Direct Functionalization of 4,5-Dichloropyridazin-6-one

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Direct functionalization of 4,5-dichloropyridazin-6-one with some nucleophiles in seven solvents gave regioselectively 5-halo-4-substituted-pyridazin-6-ones as main product. Reaction of 4,5-dichloropyridazin-6-one with 2-mercaptopyrimidine (2 equivalents) also afforded 4,5-di(pyrimidin-2-ylsulfanyl)pyridazin-6-one as the main product.

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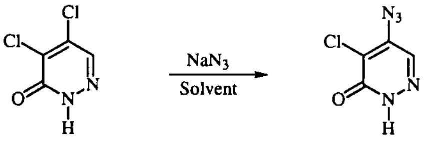
Dihalopyridazin-6-ones such as 3,4- or 4,5-dihalopyridazin-6-one are useful intermediates for the synthesis of pyridazine derivatives. However, the direct functionalization of these dihalopyridazin-6-ones is difficult because of the acidity for hydrogen at N-1 position. Recently, the functionalization of 4,5-dihalopyridazin-6-ones using 1-O, 3-N, 5-O ene-adducts [1,2] and the protecting groups [3, 4] has reported. Because the reported methods are over two steps, we attempted to investigate a more simple and convenient functionalization method of 4,5-dichloropyridazin-6-one (**1**).

Wagner, *et al.* [5] reported the direct preparation of 5-chloro-4-methoxypyridazin-6-one from 4,5-dichloropyridazin-6-one (**1**). Therefore, we investigated the direct functionalization of **1**. A nucleophile has the high nucleophilicity, but on the other hand it has relatively the low basicity in a suitable solvent to achieve the direct functionalization of 4,5-dihalopyridazin-6-ones. Therefore, we investigated the reaction of 4,5-dichloropyridazin-6-one (**1**) with some neutral nucleophiles in seven solvent systems such as tetrahydrofuran, tetrahydrofuran/water, acetonitrile, acetonitrile/water, methanol, ethanol and water.

In this paper, we report the results for the above reactions.

Reaction of **1** with sodium azide in seven solvents gave regioselectively 4-azido-5-chloropyridazin-6-one (**2**) in 64-92% yields (Scheme 1). Treatment of **1** with ethylamine hydrochloride and potassium carbonate in tetrahydrofuran, tetrahydrofuran/water, acetonitrile, acetonitrile/water or water also afforded the 4-ethylamino derivative **3** in 48-76% yields (Scheme 2). On the other hand, compound **1** was reacted with ethylamine hydrochloride and potassium carbonate in methanol or ethanol to give **3** in 19% (methanol) or in 46% (ethanol) yield and the corresponding 4-alkoxy derivatives **4** (52%) or **5** (23%) (Scheme 2). The regioselectivity of ethylamine is lower than it of the azide under our reaction conditions. In addition, an aliphatic alcohol such as methanol or ethanol is not useful for the reaction of **1** with ethylamine.

Scheme 1

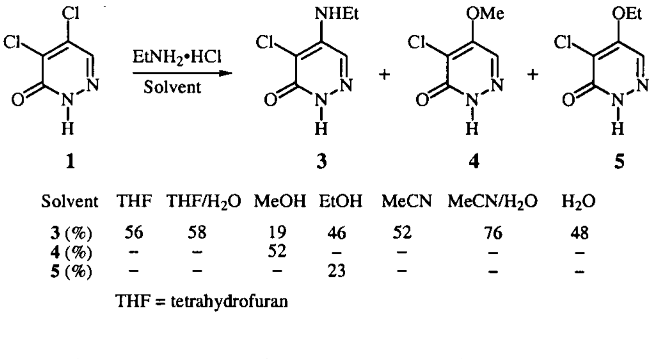


1 **2**

Solvent	THF	THF/H_2O	MeOH	EtOH	MeCN	MeCN/H_2O	H_2O
2 (%)	71	92	64	70	69	82	75

THF = tetrahydrofuran

Scheme 2



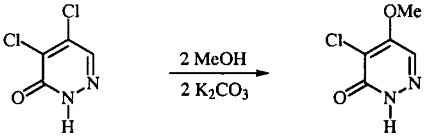
1 **3** **4** **5**

Solvent	THF	THF/H_2O	MeOH	EtOH	MeCN	MeCN/H_2O	H_2O
3 (%)	56	58	19	46	52	76	48
4 (%)	–	–	52	–	–	–	–
5 (%)	–	–	–	23	–	–	–

