Kinetic Studies on the Aminolysis of 2-(*p*-Substitutedbenzoyl)-4,5-dichloropyridazin-3-ones

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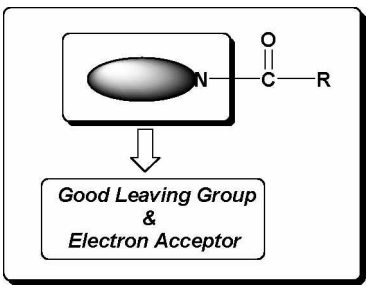
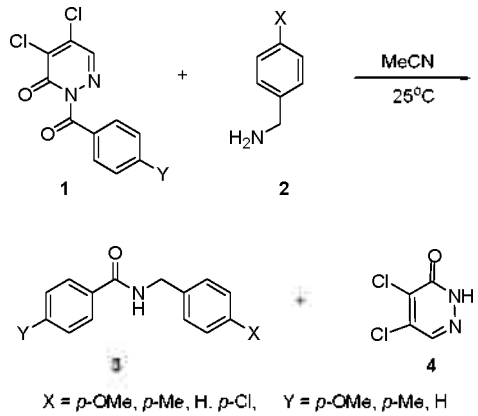
Chemoselective acylation of amino groups is an important reaction in organic synthesis.[1] Common routes to amides mostly involve the treatment of activated derivatives of carboxylic acids such as acyl halides, acid anhydrides, or esters, with ammonia or amines.[2,3] However, these methods have some problems such as exothermic reaction, formation of byproducts, complicated conditions[4] and low selectivity.[3] In order to overcome the problems a variety of reagents have been developed,[5] and continuing efforts are being made to find an ideal chemoselective and neutral reagent.[3] It is reasonably assumed that a reagent bearing a bulky, electron acceptable leaving group may satisfy such a requirement. Recently new acylation reagents (Scheme 1) composed of acyl group and aromatic hetero cyclic group which contains good electron acceptor are known .[3,6]

Furthermore, acylating ability depends on electron acceptability of hetero cyclic ring, and stereoscopic structure for neighboring of N-C(=O)R bonds affects on stereoselective acylation reactions.[4,6] Yoon and co-workers chose 4,5-dichloropyridazin-3-one as a leaving group for new acylation reaction and carried out acylation reaction of 4,5-dichloropyridazin-3-one with various nucleophilic amines successfully.[3,6] During the synthesis of pyridazine derivatives, they found that the necleophilic substitution reactions of the pyridazine derivatives rely on both structural and electronic factors.[6-8] The product yields of the substitution reaction depend on electron donating and/or withdrawing ability.[9] They also have studied aminolysis of 2-(Y-substitutedbenzoyl)-4,5-dichloropyridazin-3-ones **1**, but only approximate reaction times to complete the reaction were determined for varying solvents and substituents.[3,6-8]



Scheme 1

Therefore, it is necessary to perform the kinetic study on the nucleophilic substitution reactions of **1** with amines. In this work, we determined the second-order rate constants for the reaction of **1** with X-substitutedbenzylamines **2** in aceonitrile at 25 °C.



(1)

X = *p*-OMe, *p*-Me, H, *p*-Cl, Y = *p*-OMe, *p*-Me, H

In order to discuss the reaction mechanism and substituent effects, we also determined transition parameters, ρ_X, ρ_Y, and β_Y using Hammett equation and simple Brönsted relationships, and the cross-interaction constant.[10,11] ρ_{XY} in eq 2 are determined, where X and Y are substituents in the nucleophile and substrate, respectively.

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (2a)$$

$$\rho_{XY} = \partial\rho_Y/\partial\sigma_X = \partial\rho_X/\partial\sigma_Y \quad (2b)$$

Results and Discussion

The present reactions obeyed the kinetic law given in eq 3. Plots of pseudo-first-order rate constants k_{obs} against [benzylamines] show good linear relationship as shown at Figure 1, and the second-order rate constants k_2, were determined from the slopes of these plots. The second-order rate constants are summarized in Table 1. No third-order or higher-order terms were detected, and no complications were found in the determination of k_{obs} and also in the linear plots of eq. 3b. This suggests that there is no base-catalysis or noticeable side reactions, and the overall reaction is subject to the rate law given in eq. 3.[12]

$$\text{Rate} = k_2[\text{Benzylamines}][\text{Substrates}] = k_{obs}[\text{Substrates}] \quad (3a)$$

$$k_{obs} = k_2[\text{Benzylamines}] \quad (3b)$$

The various transition parameters, Hammett ρ_X and ρ_Y values, cross-interaction constant ρ_{XY} (eq 2), and Brönsted β_X values are summarized in Table 1. The β_X (β_{nuc}) values were determined by plotting log k_2 (MeCN) against pK_a (H_2O) of benzylamines. This procedure was found to be reliable since the pK_a (MeCN) varied in parallel with the pK_a (H_2O) with a reasonably constant difference of 7.5 (= pK_a (MeCN) – pK_a (H_2O)).[13,14] As shown in Table 1, the second-order rate constant (k_2) increases in order of X = *p*-OMe > *p*-Me > H > *p*-Cl, and also increases in the order of Y = H > *p*-Me > *p*-OMe. The large positive ρ_Y and β_X values and the large negative ρ_X values indicate that the large negative charge is developed in the substrate carbonyl carbon at the TS, and the positive charge is developed in the nucleophile nitrogen atom at the TS.[10-13] This result indicates that the rates are faster for the reaction with a stronger nucleophile and/or the substrates **1** with a stronger electron-withdrawing group in phenyl ring as found in typical nucleophilic substitution reactions. Table 1 shows that the ρ_Y values are larger than 2.5|ρ_X|. In general, the selectivity parameters (ρ_X) for benzylamines are 2 ~ 2.5 times smaller than that of anilines for the nulcleophilic substitution reactions.[11d] Thus the larger ρ_Y values indicate more advanced bond formation than the bond breaking at the TS (transition state) and/or no bond breaking at the TS. The parameter ρ_Y can be regarded as a balance of charge gained from the nucleophile in N-C bond formation ($\rho_{form} > 0$) and charge lost to the leaving group in C-LG (leaving group) bond breaking ($\rho_{break} < 0$),[15] *i.e.* eq 4.

