Facile Esterification of Alcohols with 2-Acyl-4,5-dichloropyridazin-3(2*H*)-ones under Friedel–Crafts Conditions

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Abstract: This paper describes the esterification of aromatic and aliphatic alcohols by using 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones as an acyl source under Friedel–Crafts conditions. Twelve alcohols were reacted with four 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones in the presence of $AlCl_3$ in tetrahydrofuran at room temperature to give the corresponding esters in moderate to excellent yields. Thus, 2-acylpyridazin-3(2*H*)-ones serve as good and atom-economic acyl sources for the esterification of aromatic alcohols under Friedel–Crafts conditions, representing a rapid, practical, and efficient method of esterification.

Key words: acylation, esterification, Friedel–Crafts condition, sustainable chemistry, synthetic methods

The esterification of alcohols is a staple reaction in organic synthesis.[1,2] Classical esterification, for example Fischer–Speier esterification,[3] usually involves carboxylic acid, alcohol and a strong, protic acid such as sulfuric acid, and is a key reaction for synthetic applications in both industry and academia. Classical esterification, however, often results in side reactions including dehydration, etherification, carbonization, and/or oxidation (Scheme 1, a),[4] and many esterification reactions require high temperature (reflux conditions) and relatively long reaction time (up to 60 h).[5] In addition, organic or organometallic catalysts are often used for esterification.[6]

This paper describes an alternative method for the esterification of aromatic and aliphatic alcohols using acyl chloride, as an acyl source, under mild conditions (THF at room temperature, Scheme 1, b) in a fairly short time (5–120 min). We employed *N*-acylazinone derivatives, 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones, as acyl sources, and examined their reactivity towards aromatic and aliphatic alcohols in the presence of aprotic Lewis acid, aluminum chloride (Scheme 1, c). We found that 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones serve as a good acyl carriers and their reaction leads to O-acylated products (esters) in moderate to excellent yields (50–99%; mostly >70%), and reusable 4,5-dichloropyridazin-3(2*H*)-ones, which are precursors of 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones. We did not detect byproducts that are commonly found in classical Fischer esterification reaction. Rather surprisingly, for aromatic alcohols, the optimized reaction conditions did not yield byproducts arising from C-acylation (Friedel–Crafts reaction, see below).

Although many synthetic methods for esterification have been developed to reduce the number of side reactions,[7] research in this field is still very active because of increasing demand for the synthesis of molecules with complex structures both inside and outside industry.[8,9] In this context, the development of a esterification methodology that uses another acyl source that can be performed under mild reaction conditions could offer another choice for selective esterification in molecules having multiple functional groups.

The purpose of this study was to develop a method for esterification that (i) avoids the side reactions found in classical esterification reactions, (ii) leads to high yields of O-acylated products, (iii) proceeds under mild conditions and in relatively short reaction time, and (iv) generates a reusable byproduct for atom-economic reaction. We initially designed a reaction that can be used to esterify alcohols in the presence of aprotic Lewis acid such as metal halides (those usually used for Friedel–Crafts reaction; Scheme 1, b), but found that the reaction with alcohols and acyl halide resulted in C-acylated products that were typical of Friedel–Crafts reaction (Scheme 1, b).[10]

We examined the use of another acyl source, *N*-acylazinone, for esterification under Friedel–Crafts conditions (Scheme 1, c) for two reasons: (i) It contains an amide moiety whose reactivity to aprotic Lewis acid ($AlCl_3$) is less than acid halide, and thereby allows C-acylation in the esterification of aromatic alcohols to be avoided. (ii) A ketone in the heterocyclic ring (Scheme 1) plays a role in activating the C–N amide bond, whereby the ketone reacts with an acidic proton and increases the reactivity of C–N amide bond, leading to its cleavage in the presence of a nucleophile. Furthermore, esterification using *N*-acylazinone gives pyridazinone as a byproduct, which can be isolated and subsequently recycled. We previously examined *N*-acylazinone derivatives, 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones, as acyl sources in catalyst-, additive-, and solvent-free esterification reactions under high-temperature and/or microwave conditions (130 or 150 °C, 300 W).[11] Although these conditions are not suitable for industrial processes, 2-acyl-4,5-dichloropyridazin-3(2*H*)-