THF = tetrahydrofuran

Methoxylation [6] of **1** with methanol/potassium carbonate in tetrahydrofuran/water, methanol or water afforded regioselectively the 4-methoxy derivative **4** in 62-91% yields. However, the methoxylation of **1** did not proceed in tetrahydrofuran, ethanol, acetonitrile or acetonitrile/water (Scheme 3).

Scheme 3



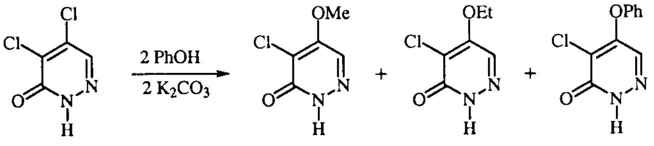
1 **4**

Solvent	THF	THF/H_2O	MeOH	EtOH	MeCN	MeCN/H_2O	H_2O
4 (%)	No Reaction	62	91	No Reaction	No Reaction	No Reaction	90

THF = tetrahydrofuran

Reaction of **1** with phenol (2-equivalents) and potassium carbonate (2-equivalents) in tetrahydrofuran/water, acetonitrile/water or water also gave regioselectively the 4-phenoxy derivative **6** in 82-90% yields instead of the 4,5-diphenoxy derivative. Compound **1** was allowed to react with phenol (2 equivalents) and potassium carbonate (2 equivalents) in methanol to give only the 4-methoxy derivative **4** (98%) instead of **6**. Treatment of **1** with phenol (2 equivalents) and potassium carbonate (2 equivalents) in ethanol provided **6** (52%) and **5** (14%) (Scheme 4). Therefore, methanol and ethanol are not satisfactory as solvents for the preparation of **6** from **1** under our reaction conditions.

Scheme 4



1 **4** **5** **6**

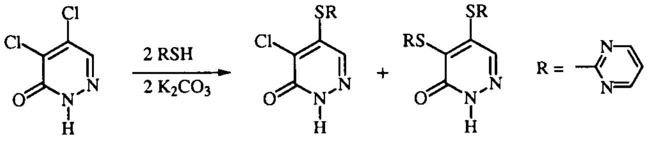
Solvent	THF	THF/H_2O	MeOH	EtOH	MeCN	MeCN/H_2O	H_2O
4 (%)	No Reaction	–	98	–	No Reaction	–	–
5 (%)		–	–	14		–	–
6 (%)		90	–	52		87	82

THF = tetrahydrofuran

On the other hand, compound **1** was reacted with 2-mercaptopyrimidine (2 equivalents) in the presence of potassium carbonate (2 equivalents) in seven solvents to give **7** as the minor and **8** as the main product. When this reaction was carried out in methanol or ethanol, compound **4** or **5** was not formed.

The structures of **2-8** were established by ir, ^{1}H nmr and elemental analyses. Compounds **2-8** were also identical an authentic compounds.

Scheme 5



1 **7** **8**

Solvent	THF	THF/H_2O	MeOH	EtOH	MeCN	MeCN/H_2O	H_2O
7 (%)	–	8	3	–	–	6	3
8 (%)	98	76	76	65	91	65	85

THF = tetrahydrofuran

Finally, water is a useful solvent for the direct functionalization of 4,5-dichloropyridazin-6-one (**1**) with some nucleophiles such as sodium azide, ethylamine, methanol, phenol and arylmercaptan. Our direct functionalization is regioselective and more convenient than the reported methods.

