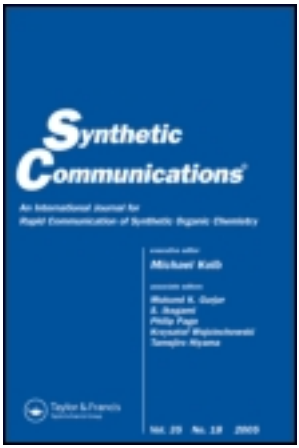

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$ZnCl_2$-Mediated Synthesis of Carboxylic Anhydrides using 2-Acyl-4,5-dichloropyridazin-3(2H)

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$ZnCl_2$-Mediated Synthesis of Carboxylic Anhydrides using 2-Acyl-4,5-dichloropyridazin-3(2*H*)-ones

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Abstract: $ZnCl_2$ is an efficient catalyst for synthesis of carboxylic acid anhydride from 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones. Treatment of 2-acyl-4,5-dichloropyridazin-3(2*H*) -ones with $ZnCl_2$ (0.5 equivalents) and air in refluxing dry THF or acetonitrile gave the corresponding symmetric acid anhydrides in good to excellent yield.

Keywords: Carboxylic acid anhydride, 2-acyl-4,5-dichloropyridazin-3(2*H*)-one, $ZnCl_2$

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Recently, we reported on the acylation ability of 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones (**1**) for amines and the synthesis of 1,3,4-oxadiazoles using 2-acylpyridazin-3(2*H*)-ones.[1,2] During the study of other synthetic applications of 2-acylpyridazin-3(2*H*)-ones, we found that the treatment of 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones (**1**) with zinc chloride and air in an organic solvent at reflux gave the corresponding carboxylic anhydrides **2**. The $ZnCl_2$-mediated synthesis of carboxylic anhydrides using *N*-acyl-heterocycle in air has not been reported to date.

Carboxylic anhydrides are useful acylating agents or intermediates in organic synthesis because of the enhanced electrophilic character of the carbonyl group.[3–10] The availability of symmetric acid anhydrides is quite important for many transacylation applications[11] because it precludes the formation of by-products from the attack at the other acyl group present in mixed anhydrides. Although many reagents for the synthesis of carboxylic acid anhydrides have been developed,[3,10–30] research in this field is still active even now. In the present study, we investigated the synthesis of carboxylic anhydrides using 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones (**1**) and report a novel method using a $ZnCl_2$-mediated reaction sequence.

RESULTS AND DISCUSSION

First, we carried out the treatment of **1a** with 0.5, 1 or 2 equivalents of zinc chloride and air in dry tetrahydrofuran at room temperature (for Entries 1–3 in Table 1) or at reflux temperature (for Entry 4 in Table 1) under an air atmosphere. Zinc chloride (0.5 equivalents)/refluxing dry tetrahydrofuran (Entry 4) was a good condition. To evaluate the solvent effect, the reaction was carried out in various organic solvents such as tetrahydrofuran, methylene chloride, acetonitrile, toluene, benzene, and methanol. From the preliminary experiments (Entries 4–9), we chose tetrahydrofuran and acetonitrile as the suitable solvent in our system. Acetonitrile was more efficient than tetrahydrofuran (Entry 4 vs. Entry 5). It may be due to the difference in the dielectric constant and/or the boiling point. We also performed the reaction of **1c** in the presence of various Lewis acids in refluxing acetonitrile (Scheme 1). The results are summarized in Table 1 (Entries 10–16).

Among the nine Lewis acids, zinc halides and samarium iodide gave **2c** in excellent yield. Therefore we selected zinc chloride as the catalyst. 2-Aroyl-4,5-dichloropyridazin-3(2*H*)-ones **1b–g** were treated with zinc chloride (0.5 equivalents) in air in refluxing dry tetrahydrofuran and acetonitrile to give the corresponding symmetric anhydrides **2b–g** in 73–97% yield, respectively (Table 2). Although the reaction of **1h** or **1i** in refluxing tetrahydrofuran did not give the corresponding anhydrides, treatment in refluxing acetonitrile afforded **2h** (91%) and **2i** (90%), respectively (Entries 16 and 18 in Table 2).