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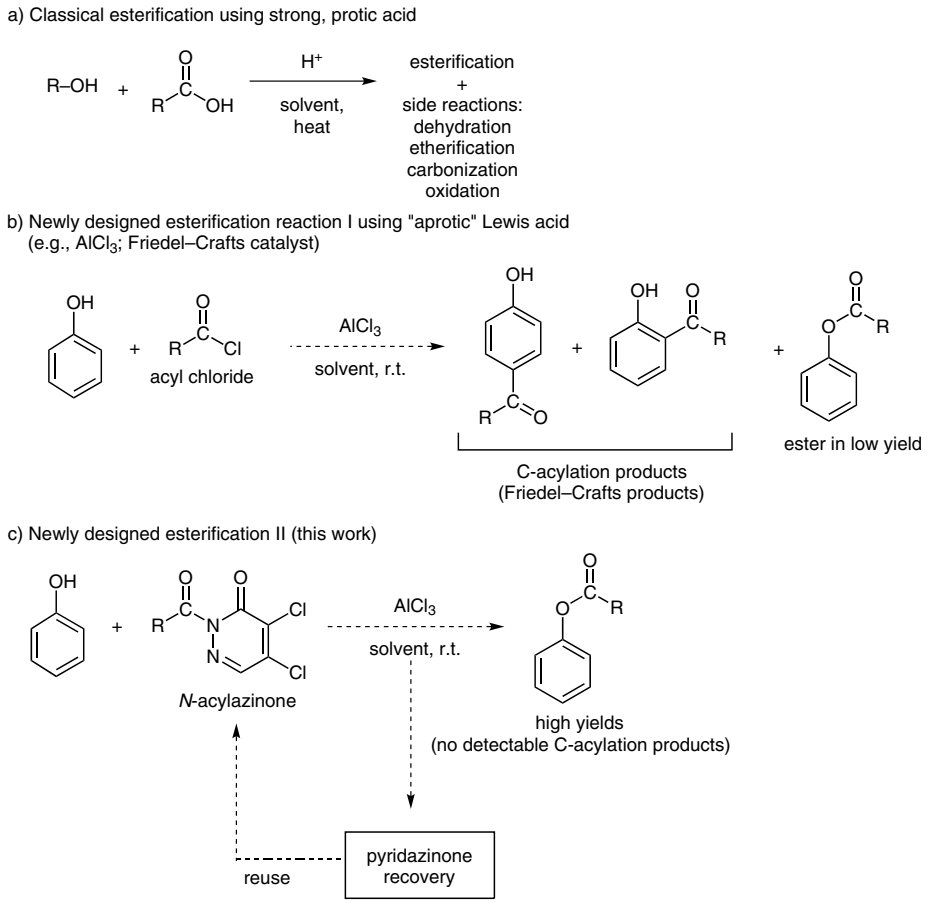


Scheme 1 (a) Classical esterification of alcohols using strong, protic acid; (b) newly designed method I for esterification using 'aprotic' Lewis acid (i.e., esterification under Friedel–Crafts conditions), and (c) newly designed method II (this work) for esterification using *N*-acylazinone, as acyl source, under Friedel–Crafts conditions.

ones are stable, nonhygroscopic, and atom-economic acyl sources.[11,12] A precursor for preparing 2-acyl-4,5-dichloropyridazin-3(2*H*)-one derivatives is 4,5-dichloropyridazin-3(2*H*)-one, which is inexpensive and stable (no observable decomposition under ambient conditions). This reagent serves as a good leaving group, and can be readily isolated and recycled at the end of the synthetic procedure.[11–13] Esterification of alcohols by *N*-acylazinone under Friedel–Crafts conditions has, to our knowledge, not been reported.