Table 1

Yields, Melting Points and Infrared Spectral Data of **2-8**

Compound No.	Method	Yield (%)	Mp (°C) (lit mp)	IR (potassium bromide) (cm^{-1}) [a]
2	AA	71	172-173 (170-172) [3]	3300-2900 (m), 2200, 2150, 1660, 1610, 1410, 1340, 1300, 1000
	AB	92		
	AC	64		
	AD	70		
	AE	69		
	AF	82		
	AG	75		
3	AH	56	203-204 (198-200) [1]	3350, 3150-2950 (m), 1680, 1660, 1620, 1460, 1350, 1320, 1030
	AI	58		
	AJ	19		
	AK	46		
	AL	52		
	AM	76		
	AN	48		
4	AJ	52	230-231 (233-235) [3]	3300-2950 (m), 1660, 1600, 1470, 1410, 1280, 1120, 950, 900
	AO	62		
	AP	91		
	AQ	90		
	AS	98		
5	AK	23	201-203	3310-2950 (m), 1660, 1625, 1610, 1405, 1335, 1285, 1020, 885, 790, 680
	AT	14		
6	AR	90	178-179 (178-179) [3]	3250-2900 (m), 1680, 1620, 1600, 1500, 1400, 1280, 1100, 780
	AT	52		
	AU	87		
	AV	82		
7	AX	8	222 dec 222 dec [1]	3200-2900 (m), 1680, 1580, 1400, 1180, 1080
	AY	3		
	BB	6		
	BC	3		
8	AW	98	174-175 (174-175) [1]	3200-2900 (m), 1640, 1500, 1400, 1180
	AX	76		
	AY	76		
	AZ	65		
	BA	91		
	BB	65		
	BC	85		

[a] m = multiplet.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 or a Bruker FTNMR-DRX 500 spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Open-bed chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

Reaction of **1** with Sodium Azide.

Method AA.

A mixture of **1** (6 g, 36.3 mmoles), sodium azide (4 g, 61.5 mmoles) and tetrahydrofuran (30 ml) was refluxed for 76 hours. After evaporating the solvent under reduced pressure, water (100 ml) was added to the resulting residue with stirring. The product was extracted with chloroform (100 ml x 2). The chloroform solution was dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm).

Table 2

NMR Spectral Data of **2-8**

Compound No	Solvent [a]	^{1}H NMR (δ, ppm) [b] N-1 (1H) (bs)	C-3 (1H) (s)	Others	^{13}C nmr (δ, ppm)
2	D	13.26	8.08	—	119.2, 131.6, 141.1, 157.8
3	C	12.42	7.63	1.31 (t, 3H), 4.39 (quin, 2H), 5.19 (bs, NH)	14.8, 37.4, 105.8, 126.2, 144.2, 158.5
4	D	13.26	8.10	4.06 (s, 3H)	58.2, 106.0, 127.9, 157.5, 159.4
5	D	13.27	8.17	1.36 (t, 3H), 4.39 (q, 2H)	14.1, 66.0, 113.9, 128.2, 154.6, 158.5
6	C	No detection	7.54	7.26-7.48 (m, Ar 5H)	119.7, 126.2, 130.5, 131.1, 153.8, 154.6, 160.5
7	D	13.59	8.14	7.42 (t, 1H), 8.74 (d, 2H, J = 4.5)	119.4, 135.6, 137.9, 139.3, 156.6, 158.8, 167.0
8	D	13.40	8.15	8.60 (d, 2H, J = 8.0), 8.70 (d, 2H, J = 8.2)	118.6, 119.4, 135.9, 138.8, 142.7, 142.8, 158.0, 158.1, 158.2, 158.7, 167.5, 168.1

[a] D = dimethyl-d_6 sulfoxide. C = Deuteriochloroform. [b] Abbreviations used: bs = broad singlet, s = singlet, d = doublet. t = triplet, q = quartet, quin = quintet, m = multiplet and Ar = Aromatic. J = Hz unit. The proton signals of NH were exchangeable with deuterium oxide.

