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Tri-component reaction of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones: synthesis of 5-cyano-5-(pyrimidin-2-yl)-2,7-dialkyl-5*H*-dipyridazino-[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione and 2-(4-cyanophenoxy) pyrimidine

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Abstract—Reaction of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones with *p*-cyanophenol and 2-mercaptopyrimidine in the presence of base gave 2,4,5-trisubstituted-pyridazin-3(2*H*)-ones **4**–**9**, 2-(4-cyanophenoxy)pyrimidine (**10**) and 5-cyano-5-(pyrimidin-2-yl)-2,7-dialkyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-diones **11** as a novel heterocycle.

1. Introduction

In the previous report,[1,2] we reported the replacement of 4-cyanophenoxy group of 2-methyl-4-halo-5-(4-cyanophenoxy)pyridazin-3(2*H*)-ones by alkoxy groups such as methoxy and ethoxy. Therefore, we tried the regioselective substitution of 4-chloro-2-methyl-5-(4-cyanophenoxy)-pyridazin-3(2*H*)-one with 2-mercaptopyrimidine. In this preliminary experiment, we detected the several products on the tlc. As part of our research program for the regioselective displacement of 4,5-dichloropyridazin-3(2*H*)-one, we studied the tri-component reactions of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones with 4-cyanophenol and 2-mercaptopyrimidine.

In this paper, we would like to report on the reaction results and new compounds in the title reaction.

2. Results and discussion

Reaction of **1a** with **2** and **3** in the presence of triethylamine in refluxing acetonitrile gave compounds **4a** (42%) and **8a** (25%) (entry 1 in Table 1), whereas this reaction was carried out in the presence of potassium carbonate instead of triethylamine to afford **6a** (22%) and **7a** (43%) (entry 2 in Table 1) (Scheme 1).

Treatment of **1b** with **2** and **3** in the presence of potassium carbonate in refluxing acetonitrile yielded **6b** (6%), **7b** (41%) and **8b** (26%) (entry 3 in Table 1). On the other hand, compound **1c** was reacted with **2** and **3** in the presence of potassium carbonate in refluxing acetonitrile afforded **6c** (7%), **7c** (32%), **8c** (28%) and phenyl pyrimidin-2-yl ether **10** (9%) as a new product (entry 4 in Table 1). Also this reaction was carried out in the presence of cesium carbonate instead of potassium carbonate to give **10** (42%) as the main and **11c** (6%) as another new product (entry 5 in Table 1). Tri-component reaction of **1d** with **2** and **3** in the presence of potassium carbonate in refluxing acetonitrile gave **5d** (15%), **7d** (44%) and **8d** (19%) (entry 6 in Table 1).

In order to elucidate the formation pathway of the new compounds **10** and **11c**, we attempted some further

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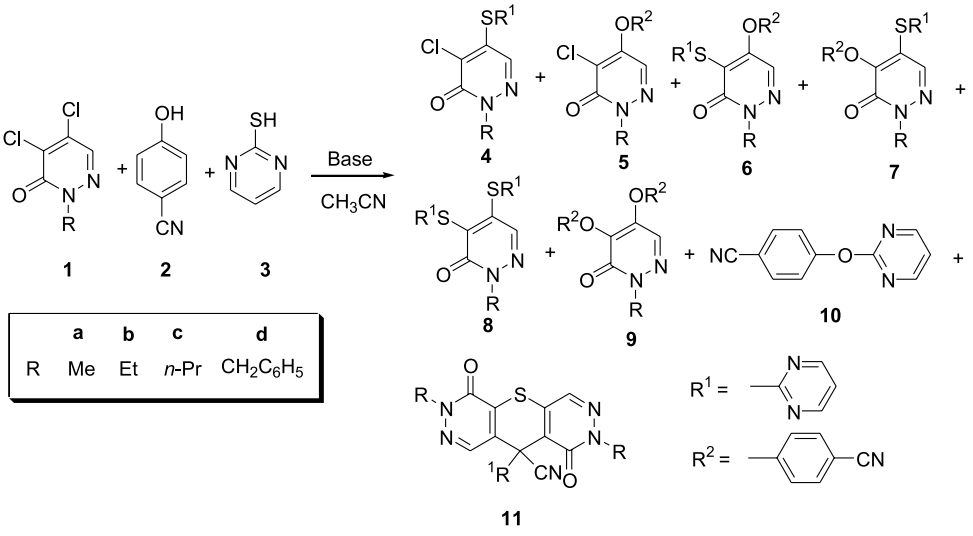
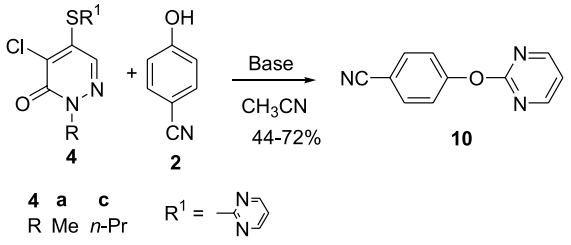
Table 1. Reaction of **1** with **2** and **3** in the presence of bases in refluxing acetonitrile

