toluene (2.4) | 96 | **3b** (80) | **4b** (7)[c] |
| 12 | | ethyl acetate (3.7) | 45 | - | **4b** (60)[c] |
| 13 | | tetrahydrofuran (4.2) | 27 | **3b** (29) | **4b** ( 5)[c] |
| 14 | | *N*,*N*-dimethylformamide (6.0) | 2 | **3b** (51) | - |
| 15 | | acetonitrile (6.2) | 4 | - | **4b** (51)[c] |
| 16 | | water (9.0) | 6 | decomposition | |
| 17 | **c**  | *n*-hexane (0.0) | 18 | - | **4c** (83) |
| 18 | | cyclohexane (0.0) | 6 | **3c** (16) | **4c** (58) |
| 19 | | toluene (2.4) | 7 | **3c** (32) | **4c** (56) |
| 20 | | ethyl acetate (3.7) | 5 | - | **4c** (86) |
| 21 | | tetrahydrofuran (4.2) | 6 | - | **4c** (82) |
| 22 | | *N*,*N*-dimethylformamide (6.0) | 1 | - | **4c** (84) |
| 23 | | acetonitrile (6.2) | 10 | - | **4c** (88) |
| 24 | | water (9.0) | 1 | - | **4c** (96) |
| 25 | **d** $NaN_3$ | *n*-hexane (0.0) | 120 | - | trace |
| 26 | | cyclohexane (0.0) | 120 | - | trace |
| 27 | | toluene (2.4) | 120 | - | trace |
| 28 | | ethyl acetate (3.7) | 30 | - | **4d** (72) |
| 29 | | tetrahydrofuran (4.2) | 5 | - | **4d** (34) |
| 30 | | *N*,*N*-dimethylformamide (6.0) | 2 | - | **4d** (64) |
| 31 | | acetonitrile (6.2) | 3 | - | **4d** (61) |
| 32 | | water (9.0) | 2 | decomposition | |

[a]Average of two or three runs. [b]The reaction was carried out in the presence of $K_2CO_3$. [c]Compound **4b** decomposed during the chromatography.

azide, 5-substituted-2-cyano derivatives yielded as the main products except for the reaction of phenol in toluene. Except for the reactions of 2-mercaptopyrimidine in acetonitrile and water, phenol in toluene and THF, aniline in cyclohexane, toluene and water, all reactions gave selectively compound **3** or **4** in moderate and excellent yields. Although we did not find any regularity for the solvent polarity, the effect of nucleophile for the regiochemistry is higher than it of the solvent. These results may be a guide-line for the reaction of 2-substituted pyridazin-3(2*H*)-ones as electrophilic agents with nucleophiles.

## Experimental Section

**General.** Melting points were determined with a capillary apparatus and uncorrected. NMR spectra were recorded on a 300 MHz spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on a Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with CHNS-932 (Leco). The open-bed chromatography was carried out on silica gel (70 - 230 mesh, Merck) using gravity flow. The column was packed with slurries made from the elution solvent.

Compound **1** was prepared from 4,5-dichloropyridazin-3(2*H*)-one by the literature method.[1j]

**Reaction of compound 1 with 2a, 2c and 2d:** A mixture of compound **1** (0.2 g, 1.05 mmol), nucleophile (1.16 mmol) and solvent (20 mL) was refluxed until the compound **1** disappeared. After cooling the reaction mixture, the solvent was evaporated under reduced pressure. The resulting residue was applied on the top of silica gel column (3 × 8 cm). The column was eluted with methylene chloride for **3a**, **3c**, **4a** and **4c** or ethyl acetate/*n*-hexane (1:1, v/v) for **3d** and **4d**. The fractions containing the product **3** or **4** were combined and evaporated under reduced pressure to give the corresponding **3** or **4**, respectively.

**2-Thiocyanatopyrimidine (3a):** mp 112 - 113 °C. $R_f$ = 0.61 (methylene chloride). IR (KBr) 3100, 3000, 2180, 1570, 1390, 1280, 1180, 820, 770, 740, 700, 630 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7.59 (t, 1H, $J$ = 4.9 Hz), 8.87 (d, 2H, $J$ = 4.9 Hz). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 107.8, 120.6, 159.7, 164.9. Elemental analysis cacld for $C_5H_3N_3S$: C, 43.78; H, 2.20; N, 30.64; found C, 43.81; H, 2.25; N, 30.67.

**4-Chloro-2-cyano-5-(pyrimidine-2-ylthio)pyridazin-3(2*H*)-**

**one (4a):** mp 145 - 146 °C. $R_f$ = 0.42 (methylene chloride). IR (KBr) 3100, 3000, 2261, 1697, 1557, 1546, 1503, 1378, 1224, 1183, 1107, 953, 906, 858, 804, 766, 747, 734 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7.50 (t, 1H, $J$ = 4.9 Hz), 8.53 (s, 1H), 8.79 (d, 2H, $J$ = 4.9 Hz). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 106.5, 120.0, 134.7, 137.8, 143.1, 154.4, 159.0, 165.7. Elemental analysis cacld for $C_9H_4N_5OSCl$: C, 40.69; H, 1.52; N, 26.36; found C, 40.70; H, 1.55; N, 26.39.