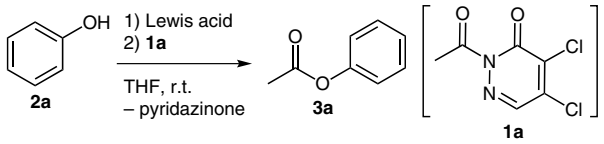
Here, we report the esterification of a range of aromatic and aliphatic alcohols with 2-acyl-4,5-dichloropyridazin-3(2*H*)-one (*N*-acylazinone; Scheme 1, c) in the presence of $AlCl_3$ in THF at room temperature. As a model reaction for testing this new protocol, we examined the reaction of phenol with 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one in the presence of Lewis acid at room temperature.

Initially, we evaluated the efficacy of several metal chlorides (Table 1). Among the eight aprotic Lewis acids investigated, $AlCl_3$ (1 equiv) in THF provided the best results (entry 2). We also evaluated five protic acids (HCl, H_2SO_4, CF_3COOH, TsOH, and TfOH) and one aprotic acid ($BF_3{\cdot}Et_2O$) under the same conditions, but the reactions did not progress (within 2 h). We then investigated the effect of solvent (Table 2). Among nine solvents tested, THF afforded the best results (entry 6). Under the optimized reaction conditions [$AlCl_3$ (1 equiv), THF (0.1 M relative to phenol), r.t.], we then evaluated the reactivity of acyl sources having different substituents: acid, ester, halide, anhydride, amide, or heterocycles (Scheme 2).

Among the eleven derivatives tested, 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one showed the best yield (98% in 10 min). Rather surprisingly, acetyl chloride (**4f**) and anhydride (**4d**) gave the esters in very low yields (20% or less) under our conditions. Based on the preliminary experimental data, we optimized the reaction conditions for further study: ROH (1 equiv), $AlCl_3$ (1 equiv), and 2-acylpyridazinone (1 equiv) in THF at room temperature.

To illustrate the versatility of the reaction method, we examined the esterification reaction with a wide range of aliphatic and aromatic alcohols, and 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones under the optimized reaction conditions (Table 3).[14] Reaction of aliphatic and aromatic alcohols with 2-acetyl- or 2-heptanoyl-4,5-dichloropyridazin-3(2*H*)-ones afforded the corresponding esters **3** in 80–99% yield (entries 1–11) except for 3-hydroxypyridine (entry 8) and 2-(4-hydroxyphenyl)ethanol (entries 9 and 10).

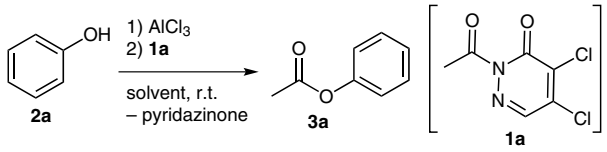
Table 1 Screening Aprotic Lewis Acids for the Esterification of Phenol with 2-Acetyl-4,5-dichloropyridazin-3(2*H*)-one



Entry	Lewis acid (equiv)	Time (min)	**3a** (%)[a]
1	none	60	no reaction
2	$AlCl_3$ (1)	5	98
3	$AlCl_3$ (0.5)	5	55[b]
4	$AlCl_3$ (0.2)	5	22[b]
5	$InCl_3$ (1)	30	51[b]
6	$SnCl_2$ (1)	30	43[b]
7	$CuCl_2$ (1)	30	trace
8	CuCl (1)	30	trace
9	$ZnCl_2$ (1)	30	24[b]
10	$FeCl_3$ (1)	30	trace
11	$TiCl_4$ (1)	30	trace

[a] Isolated yield.
[b] Unreacted starting material was detected by TLC.

