Chemistry Letters

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Advance Publication on the web November 11, 2017
doi:10.1246/cl.170975

Esterification with Aromatic Acyl-1,2,4-triazole Catalyzed by Weak Base at the Rate Comparable to Acyl Chloride

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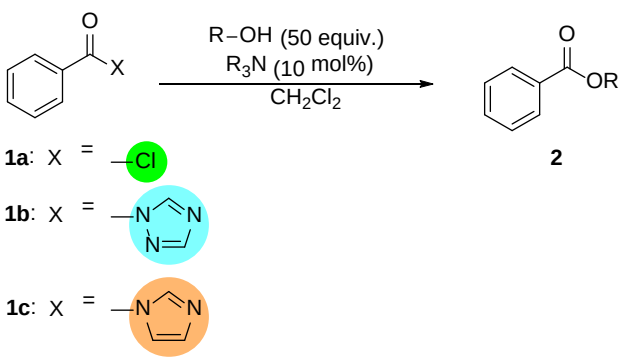
Benzoyl-1,2,4-triazole underwent the esterification with a primary alcohol in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) catalyst at the rate comparable to benzoyl chloride. The kinetic study concluded that the reaction proceeds in a similar mechanism to carboxylic acid anhydride and thus sensitive to the steric hindrance of alcohol. As the esterification of benzoyl-1,2,4-triazole did not afford acidic byproduct and require an equimolar or more amount of base, it is effective for protection of acid-sensitive alcohol and polyester synthesis.

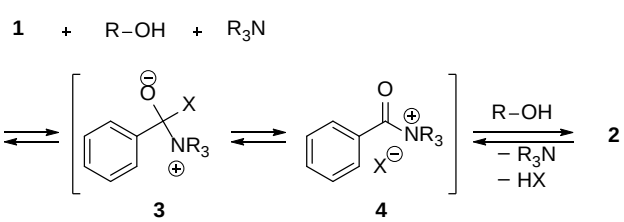
Acylazoles are known as acylating reagents alternative of acyl chlorides.[1-3] For example, acylimidazole prepared from carboxylic acid and carbonyl diimidazole is often used in peptide synthesis.[4,5] 1,2,4-Triazole that has higher acidity than imidazole is a more excellent leaving group, and thus the acyl derivatives can undergo esterification with primary alcohols in polar solvents with a strong base catalyst that generate alkoxide.[1,6] In addition, the esterification can be achieved without catalyst if much excess amount of alcohol is used.[3] Recently, we have prepared bifunctional acyl-1,2,4-triazoles that functioned as alternative monomers of dicarbonyl chlorides for polyester synthesis.[7,8]

Base-catalyzed esterification with carboxylic acid anhydrides are important tools for the protection of hydroxy group[9] and kinetic resolution of alcohols and carboxylic acids.[10] In particular, benzoates are often used as protecting groups, as the selective deprotection could be achieved in moderate conditions.[9] Compared with carboxylic acid anhydrides, the esterification with acyl-1,2,4-triazoles and acylimidazoles does not require an excess amount of auxiliary base that regenerate the base catalyst *in situ*. In addition, such acyl azoles can be prepared from the acyl chloride in a facile procedure and stored in bulk. The liberated azoles are nontoxic and can be removed from the product by washing with water. In spite of such attractive features, however, the kinetics of the esterification with benzoyl azole in the presence of weak base have not been reported. The knowledge is important to selective protection of primary alcohols, kinetic resolution, and polycondensation with aromatic bifunctional acylazoles.[7,8] It should be noted that the esterification with benzoyl 1,2,4-triazole in polar solvents in the presence of strong base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeds almost quantitatively.[10,11] However, the conditions are not suitable for the polycondensation of aromatic bifunctional acylazoles because of the poor solubility of the resulting polymer in polar solvents and the transesterification between the ester backbone and hydroxy groups at the chain end that catalyzed by strong base.[8] In this report, therefore, we have investigated the kinetics of acyl azoles with various weak base catalyst in low-polar solvents as the alternative conditions and found that esterification of benzoyl 1,2,4-triazole with 4-*N*,*N*- (dimethylamino)pyridine (DMAP) proceeds in high selectivity to primary alcohol and a similar rate constant comparable to that of benzoyl chloride.