Table 3

Elemental Analytical Data of **2-8**

Compound No	Molecular Formula	Elemental Analyses(%) (Calcd./Found) C	H	N
2	$C_4H_2N_5OCl$	28.01	1.18	40.82
		28.30	1.26	40.55
3	$C_6H_8N_3OCl$	41.51	4.64	24.20
		41.68	4.72	24.32
4	$C_5H_5N_2O_2Cl$	37.40	3.14	17.45
		37.52	3.26	17.60
5	$C_6H_7N_2O_2Cl$	41.28	4.04	16.05
		41.52	3.83	15.91
6	$C_{10}H_7N_2O_2Cl$	53.95	3.17	12.58
		54.12	3.32	12.70
7	$C_8H_5N_4SOCl$	39.93	2.09	23.28
		40.14	2.22	23.01
8	$C_{12}H_8N_6OS_2$	45.56	2.55	26.57
		45.58	2.65	26.85

The column was eluted with chloroform. Fractions containing the product were combined and evaporated under reduced pressure to give **2** in 71% (4.14 g) yield.

Method AB.

A solution of **1** (6 g, 36.3 mmoles), sodium azide (4 g, 61.5 mmoles), tetrahydrofuran (30 ml) and water (10 ml) was refluxed for 19 hours. After evaporating the solvent under reduced pressure, water (100 ml) was added to the residue with stirring. The resulting precipitate was filtered and dried in air to afford **2** in 92% (5.75 g) yield.

Method AC.

A mixture of **1** (6 g, 36.3 mmoles), sodium azide (4 g, 61.5 mmoles) and methanol (20 ml) was refluxed for 19 hours. After evaporating the solvents under reduced pressure, water (100 ml) was added to the residue with stirring. The resulting precipitate was filtered and dried in air to yield **2** in 64% (4 g) yield.

Method AD.

A mixture of **1** (2 g, 12.12 mmoles), sodium azide (0.82 g, 12.12 mmoles) and ethanol (20 ml) was refluxed for 7 hours. After evaporating the solvent under reduced pressure, water (100 ml) was added to the residue with stirring. The resulting precipitate was filtered, washed with water (20 ml x 3) and dried in air to yield **2** in 70% (1.45 g) yield.

Method AE.

A mixture of **1** (2 g, 12.12 mmoles), sodium azide (0.82 g, 12.12 mmoles) and acetonitrile (20 ml) was refluxed for 14 hours. After evaporating the solvent under reduced pressure, water (100 ml) was added to the residue with stirring. The resulting precipitate was filtered, washed with water (20 ml x 3) and dried in air to yield **2** in 69% (1.43 g) yield.

Method AF.

A mixture of **1** (1 g, 6.06 mmoles), sodium azide (0.394 g, 6.06 mmoles), acetonitrile (25 ml) and water (15 ml) was refluxed for 3.5 hours. After evaporating the solvent under reduced pressure, water (100 ml) was added to the residue with stirring. The resulting precipitate was filtered, washed with water (20 ml x 3) and dried in air to yield **2** in 82% (0.85 g) yield.

Method AG.

A solution of **1** (1 g, 6.06 mmoles), sodium azide (0.394 g, 6.06 mmoles) and water (40 ml) was refluxed for 2 hours. After cooling to room temperature, the resulting precipitate was filtered, washed with water (20 ml x 3) and dried in air to yield **2** in 75% (0.78 g) yield.

Reaction of **1** with Ethylamine.

Method AH.

A mixture of **1** (3 g, 18.18 mmoles), ethylamine hydrochloride (3 g, 36.05 mmoles), potassium carbonate (3 g, 21.71 mmoles) and tetrahydrofuran (20 ml) was refluxed for 32 hours. After evaporating the solvent under reduced pressure, water (50 ml) was added to the residue with stirring. The resulting precipitate was filtered and dissolved in chloroform (5 ml). The chloroform solution was coevaporated with silica gel (5 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 8 cm). The column was eluted with chloroform. Fractions containing **3** (Rf = 0.16, chloroform) were combined and evaporated under reduced pressure to yield **3** in 56% (1.75 g) yield.

Method AI.