Table 2 Screening Solvent for the Esterification of Phenol with 2-Acetyl-4,5-dichloropyridazin-3(2*H*)-one[a]

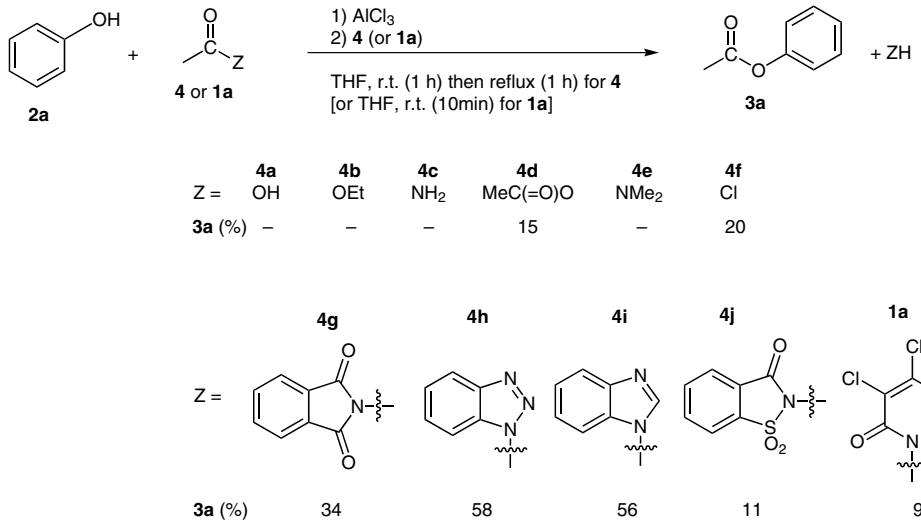


Entry	Solvent	Time (min)	**3a** (%)[b]
1	*n*-hexane	90	14[c]
2	1,4-dioxane	30	–
3	benzene	10	89
4	toluene	10	65[c]
5	Et_2O	10	85
6	THF	5	98
7	acetone	30	44[c]
8	MeCN	20	72
9	DMF	30	18

[a] Reaction procedure: After forming $AlCl_3$–phenol adduct in the corresponding solvent (20 mL), compound **1a** was then added.
[b] Isolated yield.
[c] Unreacted starting materials were detected by TLC analysis.

3-Hydroxypyridine was reacted with $AlCl_3$ (2 equiv) and then with 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one to give the ester **3i** in 56% yield [in the case of 2-(4-hydroxyphenyl)ethanol, see below]. Remarkably, no C-acylated products were detected in the reaction involving aromatic alcohols (Table 3, entries 1, 2, 4–13, and 18–20) and/or aroyl-4,5-dichloropyridazin-3(2*H*)-ones (Table 3, entries 12–20).

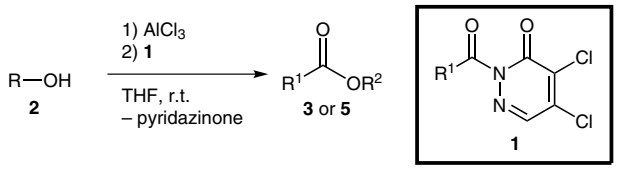
We also investigated the selectivity of the acylation for aliphatic and aromatic alcohols by using 2-(4-hydroxyphenyl)ethanol (Table 3, entries 9 and 10). When 2-(4-hydroxyphenyl)ethanol and aluminum chloride (1 equiv) was reacted with 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one (**1a**; 1 equiv), the products were monoacetyl ester **3j** (32%) (i.e., the product monoacetylated selectively in aliphatic alcohol) and diacetyl ester **3k** (24%; entry 10); the addition of **1a** (2 equiv) and aluminum chloride (2 equiv)