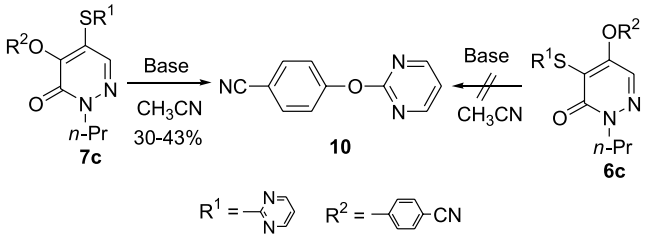
Entry	**1**(R)	Base	Reaction time (h)	Product distribution (isolated yield, %)							
				4	**5**	**6**	**7**	**8**	**9**	**10**	**11**
1	**a** Me	Et_3N	21	42	—	—	—	25	—	—	—
2	**a** Me	K_2CO_3	44	—	—	22	43	—	—	—	—
3	**b** Et	K_2CO_3	16	—	—	6	41	26	—		—
4	**c** *n*-Pr	K_2CO_3	27	—	Trace	7	32	28	—	9	—
5	**c** *n*-Pr	Cs_2CO_3	115	—	—	—	—	—	—	42	6
6	**d** CH_2Ph	K_2CO_3	5	—	15	Trace	44	19	—	—	—



Scheme 1.



Scheme 2.



Scheme 3.

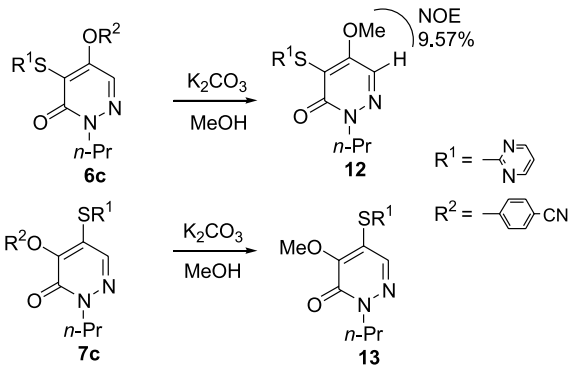
reactions. First, the reaction of **4c** with phenol **2** in the presence of potassium carbonate in refluxing acetonitrile for 8 days gave **10** in 40% yield, whereas the reaction which was carried out in the presence of cesium carbonate instead of potassium carbonate for 4 days, afforded **10** in 44% yield. The treatment of **4a** with **2** in the presence of potassium carbonate in refluxing acetonitrile also gave **10** in 72% yield. These are similar to the previously reported results.[3,4] However, **4b** and **4d** did not form compound **10** under the same conditions.

Compound **5** was also treated with **3** in the presence of potassium carbonate in refluxing acetonitrile to form compounds **6**, **7** and **10**. This reaction involved the *ipso* substitution of **5** by 2-mercaptopyrimidine anion to **4** at C5 (Scheme 2).

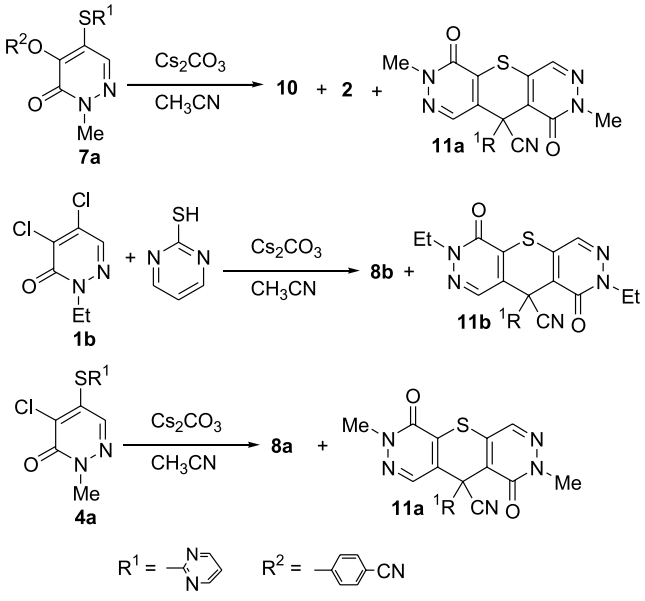
Reaction of **7c** with some other bases such as K_2CO_3, Cs_2CO_3 and Rb_2CO_3 in refluxing acetonitrile afforded **10** (30–43%) and 4-cyanophenol (**2**). However, treatment of compound **6c** with these bases did not form compound **10** (Scheme 3).

Thus, it is possible that compound **10** may have been formed via two pathways. *Pathway A*: **1**→**4**→**7**→**10**. *Pathway B*: **1**→**5**→**4**→**7**→**10**. Compound **7** is a key intermediate for the synthesis of **10**. The formation of **10** from **7** under our condition was an unusual reaction.