A mixture of **1** (5 g, 30.3 mmoles), ethylamine hydrochloride (2.5 g, 30.3 mmoles), potassium carbonate (15.45 g, 60.6 mmoles), water (10 ml) and tetrahydrofuran (30 ml) was refluxed for 32 hours. After evaporating the solvent under reduced pressure, water (100 ml) was added to the residue with stirring. The resulting precipitate was filtered, washed with chloroform (10 ml x 5) and dried in air to give **3** in 58% (3.04 g) yield.

Method AJ.

A mixture of **1** (1 g, 6.06 mmoles), ethylamine hydrochloride (1 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and methanol (40 ml) was refluxed for 27 hours. After evaporating the solvent under reduced pressure, water (20 ml) was added to the residue with stirring. The solution was neutralized by concentrated hydrochloric acid. After evaporating the solvent under reduced pressure, the product was extracted with methanol (40 m). The methanol solution was coevaporated with silica gel (3 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **4** (Rf = 0.25, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure to yield **5** in 52% (0.4 g) yield. Fractions involving **3** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined and evaporated under reduced pressure to give **3** in 19% (0.16 g) yield.

Method AK.

A mixture of **1** (1 g, 6.06 mmoles), ethylamine hydrochloride (1 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and ethanol (20 ml) was refluxed for 27 hours. After evaporating the solvent under reduced pressure, water (20 ml) was added to the residue with stirring. The solution was neutralized with concentrated hydrochloric acid. After evaporating the solvent under reduced pressure, the product was extracted with methanol (50 ml). The methanol solution was coevaporated with silica gel (3 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **5** (Rf = 0.3, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure. The product was recrystallized from diethyl ether to yield **5** in 23% (0.2 g) yield. Fractions containing **3** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined and evaporated under reduced pressure. The product was recrystallized from ethyl acetate to give **3** in 46% (0.4 g) yield.

Method AL.

A solution of **1** (1 g, 6.06 mmoles), ethylamine hydrochloride (1 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and acetonitrile (20 ml) was refluxed for 16 hours. After evaporating the solvent under reduced pressure, water (20 ml) was added to the residue with stirring. The solution was neutralized by concentrated hydrochloric acid. After evaporating the solvent under reduced pressure, the product was extracted with methanol (50 ml). The methanol solution was coevaporated with silica gel (3 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 15 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **3** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined, evaporated under reduced pressure and washed with ethyl acetate (5 ml) to give **3** in 52% (0.55 g) yield.

Method AM.

A mixture of **1** (1 g, 6.06 mmoles), ethylamine hydrochloride (1 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles), acetonitrile (25 ml) and water (15 ml) was refluxed for 80 hours. After evaporating acetonitrile under reduced pressure, the resulting solution was neutralized by concentrated hydrochloric acid. After evaporating the solvent under reduced pressure, the product was extracted with methanol (30 ml). The methanol solution was coevaporated with silica gel (3 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **3** were combined and evaporated under reduced pressure. The product was recrystallized from methanol/diethyl ether (1:3, v/v) to yield **3** in 76% (0.6 g) yield.

Method AN.

A solution of **1** (1 g, 6.06 mmoles), ethylamine hydrochloride (1 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and water (15 ml) was refluxed for 28 hours. After cooling to room temperature, the solution was neutralized by concentrated hydrochloric acid. After evaporating the solvent under reduced pressure, the product was extracted with methanol (50 ml). The methanol solution was coevaporated with silica gel (3 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions involving **3** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined and evaporated under reduced pressure. The product was recrystallized from ethyl acetate to give **3** in 48% (0.5 g) yield.

Reaction of **1** with Methanol.

Method AO.

A solution of **1** (1 g, 6.06 mmoles), methanol (10 ml), potassium carbonate (1.67 g, 12.12 mmoles), tetrahydrofuran (25 ml) and water (15 ml) was refluxed for 24 hours. After evaporating the solvent under reduced pressure, water (20 ml) was added to the residue. The solution was neutralized by concentrated hydrochloric acid. The resulting precipitate was filtered. The product was washed with water (60 ml) and then with diethyl ether (5 ml) to give **4** in 62% (0.6 g) yield.