Benzoyl-1,2,4-triazole (**1b**) was prepared from the respective chloride (**1a**).[13] The esterification of **1b** was conducted with alcohol (50 equiv.) in CH_2Cl_2 in the presence of base catalyst (10 mol%) and monitored by gas chromatography (Scheme 1).[14] Similar experiments were also conducted with **1a** and its imidazole derivative (**1c**).[15]



Scheme 1. Esterification of benzoyl chloride and its derivatives catalyzed by base.



Scheme 2. Reaction mechanism of the esterification.

The pathway of the esterification of carboxylic acid anhydride has been proposed by the quantum calculation with polarizable continuum model-united atom for Hartree-Fock (PCM-UAHF).[16] Similar mechanism can be applied for the case of acylazole **1** (Scheme 2). Since the alcohol associate with the intermediate, quaternary amide **4**, the reaction rate should be discussed according to the following equation[16,17];

$$r = k_1[\mathbf{1}][\mathrm{alcohol}] + k_2[\mathbf{1}][\mathrm{alcohol}][\mathrm{base}] \qquad (1)$$

The first and second members are for the uncatalyzed and the catalyzed pathway, respectively. k_1 and k_2 are rate constant. Since much excess amount of alcohol was used, [alcohol] can be treated as a constant. In the case of **1a**, the base catalyst became hydrochloric salt and did not regenerated, and thus the second member should be ignored in the late stage of esterification ([base] = 0). For others, base is catalyst and thus [base] is constant. Consequently, equation (1) can be rewrite as follows;

Table 1. Pseudo-first-order kinetic constant in the esterification of benzoyl chloride and its derivatives with various alcohols.

Entry[a]	Alcohol	Base	1	k_1'[b] [10^{-5} s^{-1}]	k_2'[b] [10^{-5} s^{-1}]
1	EtOH	-	**1a**	63.2	-
2	EtOH	-	**1b**	No reaction	
3	EtOH	-	**1c**	No reaction	
4	EtOH	pyridine	**1a**	63.1	-
5	EtOH	pyridine	**1b**	-	2.18
6	EtOH	pyridine	**1c**	No reaction	
7	EtOH	Et_3N	**1a**	52.8	-
8	EtOH	Et_3N	**1b**	-	4.43
9	EtOH	Et_3N	**1c**	-	1.71
10	EtOH	DMAP	**1a**	50.8	-
11	EtOH	DMAP	**1b**	-	56.1
12	EtOH	DMAP	**1c**		5.68
13	EtOH	PPY	**1a**	61.5	-
14	EtOH	PPY	**1b**	-	134
15	EtOH	PPY	**1c**	-	5.34
16	*i*PrOH	DMAP	**1b**	-	2.05
17	*i*PrOH	DMAP	**1c**	No reaction	
18	*t*BuOH	DMAP	**1b**	No reaction	
19	*t*BuOH	DMAP	**1c**	No reaction	

a) $[\text{Acylating agent}]_0$ = 1.0 M, $[\text{alcohol}]_0/[\text{acylating agent}]_0/[\text{base}]_0$ = 50/1/0.10, CH_2Cl_2, 25 °C. b) Determined by GC.

$$r = (k_1' + k_2')[\mathbf{1}] \qquad (2)$$

In order to estimate k_1', the rate constant for uncatalyzed pathway, esterification of **1** with ethanol were conducted in the absence of base (Table 1, Entries 1-3). k_1' for **1a** was determined from the pseudo-first-order kinetic plots as 63.2 × 10^{-5} s^{-1}, while **1b** and **1c** did not afford the ester. This is contractive to the esterification in polar solvents, where **1b** yielded esters even in the absence of catalyst.[3] In the presence of pyridine, **1a** and **1b** afforded the ester (Entries 4 and 5). In the case of **1a**, the pseudo-first-order kinetic plot should give k_1' as mentioned before, and the determined value (63.1 × 10^{-5} s^{-1}) was actually similar to that of Entry 1. Since **1b** did not yield the ester in the absence of pyridine (Entry 2), k_1' for **1b** is enough low to be ignored and the pseudo-first-order kinetic plot for the current experiment should give k_2'. In fact, the plot obeyed liner relationship and the determined k_2' was 2.18 × 10^{-5} s^{-1}, which was less than 1/10 of k_1' for **1a**. Et_3N accelerated the reaction more efficiently (Entry 8), and **1c** also afforded the ester although the reaction was slower (Entry 9).

