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Eco-friendly atom-economical synthesis of 2-substituted-benzo[*d*]thiazoles and 2-substituted-benzo[*d*]oxazoles using 2-acylpyridazin-3(2*H*)-ones

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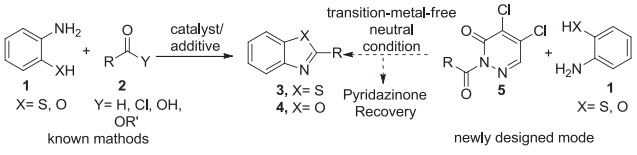
ABSTRACT

Efficient and green syntheses of heterocycles are of great importance. In this work, we have demonstrated the synthesis of benzo[*d*]thiazoles and benzo[*d*]oxazoles using 2-acylpyridazin-3(2*H*)-ones as acyl transfer agents under transition-metal-free and eco-friendly conditions. It is worthy to note that the reaction is efficient, green, and economical, and will find several applications in organic synthesis, medicinal chemistry, and industrial chemistry.

1. Introduction

Molecules that contain benzothiazole and benzoxazole moieties are attractive targets for synthesis because they often exhibit diverse and important biological properties. Because of their importance in medicinal and synthetic chemistry,[1,2] various methods to synthesize these azoles have been developed. Synthesis methods based on the condensation of 2-aminothiophenol with carbonyl derivatives such as aldehydes,[2e,3] carboxylic acids,[4] acid chlorides[5] or esters[6] as well as cyclization of thiobenzanilides[7] have been reported. However, these methods suffer from one or more disadvantages such as the requirement of harsh reaction conditions and metal catalysts and/or additional reagents, use of air sensitive and/or toxic substances cumbersome work-up procedures, and generation of acidic and metallic wastes. Therefore, their utility is limited, especially in industrial applications. Thus, there is significant interest in developing eco-friendly, economical, and atom-economic methods.[8]

To prevent the generation of wastes in eco-friendly synthesis, the use of catalysts and additional agents should be avoided or reduced. Thus, we investigated the synthesis of benzo[*d*]thiazoles and benzo[*d*]oxazoles using 2-acylpyridazin-3(2*H*)-ones as acyl transfer agents under transition-metal-free, atom-economic, and eco-friendly conditions (Scheme 1).



Scheme 1. Known and newly designed modes for synthesis of benzo[*d*]azoles **3** and **4**.

Pyridazin-3(2*H*)-ones are inexpensive, stable, and easy-to-synthesize heterocycles, whose utility as synthetic auxiliaries was recently demonstrated by Yoon et al.[9] The ease with which pyridazin-3(2*H*)-ones can be removed and/or recycled spurred our interest in their use for other transformations. Since pyridazin-3(2*H*)-ones readily form stable anions[9,11] and can act as good leaving groups,[9] we previously explored and reported[9,10] the use of 2-acylpyridazin-3(2*H*)-ones as a eco-friendly acyl source.

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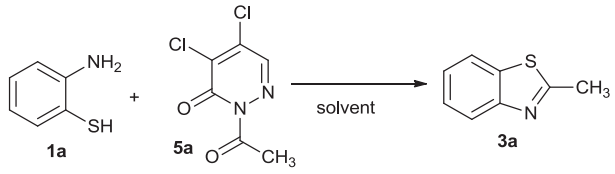
Herein, we report the synthesis of 2-substituted-benzo[*d*]thiazoles and 2-substituted-benzo[*d*]oxazoles using 2-acylpyridazin-3(2*H*)-ones as acyl transfer agents.

2. Results and discussion

Acylpyridazizn-3(2*H*)-ones were easily prepared according to the literature methods.[10g] As a model reaction to test newly designed cyclization procedure, we studied the effect of solvent in the reaction of 2-aminothiophenol with 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one at room temperature (Table 1). Among the nine solvents investigated, toluene showed the best results (entry 1, Table 1).

Table 1
Screening of solvents for the synthesis of 2-methylbenzo[*d*]thiazole (**3a**)[a]

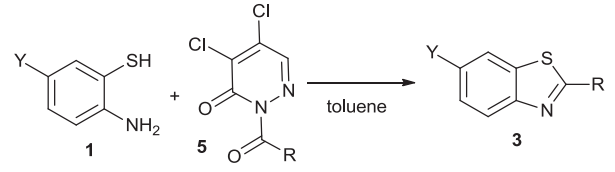


Entry	Solvent	Time (min)	**3a**[b] (%)
1	Toluene	30	90
2	*n*-Hexane	30	68
3	Chloroform	30	70
4	Tetrahydrofuran	30	64
5	Dichloromethane	30	63
6	Acetonitrile	30	68
7	2-Propanol	30	52
8	Methanol	30	54
9	Water	30	59

[a] Reaction condition: **1a** (1.2 equiv) and **5a** (1 equiv) in solvent (25 mL) at rt.
[b] Isolated yields.