In order to establish the structures of compound **6** and **7**, we attempted methoxylation of **6c** and **7c**. Compound **6** and **7** were treated with potassium carbonate in methanol to **12** and **13**, respectively.[5] The substituted position of the methoxy group for **12** and **13** was established easily by



Scheme 4.



Scheme 5.

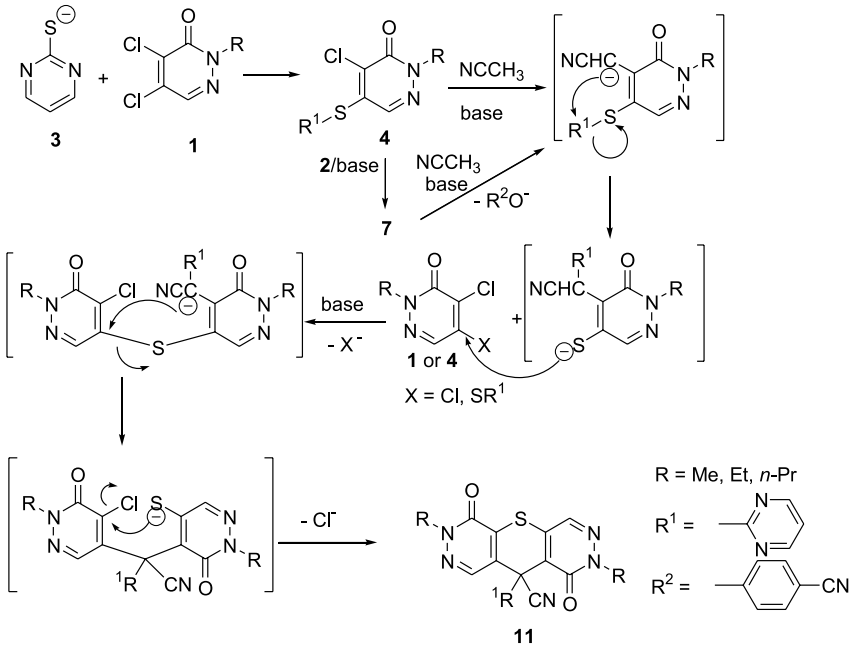
the NOE (between C5–OMe protons and C6–H proton for **12** in Scheme 4). The structures of **4**, **5**, **8**, **9** and **10** were established by IR, NMR, and elemental analysis.

On the other hand, we also attempted further reactions in order to elucidate the formation pathway(mechanism) of the new type heterocycles **11**. Reaction of **7a** with cesium carbonate in refluxing acetonitrile gave **10** (17%), **11a** (12%) and 4-cyanophenol (**2**, 69%). Compound **1b** was reacted with **3** in the presence of cesium carbonate in refluxing acetonitrile and it gave **8b** (36%) and **11b** (13%). Treatment of **4a** with cesium carbonate in refluxing acetonitrile afforded **11a** (55%) and **8a** (40%) (Scheme 5).

However, compound **5**, **6**, **8** and **9** did not form **11** under our condition. Thus, compound **11** may have been formed via two pathways. *Pathway A*: **1**→**4**→**7**→**11**. *Pathway B*: **1**→**4**→**11**. The synthetic mechanism of **11** under our condition is also showed in Scheme 6. The structures of **11** were established by IR, NMR, elemental analysis and X-ray diffraction for **11a** (Fig. 1).[6]

3. Conclusion

In summary, we report herein the results of the tri-component reaction of 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones with *p*-cyanophenol and 2-mercaptopyrimidine to give 2,4,5-trisubstituted-pyridazin-3(2*H*)-ones (**4**-**9**), 2-(4-cyanophenoxy)pyrimidine (**10**) and 5-cyano-5-(pyrimidin-2-yl)-2,7-dialkyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-diones **11**. The formation of ether **10** and tricyclic fused heterocycles **11** from 2-alkyl-4,5-dichloropyridazin-3(2*H*)-ones is a new type of reaction. Also compound **11** is a novel heterocycle. Further work including the chemical transformation and application of novel compounds are under way in our laboratory.



Scheme 6. Proposed mechanism for the synthesis of **11**.