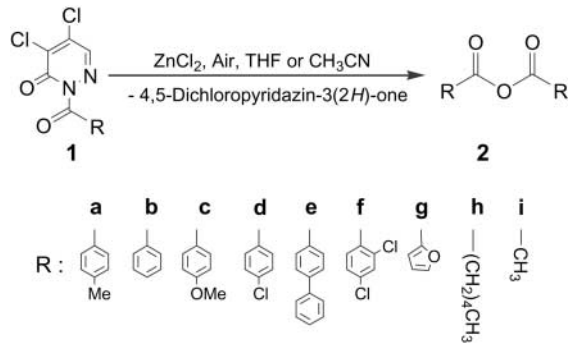
Table 1. Reactions of carboxylic anhydrides with **1a-c** in the presence of some Lewis acids

Entry	1	Lewis acid (equiv)	Reaction condition[a]	Time (h)	2 (%)[b]
1	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (2)	THF, rt	144	**2a** (46)
2	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (1)	THF, rt	120	**2a** (90)
3	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (0.5)	THF, rt	176	**2a** (89)
4	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (0.5)	THF, rf	34	**2a** (89)
5	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (0.5)	CH_3CN, rf	6	**2a** (93)
6	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (0.5)	CH_2Cl_2,rf	35	**2a** (85)
7	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (0.5)	$C_6H_5CH_3$,rf	36	**2a** (50)[c]
8	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (0.5)	C_6H_6,rf	36	**2a** (40)[c]
9	**1a** -C_6H_4-Me(*p*)	$ZnCl_2$ (0.5)	MeOH,rf	1	—[d]
10	**1c** -C_6H_4-OMe(*p*)	Zn (0.5)	CH_3CN, rf	17	**2c** (53)
11	**1c** -C_6H_4-OMe(*p*)	ZnF_2 (0.5)	CH_3CN, rf	115	**2c** (42)
12	**1c** -C_6H_4-OMe(*p*)	$ZnBr_2$ (0.5)	CH_3CN, rf	10	**2c** (96)
13	**1c** -C_6H_4-OMe(*p*)	ZnI_2 (0.5)	CH_3CN, rf	10	**2c** (96)
14	**1c** -C_6H_4-OMe(*p*)	SmI_2 (0.5)	CH_3CN, rf	8	**2c** (95)
15	**1c** -C_6H_4-OMe(*p*)	$CuCl_2$ (0.5)	CH_3CN, rf	24	**2c** (trace)
16	**1c** -C_6H_4-OMe(*p*)	$SnCl_2$ (0.5)	CH_3CN, rf	24	**2c** (trace)

[a]rt = Room temperature; rf = Reflux.
[b]Isolated yields.
[c]Unknown product was formed. And the reaction did not finished for 36 h.
[d] Methyl *p*-methylbenzoate was obtained in 83% yield.

The other product in this reaction, 4,5-dichloropyridazin-3(2*H*)-one could be recovered quantitatively.

To provide evidence for the need of an oxygen source, we studied the reaction of **1c** in the presence of zinc chloride under three conditions.



Scheme 1.

Table 2. $ZnCl_2$-Mediated synthesis of carboxylic anhydrides using 2-aroylpyridazin-(2**H**)-ones **1**

Entry	**1**	$ZnCl_2$ (equiv)	Solvent[a]	Time (h)	**2** (%)[b]
1	**a** -C_6H_4-Me(*p*)	0.5	THF	34	**2a** (89)
2	**a** -C_6H_4-Me(*p*)	0.5	CH_3CN	6	**2a** (93)
3	**b** -C_6H_5	0.5	THF	45	**2b** (96)
4	**b** -C_6H_5	0.5	CH_3CN	7	**2b** (97)
5	**c** -C_6H_4-OMe(*p*)	0.5	THF	49	**2c** (97)
6	**c** -C_6H_4-OMe(*p*)	0.5	CH_3CN	7	**2c** (98)
7	**d** -C_6H_4-Cl(*p*)	0.5	THF	23	**2d** (92)
8	**d** -C_6H_4-Cl(*p*)	0.5	CH_3CN	7	**2d** (95)
9	**e** -C_6H_4-C_6H_5(*p*)	0.5	THF	14	**2e** (91)
10	**e** -C_6H_4-C_6H_5(*p*)	0.5	CH_3CN	8	**2e** (93)
11	**f** -C_6H_3-Cl_2 -2,4	0.5	THF	146	**2f** (73)
12	**f** -C_6H_3-Cl_2 -2,4	0.5	CH_3CN	8	**2f** (87)
13	**g** -C_4H_3O[c]	0.5	THF	11	**2g** (95)
14	**g** -C_4H_3O[c]	0.5	CH_3CN	7	**2g** (97)
15	**h** –$(CH_2)_4CH_3$	0.5	THF	—	**2h** (—)
16	**h** –$(CH_2)_4CH_3$	0.5	CH_3CN	6	**2h** (91)
17	**i** –CH_3	0.5	THF	—	**2i** (—)
18	**i** –CH_3	0.5	CH_3CN	7	**2i** (90)

[a]Reaction temperature = Reflux.
[b]Isolated yield. [c]2-Furyl.

