

Rapid and Ecofriendly Esterification of Alcohols with 2-Acylpyridazinones

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Atom-economical esterification is of great importance in green chemistry. In this work, we demonstrated the catalyst and additive free esterification of alcohols by their reaction with 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones without solvent at 100 °C. Aliphatic and aromatic alcohols were converted into the corresponding esters in good to excellent yields. It is noteworthy that the reaction is solvent-free, atom-economic, easy-workup, and rapid and that the process is inexpensive.

Key Words : Esterification, 2-Acylpyridazin-3(2*H*)-one, Atom-economical reaction, Green chemistry, Heterocycles

Introduction

The importance of green chemistry was recently highlighted in a cover story in *Chemical and Engineering News*.¹ Green chemistry is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.^{2,3} In 2005, the ACS Green Chemistry Institute joined with global pharmaceutical corporations to develop the ACS GCI Pharmaceutical Roundtable, an initiative to encourage the integration of green chemistry into the pharmaceutical industry.⁴ Therefore, the development of ecofriendly and atom-economical synthesis within the fields of green chemistry and organic synthesis remains an active area of research.

In connection with the research on synthetic applications of 2-substituted pyridazin-3(2*H*)-ones, we found 2-acylpyridazin-3(2*H*)-ones serve as a good acyl source in green esterification transformations (Scheme 1).⁵⁻¹⁰

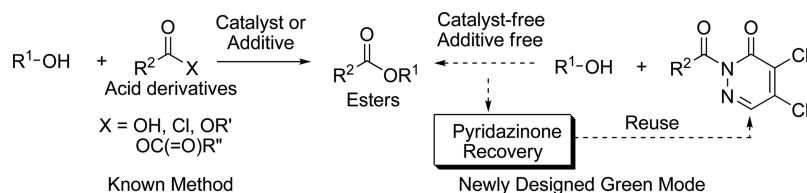
In previous accounts,^{5,11} we also reported the amidation reaction of amines, along with the mechanism of aminolysis using 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones at room

temperature. Therefore, it may be postulated that the reaction progress of alcohols and 2-acylpyridazin-3(2*H*)-ones may follow a similar mechanistic pathway (Scheme 2).

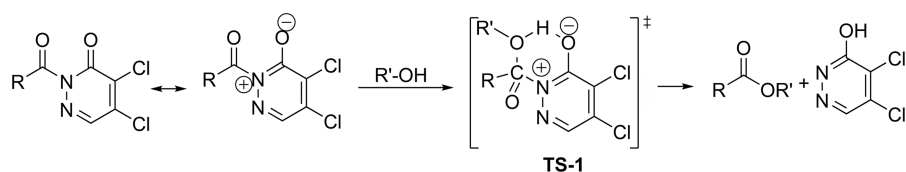
2-Acyl-4,5-dichloropyridazin-3(2*H*)-ones are inexpensive and easily prepared heterocycles. Since pyridazin-3(2*H*)-one species readily form stable anions,⁵⁻¹¹ they can act as good leaving groups. In addition, the ease with which pyridazin-3(2*H*)-ones can be removed and/or recycled has further stimulated our interest in their use in green synthesis. Therefore, we attempted to synthesize directly the esters from alcohols and 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones under catalyst and additive free conditions. Herein, we report a rapid, direct and green conversion of alcohols with 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones into esters. The introduction should state the purpose of the research and should include appropriate citations of previous and relevant works.

Experimental

General Methods. Melting points were determined with a capillary apparatus and uncorrected. NMR spectra were



Scheme 1. Green esterification of alcohols with 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones.