To illustrate the versatility of the eco-friendly synthesis of 2-substituted-benzo[*d*]thiazoles, the reaction of 2-aminothiophenols with 2-acylpyridazin-3(2*H*)-ones under catalyst-free and neutral conditions was been examined (Table 2). 2-Aminobenzenethiol and 2-amino-4-chlorothiophenol were reacted with 2-alkanoyl-4,5-dichloropyridazin-3(2*H*)-ones in toluene under catalyst-free, neutral conditions at room temperature afforded the corresponding benzo[*d*]thiazoles in 69–94% yield (entries 1–6, Table 2), whereas 2-aminothiophenol and 2-amino-4-chlorothiophenol reacted with 2-aroyl-4,5-dichloropyridazin-3(2*H*)-ones under the same conditions to afford the corresponding 2-substituted-benzo[*d*]thiazoles in 50–86% yield (entries 7–14, Table 2).

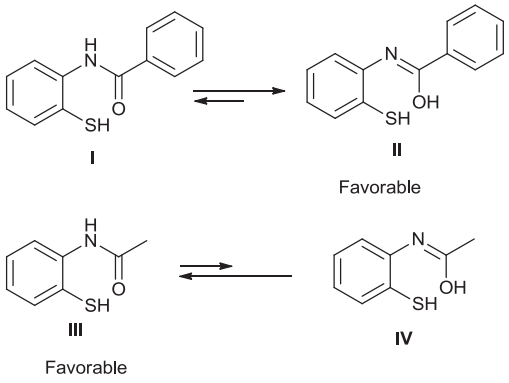
Table 2
Synthesis of benzo[*d*]thiazoles[a]



Entry	Y	R	Conditions	**3** (Yield, %)[b]
1	H	CH_2CH_3	30 min, rt	**3b** (82)
2	H	$CH_2(CH_2)_3CH_3$	30 min, rt	**3c** (83)
3	H	*c*-C_6H_{11}[c]	30 min, rt	**3d** (78)
4	Cl	CH_3	10 min, reflux	**3e** (94)
5	Cl	$CH_2(CH_2)_3CH_3$	20 min, reflux	**3f** (77)
6	Cl	*c*-C_6H_{11}[c]	40 min, reflux	**3g** (69)
7	H	C_6H_5	45 min, rt	**3h** (86)
8	H	C_6H_5(*p*-CH_3)	1.5 h, rt	**3i** (80)
9	H	C_6H_5(*p*-OCH_3)	3.5 h, rt	**3j** (62)
10	H	C_6H_5(*p*-Br)	20 min, rt	**3k** (75)
11	Cl	C_6H_5	2 h, reflux	**3l** (60)
12	Cl	C_6H_5(*p*-OCH_3)	7 h, reflux	**3m** (53)
13	Cl	C_6H_5(*p*-Br)	30 min, reflux	**3n** (50)
14	Cl	C_4H_3O[d]	30 min, reflux	**3o** (52)

[a] Reaction condition: **1** (1.2 equiv) and **5** (1 equiv) in toluene (25 mL).
[b] Isolated yields.
[c] Cyclohexyl.
[d] Furoyl.

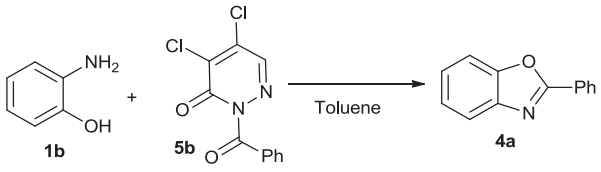
Interestingly in our system, the yields of 2-alkylbenzo[*d*]thiazoles are higher than those of the 2-aryl derivatives. This may be due to the difference in the reactivity of the carbonyl carbon of the intermediate amide in the cyclization step (Scheme 2), such that the enol configuration is favored in the benzamide tautomers, whereas the equilibrium lies toward the keto configuration in the acetamide tautomers. We detected the benzamide derivatives by TLC. The structures of the synthesized 2-substituted-benzo[*d*]thiazoles were established by IR, NMR, and HRMS.



Scheme 2. Tautomer structures of intermediates.