**5-Azido-4-chloro-2-cyanopyridazin-3(2*H*)-one (4c):** mp 114 - 116 °C. $R_f$ = 0.45 (methylene chloride). IR (KBr) 3065, 2255, 2160, 2118, 1693, 1680, 1600, 1526, 1384, 1321, 1234, 1139, 1007, 881, 864, 734, 702, 638 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8.50 (s, 1H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 106.5, 117.1, 148.1, 142.2, 155.8. Elemental analysis cacld for $C_5HN_5OCl$: C, 30.55; H, 0.51; N, 42.76; found C, 30.56; H, 0.54; N, 42.80.

***N*-Phenylcyanamide (3d):** Liquid, $R_f$ = 0.69 (ethyl acetate/*n*-hexane = 1:1, v/v) IR (KBr) 3200, 3171, 3099, 2986, 2918, 2226, 1600, 1500, 1432, 1275, 1240, 748 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.01-7.06 (m, 3H), 7.29-7.34 (m, 2H), NH (no detection). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 111.9, 115.4, 123.5, 129.7, 137.3. Elemental analysis cacld for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71; found C, 71.19; H, 5.15; N, 23.73.

**4-Chloro-2-cyano-5-phenylaminopyridazin-3(2*H*)-one (4d):** mp 216 - 218 °C. $R_f$ = 0.57 (ethyl acetate/*n*-hexane = 1:1, v/v). IR (KBr) 3297, 2255, 1695, 1676, 1609, 1593, 1540, 1493, 1414, 1329, 1313, 1284, 1247, 900, 867, 742 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7.31 (t, 3H, $J$ = 5.1 Hz), 7.46 (t, 2H, $J$ = 7.8 Hz), 7.92 (s, 1H), 9.69 (s, NH). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 104.0, 107.1, 124.7, 126.4, 129.5, 136.0, 137.0, 143.6, 155.7. Elemental analysis cacld for $C_{11}H_7N_3OCl$: C, 53.56; H, 2.86; N, 22.71; found C, 53.57; H, 2.88; N, 22.74.

**Reaction of compound 1 with phenol (2b):** A mixture of compound **1** (0.2 g, 1.05 mmol), phenol (0.11 g, 1.16 mmol), potassium carbonate (0.16 g, 1.16 mmol) and solvent (20 mL) was refluxed until the compound **1** disappeared. After cooling the reaction mixture, the solvent was evaporated under reduced pressure. The resulting residue was applied on the top of silica gel column (3 × 8 cm). The column was eluted with methylene chloride. The fractions containing the product **3b** or **4b** were combined and evaporated under reduced pressure to give the corresponding **3b** or **4b**, respectively.

**Cyanatobenzene (3b):** Liquid. $R_f$ = 0.7 (methylene chloride). IR (KBr) 3086, 3061, 2279, 2234, 1604, 1585, 1487, 1460, 1185, 1162, 1082, 1022, 1004, 781, 750, 683 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7.42-7.48 (m, 3H), 7.56-7.61 (m, 2H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 108.6, 115.4, 127.1, 130.8, 152.5. Elemental analysis cacld for $C_7H_5NO$: C, 70.58; H, 4.23; N, 11.76; found C, 70.60; H, 4.26; N, 11.78.

**4-Chloro-2-cyano-5-phenyloxypyridazin-3(2*H*)-one (4b):** mp 117 - 119 °C. $R_f$ = 0.63 (methylene chloride). IR (KBr) 3100, 3000, 2257, 1700, 1615, 1585, 1483, 1372, 1274, 1218, 1156 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 7.26-7.33 (m, 3H), 7.51 (t, 2H, $J$ = 7.74 Hz), 8.14 (s, 1H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ 107.0, 119.3, 120.1, 126.5, 131.1, 138.4, 153.6, 154.0, 158.0. Elemental analysis cacld for $C_{11}H_6N_3O_2Cl$: C, 53.35; H, 2.44; N, 16.97; found C, 53.37; H, 2.48; N, 16.98.