Scheme 2 Esterification of acetic acid derivatives with phenol and $AlCl_3$ in 0.1 M THF (relative to **2a**) at room temperature and then heated to reflux for **4** or at room temperature for **1a**

produced only **3k** in 98% yield (entry 11). We obtained only **3j** (66%) when the reaction was conducted at low temperature (entry 9): complexation between alcohol and aluminum chloride proceeded first in THF at 0 °C, and subsequent addition of 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one at 0 °C resulted in formation of the desired esterified product **3j** in a relatively high yield (66%). According to TLC analysis, acylation of the aliphatic alcohol was more favorable than acylation of the aromatic alcohol in our system. We further determined whether our reaction method gives aliphatic or aromatic benzoates products. Esterification of aliphatic and aromatic alcohols with 2-aroyl-4,5-dichloropyridazin-3(2*H*)-ones under the optimized conditions gave the corresponding esters **5** in 51–95% yield (Table 3, entries 12–20). In the reaction of 2-mercaptoethanol, the yield of the reaction with $AlCl_3$ (1 equiv) was low (24%); however, the reaction with $AlCl_3$ (2 equiv) gave the product acylated at both thiol and alcohol (**5d**) in 72% yield (Table 3, entry 15). Although the esterification using our reaction method is not chemoselective for amino and mercapto groups, it showed selectivity between aliphatic and aromatic alcohols: when the reactant contains both aliphatic and aromatic alcohols, the

Table 3 Esterification of Alcohols with 2-Alkanoyl (or Aroyl)-4,5-dichloropyridazin-3(2*H*)-ones in the Presence of $AlCl_3$ in THF at Room Temperature[a]

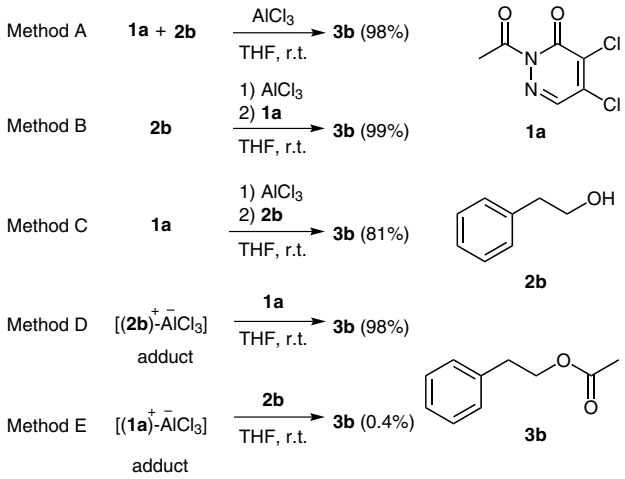


Entry	R	R^1	R^2	Time (min)	Product	Yield (%)[a]
1	$Ph(CH_2)_2$	Me	R	10	**3b**	90
2	*p*-$(H_2N)C_6H_4(CH_2)_2$	Me	*p*-$(AcNH)C_6H_4(CH_2)_2$	10	**3c**	86[b]
3	*c*-C_6H_{11}	Me	R	10	**3d**	80
4	*p*-$(MeO)C_6H_4$	Me	R	5	**3e**	98
5	*p*-$(O_2N)C_6H_4$	Me	R	5	**3f**	70
6	*p*-$(MeO)C_6H_4$	$CH_3(CH_2)_5$	R	20	**3g**	98
7	*p*-$(OHC)C_6H_4$	Me	R	30	**3h**	98
8	C_5H_4N	Me	R	6	**3i**	56[c]
9	*p*-$(HO)C_6H_4(CH_2)_2$	Me	R	30	**3j**	66[d]
10	*p*-$(HO)C_6H_4(CH_2)_2$	Me	R *p*-$(AcO)C_6H_4(CH_2)_2$	30	**3j** **3k**	32 24
11	*p*-$(HO)C_6H_4(CH_2)_2$	Me	*p*-$(AcO)C_6H_4(CH_2)_2$	10	**3k**	98[b]
12	*p*-$(H_2N)C_6H_4(CH_2)_2$	Ph	*p*-$(C_6H_4COHN)C_6H_4(CH_2)_2$	90	**5a**	72[b]
13	*p*-$(PhNH)C_6H_4$	Ph	R	120	**5b**	51
14	$HS(CH_2)_2$	Ph	R $PhC(O)S(CH_2)_2$	20	**5c** **5d**	24 24
15	$HS(CH_2)_2$	Ph	$PhC(O)S(CH_2)_2$	20	**5d**	72[e]
16	*i*-Pr	Ph	R	40	**5e**	73
17	Et	Ph	R	15	**5f**	72
18	*p*-$(MeO)C_6H_4$	Ph	R	5	**5g**	95
19	*p*-$(MeO)C_6H_4$	*p*-$(NC)C_6H_4$	R	5	**5h**	93
20	*p*-$(MeO)C_6H_4$	*p*-$(MeO)C_6H_4$	R	10	**5i**	70