Since the values of k_2' were dependent on the acylating agent, **1b** or **1c**, and on the basicity of catalyst, the rate-determining step is the formation of quaternary amide **4** as expected. 4-(*N*,*N*-Dimethyl)aminopyridine (DMAP) is an effective catalyst for the esterification of active ester and carboxylic acid anhydride, because it provides a stable quaternary amide as an intermediate. Similarly, DMAP was found effective against **1b** and **1c** (Entries 11 and 12). It is notable that the k_2' of **1b** (56.1 × 10^{-5} s^{-1}) is comparable to k_1' of **1a** (50.8 × 10^{-5} s^{-1}). 4-Pyrrolidinopyridine (PPY) is known as a more effective catalyst than DMAP for acylation.[18] Remarkably, the k_2' of **1b** catalyzed by PPY (134 × 10^{-5} s^{-1}) was almost twice of that of **1a** (61.5 × 10^{-5} s^{-1}). That is, **1b** is more reactive acylating agent than **1a** in the presence of suitable catalyst.

Although the reactivity order among the three compounds, *i.e.* **1a** > **1b** > **1c**, are reported,[1] the detailed mechanism has not been discussed. If the elimination of azole from the intermediate **3** is the rate-determining step, the pK_a of the liberated azole should be suitable to explain the reactivity of **1b** and **1c**. However, they exhibit higher reactivity than phenyl ester that undergoes esterification in equilibrium even in the presence of catalyst.[19] The pK_a of phenol is 9.95, while those of 1,2,4-triazole and imidazole are 10.3 and 14.5. Therefore, pK_a of azole is not suitable to explain the reactivity. Staab has reported that the reaction rate of the aminolysis of acylazole obey the two-molecules (addition-elimination) model.[1] Moreover, the recent reports on the esterification of carboxylic acid theoretically[16] and experimentally[16,17] supported the two-molecules model. Therefore, the reaction rate orders of **1** should be discussed on the basis of two-molecules model. In order to support this presumption, the structures of **1** were optimized by DFT calculation under B3LYP/6-31G*. In the optimized conformation (Figure 1), the dihedral angle of the carbonyl group of **1b** and the phenyl group is 18°, whereas that in **1c** is 36°. That is, **1c** has more twisted structure due to the steric repulsion of 2-CH of the imidazole ring and 2'-CH of the benzene ring. The twisted structure of **1c** was also implied by ^{1}H NMR spectrum (Figure 2). The 2'-CH signal of the phenyl group of **1b** (signal a, 8.24-8.21 ppm) was observed in much lower magnet field than that of **1c** (7.80 ppm). Since **1b** has planner structure, the resonance of the carbonyl group and benzene ring would strongly affect the chemical shift of 2'-CH. As well known, a nucleophile attack to carbonyl group at an angle ca. 45° against the carbonyl planner. The twisted structure of **1c**, therefore, has much steric hindrance to the nucleophile, DMAP, and the reaction rate would become much slower than **1b**.

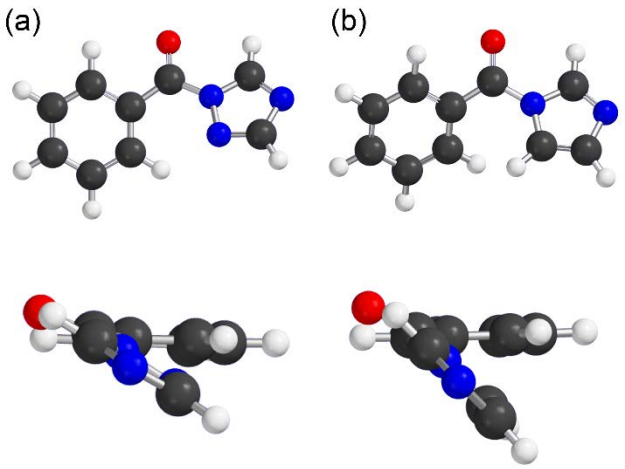


Figure 1. Optimized structure of (a) **1b** and (b) **1c** by DFT calculation (B3LYP/6-31G*).