Method AP.

A mixture of **1** (1 g, 6.06 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and methanol (30 ml) was refluxed for 86 hours. After evaporating the solvent under reduced pressure, water (20 ml) was added to the residue. The solution was neutralized by acetic acid. The resulting precipitate was filtered and washed with diethyl ether (5 ml) to give **4** in 91% (0.88 g) yield.

Method AQ.

A solution of **1** (1 g, 6.06 mmoles), methanol (10 ml), potassium carbonate (1.67 g, 12.12 mmoles) and water (40 ml) was refluxed for 15 hours. After cooling to temperature, the solution was neutralized by concentrated hydrochloric acid. The resulting precipitate was filtered and washed with water (30 ml) to give **4** in 90% (0.87 g) yield.

Reaction of **1** with Phenol.

Method AR.

A mixture of **1** (1 g, 6.06 mmoles), phenol (1.2 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles), tetrahydrofuran (30 ml) and water (20 ml) was refluxed for 72 hours. After evaporating tetrahydrofuran under reduced pressure, the solution was neutralized by concentrated hydrochloric acid. The resulting precipitate was filtered. The product was washed with water (100 ml) and then with *n*-hexane (5 ml) to give **6** in 90% (1.22 g) yield.

Method AS.

A solution of **1** (1 g, 6.06 mmoles), phenol (1.2 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and methanol (20 ml) was refluxed for 72 hours. After evaporating methanol under reduced pressure, water (50 ml) was added to the residue. The solution was neutralized by concentrated hydrochloric acid. The resulting precipitate was filtered. The product was washed with water (100 ml) and then with *n*-hexane (5 ml) to give **4** in 98% (0.95 g) yield.

Method AT.

A mixture of **1** (1 g, 6.06 mmoles), phenol (1.2 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and ethanol (20 ml) was refluxed for 96 hours. The mixture was coevaporated with silica gel (4 g). The resulting residue was applied to the top of an open-bed silica gel column (2 x 12 cm). The column was eluted with chloroform/diethyl ether (1:1, v/v). Fractions containing **6** (Rf = 0.6, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure. The resulting precipitate was washed with diethyl ether (5 ml) to give **6** in 52% (0.7 g) yield. Fractions involving **5** (Rf = 0.3, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure. The product was recrystallized from ethyl acetate/*n*-hexane to afford **5** in 14% (0.15 g) yield.

Method AU.

A solution of **1** (1 g, 6.06 mmoles), phenol (1.2 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles), acetonitrile (25 ml) and water (15 ml) was refluxed for 46 hours. After evaporating acetonitrile under reduced pressure, the solution was neutralized by concentrated hydrochloric acid. The resulting precipitate was filtered. The product was washed with water (60 ml) and then with diethyl ether (10 ml) to give **6** in 87% (1.17 g) yield.

Method AV.

A mixture of **1** (1 g, 6.06 mmoles), phenol (1.2 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and water (30 ml) was refluxed for 5 hours. After cooling to room temperature, the solution was neutralized by concentrated hydrochloric acid. The resulting precipitate was filtered and washed with water (60 ml) to give **6** in 82% (1.11 g) yield.

Reaction of **1** with 2-Mercaptopyrimidine.

Method AW.

A solution of **1** (1 g, 6.06 mmoles), 2-mercaptopyrimidine (1.4 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and tetrahydrofuran (30 ml) was refluxed for 19 hours. After cooling to room temperature, the resulting mixture was filtered and washed with methanol (50 ml). The filtrate was evaporated under reduced pressure. Methanol (3 ml) was added to the residue. The resulting crystals were filtered and washed with ethyl acetate (5 ml x 2) to give **8** in 98% (1.87 g) yield.

Method AX.