[a] Isolated yield.
[b] $AlCl_3$ (2 equiv) and **1** (2 equiv) were used.
[c] C_5H_4N = Pyridin-3-yl. $AlCl_3$ (2 equiv) was used, and unreacted **1a** was detected by TLC analysis.
[d] ROH–$AlCl_3$ adduct (1 equiv) was synthesized at low temperature (below 0 °C), then **1** (1 equiv) in THF was added at 0 °C to room temperature.
[e] $AlCl_3$ (2 equiv) and **1** (3 equiv) were used.

reaction conditions enabled the selective acylation of aliphatic alcohol rather than the aromatic alcohol.

To understand the mechanism of esterification for our method, we carried out five control experiments[15] (Scheme 3) using a reaction of **1a**, 2-phenylethyl alcohol (**2b**), and aluminum chloride in THF at room temperature. Initial investigations focused on two facets of the protocol: (i) The order of addition of starting compounds (**1a**, **2b** and $AlCl_3$ for Methods A–C in Scheme 3) was altered and the effect of this change on the yield of reaction was assessed, and (ii) The $(ROH)^+$–$(AlCl_3)^-$ adduct (Scheme 3, Method D) and $(\mathbf{1a})^+$–$(AlCl_3)^-$ adduct (Scheme 3, Method E) were prepared and used for esterification. In the latter experiments, we wished to determine whether complexation between aluminum chloride and alcohol (or *N*-acylazinone) occurs immediately at the beginning of the reaction and whether this plays a crucial role in the esterification of the alcohol under the Friedel–Crafts conditions. All of the methods we tested, except Method E, exhibited high yields (>80%); almost no reaction occurred in Method E (0.4%). The comparison of yield between the Methods D and E suggests that the formation of $(ROH)^+$–$(AlCl_3)^-$ adduct is likely more favorable than that of the *N*-acylazinone (**1a**)–$AlCl_3$ adduct under our conditions, and that the $(ROH)^+$–$(AlCl_3)^-$ adduct, not the *N*-acylazinone-$AlCl_3$ adduct, serves as a key component for high yields of esterification of alcohols in this synthetic method.



Scheme 3 Control experiments aimed at understanding the mechanism of esterification reaction using 2-phenylethyl alcohol (**2b**), aluminum chloride, and 2-acetyl-4,5-dichloropyridazin-3(2*H*)-one (**1a**). We changed the order of addition of starting compounds (**1a**, **2b** and $AlCl_3$), or used **1a**–$AlCl_3$ or **2b**–$AlCl_3$ adducts as starting compounds (see the experimental section for detailed information)

The above conclusion is supported by the fact that both Method A (one-pot, one-step reaction), B (one-pot, two-step reaction), and C (one-pot, two-step reaction with different sequence) gave the corresponding ester **3b** in high yields (81–99%). Based on the results of the control experiments, a plausible mechanism for the esterification is outlined in Scheme 4. The ROH–$AlCl_3$ adduct used in this system may act as the equivalent of an alkoxide, and it is speculated that the pyridazinone anion acts as the proton acceptor. Therefore, 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones are both acylation agents and proton acceptor, and faciliate esterification reactions under Friedel–Crafts conditions.

In all experiments, we isolated the 4,5-dichloropyridazin-3(2*H*)-one in reusable form in good to excellent yields. The structures of the synthesized esters were established on the basis of FTIR, NMR, and HRMS analysis (or elemental analysis).