Scheme 2. Plausible mechanism for the esterification reaction of alcohols with 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones.

recorded on a 300 MHz spectrometer (Bruker) with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on a Varian 640-IR spectrophotometer. Mass spectra were obtained on a GC MSD (HP6890 & 5973) under electron ionization (EI). The open-bed chromatography was carried out on silica gel (70-230 mesh, Merck) using gravity flow. The column was packed with slurries. Chemicals were purchased from the Aldrich or TCI chemical company. 2-Acyl-4,5-dichloropyridazin-3(2H)-ones were prepared from the corresponding acyl chloride according to the reported procedure.⁵

General Procedure for the Conversion of *N*-Acylpyridazin-3(2H)-ones into the Corresponding Ester. Alcohol (**1**, 5.31 mmol, 1 equiv.) and 2-acylpyridazin-3(2H)-ones (**2**, 6.37 mmol, 1.2 equiv.) were placed in a culture tube (Pyrex brand 9825 culture tube with screw cap), sealed, and heated to 100 °C. The resulting mixture was kept at this temperature until **1** disappeared (as determined by TLC analysis). After cooling of the tube, dichloromethane (5-6 mL) was added to the mixture with stirring until the reaction mixture was dissolved. After removing 4,5-dichloropyridazin-3(2H)-one by filtration, the resulting filtrate was evaporated under reduced pressure. The resulting residue was further purified by silica gel column chromatography to give the corresponding esters **3**.

Compounds Characterization.

Phenyl Acetate (3a): Yield: 266 mg (92%). Colorless oil; IR (KBr) 3069, 3042, 2927, 2853, 1765, 1593, 1492, 1370, 1213, 1195, 1010, 924, 891, 813, 748, 691, 664 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.25 (s, 3H), 7.03-7.08 (m, 2H), 7.17-7.22 (m, 1H), 7.31-7.37 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.0, 121.7, 125.9, 129.5, 150.9, 169.4; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_8\text{H}_8\text{O}_2$ 136.0524. found: 136.0525.

4-Methoxyphenyl Benzoate (3b): Yield: 360 mg (98%). White solid. mp 84-85 °C (lit.¹² 85.5-86.5 °C); IR (KBr) 3066, 2997, 2960, 2934, 2834, 1730, 1599, 1503, 1271, 1248, 1194, 1177, 1031, 869, 807 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.81 (s, 3H), 6.91-6.96 (m, 2H), 7.10-7.15 (m, 2H), 7.47-7.64 (m, 3H), 8.17-8.20 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.6, 114.5, 122.5, 128.6, 128.9, 129.7, 130.1, 130.6, 133.5, 144.5, 157.3, 165.5; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{12}\text{O}_3$ 228.0786. Found: 228.0787.

4-Acetamidophenethyl Acetate (3c): Yield: 302 mg (93%). White solid. mp 96-98 °C (lit.¹³ 95 °C); IR (KBr) 3293, 3186, 3119, 3061, 2952, 2928, 2885, 1732, 1663, 1603, 1534, 1408, 1368, 1315, 1262, 1034, 835, 753 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.03 (s, 3H), 2.15 (s, 3H), 2.89 (t, 2H, $J_1 = J_2 = 7.0$ Hz), 4.24 (t, 2H, $J_1 = J_2 = 7.0$ Hz), 7.15 (d, 2H, $J = 8.4$ Hz), 7.43 (d, 2H, $J = 8.4$ Hz), 7.55 (bs, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, CDCl_3) δ 20.9, 24.5, 34.5, 54.9, 120.1, 129.4, 133.8, 136.5, 168.5, 171.1; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3$ 221.1052. Found: 221.1056.

Cyclohexyl Acetate (3d): Yield: 560 mg (80%). Colorless oil; IR (KBr) 2938, 3859, 1734, 1448, 1367, 1241, 1123, 1044, 1021, 962, 901 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.22-1.87 (m, 10H), 2.02 (s, 3H), 4.69-4.76 (m, 1H); ^{13}C

NMR (75 MHz, CDCl_3) δ 21.4, 23.9, 25.4, 30.3, 31.7, 72.7, 170.6; MS (EI, 70 eV): m/z 142 (M^+)(1), 127 ($\text{M}-\text{CH}_3$)⁺ (0.5), 99 ($\text{M}-\text{OC}_2\text{H}_5$)⁺ (7), 82 (C_6H_{10})⁺ (100), 67 (C_5H_7)⁺ (73), 54 (C_4H_6)⁺ (15).¹⁴