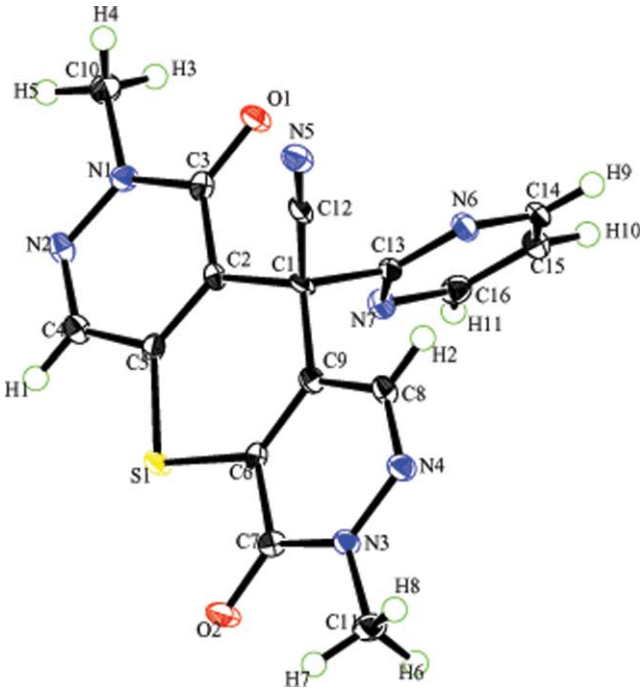


Figure 1. ORTEP plot for X-ray crystal structures of **11a**.

4. Experimental

4.1. General

Melting points were determined with a Thomas-Hoover capillary apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker FT NMR-DRX 500 or Varian Inova 500 spectrometer and with chemical shift values reported in δ units (part per million) relative to an internal standard (teteramethylsilane). IR spectra were obtained on a Hitachi 270-50 or Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with a Perkin–Elmer 240C. X-ray diffraction data were obtained with a Rigaku AFC7R diffractometer with filtered Cu Kα radiation and a rotating anode generator. TLC was performed on SiO_2 (silica gel 60 F254, Merck). The spots were located by UV light. Column chromatography was carried out on SiO_2 (silica gel 60, 70–230 mesh). Compounds **1** were prepared from 4,5-dichloropyridazin-3(2*H*)-one by the literature method.[7]

4.2. Reaction of 1 with 2 and 3

Method A. A mixture of **1** (5.586 mmol), **2** (5.586 mmol), **3** (5.586 mmol), base (5.586 mmol) and acetonitrile (50 mL) was refluxed until **1** was disappeared. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (35 mL×2). The combined filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×22 cm). The column was eluted with ethyl acetate/n-hexane (1:1, v/v). Fractions involving each product were combined and evaporated under reduced pressure to give the product.

4.2.1. 2-Methyl-4-chloro-5-(pyirimidin-2-ylsulfanyl)-pyridazin-3(2*H*)-one (4a). Mp 134–135 °C; IR (potassium bromide): ν 3030, 2970, 1650, 1549, 1497, 1376, 1313, 1229, 1172, 1018, 954, 873, 797, 769, 748, 707, 628 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.87 (s, 3H), 7.17 (t, 1H, J=4.9 Hz), 7.98 (s, 1H), 8.60 (d, 2H, J =4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 41.4, 119.0, 135.5, 138.6, 138.8, 157.2, 158.5, 168.7. Anal. Calcd for $C_9H_7ClN_4OS$: C, 42.44; H, 2.77; N, 22.00; S, 12.59. Found: C, 42.15; H, 2.24; N, 21.97; S, 12.51.

4.2.2. 2-Benzyl-4-chloro-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (5d). Mp 196–197 °C; IR (potassium bromide): ν 3090, 2970, 2950, 2232, 1659, 1608, 1587, 1489, 1395, 1330, 1311, 1260, 1224, 1151, 1100, 1076, 1007, 938, 858, 747, 699, 559 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 5.36 (s, 2H), 7.09–7.15 (m, 2H), 7.30–7.38 (m, 3H), 7.44–7.48 (m, 2H), 7.58 (s, 1H), 7.69–7.73 (m, 2H); ^{13}C NMR (deuteriochloroform) δ 56.4, 109.1, 117.9, 119.0, 123.4, 128.4, 128.7, 129.2, 130.5, 134.7, 135.2, 151.5, 157.3, 158.2. Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44; Cl, 10.50. Found: C, 64.04; H, 3.61; N, 12.49; Cl, 10.56.

4.2.3. 2-Methyl-4-(pyirimidin-2-ylsulfanyl)-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (6a). Mp 207–208 °C; IR (potassium bromide): ν 3117, 3072, 2226, 1648, 1586, 1551, 1497, 1375, 1267, 1229, 1172, 1069, 840, 769, 543 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 3.82 (s, 3H), 7.03 (t, 1H, J=4.8 Hz), 7.14–7.18 (m, 2H), 7.61 (s, 1H), 7.61–7.67 (m, 2H), 8.46 (d, 2H, J=4.8 Hz); ^{13}C NMR (deuteriochloroform) δ 41.0, 108.7, 117.9, 118.0, 119.1, 120.2, 130.2, 134.4, 156.8, 157.6, 158.0, 160.1, 168.9. Anal. Calcd for $C_{16}H_{11}N_5O_2S$: C, 56.96; H, 3.29; N, 20.76; S, 9.50. Found: C, 57.00; H, 3.32; N, 20.82; S, 9.55.