Next, we attempted to synthesize 2-substituted-benzo[*d*]oxazoles by reacting 2-aminophenol (**1b**) with 2-acylpyridazin-3(2*H*)-ones under the same conditions. The reaction of **1b** with 2-benzoyl-4,5-dichloropyridazin-3(2*H*)-one (**5b**) under neutral conditions did not give any products. Therefore, we optimized the conditions for the reaction of **1b** with **5b** as the model reaction using $POCl_3$, P_2O_5, acetic acid, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as catalyst and/or dehydrating agent (Table 3). Among the five entries, the

Table 3
Optimization of reaction conditions for the synthesis of 2-phenylbenzo[*d*]oxazole (**4a**)[a]

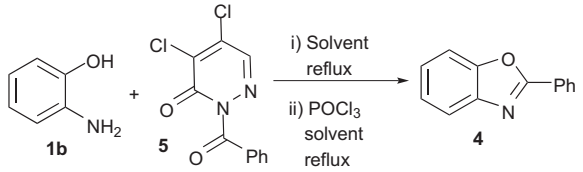


Entry	Conditions	Time (h)	**4a**[b] (%)
1	Room temperature	7	—
2	Reflux	2	—
3	Microwave irradiation[c]	0.5	—
4	(i) Reflux (0.7 h), (ii) $POCl_3$ (0.5 equiv), reflux (7 h)	7.7	61
5	(i) Reflux (0.7 h), (ii) $POCl_3$ (1.0 equiv), reflux (2.8 h)	3.5	92
6	(i) Reflux (0.7 h), (ii) P_2O_5 (1.0 equiv), reflux (8.3 h)	9	63
7	(i) Reflux (0.7 h), (ii) AcOH (1.0 equiv), reflux (47.3 h)	48	60[d]
8	(i) Reflux (0.7 h), (ii) DDQ[e] (1.0 equiv), reflux (11.3 h)	12	—

[a] Reaction condition: **1b** (1 equiv) and **5b** (1.2 equiv) in solvent (25 mL).
[b] Isolated yields.
[c] 300 W, 150 °C, run time: 5 min.
[d] Starting material remained.
[e] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

reaction using 1 equiv of $POCl_3$ gave the best yield (92%, entry 5, Table 3). In addition, we screened nine solvents (Table 4), among which, toluene gave the best results (entry 1, Table 4). Thus, the reaction of **1b** (1 equiv) with **5b** (1.2 equiv) in refluxing toluene, in the presence of $POCl_3$ (1 equiv) represents our optimized reaction system.

Table 4
Solvent screening for the synthesis of 2-phenylbenzo[*d*]oxazole (**4a**)[a]

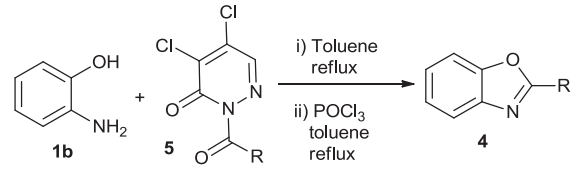


Entry	Conditions	Time (h)	**4a**[b] (%)
1	Toluene	3.5	92
2	*n*-Hexane	25	74
3	Chloroform	9	69
4	Methylene chloride	23	68
5	Tetrahydrofuran	10	65
6	Ethyl acetate	6	64
7	*N*,*N*-Dimethylformamide	7	37
8	2-Propanol	6	82
9	Water	48	25

[a] Reaction condition: a mixture of **1b** (1.2 equiv) and **5b** (1 equiv) in solvent (25 mL) was refluxed until **5b** was disappeared, and after adding $POCl_3$(1 equiv) then refluxed.
[b] Isolated yields.

With the established optimal conditions, we explored the scope of both 2-aminophenols and 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones. As shown in Table 5, the reaction of six 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones with **1b** under the optimized conditions afforded the corresponding benzo[*d*]oxazoles in 71–91% yield (Table 5). We also isolated quantitatively reusable 4,5-dichloropyridazin-3(2*H*)-one from the reaction mixture.

Table 5
Synthesis of 2-substituted-benzo[*d*]oxazoles[a]



Entry	R	Time (h)	**4** (Yield, %)[b]
1	C_6H_5(*p*-OCH_3)	6	**4b** (71)
2	C_6H_5(*p*-Br)	9	**4c** (78)
3	C_4H_3O[c]	2	**4d** (91)
4	CH_2CH_3	0.3	**4e** (81)
5	$CH_2(CH_2)_4CH_3$	0.3	**4f** (84)
6	*c*-C_6H_{11}[d]	1	**4g** (73)

[a] Reaction condition: a mixture of **1b** (1 equiv) and **5** (1.2 equiv) in toluene (25 mL) was refluxed until **5** was disappeared, and after adding $POCl_3$(1 equiv) then refluxed.
[b] Isolated yields.
[c] Furoyl.
[d] Cyclohexyl.

The structures of the prepared 2-substituted-benzo[*d*]oxazoles were confirmed by IR, NMR, and HRMS.