4-Nitrophenyl Acetate (3e): Yield: 251 mg (96%). White solid. mp 77-79 °C (lit.¹⁵ 78-79 °C); IR (KBr) 3110, 3084, 2936, 2857, 1762, 1615, 1592, 1524, 1490, 1369, 1348, 1189, 1160, 1108, 1101, 911, 866, 851 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.34 (s, 3H), 7.25-7.30 (m, 2H), 8.22-8.27 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 21.1, 122.5, 125.2, 145.3, 155.5, 168.5; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_8\text{H}_7\text{NO}_4$ 181.0375. Found: 181.0377.

4-Methoxyphenyl Acetate (3f): Yield: 258 mg (96%). Colorless oil; IR (KBr) 3005, 2955, 2938, 2911, 2837, 1761, 1596, 1506, 1465, 1369, 1249, 1217, 1193, 1003, 905, 841, 760 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.21 (s, 3H), 3.72 (s, 3H), 6.82-6.87 (m, 2H), 6.94-7.00 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.9, 55.5, 114.4, 122.3, 144.2, 157.3, 169.8; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_{10}\text{O}_3$ 166.0630. Found: 166.0629.

4-Formylphenyl Acetate (3g): Yield: 260 mg (97%). Colorless oil; IR (KBr) 2942, 2853, 2737, 1763, 1701, 1597, 1502, 1369, 1191, 1155, 1011, 909, 858, 827, 763, 749 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.33 (s, 3H), 7.25-7.28 (m, 2H), 7.90-7.92 (m, 2H), 9.98 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 21.1, 122.4, 131.1, 133.9, 155.3, 168.7, 190.9; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_8\text{O}_3$ 164.0473. Found: 164.0474.

Pyridin-3-yl Acetate (3h): Yield: 262 mg (90%). Colorless oil; IR (KBr) 2926, 2852, 1767, 1633, 1580, 1474, 1423, 1370, 1274, 1195, 1022, 897, 749, 705 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.19 (s, 3H), 7.18-7.38 (m, 2H), 8.33-8.36 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.8, 123.9, 129.3, 143.3, 146.7, 147.3, 168.8. HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_7\text{H}_7\text{NO}_2$ 137.0477. Found: 137.0474.

Se-Phenyl Ethaneselenoate (3i): Yield: 55 mg (44%, 0.1 g scale). Colorless oil; IR (KBr) 3056, 2997, 2918, 1721, 1576, 1475, 1436, 1347, 1098, 1071, 1019, 997, 936, 738, 688, 572 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.46 (s, 3H), 7.36-7.39 (m, 3H), 7.50-7.52 (m, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 34.0, 126.4, 128.9, 129.5, 135.5, 196.4; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_8\text{H}_8\text{OSe}$ 199.9740. Found: 199.9739.

4-Methoxyphenyl Heptanoate (3j): Yield: 379 mg (99%). Colorless oil; IR (KBr) 2954, 2930, 2857, 1755, 1504, 1463, 1373, 1248, 1194, 1142, 1101, 1033, 839, 749, 518 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.89 (t, 3H, $J_1 = 6.7$ Hz, $J_2 = 6.6$ Hz), 1.28-1.43 (m, 6H), 1.66-1.76 (m, 2H), 2.49 (t, 2H, $J_1 = 7.5$ Hz, $J_2 = 7.4$ Hz), 3.72 (s, 3H), 6.82-6.87 (m, 2H), 6.94-6.99 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.0, 22.5, 24.9, 28.8, 31.5, 34.3, 55.4, 114.4, 122.3, 144.3, 157.2, 172.6; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ 236.1412. Found: 236.1411.