Firstly, **1c** was refluxed in the presence of zinc chloride in dry acetonitrile to give only anhydride **2c** in excellent yield under an air atmosphere. However, treatment of **1c** in the presence of zinc chloride in refluxing dry acetonitile under an argon atmosphere did not yield **2c**. A mixture of **1c**, zinc chloride, a small amount of water (one drop), and acetonitrile was also refluxed to afford **2c** in excellent yield under an air atmosphere. In the presence of excess water, however, **1c** was transformed under the same condition to *p*-methoxybenzoic acid as the main product and anhydride **2c**. The reaction of **1c** and zinc chloride in the presence of a small amount of water under an argon atmosphere did not provide **2c**. Although the reaction was accelerated by water, **1c** competitively decomposed to *p*-methoxybenzoic acid in the presence of excess water. These findings indicate that the oxygen in our system is necessary for the formation of anhydrides **2**.

In summary, we demonstrated a novel access and a simple method synthesizing carboxylic anhydrides **2** from 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones and zinc chloride in air under neutral reaction conditions. The method offers some advantages including easy preparation of **1** from

commercially available 4,5-dichloropyridazin-3(2*H*)-one, stability of **1** in air, high yields of products, simple and convenient procedures, and a quantitative recovery of reusable 4,5-dichloropyridazin-3(2*H*)-one. We are currently investigating the detailed mechanism of this reaction.

EXPERIMENTAL

Reagents and solvents were used as received from the commercial sources. TLC was performed on plates coated with silica gel (silica gel 60 F254, Merck). The spots were located by UV light. Column chromatography was carried out on silica gel (silica gel 60, 70–230 mesh). Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Brüker FT NMR-DRX 500 or Varian Inova 300 Spectrometer. The chemical shift values were reported in δ units (part per million) relative to TMS as an internal standard. IR spectra were obtained on a Hitachi 270-50 or Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240 C.

General Procedure

2a-g: A mixture of compound **1** (1.67 mmol), zinc chloride (0.83 mmol), and dry tetrahydrofuran (30 mL) or dry acetonitrile (30 mL) was refluxed in air until **1** disappeared by TLC monitoring. After cooling the mixture to room temperature, the solvent was removed under reduced pressure. Diethyl ether (30 mL) was added, the mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (2.5 × 3 cm) using methylene chloride as eluent. Fractions containing anhydride **2** were combined and evaporated under reduced pressure to give pure anhydride **2**. Fractions containing pyridazinone were also combined and evaporated under reduced pressure to afford 4,5-dichloropyridazin-3(2*H*)-one quantitatively.

2h-i: A mixture of compound **1** (11.5 mmol), zinc chloride (5.7 mmol), and dry acetonitrile (60 mL) was refluxed in air until **1** disappeared. After cooling the mixture to room temperature, the solvent was removed under reduced pressure. Dry diethyl ether (30 mL) was added to the stirred mixture. The mixture was filtered and concentrated. The residue was purified by vacuum distillation to give the corresponding anhydride **2**. The filter residue was also dried in air to afford 4,5-dichloropyridazin-3(2*H*)-one.

4-Methylbenzoic anhydride (2a). Light yellow solid, mp 88–90°C [Lit.[22] mp 89–90°C]; ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 6H), 7.27 (d, 4H, $J = 8$ Hz), 8.03 (d, 4H, $J = 8$ Hz); ^{13}C NMR ($CDCl_3$) δ: 21.8, 126.3, 129.6, 130.6, 145.6, 162.6; IR (KBr): 3010, 2990, 1780, 1720, 1620, 1300, 1220,

1180, 1040, 1000 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found C, 75.68; H, 5.61.

Benzoic anhydride (2b). Yellow solid, mp 40–41°C [Lit.[22] mp 40–41 °C]; ^{1}H NMR ($CDCl_3$) δ: 7.50–7.54 (m, 4H), 7.66–7.69 (m, 2H), 8.16–8.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 128.9, 129.0, 130.6, 134.5, 162.4; IR (KBr): 3065, 1785, 1725, 1598, 1451, 1213, 1039, 720 cm^{-1}. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found C, 74.41; H, 4.50.