3. Conclusions

In summary, we have developed an efficient and eco-friendly method for the synthesis of 2-substituted-benzo[*d*]thiazole and benzo[*d*]oxazole in toluene in moderate-to-good yields without using transition-metal catalyst. The advantages of our method over those described in the literature include a better efficiency, neutral and ambient conditions for benzo[*d*]thiazoles, a very simplified procedure, the use of toluene as the solvent and the quantitative isolation of reusable 4,5-dichloropyridazin-3(2*H*)-one. Thus we have provided eco-friendly atom-economic alternative to the available methods. Further applications of 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones in the synthesis of other heterocycles are currently under investigation in our laboratory.

4. Experimental

4.1. General

Melting points were determined with a capillary apparatus and were not further corrected. NMR spectra were recorded with a Bruker FT NMR Avance-300 spectrometer at 300 and 75 MHz, with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained using a Varian 640-IR spectrophotometer. Mass spectra were obtained using a GC Mate 2, JEOL instrument. 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.

2-Acyl-4,5-dichloropyridazin-3(2*H*)-ones were synthesized according to the literature procedures.[10g]

4.2. Typical procedure for the synthesis of 2-substituted-benzo[*d*]thiazoles 3

A mixture of 2-acyl-4,5-dichloropyridazin-3(2*H*)-one (**5**, 1 equiv, 2.4 mmol), 2-aminothiophenol (**1**, 1.2 equiv, 0.3 mmol), and toluene (25 mL) was stirred at room temperature (or at reflux conditions) until **5** was disappeared as determined by TLC. Water (50 mL) and dichloromethane (150 mL) were added with stirring to the reaction mixture. The organic layer was extracted and dried over anhydrous magnesium sulfate, and the solvent was evaporated under the reduced pressure. The resulting residue was transferred to an open-bed silica gel column (3×6 cm). The column was eluted with *n*-hexane/tetrahydrofuran (5:1, v/v) for **3** and then ethyl acetate for 4,5-dichloropyridazin-3(2*H*)-one. Fractions containing compound **3** were combined and evaporated under reduced pressure to give the product. Fractions containing 4,5-dichloropyridazin-3(2*H*)-one were also combined and evaporated under reduced pressure to afford quantitatively the recyclable 4,5-dichloropyridazin-3(2*H*)-one.

*4.2.1. 2-Methylbenzo[d]thiazole (**3a**).* Yellow oil. IR (KBr) 3060, 3036, 2990, 2958, 2921, 2849, 1715, 1686, 1672, 1595, 1527, 1455, 1432, 1310, 1285, 1241, 1173, 1126, 1065, 1015, 870, 758, 729, 706, 641 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 2.81 (s, 3H), 7.38–7.52 (m, 2H), 8.01 (t, 2H, J_1=6.58 Hz, J_2=6.13 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 19.75, 121.86, 122.10, 124.70, 125.94, 135.46, 153.23, 166.74. HRMS (*m*/*z*): $[M]^+$ calcd for C_8H_7NS 149.0299. Found: 149.0299.

*4.2.2. 2-Ethylbenzo[d]thiazole (**3b**).* Yellow oil. IR (KBr) 2955, 2922, 2867, 1731, 1700, 1651, 1558, 1540, 1509, 1457, 1433, 1361, 1311, 1230, 1156, 1118, 1021, 860, 758, 668, 615 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 1.36–1.41 (m, 3H), 3.08–3.16 (m, 2H), 7.38–7.43 (m, 1H), 7.47–7.52 (m, 1H), 7.97–8.04 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm) 13.46, 27.17, 121.99, 122.28, 124.74, 125.98, 134.84, 153.10, 172.8. HRMS (*m*/*z*): $[M]^+$ calcd for C_9H_9NS 163.0456. Found: 163.0456.

*4.2.3. 2-Pentylbenzo[d]thiazole (**3c**).* Yellow oil. IR (KBr) 3060, 2953, 2925, 2855, 1731, 1718, 1698, 1556, 1518, 1454, 1433, 1373, 1308, 1239, 1277, 1239, 1200, 1149, 1126, 1080, 1058, 1010, 871, 756, 726, 704 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 0.84–0.89 (m, 3H), 1.32–1.37 (m, 4H), 1.75–1.84 (m, 2H), 3.08 (t, 2H, J_1=7.8 Hz, J_2=7.2 Hz), 7.39 (t, 1H, J_1=7.2 Hz, J_2=7.8 Hz), 7.48 (t, 1H, J_1=7.8 Hz, J_2=7.2 Hz), 7.93 (d,

1H, J=8.1 Hz), 8.04 (d, 1H, J=8.1 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 14.30, 22.28, 29.11, 31.11, 33.79, 122.50, 122.57, 125.20, 126.44, 135.10, 153.29, 172.25. HRMS (m/z): $[M]^+$ calcd for $C_{12}H_{15}NS$ 205.0925. Found: 205.0927.