A mixture of **1** (1 g, 6.06 mmoles), 2-mercaptopyrimidine (1.4 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles), tetrahydrofuran (25 ml) and water (25 ml) was refluxed for 34 hours. After evaporating tetrahydrofuran under reduced pressure, the solution was neutralized by concentrated hydrochloric acid. The resulting precipitate was dissolved in chloroform (10 ml). The solution was coevaporated with silica gel (5 g). The resulting residue was applied to the top of an open-bed silica gel column (2 x 8 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **7** (Rf = 0.4, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure. The resulting precipitate was washed with diethyl ether (3 ml) to give **7** in 8% (0.12 g) yield. Fractions containing **8** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined and evaporated under reduced pressure. The product was washed with ethyl acetate (10 ml) to afford **8** in 76% (1.45 g) yield.

Method AY.

A solution of **1** (1 g, 6.06 mmoles), 2-mercaptopyrimidine (1.4 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and methanol (40 ml) was refluxed for 40 hours. After cooling to room temperature, the solution was coevaporated with silica gel (4 g). The resulting residue was applied to the top of an open-bed silica gel column (2 x 10 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **7** (Rf = 0.4, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure. The resulting precipitate was washed with *n*-hexane (7 ml) to give **7** in 3% (0.04 g) yield. This column was then eluted with methanol. Fractions containing **8** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined. The solution was concentrated to 30 ml. Water (90 ml) was added to the solution. After evaporating methanol under reduced pressure, the resulting product was filtered and washed with water (50 ml) to afford **8** in 76% (1.45 g) yield.

Method AZ.

A mixture of **1** (1 g, 6.06 mmoles), 2-mercaptopyrimidine (1.4 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and ethanol (30 ml) was refluxed for 0.5 hours. After evaporating ethanol under reduced pressure, water (50 ml) was added. The solution was neutralized by concentrated hydrochloric acid. The resulting crystals were filtered and washed with water (30 ml). The product was recrystallized from ethyl acetate to give **8** in 65% (1.25 g) yield.

Method BA.

A mixture of **1** (1 g, 6.06 mmoles), 2-mercaptopyrimidine (1.4 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and acetonitrile (40 ml) was refluxed for 1.5 hours. After cooling to room temperature, methanol (50 ml) was added with stirring. The resulting mixture was filtered. The filtrate was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/methanol (1:3, v/v) to give **8** in 91% (1.75 g) yield.

Method BB.

A solution of **1** (1 g, 6.06 mmoles), 2-mercaptopyrimidine (1.4 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles), acetonitrile (25 ml) and water (15 ml) was refluxed for 6 hours. After evaporating acetonitrile under reduced pressure, the solution was neutralized by concentrated hydrochloric acid. The product was extracted with chloroform (50 ml x 3). The solution was dried over anhydrous magnesium sulfate. The solution was coevaporated with silica gel (4 g). The resulting residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **7** (Rf = 0.4, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure. The resulting precipitate was washed with methanol (10 ml) to give **7** in 6% (0.08 g) yield. Fractions involving **9** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined and evaporated under reduced pressure. The resulting product was filtered and washed with ethyl acetate (5 ml) to afford **8** in 65% (1.25 g) yield.

Method BC.

A solution of **1** (1 g, 6.06 mmoles), 2-mercaptopyrimidine (1.4 g, 12.12 mmoles), potassium carbonate (1.67 g, 12.12 mmoles) and water (15 ml) was refluxed for 1 hour. After cooling to room temperature, the resulting precipitate was filtered. The precipitate was washed with water (10 ml), with methanol (3 ml) and then with ethyl acetate (20 ml) to give **8** (0.7 g). The filtrate was evaporated under reduced pressure and applied to the top of an open-bed silica gel column (2 x 7 cm) The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing **7** (Rf = 0.4, ethyl acetate/*n*-hexane = 1:1, v/v) were combined and evaporated under reduced pressure. The resulting precipitate was recrystalllized from *n*-hexane/diethyl ether (1:2, v/v) to give **7** in 3% (0.04 g) yield. Fractions containing **8** (Rf = 0.1, ethyl acetate/*n*-hexane = 1:1, v/v) were also combined and evaporated under reduced pressure. The resulting product was filtered and recrystallized from methanol to afford **8** (0.94 g). The total yield of **8** was 85% (1.64 g).

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