4.2.4. 2-Ethyl-5-(4-cyanophenoxy)-4-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (6b). Mp 183–184 °C; IR (potassium bromide): ν 3070, 2970, 2250, 1650, 1600, 1550, 1500, 1380, 1320, 1260, 1230, 1170, 1070, 840, 760, 540 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 1.40 (t, 3H, J=7.2 Hz), 4.25 (q, 2H, J=7.2 Hz), 6.99 (t, 1H, J= 4.9 Hz), 7.13–7.15 (m, 2H), 7.60 (s, 1H), 7.60–7.64 (m, 2H), 8.44 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 13.4, 48.1, 108.8, 117.8, 118.0, 119.2, 120.7, 130.3, 134.4, 156.5, 157.6, 158.1, 159.7, 169.2. Anal. Calcd for $C_{17}H_{13}N_5SO_2$: C, 58.11; H, 3.73; N, 19.93; S, 9.13. Found: C, 58.14; H, 3.80; N, 20.00; S, 9.16.

4.2.5. 2-Propyl-4-(pyrimidin-2-ylsulfanyl)-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (6c). Mp 109–110 °C; IR (potassium bromide): ν 3008, 2969, 2229, 1649, 1590, 1550, 1499, 1375, 1310, 1255, 1225, 1174, 1079, 841, 770, 750 cm^{-1}; ^{1}H NMR (deuteriochloroform): δ 0.97 (t, 3H, J=7.4 Hz), 1.83–1.88 (m, 2H), 4.17 (t, 2H, J=7.4 Hz), 7.00 (t, 1H, J=4.9 Hz), 7.13–7.17 (m, 2H), 7.60 (s, 1H), 7.63–7.66 (m, 2H), 8.45 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 11.3, 21.7, 53.8, 108.3, 117.9, 118.3, 119.1, 121.2, 130.7, 134.9, 154.3, 157.4, 158.3, 159.9, 168.9. Anal. Calcd for $C_{18}H_{15}N_5SO_2$: C, 59.16; H, 4.14; N, 19.17; S, 8.78. Found: C, 59.21; H, 4.20; N, 19.21; S, 8.82.

4.2.6. 2-Methyl-4-(pyirimidin-2-ylsulfanyl)-5-(4-cyanophenoxy)pyridazin-3(2*H*)-one (7a). Mp 160–161 °C; IR (potassium bromide): ν 3100, 3070, 2945, 2226, 1650, 1549,

1501, 1384, 1298, 1240, 951, 826, 765 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.82 (s, 3H), 7.01–7.06 (m, 2H), 7.11 (t, 1H, J=4.8 Hz), 7.55–7.60 (m, 2H), 8.00 (s, 1H), 8.52 (d, 2H, J=4.8 Hz); ^{13}C NMR (deuteriochloroform) δ 40.2, 107.3, 117.4, 118.4, 118.5, 125.8, 133.8, 139.8, 150.4, 155.8, 158.0, 158.9, 168.7. Anal. Calcd for $C_{16}H_{15}N_5O_2S$: C, 56.96; H, 3.29; N, 20.76; S, 9.50. Found: C, 57.01; H, 3.34; N, 20.80; S, 9.59.

4.2.7. 2-Ethyl-4-(4-cyanophenoxy)-5-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (7b). Mp 110–111 °C; IR (potassium bromide): ν 3080, 3000, 2250, 1660, 1600, 1560, 1500, 1460, 1380, 1310, 1260, 1170, 1020, 960, 840, 780, 750, 630, 550 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.41 (t, 3H, J=7.2 Hz), 4.22 (q, 2H, J=7.2 Hz), 7.01–7.03 (m, 2H), 7.08 (t, 1H, J=4.9 Hz), 7.52–7.57 (m, 2H), 8.02 (s, 1H), 8.51 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 13.4, 47.4, 107.4, 117.4, 118.4, 118.5, 125.6, 133.9, 139.7, 150.4, 155.4, 158.0, 159.0, 168.9. Anal. Calcd for $C_{17}H_{13}N_5SO_2$: C, 58.11; H, 3.73; N, 19.93; S, 9.13. Found: C, 58.15; H, 3.78; N, 20.01; S, 9.18.

4.2.8. 2-Propyl-4-(4-cyanophenoxy)-5-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (7c). Mp 91–92 °C; IR (potassium bromide): ν 3062, 2962, 2875, 2228, 1650, 1590, 1553, 1496, 1381, 1306, 1248, 1169, 945, 843, 767 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.97 (t, 3H, J=7.4 Hz), 1.83–1.88 (m, 2H), 4.13 (t, 2H, J=7.4 Hz), 7.00–7.04 (m, 2H), 7.09 (t, 1H, J=4.9 Hz), 7.55–7.59 (m, 2H), 8.02 (s, 1H), 8.51 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 11.1, 21.7, 53.7, 107.3, 117.4, 118.4, 118.5, 125.5, 133.8, 139.6, 150.4, 155.6, 158.0, 158.9, 168.8. Anal. Calcd for $C_{18}H_{15}N_5SO_2$: C, 59.16; H, 4.14; N, 19.17; S, 8.78. Found: C, 59.22; H, 4.21; N, 19.22; S, 8.84.