*4.2.4. 2-Cyclohexylbenzo[d]thiazole (**3d**).* Yellow oil. IR (KBr) 3060, 2926, 2851, 1559, 1514, 1455, 1447, 1436, 1313, 1244, 1146, 1124, 1094, 1067, 1014, 991, 889, 846, 757, 728, 709, 667 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ ppm) 1.20–1.41 (m, 3H), 1.52–1.70 (m, 3H), 1.78–1.82 (m, 2H), 2.14 (d, 2H, J=12.94 Hz), 2.97–3.07 (m, 1H), 7.20–7.25 (m, 1H), 7.33–7.38 (m, 1H), 7.74 (d, 1H, J=7.96 Hz), 7.96 (d, 1H, J=8.18 Hz). ^{13}C NMR ($CDCl_3$, δ ppm) 25.79, 26.02, 33.32, 43.31, 121.43, 122.57, 124.39, 125.67, 134.57, 153.20, 177.12. HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{15}NS$ 217.0925. Found: 217.0923.

*4.2.5. 5-Chloro-2-methylbenzo[d]thiazole (**3e**).* Light yellow solid. Mp 68–69 °C (lit.[12] 68–69 °C). IR (KBr) 3082, 3062, 3009, 2921, 1583, 1544, 1477, 1408, 1369, 1300, 1254, 1171, 1144, 1072, 1060, 996, 939, 903, 885, 801, 734, 644, 609 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 2.83 (s, 3H), 7.43–7.46 (m, 1H), 7.99–8.08 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm) 19.76, 121.37, 123.26, 124.71, 130.71, 133.92, 153.81, 169.49. HRMS (m/z): $[M]^+$ calcd for C_8H_6ClNS 182.9909. Found: 182.9908.

*4.2.6. 5-Chloro-2-pentylbenzo[d]thiazole (**3f**).* Yellow oil. IR (KBr) 2952, 2924, 2853, 1586, 1543, 1514, 1459, 1433, 1410, 1374, 1297, 1245, 1188, 1139, 1067, 912, 866, 796, 735, 617, 646, 612 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 0.85 (s, 3H), 1.26–1.34 (m, 6H), 1.74–1.79 (m, 2H), 3.07 (t, 2H, J_1=7.44 Hz, J_2=7.38 Hz), 7.41–7.44 (d, 1H, J=8.38 Hz), 8.03 (t, 2H, J_1=8.30 Hz, J_2=8.53 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 13.90, 22.13, 28.32, 28.96, 31.08, 33.65, 121.75, 123.33, 124.84, 130.93, 133.53, 153.93, 174.23. HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{16}ClNS$ 253.0692. Found: 253.0694.

*4.2.7. 5-Chloro-2-cyclohexylbenzo[d]thiazole (**3g**).* White solid. Mp 80–82 °C (lit.[13] 58–61 °C). IR (KBr) 2924, 2849, 1633, 1542, 1493, 1431, 1406, 1360, 1294, 1245, 1186, 1143, 1067, 983, 890, 843, 793, 734, 713, 685, 651, 613 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ ppm) 1.23–1.32 (m, 1H), 1.35–1.50 (m, 2H), 1.55–1.68 (m, 2H), 1.75–1.78 (m, 1H), 1.86–1.91 (m, 2H), 2.19 (d, 2H, J=11.29 Hz), 3.03–3.13 (m, 1H), 7.30 (dd, 1H, J_1=1.98 Hz, J_2=1.99 Hz), 7.73 (d, 1H, J=8.50 Hz), 7.94 (d, 1H, J=1.93 Hz). ^{13}C NMR ($CDCl_3$, δ ppm) 25.77, 26.02, 33.36, 43.52, 122.23, 122.50, 124.98, 131.82, 132.88, 154.09, 179.61. HRMS (m/z): $[M]^+$ calcd for $C_{13}H_{14}ClNS$ 251.0535. Found: 251.0535.

*4.2.8. 2-Phenylbenzo[d]thiazole (**3h**).* Light yellow solid. Mp 108–110 °C (lit.[14] 109–111 °C). IR (KBr) 3062, 2951, 2921, 2851, 1698, 1650, 1556, 1506, 1475, 1453, 1432, 1311, 1283, 1250, 1222, 1157, 1069, 961, 761, 729, 685, 667, 650, 621 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 7.46–7.60 (m, 5H), 8.09–8.16 (m, 4H). ^{13}C NMR (DMSO-d_6, δ ppm) 122.26, 122.87, 125.49, 126.60, 127.16, 129.33, 131.34, 132.85, 134.45, 153.56, 167.26. HRMS (m/z): $[M]^+$ calcd for $C_{13}H_9NS$ 211.0456. Found: 211.0455.