4-Methoxyphenyl 4-Bromobenzoate (3k): Yield: 245 mg (99%). White solid. mp 116-119 °C (lit.¹⁶ 122-124 °C); IR (KBr) 3096, 2957, 2931, 2903, 2834, 1732, 1586, 1395, 1266, 1193, 1100, 1074, 1032, 872, 849, 816, 748 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.81 (s, 3H), 6.90-6.96 (m, 2H),

7.08-7.14 (m, 2H), 7.61-7.66 (m, 2H), 8.02-8.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.6, 114.6, 122.4, 128.6, 128.7, 131.6, 131.9, 144.2, 157.4, 164.9; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{BrO}_3$ 305.9892. Found: 305.9893.

4-Methoxyphenyl 4-Cyanobenzoate (3l): Yield: 208 mg (51%). Pale yellow solid. mp 123-125 °C (lit.¹⁷ 122-124 °C); IR (KBr) 3072, 2965, 2912, 2841, 2228, 1742, 1601, 1504, 1292, 1256, 1195, 1071, 1017, 867, 819, 759, 681 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.81 (s, 3H), 6.91-6.96 (m, 2H), 7.10-7.16 (m, 2H), 7.77-7.80 (m, 2H), 8.16-8.29 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.6, 114.6, 116.9, 117.9, 122.2, 130.6, 132.4, 133.5, 144.0, 157.6, 163.9; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_3$ 253.0739. Found: 253.0737.

4-Methoxyphenyl 4-Methoxybenzoate (3m): Yield: 256 mg (62%). White solid. mp 123-124 °C (lit.¹⁸ 123-123.5 °C); IR (KBr) 3016, 2964, 2933, 2907, 2837, 1721, 1604, 1510, 1453, 1319, 1274, 1248, 1193, 1163, 1071, 1023, 867, 843, 812, 787, 761, 743 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.80 (s, 3H), 3.86 (s, 3H), 6.90-6.97 (m, 4H), 7.08-7.12 (m, 2H), 8.13 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 55.5, 55.6, 113.8, 114.5, 121.9, 122.6, 132.3, 144.6, 157.2, 163.9, 165.3; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{14}\text{O}_4$ 258.0892. Found: 258.0890.

Phenyl Benzoate (3n): Yield: 348 mg (83%). White solid. mp 66-68 °C (lit.¹⁹ 85.5-86.5 °C); IR (KBr) 3086, 3057, 1730, 1453, 1265, 1194, 1177, 1080 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.18-7.27 (m, 3H), 7.36-7.50 (m, 4H), 7.57-7.63 (m, 1H), 8.18-8.21 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 121.7, 125.9, 128.5, 129.5, 129.6, 130.2, 133.5, 151.0; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{10}\text{O}_2$ 198.0681. Found: 198.0687.

Ethyl Benzoate (3o): Yield: 601 mg (92%). Colorless oil; IR (KBr) 3064, 3032, 2982, 2936, 2903, 1717, 1599, 1450, 1391, 1366, 1308, 1272, 1171, 1107, 1069, 1024, 871, 849 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.28 (t, 3H, $J_1 = J_2 = 7.1$ Hz), 4.33-4.40 (m, 2H), 7.38-7.43 (m, 2H), 7.50-7.55 (m, 1H), 8.02-8.05 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 14.3, 60.9, 128.3, 129.5, 130.5, 132.8, 166.6; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_{10}\text{O}_2$ 150.0681. Found: 150.0685.

Isopropyl Benzoate (3p): Yield: 1.35 g (99%, 0.5 g scale). Colorless oil; IR (KBr) 3065, 2980, 2935, 1715, 1599, 1454, 1374, 1347, 1311, 1276, 1175, 1102, 1062, 1024, 919, 849, 711 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.36 (d, 6H, $J = 3.0$ Hz), 5.21-5.29 (m, 1H), 7.38-7.43 (m, 2H), 7.49-7.54 (m, 1H), 8.02-8.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.9, 68.3, 128.2, 129.5, 130.9, 132.7, 166.0; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2$ 164.0837. Found: 164.0834.