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## References and Notes

1. (a) Jung, K. J.; Kang, S. B.; Won, J. E.; Park, S. E.; Park, K. H.; Park, J. G.; Lee, S. G.; Yoon, Y. J. *Synlett* **2009**, 490. (b) Lee, H. G.; Kim, M. J.; Park, S. E.; Jung, K. J.; Kim, B. R.; Lee, S. G.; Yoon, Y. J. *Synlett* **2009**, 2809. (c) Kim, B. R.; Lee, H. G.; Kim, E. J.; Lee, S. G.; Yoon, Y. J. *J. Org. Chem.* **2010**, *75*, 484. (d) Kang, S. B.; Yim, H. S.; Won, J. E.; Kim, M. J.; Kim, J. J.; Kim, H. K.; Lee, S. G.; Yoon, Y. J. *Bull. Korean Chem. Soc*. **2008**, *29*, 1025. (e) Kim, M. J.; Yim, H. S.; Won, J. E.; Sung, G. H.; Kim, H. K.; Kim, J. J.; Kang, S. B.; Lee, S. G.; Yoon, Y. J. *Bull. Korean Chem. Soc.* **2008**, *29*, 2247. (f) Won, J. E.; Kim, H. K.; Kim, J. J.; Yim, H. S.; Kim, M. J.; Kang, S. B.; Chung, H. A; Lee, S. G.; *Tetrahedron* **2007**, *63*, 12720. (g) Park, Y. D.; Kim, J. J.; Kim, H. K.; Cho, S. D.; Kang, Y. J.; Park, K. H.; Lee, S. G.; Yoon, Y. J. *Synth. Commun*. **2005**, *35*, 371. (h) Kim, J. J.; Park, Y. D.; Kim, H. K.; Cho, S. D.; Kim, J. K.; Lee, S. G.; Yoon, Y. J. *Synth. Commun.* **2005**, *35*, 731. (i) Kim, S. K.; Kweon, D. H.; Cho, S. D.; Kang, Y. J.; Park, K. H.; Lee, S. G.; Yoon, Y. J. *J. Heterocyclic Chem.* **2005**, *42*, 353. (j) Kim, J. J.; Kweon, D. H.; Cho, S. D.; Kim, K.; Chung, H. A.; Lee, S. G.; Falck, J. R.; Yoon, Y. J. *Tetrahedron* **2005**, *61*, 5889. (k) Park, Y. D.; Kim, J. J.; Cho, S. D.; Lee, S. G.; Falck, J. R.; Yoon, Y. J. *Synthesis* **2005**, 1136. (l) Kim, J. J.; Park, Y. D.; Kweon, D. H.; Kang, Y. J.; Kim, H. K.; Lee, S. G.; Cho, S. D.; Lee, W. S.; Yoon, Y. J. *Bull. Korean Chem. Soc.* **2004**, *25*, 501. (m) Kim, J. J.; Park, Y. D.; Cho, S. D.; Kim, H. K.; Kang, Y. J.; Lee, S. G.; Falck, J. R.; Shiro, M.; Yoon, Y. J. *Bull. Korean Chem. Soc*. **2004**, *25*, 1273. (n) Lee, S. G.; Kim, J, J.; Kang, Y. J.; Park, Y. D.; Cho, S. D.; Kim, S. K.; Yoon, Y. J. *Current Org. Chem.* **2004**, *8*, 1463. (o) Kim, J. J.; Park, Y. D.; Lee, W. S.; Cho, S. D.; Yoon, Y. J. *Synthesis* **2003**, 1517. (p) Kim, H. K.; Park, Y. D.; Kim, J, J.; Lee, M. H.; Chung, H. A.; Kweon, D. H.; Cho, S. D.; Yoon, Y. J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1655. (q) Park, Y. D.; Kim, H. K.; Kim, J. J.; Cho, S. D.; Kim, S. K.; Shiro, M. Yoon, Y. J. *J. Org. Chem.* **2003**, *68*(23), 9113. (r) Park, Y. D.; Kim, J. J.; Chung, H. A.; Kweon, D. H.; Cho, S. D.; Lee, S. G.; Yoon, Y. J. *Synthesis* **2003**, 560. (s) Kang, Y. J.; Chung, H. A.; Kim, J. J.; Yoon, Y. J. *Synthesis* **2002**, 733. (t) Kim, H. K.; Park, Y. D.; Kim, J. J.; Lee, M. H.; Chung, H. A.; Kweon, D. H.; Cho, S. D.; Yoon, Y. J. *Bull. Korean Chem. Soc*. **2003**, *24*, 1655. (u) Kweon, D. H.; Kim, H. K.; Kim, J. J.; Chung, H. A.; Lee, W. S.; Kim, S. K.; Yoon, Y. J. *J. Heterocycl. Chem.* **2002**, *39*, 203.
2. Kim, S. K.; Cho, S. D.; Kweon, D. H.; Yoon, Y. J.; Kim, J. H.; Heo, J. N. *J. Heterocycl. Chem.* **1997**, *34*, 209.
3. Hwang, J.; Hwang, Y.; Yang, K.; Yoon, Y. J.; Koo, I. S. *Bull. Korean Chem. Soc.* **2009**, *30*, 2779.
4. Yoon, Y. J.; Koo, I. S.; Park, J. K. *Bull. Korean Chem. Soc.* **2007**, *28*, 1363.
5. Schirmer, R. E. *Modern methods of pharmaceutical analysis*, 2nd ed.; CRC press: Vol. II, p 305.