*4.2.9. 2-(p-Tolyl)benzo[d]thiazole (**3i**).* Light yellow solid. Mp 77–79 °C (lit.[15] 79.3–81.2 °C). IR (KBr) 2949, 2916, 2846, 1693, 1604, 1546, 1478, 1427, 1402, 1306, 1269, 1253, 1221, 955, 811, 750, 721, 703, 685, 662 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 2.39 (s, 3H), 7.38 (d, 2H, J=8.09 Hz), 7.45 (t, 1H, J_1=7.21 Hz, J_2=7.87 Hz), 7.54 (t, 1H, J_1=7.97 Hz, J_2=7.13 Hz), 7.99 (d, 2H, J=8.03 Hz), 8.04 (d, 1H, J=8.09 Hz), 8.14 (d, 1H, J=7.96 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 21.52, 122.78, 123.17, 125.85, 127.07, 127.61, 130.42, 130.69, 134.76, 141.98, 154.04, 167.81. HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{11}NS$; 225,0612. Found: 225,0611.

*4.2.10. 2-(4-Methoxyphenyl)benzo[d]thiazole (**3j**).* Light yellow solid. Mp 108–111 °C (lit.[16] 106–108 °C). IR (KBr) 2952, 2921, 2851, 1601, 1518, 1480, 1456, 1431, 1408, 1374, 1306, 1256, 1221, 1167, 1110, 1025, 1007, 964, 829, 787, 756, 726, 687, 621 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 3.86 (s, 3H), 7.10–7.15 (m, 2H), 7.40–7.46 (m, 1H), 7.50–7.56 (m, 1H), 8.01–8.11 (m, 4H). ^{13}C NMR (DMSO-d_6, δ ppm) 55.43, 114.68, 122.09, 122.43, 125.02, 125.54, 126.43, 128.82, 134.22, 153.68, 161.75, 166.99. HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{11}NOS$ 241.0561. Found: 241.0560.

*4.2.11. 2-(4-Bromophenyl)benzo[d]thiazole (**3k**).* White solid. Mp 129–131 °C (lit.[17] 129–131 °C). IR (KBr) 3053, 3025, 1620, 1577, 1554, 1500, 1470, 1451, 1426, 1390, 1307, 1281, 1242, 1220, 1098, 1063, 1006, 963, 929, 823, 750, 716, 677, 614 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 7.47–7.60 (m, 2H), 7.77 (d, 2H, J=8.21 Hz), 8.02–8.17 (m, 4H). ^{13}C NMR (DMSO-d_6, δ ppm) 121.51, 123.24, 125.29, 126.34, 128.72, 132.04, 132.38, 134.94, 153.97, 166.43. HRMS (m/z): $[M]^+$ calcd for $C_{13}H_8BrNS$ 288.9561. Found: 288.9560.

*4.2.12. 5-Chloro-2-phenylbenzo[d]thiazole (**3l**).* White solid. Mp 137–138 °C (lit.[18] 138–139 °C). IR (KBr) 3079, 1582, 1541, 1504, 1476, 1431, 1314, 1262, 1251, 1221, 1063, 966, 918, 899, 882, 806, 762, 733, 686, 626 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 7.53 (dd, 1H, J_1=2.01 Hz, J_2=2.03 Hz), 7.58–7.62 (m, 3H), 8.09–8.12 (m, 2H), 8.16 (d, 1H, J=1.97 Hz), 8.21 (d, 1H, J=8.59 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 122.19, 123.79, 125.56, 127.24, 129.39, 131.34, 131.72, 132.42, 133.17, 154.37, 169.59. HRMS (m/z): $[M]^+$ calcd for $C_{13}H_8ClNS$ 245.0066. Found: 245.0066.

*4.2.13. 5-Chloro-2-(4-methoxyphenyl)[d]thiazole (**3m**).* White solid. Mp 149–150 °C. IR (KBr) 2961, 2934, 2837, 1603, 1572, 1542, 1522, 1479, 1455, 1432, 1412, 1308, 1259, 1222, 1171, 1111, 1062, 1028, 968, 883, 830, 807, 792, 627 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 3.86 (s, 3H), 7.12–7.15 (m, 2H), 7.48 (dd, 1H, $J_{1,2}$=2.08 Hz), 8.03–8.09 (m, 3H), 8.15 (d, 1H, J=8.54 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 55.57, 114.72, 121.98, 123.34, 125.13, 125.43, 129.11, 131.50, 133.14, 154.82, 162.24, 169.55. HRMS (m/z): $[M]^+$ calcd for $C_{14}H_{10}ClNOS$ 275.0172. Found: 275.0273.