8-Chlorooctyl Heptanoate (3q): Yield: 330 mg (94%). Colorless oil; IR (KBr) 2931, 2858, 1735, 1641, 1461, 1265, 1234, 1170, 1105, 750, 649, 538 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.88 (t, 3H, $J_1 = 6.8$ Hz, $J_2 = 6.6$ Hz), 1.26-1.37 (m, 12H), 1.41-1.48 (m, 2H), 1.57-1.67 (m, 4H), 1.72-1.81 (m, 2H), 2.29 (t, 2H, $J_1 = 7.6$ Hz, $J_2 = 7.4$ Hz), 3.53 (t, 2H, $J_1 = J_2 = 6.7$ Hz), 4.05 (t, 2H, $J_1 = J_2 = 6.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 13.9, 22.5, 24.9, 25.8, 26.8, 28.6, 28.7, 28.8, 29.3, 31.4, 32.6, 34.4, 45.0, 64.2, 173.9; HRMS (m/z): $[\text{M}]^+$ calcd

for $\text{C}_{15}\text{H}_{29}\text{ClO}_2$ 276.1856. Found: 276.1853.

2-Ethylhexyl Benzoate (3r): Yield: 345 mg (96%). Colorless oil; IR (KBr) 2960, 2929, 2865, 1724, 1457, 1382, 1313, 1276, 1112, 1068, 1025, 711 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.88-0.97 (m, 6H), 1.16-1.54 (m, 8H), 1.66-1.76 (m, 1H), 4.12-4.29 (m, 2H), 7.41-7.46 (m, 2H), 7.52-7.57 (m, 1H), 8.02-8.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 11.1, 14.0, 22.9, 24.0, 29.0, 30.6, 38.9, 67.3, 138.3, 129.5, 130.6, 132.7, 166.7; HRMS (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$ 234.1620. Found: 234.1623.

2-Mercaptoethyl Benzoate (3s): Yield: 218 mg (47%). Colorless oil; IR (KBr) 3064, 2947, 2890, 2570, 1720, 1061, 1583, 1451, 1378, 1313, 1272, 1176, 1113, 1069, 1206, 958, 911, 711 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.56 (t, 1H, SH, $J_1 = 8.7$ Hz, $J_2 = 8.4$ Hz), 2.84-2.91 (m, 2H), 4.43 (t, 2H, $J_1 = J_2 = 6.6$ Hz), 7.41-7.46 (m, 2H), 7.52-7.58 (m, 1H), 8.03-8.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 23.4, 66.2, 128.4, 129.6, 129.9, 133.1, 166.2. [Unstable. Storage in freezer under Ar (g)].

2-(Benzoylthio)ethyl Benzoate (3t): Yield: 210 mg (29%). White solid. mp 30-33 °C (lit.²⁰ 39 °C); IR (KBr) 3061, 3034, 2952, 1720, 1666, 1450, 1271, 1206, 1175, 1111, 1070, 911, 744, 710, 687, 647 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.48 (t, 2H, $J_1 = 6.3$ Hz, $J_2 = 6.6$ Hz), 4.53 (t, 2H, $J_1 = 6.3$ Hz, $J_2 = 6.6$ Hz), 7.41-7.47 (m, 4H), 7.52-7.60 (m, 2H), 7.97-7.98 (m, 2H), 8.03-8.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 27.8, 63.6, 127.3, 128.4, 128.6, 129.7, 129.9, 133.1, 133.6, 136.7, 166.2, 190.9; Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{O}_3\text{S}$: C, 67.11; H, 4.93; S, 11.20. Found: C, 67.65; H, 4.92; S, 11.04. [Storage in freezer under Ar (g)].

Results and Discussion

Initially, we examined the reaction of phenol (**1a**) with eleven acetic acid derivatives including acetic acid (**2a**), ethyl acetate (**2b**), acetic anhydride (**2c**), acetyl chloride (**2d**), acetamide (**2e**), *N,N*-dimethylacetamide (**2f**), 1-acetylbenzotriazole (**2g**), 1-acetyl-1*H*-benzo[d]imidazole (**2h**), *N*-acetylphthalimide (**2i**), 1-acetylsaccharin (**2j**) and 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one (**2k**) in refluxing THF (Method A) and without solvent at 150 °C (Method B). Among 22 preliminary experiments, the reaction of phenol with **2k** without solvent at 150 °C showed the best result (Entry 11, Method B, Table 1).