4.2.9. 2-Benzyl-4-(4-cyanophenoxy)-5-(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (7d). Mp 106–107 °C; IR (potassium bromide): ν 3061, 3000, 2225, 1657, 1590, 1553, 1494, 1379, 1303, 1244, 1165, 951, 835, 760, 736, 700, 627 cm^{-1}; ^1H NMR (deuteriochloroform): δ 5.32 (s, 2H), 6.99–7.01 (m, 2H), 7.08 (t, 1H, J=4.9 Hz), 7.30–7.34 (m, 3H), 7.44–7.45 (m, 2H), 7.55–7.57 (m, 2H), 8.03 (s, 1H), 8.50 (d, 2H, J =4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 55.6, 103.3, 117.3, 118.4, 118.5, 126.0, 128.3, 128.7, 129.1, 133.8, 135.5, 139.9, 150.5, 155.5, 158.0, 158.8, 168.7. Anal. Calcd for $C_{22}H_{15}N_5O_2S$: C, 63.91; H, 3.66; N, 16.94; S, 7.76. Found: C, 64.13; H, 3.72; N, 17.11.

4.2.10. 2-Methyl-4,5-di(pyirimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8a). Mp 125–126 °C; IR (potassium bromide): ν 3064, 2980, 1660, 1554, 1383, 1250, 1167, 1024, 947, 865, 806, 769, 745, 625 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.82 (s, 3H), 7.02–7.16 (m, 2H), 8.05 (s, 1H), 8.47–8.58 (m, 4H); ^{13}C NMR (deuteriochloroform) δ 40.9, 117.9, 118.5, 136.6, 138.2, 141.9, 157.6, 158.0, 158.2, 168.9, 169.2. Anal. Calcd for $C_{13}H_{10}N_6OS_2$: C, 47.26; H, 3.05; N, 25.44; S, 19.41. Found: C, 47.30; H, 3.12; N, 25.51; S, 19.47.

4.2.11. 2-Ethyl-4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8b). Mp 121–123 °C; IR (potassium bromide): v 3100, 3050, 3000, 1740, 1650, 1560, 1450, 1430, 1380, 1240, 1170, 1050, 990, 940, 840, 810, 770, 750, 700, 630 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.43 (t, 3H, J=7.2 Hz), 4.24 (q, 2H, J=7.2 Hz), 7.02 (t, 1H, J=4.9 Hz), 7.12 (t, 1H, J=5.0 Hz), 8.07 (s, 1H), 8.49 (d, 2H, J=4.8 Hz), 8.57 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 13.3, 48.0, 117.8, 118.4, 137.1, 138.2, 141.5, 157.5, 157.8, 158.0, 169.3, 169.6. Anal. Calcd for $C_{14}H_{12}N_6OS_2$: C, 48.82; H, 3.51; N, 24.40; S, 18.62. Found: C, 48.90; H, 3.61; N, 24.51; S, 18.70.

4.2.12. 2-Propyl-4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8c). Mp 98–100 °C; IR (potassium bromide): ν 3057, 2963, 2930, 1655, 1548, 1426, 1373, 1300, 1268, 1167, 1056, 945, 805, 768, 745, 625 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.97 (t, 3H, J=7.4 Hz), 1.84–1.90 (m, 2H), 4.14 (t, 2H, J=7.4 Hz), 7.02 (t, 1H, J = 4.9 Hz), 7.11 (t, 1H, J=4.9 Hz), 8.05 (s, 1H), 8.48 (d, 2H, J=4.9 Hz), 8.56 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 11.5, 22.0, 54.7, 118.2, 118.8, 137.5, 138.4, 141.6, 157.9, 158.3, 158.4, 169.5, 169.8. Anal. Calcd for $C_{15}H_{14}N_6OS_2$: C, 50.26; H, 3.94; N, 23.45; S, 17.89. Found: C, 50.31; H, 4.02; N, 23.51; S, 17.93.

4.2.13. 2-Benzyl-4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-3(2*H*)-one (8d). Mp 167–168 °C; IR (potassium bromide): ν 3115, 3075, 3028, 1660, 1549, 1454, 1350, 1164, 967, 876, 824, 769, 723, 627 cm^{-1}; ^1H NMR (deuteriochloroform): δ 5.34 (s, 2H), 7.00 (t, 1H, J=4.9 Hz), 7.10 (t, 1H, J=4.9 Hz), 7.29–7.34 (m, 3H), 7.40–7.49 (m, 2H), 8.06 (s, 1H), 8.44 (d, 2H, J=4.6 Hz), 8.55 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 56.1, 117.8, 118.5, 128.0, 128.6, 128.9, 135.9, 137.2, 138.3, 141.9, 157.5, 157.9, 158.0, 169.0, 169.4. Anal. Calcd for $C_{19}H_{14}N_6OS_2$: C, 56.14; H, 3.47; N, 20.67; S, 15.78. Found: C, 56.21; H, 3.52 N, 20.71; S, 15.83.