*4.2.14. 5-Chloro-2-(4-bromophenyl)benzo[d]thiazole (**3n**).* White solid. Mp 147–149 °C. IR (KBr) 3491, 3465, 3435, 1626, 1576, 1534, 1497, 1464, 1423, 1387, 1295, 1251, 1214, 1172, 1135, 1107, 1061, 1002, 959, 893, 861, 820, 792, 727, 690 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 7.54 (d, 2H, J=8.51 Hz), 7.79 (d, 2H, J=8.36 Hz), 8.03 (d, 2H, J=8.31 Hz), 8.15 (s, 1H), 8.20 (d, 2H, J=8.58 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 122.30, 123.12, 125.86, 125.90, 128.90, 132.16, 132.29, 132.54, 133.26, 154.91, 168.47. HRMS (m/z): $[M]^+$ calcd for $C_{13}H_7BrClNS$ 322.9171. Found: 322.9173.

*4.2.15. 5-Chloro-2-(furan-2-yl)benzo[d]thiazole (**3o**).* Yellow solid. Mp 119–120 °C. IR (KBr) 3347, 3129, 3097, 1683, 1565, 1506, 1433, 1404, 1377, 1282, 1153, 1092, 1066, 1011, 910, 879, 839, 804, 753, 716, 631 cm^{-1}. ^{1}H NMR (DMSO-d_6, δ ppm) 6.81–6.83 (m, 1H), 7.40 (d, 1H, J=3.51 Hz), 7.51 (dd, 1H, J_1=1.87 Hz, J_2=2.04 Hz), 8.05 (d, 1H, J=1.58 Hz), 8.10 (d, 1H, J=2.04 Hz), 8.19 (d, 1H, J=8.61 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 112.52, 113.12, 121.99, 123.65, 125.36, 131.54, 132.49, 146.44, 147.68, 154.30, 158.91. HRMS (m/z): $[M]^+$ calcd for $C_{11}H_6ClNOS$ 234.9859. Found: 234.9859.

4.3. Typical procedure for the synthesis of 2-substituted-benzo[*d*]oxazoles 4

A mixture of 2-acyl-4,5-dichloropyridazin-3(2*H*)-one (**5**, 1.2 equiv, 5 mmol), 2-aminophenol (**1b**, 1 equiv, 4.2 mmol), and toluene (25 mL) was refluxed until **1b** disappeared, as determined by TLC. After adding $POCl_3$ (1 equiv, 4.2 mmol), the reaction mixture was refluxed until the intermediate amide disappeared. Water (50 mL) and dichloromethane (100 mL) were added with stirring to the reaction mixture. The organic layer was extracted, washed with

water, and then, with saturated NaCl solution (40 mL×6) and finally, dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was transferred an open-bed silica gel column (4×9 cm). The column was eluted with *n*-hexane/ethyl acetate (3:1, v/v) for compound **4** and then with ethyl acetate for 4,5-dichloropyridazin-3(2*H*)-one. Fractions containing **4** were combined and evaporated under reduced pressure to give **4**. Fractions containing 4,5-dichloropyridazin-3(2*H*)-one were also combined and evaporated under reduced pressure to afford recyclable 4,5-dichloropyridazin-3(2*H*)-one.

*4.3.1. 2-Phenylbenzo[d]oxazole (**4a**).* White solid. Mp 101–102 °C (lit.[19] 101–102 °C). IR (KBr) 3061, 2955, 1612, 1549, 1479, 1446, 1341, 1318, 1283, 1239, 1192, 1144, 1109, 1078, 1048, 1017, 922, 888, 858, 807, 741, 693, 689, 629 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 7.44–7.47 (m, 2H), 7.63–7.65 (m, 3H), 7.77–7.87 (m, 2H), 8.23–8.26 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm) 110.90, 119.87, 124.84, 125.48, 126.54, 127.29, 129.26, 131.88, 141.63, 150.30, 162.29. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_9NO$ 195.0684. Found: 195.0690.

*4.3.2. 2-(4-Methoxyphenyl)benzo[d]oxazole (**4b**).* White solid. Mp 98–99 °C (lit.[20] 97–99 °C). IR (KBr) 3044, 2951, 2910, 2840, 1613, 1578, 1498, 1449, 1417, 1341, 1315, 1240, 1185, 1165, 1104, 1055, 1014, 918, 828, 780, 734, 628 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 3.88 (s, 3H), 7.16 (d, 2H, J=8.69 Hz), 7.39–7.42 (m, 2H), 7.74–7.79 (m, 2H), 8.15 (d, 2H, J=8.68 Hz). ^{13}C NMR (DMSO-d_6, δ ppm) 55.45, 110.63, 114.70, 118.75, 119.38, 124.63, 124.90, 129.08, 141.70, 150.10, 162.13, 162.36. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{11}NO_2$ 225.0790. Found: 225.0790.