Next, we optimized the effect of the solvent and reaction temperature on the reaction of *p*-methoxyphenol (**1b**) with **2k** in both the presence and absence of solvent. The reaction temperatures investigated were 80 °C, 100 °C and 150 °C (Entry 3-5, Table 2). The reaction failed to occur in solvents including *n*-hexane, toluene, benzene, diethyl ether, chloroform, acetone, DMF, acetonitrile and water, with the exception of refluxing methylene chloride (56% yield), whereas the yields and reaction time at 100 °C and 150 °C without solvent were excellent. Therefore, we selected ROH (1 equiv.)/2-acylpyridazinone (1.2 equiv.) without solvent in a culture tube (Pyrex brand 9825 culture tube with screw cap) at 100 °C as the optimized system.

Table 1. Reaction of phenol (**1a**) with acetic acid derivatives **2** in refluxing THF (Method A) and without solvent at 150 °C (Method B)^a

$\text{X} = \text{OH} \quad \text{a} \quad \text{b} \quad \text{c} \quad \text{d} \quad \text{e} \quad \text{f}$ $\text{X} = \text{OH} \quad \text{OEt} \quad \text{CH}_3\text{C(=O)O} \quad \text{Cl} \quad \text{NH}_2 \quad (\text{CH}_3)_2\text{N}$				
$\text{X} = \text{g} \quad \text{h} \quad \text{i} \quad \text{j} \quad \text{k}$ 				
Entry	2	Ester 3a (%) ^b		
		Method A	Method B	
1	2a	NR ^c	NR ^c	
2	2b	NR ^c	NR ^c	
3	2c	trace	55	
4	2d	trace	76	
5	2e	NR ^c	NR ^c	
6	2f	NR ^c	NR ^c	
7	2g	NR ^c	NR ^c	
8	2h	NR ^c	77	
9	2i	NR ^c	78	
10	2j	NR ^c	87	
11	2k	trace	92	

^aMethod A: refluxing THF, 1 h; Method B: neat, 1 h at 150 °C. ^bIsolated yields. ^cNR = no reaction.

To illustrate the versatility of the ecofriendly and atom-economical esterification, we converted aliphatic and aromatic alcohols using 2-alkanoyl (or aroyl)-4,5-dichloropyridazin-3(2*H*)-ones into the corresponding esters under the optimized conditions.

Aliphatic and aromatic alcohols were reacted with 2-acetyl- or 2-heptanoyl-4,5-dichloropyridazin-3(2*H*)-one under the optimized conditions to give the corresponding esters **3c-3h** in good to excellent yields with the exception of benzeneselenol (Entries 1-6 and 8, Table 3). Although the reaction of benzeneselenol with 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one under the optimized conditions afforded Sphenyl ethaneselenoate (**3i**) in 44% yield, this reaction did not proceed to completion (Entry 7, Table 3). Esterification

Table 2. Optimization for the reaction of **1b** with **2l**

Entry	Solvent	Condition	Time	Ester 3b (%) ^b
1	CH ₂ Cl ₂	room temp.	24 h	trace
2	CH ₂ Cl ₂	reflux	24 h	56
3	—	80 °C	2.5 h	80
4	—	100 °C	10 min	97
5	—	150 °C	5 min	98

^aReaction conditions: **1b** (1 equiv.), **2l** (1.2 equiv.) in solvent or without solvent. ^bIsolated yields.