In conclusion, we have demonstrated the esterification of alcohols with 2-acyl-4,5-dichloropyridazin-3(2*H*)-ones in the presence of aluminum chloride in THF at room temperature in moderate to excellent yields. Despite the use of Friedel–Crafts conditions, the reaction of 2-acyl-4,5-pyridazin-3(2*H*)-ones with aromatic alcohols give only the corresponding esters in good to excellent yields. Thus, 2-acylpyridazin-3(2*H*)-ones are good acylation agents under Friedel–Crafts conditions. The reaction conditions described in this work allow selective acylation of an aliphatic alcohol in preference to an aromatic alcohol in a reactant having both aromatic and aliphatic alcohols.

The reaction method described in this work enables rapid, convenient, efficient and atom-economic esterification of alcohols and, interestingly, shows an example of an alkoxide equivalent resulting from complexation between alcohol and metal halide. A study on the mechanism of esterification under the present conditions leads to the conclusion that alcohols first react with aluminum chloride to form the ROH–$AlCl_3$ adduct, which plays a key role in the esterification reaction under the mild reaction conditions. The reaction protocol reported here takes advantage of 2-acylpyridazin-3(2*H*)-ones. Such compounds are synthesized easily,[11b,12] and the esterification procedure allows quantitative isolation of 4,5-dichloropyridazin-3(2*H*)-one, which is reusable. We believe that the procedure described herein will find a broad range of applications in synthetic chemistry.

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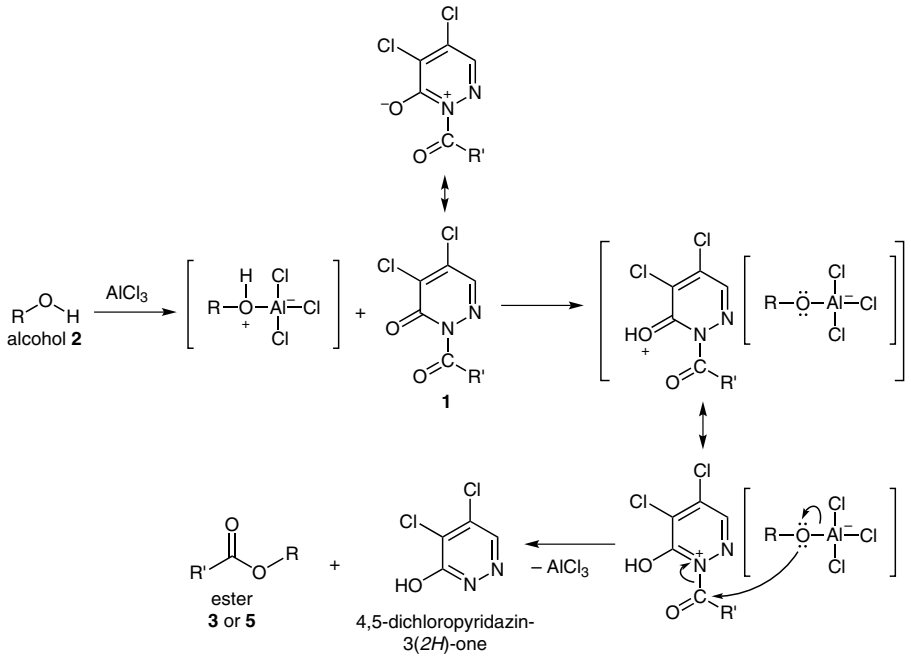

Scheme 4 Plausible mechanism for the esterification of alcohols with 2-acyl-4,5-dichloropyridazin-3(2*H*)-one in the presence of $AlCl_3$