*4.3.3. 2-(4-Bromophenyl)benzo[d]oxazole (**4c**).* Light yellow solid. Mp 157–158 °C (lit.[21] 157–158 °C). IR (KBr) 2952, 2927, 2895, 2853, 1612, 1592, 1548, 1458, 1398, 1375, 1342, 1294, 1275, 1242, 1196, 1175, 1109, 1068, 1050, 1005, 925, 890, 830, 808, 739, 625 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 7.43–7.47(m, 2H), 7.79–7.85(m, 4H), 8.12–8.15(m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm) 110.94, 119.87, 124.98, 125.57, 125.74, 129.08, 132.36, 141.34, 150.19, 161.40. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_8BrNO$ 272.9789. Found: 272.9785.

*4.3.4. 2-(Furan-2-yl)benzo[d]oxazole (**4d**).* Light yellow solid. Mp 85–86 °C (lit.[22] 85–86 °C). IR (KBr) 3107, 3062, 3040, 1640, 1586, 1532, 1474, 1447, 1391, 1338, 1296, 1241, 1154, 1108, 1079, 1057, 1011, 935, 898, 880, 826, 791, 756, 739, 620 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 6.86–6.88 (m, 1H), 7.43–7.51 (m, 3H), 7.78–7.84 (m, 2H), 8.14 (s, 1H). ^{13}C NMR (DMSO-d_6, δ ppm) 110.86, 112.79, 115.10, 119.80, 125.06, 125.56, 141.21, 141.68, 147.09, 149.61, 154.69. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{11}H_7NO_2$ 185.0477. Found: 185.0478.

*4.3.5. 2-Ethylbenzo[d]oxazole (**4e**).* Yellow oil. IR (KBr) 3061, 2981, 2935, 2880, 2848, 1612, 1570, 1517, 1453, 1372, 1286, 1264, 1239, 1156, 1102, 1066, 1027, 1001, 969, 924, 889, 822, 747, 624 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 1.27–1.40 (m, 3H), 2.87–3.00 (m, 2H), 7.28–7.36 (m, 2H), 7.62–7.70 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm) 10.67, 21.43, 110.40, 119.21, 124.13, 124.55, 141.03, 150.30, 167.81. HRMS (*m*/*z*): $[M]^+$ calcd for C_9H_9NO 147.0684. Found: 147.0687.

*4.3.6. 2-Hexylbenzo[d]oxazole (**4f**).* Yellow oil. IR (KBr) 2955, 2928, 2856, 1615, 1573, 1455, 1439, 1378, 1345, 1264, 1241, 1149, 1103, 1002, 928, 836, 816, 745, 621 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 0.85 (t, 3H, J_1=6.97 Hz, J_2=6.73 Hz), 1.24–1.38 (m, 6H), 1.76–1.85 (m, 2H), 2.90 (t, 2H, J_1=7.52 Hz, J_2=7.49 Hz), 7.30–7.34 (m, 2H), 7.59–7.64 (m, 1H), 7.70–7.73 (m, 1H). ^{13}C NMR (DMSO-d_6, δ ppm) 14.00, 22.37, 26.51, 28.18, 28.63, 31.32, 110.49, 119.52, 124.21, 124.62, 141.58, 150.71, 166.97. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{17}NO$ 203.1310. Found: 203.1312.

*4.3.7. 2-Cyclohexylbenzo[d]oxazole (**4g**).* Light yellow solid. Mp 35–36 °C (lit.[23] 35 °C). IR (KBr) 2930, 2854, 1609, 1565, 1451, 1375, 1343, 1269, 1241, 1156, 1125, 1101, 1007, 932, 888, 864, 834, 791, 742, 606 cm^{-1}. ^1H NMR (DMSO-d_6, δ ppm) 1.24–1.42 (m, 3H), 1.61–1.80 (m, 5H), 2.06–2.11 (m, 2H), 2.97–3.02 (m, 1H), 7.32–7.38 (m, 2H), 7.65–7.72 (m, 2H). ^{13}C NMR (DMSO-d_6, δ ppm) 24.95, 25.37, 29.98, 36.90, 110.47, 119.36, 124.11, 124.56, 140.95, 150.10, 169.63. HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{15}NO$ 201.1154. Found: 201.1154.

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