4.2.14. 2-(4-Cyanophenoxy)pyrimidine (10). Mp 108–109 °C; IR (potassium bromide): ν 3095, 3059, 2231, 1602, 1568, 1503, 1405, 1289, 1222, 1161, 1017, 901, 862, 820, 791, 626 cm^{-1}; ^1H NMR (deuteriochloroform): δ 7.12 (t, 1H, J=4.8 Hz), 7.32–7.36 (m, 2H), 7.72–7.75 (m, 2H), 8.60 (d, 2H, J=4.8 Hz); ^{13}C NMR (deuteriochloroform) δ 109.2, 117.2, 118.4, 122.6, 133.9, 156.3, 159.9, 164.5. Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 67.03; H, 3.62; N, 21.36.

4.2.15. 5-Cyano-5-(pyrimidin-2-yl)-2,7-dipropyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione (11c). Mp 185–186 °C; IR (potassium bromide): ν 3060, 2970, 2880, 1640, 1610, 1570, 1400 cm^{-1}; ^1H NMR (deuteriochloroform): δ 0.88 (t, 3H, J=4.5 Hz), 0.95 (t, 3H, J=4.5 Hz), 1.76 (q, 2H, J=4.5 Hz), 1.82 (q, 2H, J=4.5 Hz), 4.00–4.06 (m, 4H), 7.26–7.30 (m, 1H), 7.79 (s, 1H), 8.18 (s, 1H), 8.77 (d, 2H, J=4.9 Hz); ^{13}C NMR (deuteriochloroform) δ 10.9, 11.1, 21.5, 21.6, 49.2, 53.6, 53.9, 116.9, 120.4, 124.4, 128.4, 131.8, 133.1, 134.9, 135.5, 155.4, 156.3, 158.3, 166.4. Anal. Calcd for $C_{20}H_{19}N_7O_2S$: C, 56.99; H, 4.54; N, 23.26; S, 7.61. Found: C, 57.02; H, 4.61; N, 23.32; S, 7.70.

4.3. Synthesis of compound 10

Method B. Reaction of **4a** or **4c** with **2**. A mixture of **4** (0.393 mmol), **2** (47 mg, 0.393 mmol) and base (potassium

carbonate for **4a**; cesium carbonate for **4c**, 0.393 mmol) and acetonitrile (20 mL) was refluxed until **4** was disappeared. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (35 mL×2). The combined filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3× 12 cm). The column was eluted with methylene chloride. Fractions involving **10** were combined and evaporated under reduced pressure to give **10** as yellowish crystal in 44% (for **4c**) and 72% (for **4a**) yield, respectively.

Method C. Reaction of **7** with base. A mixture of **7** (2.74 mmol) and base such as K_2CO_3, Cs_2CO_3 and Rb_2CO_3 (5.9 mmol) and acetonitrile (50 mL) was refluxed until **7** was disappeared. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (25 mL× 2). The combined filtrate was evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (5×18 cm). The column was eluted with ethyl acetate/n-hexane (1:2, v/v). Fractions involving **10** were combined and evaporated under reduced pressure to give **10** in 43% yield. Fractions involving 4-cyanophenol were combined and evaporated under reduced pressure to afford 4-cyanophenol (39%).

4.4. Reaction of 6c or 7c with potassium carbonate/ methanol

A mixture of **6c** or **7c** (1.375 mmol), potassium carbonate (228 mg, 1.65 mmol) and MeOH (30 mL) was stirred until **6c** or **7c** was disappeared at room temperature. The mixture was coevaporated with silica gel (600 mg) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×12 cm). The column was eluted with methylene chloride/diethyl ether (30:1, v/v). Fractions involving 4-cyanophenol were combined and evaporated under reduced pressure to give 4-cyanophenol. Fractions involving **12** or **13** were combined and evaporated to afford **12** (74%) or **13** (58%).

4.5. Synthesis of 11a and 11b from 7a, 1b and 4a

Method D. A mixture of **7a** (0.35 g, 1.04 mmol), cesium carbonate (0.74 g, 2.28 mmol) and acetonitrile (20 mL) was refluxed for 24 hours. After cooling to the room temperature, the mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×12 cm). The column was eluted with methylene chloride. Fractions involving **10** were combined and evaporated under reduced pressure to give **10** (17%). Fractions involving 4-cyanophenol were combined and evaporated under reduced pressure to give 4-cyanophenol (**2**, 69%). Fractions involving **11a** were combined and evaporated to afford **11a** (12%).