Table 3. Conversion of 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones **2** and **1** into the corresponding esters **3**^a

Entry	R ¹	R ²	Time (min)	Ester 3 (%) ^b
1	AcHN-(CH ₂) ₂ -	CH ₃ -	10	3c (93)
2	Cyclohexyl-	CH ₃ -	10	3d (80)
3	O ₂ N-(CH ₂) ₂ -	CH ₃ -	5	3e (96)
4	MeO-(CH ₂) ₂ -	CH ₃ -	10	3f (96)
5	OHC-(CH ₂) ₂ -	CH ₃ -	5	3g (97)
6	Pyridin-2-yl-	CH ₃ -	5	3h (90)
7	Ph-Se-	CH ₃ -	10	3i (44) ^c
8	MeO-(CH ₂) ₂ -	CH ₃ (CH ₂) ₄ CH ₂ -	10	3j (99)
9	MeO-(CH ₂) ₂ -	Br-(CH ₂) ₂ -	10	3k (99)
10	MeO-(CH ₂) ₂ -	NC-(CH ₂) ₂ -	15	3l (51) ^d
11	MeO-(CH ₂) ₂ -	MeO-(CH ₂) ₂ -	5	3m (62)
12	Ph-	Ph-	20	3n (83)
13	CH ₃ CH ₂ -	Ph-	120	3o (86)
14	(CH ₃) ₂ CH-	Ph-	50	3p (92)
15	Cl(CH ₂) ₇ CH ₂ -	CH ₃ (CH ₂) ₄ CH ₂ -	5	3q (99)
16	CH ₃ (CH ₂) ₃ CH(C ₂ H ₅)CH ₂ - ^g	Ph-	5	3r (96)
17	HSCH ₂ CH ₂ -	Ph-	10	3s (47) ^e 3t (29) ^f

^aReaction conditions: neat in culture tube (Pyrex brand 9825 culture tube with screw cap) at 100 °C. ^bIsolated yields. ^cUnreacted starting material remained. ^dUnknown products were detected. ^e2-Mercaptoethyl benzoate. ^f2-(Benzoylthio)ethyl benzoate. ^g2-Ethyl-1-hexanol.

of aromatic and aliphatic alcohols with some 2-benzoyl-, 2-heptanoyl- or 2-(4-substituted-benzoyl)-4,5-dichloropyridazin-3(2*H*)-ones under the optimized conditions also gave the corresponding esters **3k**, **3l** and **3n-3s** in good to excellent yields (Entries 9, 10 and 12-17, Table 3) with the exception of the reaction of 4-methoxyphenol; although its reaction with 2-(4-cyanobenzoyl)-4,5-dichloropyridazin-3(2*H*)-one yielded the corresponding ester **3l** in 51% yield (Entry 10, Table 3), the requisite ester was accompanied by unknown side products. 2-Mercaptoethanol was also reacted with one equivalent of 2-benzoyl-4,5-dichloropyridazin-

3(2*H*)-one to afford mercaptoethyl benzoate (**3s**, 47%) and 2-(benzoylthio)ethyl benzoate (**3t**, 29%) (Entry 17, Table 3). In the reaction of 2-benzoyl-4,5-dichloropyridazin-3(2*H*)-ones and phenols, we could not observe the effect of aryl substitution on the reaction outcome. On the other hand, the reusable 4,5-dichloropyridazin-3(2*H*)-one could be isolated from all reactions by filtration in quantitative yield. The structures of the products were established by IR, NMR and HRMS.

Conclusion

In conclusion, we have developed a new method for the direct conversion of alcohols into the corresponding esters under catalyst and additive-free conditions. Through the reaction of 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones easily prepared from commercially inexpensive 4,5-dichloropyridazin-3(2*H*)-one with alcohols, the corresponding esters can be readily obtained. This method is a very rapid, cheap, green and effective process. Since 4,5-dichloropyridazin-3(2*H*)-one can be isolated from the reaction mixture and subsequently reused for the synthesis of 2-acylpyridazin-3(2*H*)-ones, this reaction, therefore, is an atom-economical process. This first publication raise the prospect that 2-acylpyridazinones may become a viable alternative to the unstable, less reactive, expensive and/or environmentally toxic acyl sources. Further research on expanding substrate scope and on the application of this reagent as an acyl source in organic synthesis is currently under way in our laboratory.

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