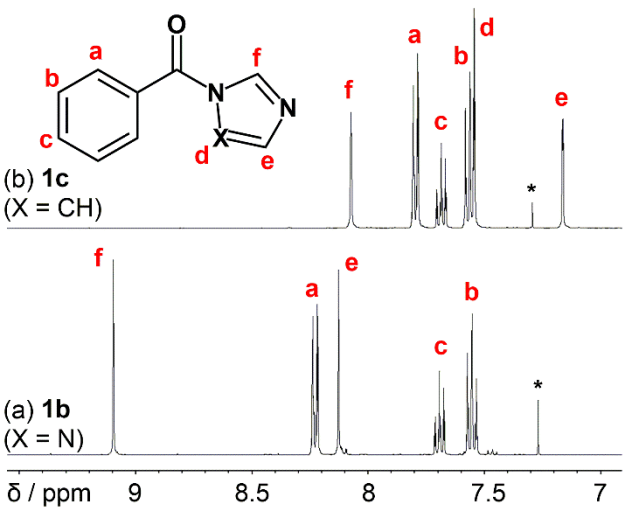


Figure 2. ^{1}H NMR spectra of (bottom) **1b** and (top) **1c** (400 MHz, $CDCl_3$, 26 °C). *: Signal of $CHCl_3$.

Esterification with sterically hindered alcohol, *i.e.* *i*PrOH and *t*BuOH were also investigated. **1b** reacted with *i*PrOH in the presence of DMAP (Entry 16). Since the k_2' against *i*PrOH was ca. 30times smaller than that against EtOH. **1b** did not react with *t*BuOH (Entry 18). Consequently, **1b** can esterify the primary alcohol in high selectivity. **1c** did not yield the esters under the same condition (Entry 17 and 19). These results indicated that the rate-determining step in the esterification is not a simple reaction between **1** and DMAP, otherwise k_2' should be agreed with that with EtOH. Zipse *et al.* have reported similar phenomena on the esterification of carboxylic acid anhydride, where the hydrogen bond of alcohol molecules to DMAP has an important role to determine the reaction rate[16] and thus the reaction rate is sensitive to the steric hindrances of both alcohol and carboxylic acid anhydride.[17] Therefore, the esterification with **1b** may proceed in a similar pathway to that of carboxylic acid anhydride.

In conclusion, **1b** has a similar reactivity to carboxylic anhydride and afforded the ester with primary alcohol in the presence of DMAP at the rate comparable to acyl chloride. Since the reaction proceeds under ambient conditions and the byproduct, 1,2,4-trizole, is non-toxic and water soluble, the esterification with acylazole might be a strong tool for the selective functionalization or protection of primary alcohol. In fact, we have succeeded the polyester synthesis with bifunctional acylazoles. The detail will be reported in our next paper.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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13 Synthesis of **1b**: Benzoyl chloride (1.25 g, 8.89 mmol) was added dropwise to a solution of 1,2,4-triazole (1.23 g, 17.8 mmol) in *N*,*N*-dimethylformamide (25 mL) and dichloromethane (10 mL). The reaction mixture was stirred for 3 h, and the resulting precipitate was removed by filtration. The filtrate was washed with cold water (≤ 5 °C, 10 mL × 3) and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (heater temperature: 160 °C, 80 mmHg) to yield **1b** (1.20 g, 78% yield) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 26 °C) δ/ppm 9.10 (s, 1H, f), 8.24-8.21 (m, 2H, a), 8.13(s, 1H, e), 7.69 (tt, J_1 = 7.5 Hz, J_2 = 1.3 Hz, 1H, c), 7.57-7.53 (m, 2H, b). See Figure 2(a).
14 See Supporting Information for the experimental detail.
15 Synthesis of **1c**: Benzoyl chloride (4.99 g, 35.5 mmol) was added dropwise to a solution of imidazole (4.83 g, 7.1. mmol) in dichloromethane (25 mL). The reaction mixture was stirred for 3 h, and the resulting precipitate was removed by filtration. The filtrate was washed with cold water (≤ 5 °C, 10 mL × 3) and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (heater temperature: 160 °C, 80 mmHg) to yield **1c** (4.33 g, 71% yield) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 26 °C) δ/ppm 8.07 (t, J = 1.0 Hz, 1H, f), 7.81-7.79 (m, 2H, a), 7.69 (tt, J_1 = 7.4 Hz, J_2 = 1.8 Hz, 1H, c), 7.58-7.54 (m, 3H, b and d), 7.16 (dd, J_1 = 1.8 Hz, J_2 = 1.0 Hz, 1H, e). See Figure 2(b).
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