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(14) (a) **Synthesis of 3 and 5a–d; General Procedure:** To a solution of alcohol **2** (1 equiv, 2 mmol) in THF (20 mL), $AlCl_3$ (1 equiv) was added followed by stirring for 1 min. 2-Acyl-4,5-pyridazin-3(2*H*)-one **1** (1 equiv) was then added and the mixture was stirred at room temperature until the alcohol was consumed. The reaction was quenched by the addition of H_2O (20 mL), and the mixture was stirred for 10 min at room temperature. After the addition of CH_2Cl_2 (40 mL), the organic layer was separated and dried over

anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the resulting residue was applied to the top of an open-bed silica gel column. The column was eluted with CH_2Cl_2 (for **3a**–**g**, **5a** and **5b**), MeCN–CH_2Cl_2 (1:5 v/v for **3h**), EtOAc–CH_2Cl_2 (1:1 v/v for **3i**), *n*-hexane–CH_2Cl_2–EtOAc (4:2:1 v/v for **3j** and **3k**), or *n*-hexane–EtOAc (10:1 v/v for **5c** and **5d**). Fractions containing the product were combined and evaporated under reduced pressure to give the desired esters. Fractions containing 4,5-dichloropyridazin-3(2*H*)-one were combined and evaporated under reduced pressure to quantitatively give reusable 4,5-dichloropyridazin-3(2*H*)-one.

(b) **Synthesis of 5e–i; General Procedure:** To a solution of alcohol **2** (1 equiv, 2 mmol) in THF (20 mL), $AlCl_3$ (1 equiv) was added followed by stirring for 1 min. 2-Aroyl-4,5-dichloropyridazin-3(2*H*)-one **1** (1 equiv) was added and the mixture was stirred at room temperature until the alcohol was consumed. The reaction was quenched by the addition of H_2O (20 mL), followed by stirring for 10 min at room temperature, and then neutralized with a saturated solution of $NaHCO_3$. After the addition of further H_2O (20 mL) and CH_2Cl_2 (40 mL), the resulting organic layer was separated, and H_2O (10 mL) and a saturated solution of NaCl (20 mL) were added. The organic layer was then separated and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting residue was applied to the top of an open-bed silica gel column. The column was eluted with CH_2Cl_2 (for **5g**–**i**) or *n*-hexane–EtOAc (3:1 v/v for **5e** and **5f**). Fractions containing the product were combined and evaporated under reduced pressure to give the desired esters. Fractions containing 4,5-dichloropyridazin-3(2*H*)-one were combined and evaporated under reduced pressure to quantitatively give reusable 4,5-dichloropyridazin-3(2*H*)-one.

(15) Procedures for Methods A–E in Scheme 3

Method A: To a solution of **1a** (1 equiv) in THF (20 mL), **2b** (1 equiv, 2 mmol) was added followed by stirring for 5 min. $AlCl_3$ (1 equiv) was added and the mixture was stirred for 10 min at room temperature.

Method B: To a solution of **2b** (1 equiv, 2 mmol) in THF (20 mL), $AlCl_3$ (1 equiv) was added followed by stirring for 30 min. **1a** (1 equiv) was added and the mixture was stirred for 10 min at room temperature.

Method C: To a solution of **1a** (1 equiv) in THF (20 mL), $AlCl_3$ (1 equiv) was added followed by stirring for 30 min. **2b** (1 equiv, 2 mmol) was added and the mixture was stirred for 10 min at room temperature.

Method D: To a solution of **2b** (1 equiv, 2 mmol) in THF (20 mL), $AlCl_3$ (1 equiv) was added followed by stirring for 30 min at room temperature. The solvent was evaporated under reduced pressure to give ROH–$AlCl_3$ adducts. After drying by vacuum pump for 1 h at room temperature, the adduct was used without further purification. Crude salt was dissolved in THF (20 mL), **1a** (1 equiv) was added, and the mixture was stirred at room temperature at 10 min.

Method E: To a solution of **1a** (1 equiv) in THF (20 mL), $AlCl_3$ (1 equiv) was added followed by stirring for 30 min at room temperature. The solvent was evaporated under reduced pressure to give **1a**–$AlCl_3$ adducts. After drying by vacuum pump for 1 h at room temperature, the adduct was used without further purification. Crude salt was dissolved in THF (20 mL), **2b** (1 equiv 2 mmol) was added, and the mixture was stirred at room temperature at 10 min.