4-Methoxybenzoic anhydride (2c). Light yellow solid, mp 89–90°C [Lit.[22] mp 89–90°C]; ^{1}H NMR ($CDCl_3$) δ: 3.89 (s, 6H), 6.98 (m, 4H), 8.09 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 55.6, 114.2, 121.3, 132.8, 162.3, 164.6; IR (KBr): 3010, 2990, 1790, 1720, 1620, 1300, 1220, 1180, 1040, 1000 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found C, 67.20; H, 5.01.

4-Chlorobenzoic anhydride (2d). Yellow solid, mp 184–185°C; ^{1}H NMR ($CDCl_3$) δ: 7.50–7.52 (m, 4H), 8.06–8.08 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 127.1, 129.4, 131.9, 141.4, 161.3; IR (KBr): 3010, 1800, 1720, 1600, 1500, 1400, 1220, 1180, 1060, 1000 cm^{-1}; Anal. Calcd for $C_{14}H_8O_3Cl_2$: C, 56.98; H, 2.73; Cl, 24.03. Found C, 57.02; H, 2.81; Cl, 24.12.

4-Phenylbenzoic anhydride (2e). Light yellow solid, mp 137–139°C [Lit.[22] mp 138–140°C]; ^{1}H NMR ($CDCl_3$) δ: 7.43 (d, 2H, $J = 7.5$ Hz), 7.49 (t, 4H, $J = 7.5$ Hz), 7.65 (d, 4H, $J = 7.5$ Hz), 7.75 (d, 4H, J = 8 Hz), 8.24 (d, 4H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$) δ: 127.4, 127.6, 127.7, 128.6, 129.1, 131.2, 139.6, 147.4, 162.4; IR (KBr): 3010, 1770, 1730, 1600, 1500, 1400, 1300, 1220, 1170, 1050, 980 cm^{-1}; Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found C, 67.20; H, 5.01.

2,4-Dichlorobenzoic anhydride (2f). Light yellow solid, mp 120–121°C; ^{1}H NMR ($CDCl_3$) δ: 7.38 (dd, 2H, $J = 10.0$ Hz), 7.56 (d, 2H, $J = 5.0$ Hz), 7.97 (d, 2H, $J = 10.0$ Hz); ^{13}C NMR ($CDCl_3$) δ: 126.2, 127.5, 131.5, 133.6, 136.3, 140.5, 159.4; IR (KBr): 3010, 1800, 1740, 1600, 1560, 1480, 1380, 1300, 1200, 1140, 1070, 1020 cm^{-1}; Anal. Calcd for $C_{14}H_6Cl_4O_3$: C, 46.19; H,1.66; Cl, 38.96. Found C, 46.23; H, 1.71; Cl, 39.00.

Furan-2-carboxylic anhydride (2g). Light yellow solid, mp 68–69°C; ^{1}H NMR ($CDCl_3$) δ: 6.61–6.62 (m, 2H), 7.42 (d, 2H, $J = 2.5$ Hz), 7.71 (d, 2H, $J = 1.0$ Hz); ^{13}C NMR ($CDCl_3$) δ: 112.9, 121.9, 143.2, 148.8, 153.1; IR (KBr): 3150, 1800, 1740, 1680, 1580, 1480, 1400, 1320, 1280, 1180, 1100, 1060, 1020 cm^{-1}; Anal. Calcd for $C_{10}H_6O_5$: C, 58.26; H, 2.93. Found C, 58.36; H, 2.98.

Hexanoic anhydride (2h). Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 0.88–0.92 (m, 6H), 1.33–1.35 (m, 8H), 1.62–1.67 (m, 4H), 2.35 (t, 4H, $J = 7.8$); ^{13}C NMR ($CDCl_3$) δ: 13.9, 22.3, 24.4, 31.2, 33.9, 179.9; IR (KBr): 2900, 2850, 1820, 1750, 1480, 1420, 1050 cm^{-1}; Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H,10.35. Found C, 67.26; H, 10.35.

Acetic anhydride (2i). Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 2.20 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 16.8, 166.0; IR (KBr): 2900, 2850, 1780, 1690, 1480,

1420, 1050 cm^{-1}; Anal. Calcd for $C_4H_6O_3$: C, 47.06; H,5.92. Found C, 47.16; H, 6.04.

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