Method E. A mixture of **1b** (1 g, 5.19 mmol), **3** (582 mg, 5.19 mmol), cesium carbonate (3.38 g, 10.38 mmol) and acetonitrile (30 mL) was refluxed for 48 hours. After cooling to the room temperature, the mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3× 12 cm). The column was eluted with methylene chloride. Fractions involving **11b** were combined and evaporated under reduced pressure to give **11b** (13%). Fractions involving **8b** were also combined and evaporated to afford **8b** (36%).

Method F. A mixture of **4a** (50 mg, 0.2 mmol), cesium carbonate (130 mg, 0.4 mmol) and acetonitrile (30 mL) was refluxed for 20 hours. After cooling to the room temperature, the mixture was filtered and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3×12 cm). The column was eluted with methylene chloride. Fractions involving **11a** were combined and evaporated under reduced pressure to give **11a** (55%). Fractions involving **8a** were also combined and evaporated to afford **8a** (40%).

4.5.1. 5-Cyano-5-(pyrimidin-2-yl)-2,7-dimethyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione (11a). Mp 186 °C; IR (potassium bromide): ν 3080, 3020, 2970, 1650, 1580, 1420, 1280, 1250, 1040, 875, 780 cm^{-1}; ^1H NMR (deuteriochloroform): δ 3.72 (s, 3H), 3.78 (s, 3H), 7.29 (t, 1H, J=4.90 Hz), 7.79 (s, 1H), 8.17 (s, 1H), 8.77 (d, 2H, J=4.89 Hz); ^{13}C NMR (deuteriochloroform) δ 40.20, 40.25, 53.45, 116.79, 120.47, 124.18, 128.63, 131.56, 133.08, 134.90, 135.81, 155.59, 156.56, 158.35, 166.24. Anal. Calcd for $C_{16}H_{11}N_7O_2S$: C, 52.60; H, 3.03; N, 26.84; S, 8.78. Found: C, 52.66; H, 3.09; N, 26.88; S, 8.90.

4.5.2. 5-Cyano-5-(pyrimidin-2-yl)-2,7-diethyl-5*H*-dipyridazino[4,5-*b*:4,5-*e*]-4*H*-thiopyran-1,6-dione (11b). Mp 227–228 °C; IR (potassium bromide): ν 3080, 3050, 2990, 2950, 2880, 1640, 1600, 1570, 1450, 1410, 1380, 1350, 1310, 1270, 1240, 1220, 1180, 1150, 1090, 1060, 1010, 1000, 960, 880, 850, 830, 760, 740, 700 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.29–1.41 (m, 6H), 4.08–4.24 (m, 4H), 7.30 (t, 1H, J=5.0 Hz), 7.83 (s, 1H), 8.18 (s, 1H), 8.78 (d, 2H, J=5.0 Hz); ^{13}C NMR (deuteriochloroform) δ 13.2, 13.3, 47.2, 47.6, 49.1, 116.9, 120.5, 124.3, 128.4, 131.8, 133.2, 135.0, 135.6, 155.1, 156.1, 158.3, 166.3. Anal. Calcd for $C_{18}H_{15}N_7O_2S$: C, 54.95; H, 3.84; N, 24.92; S, 8.15. Found: C, 55.02; H, 3.90; N, 24.99; S, 8.21.

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6. Crystal data for **11a**: $C_{36}H_{32}N_{14}O_5S_2$, formula weight = 804.86, Crystal system = triclinic, lattice type = primitive, lattice parameters $a = 9.410(2)$ Å, $b = 13.055(3)$ Å, $c = 16.915(3)$ Å, $\alpha = 103.96(5)^\circ$ $\beta = 101.55(3)^\circ$, $\gamma = 109.33(7)^\circ$, $V = 1811.7(14)$ Å^3, space group *P*-1 (#2), *Z* value = 2, $D_{calc} = 1.475$ g/cm^3, $F_{000} = 836.00$, μ(Mo Kα) 2.14 cm^{-1}, Data were collected on a Rigaku RAXIS-RAPID imaging plate diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71075$ Å). Detector aperture = 270 mm × 256 mm, Data images = 44 exposures, ω oscillation range ($\chi = 45.0$, ($\Phi = 0.0$) = 130.0–190.0°, exposure rate = 12.0 s/°, ω oscillation range ($\chi = 45.0$, $\Phi = 180.0$) = 0–160.0°, exposure rate = 12.0 s/°, detector position = 127.40 mm, pixel size = 0.100 mm, $2\theta_{max} = 60.1^\circ$, no. of reflections measured = total: 21,521, unique: 10,443 ($R_{int} = 0.096$), corrections Lorentz-polarizationabsorption (trans. factors: 0.902–0.989), no. observations (all reflections) = 10,443, reflection/parameter ratio = 20.28, residuals: *R*1 ($I > 2.00\sigma(I)$) = 0.053, residuals: *R* (all reflections) = 0.124, residuals: *wR*2 (all reflections) = 0.097, goodness of fit indicator = 0.924, max shift/error in final cycle = 0.001, maximum peak in final diff. map = 0.50 e/Å^3, minimum peak in final diff. map = −0.41 e/Å^3.
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