Table 1. Rate constants, k_2 ($M^{-1}s^{-1}$), for the reactions of 2-(Y-benzoyl)-4,5-dichloro-pyridazine-3-ones with X-benzylamines in MeCN at 25 °C.

X	Y			ρ_Y (r)
	p-OMe	*p*-Me	H	
p-OMe	11.8	40.1	115	3.56 (0.963)
p-Me	10.2	33.8	107	3.69 (0.974)
H	6.57	24.2	61.7	3.47 (0.962)
p-Cl	4.43	15.6	33.8	3.13 (0.936)
ρ_X (r)	−0.86 (0.991)	−0.83 (0.999)	−1.1 (0.981)	ρ_{XY} = −0.71
β_X (r)	0.83 (0.983)	0.79 (0.996)	1.1 (0.967)	(0.824)

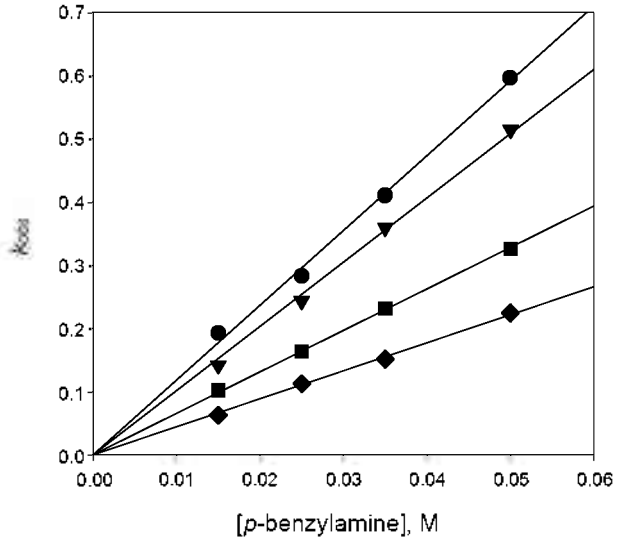


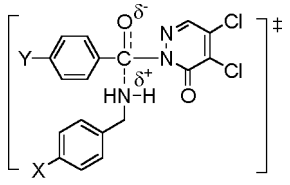
Figure 1. The plots of the *p*-methoxybenzylamine concentration *vs.* rate constants (k_{obs}) for the reactions of 2-(Y-substitutedbenzoyl)-4,5-dichloropyridazine-3-ones with *p*-methoxybenzylamines in MeCN at 25 °C (Y: ● = *p*-OMe, ▼ = *p*-Me, ■ = H, ◆ = *p*-Cl).

$$\rho_Y = \rho_{form} + \rho_{break} > 0 \quad (4)$$

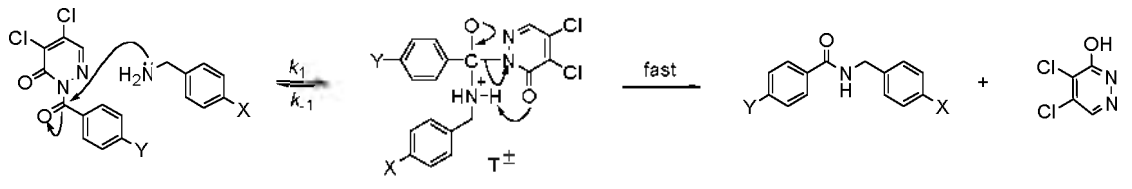
Since ρ_Y is positive, the magnitude of ρ_{form} is grater than that of ρ_{break} as can be seen in Table 1. This result indicates that the N-C bond making is ahead of C-LG (leaving group) bond breaking at the TS as shown in Scheme 2.

The negative value of cross-interaction constant ρ_{XY} (−0.71) implies that more electron-withdrawing substituent ($\delta\sigma_Y > 0$) in the substrate leads to greater degree of bond formation ($\delta\sigma_X < 0$).[11(a),(b),16] This value is comparable to those found in the reaction where the bond making takes place prior to the bond breaking process in the associative S_N2 and/or the carbonyl addition-elimination mechanism.[10-13] We proposed that aminolysis of **1** proceeds through the mechanism shown in Scheme 3 based on the Hammett ρ_X, ρ_Y and Brönsted β_X values and cross-interaction constant, ρ_{XY} value for the present work.

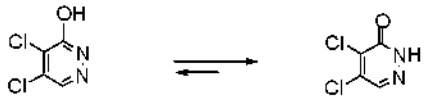
The first step is nucleophilc addition by **2** through a tetrahedral intermediate, $T^{\pm}$. Then the **3** is formed directly by losing of enol pyridazine **6** from $T^{\pm}$. However, this procedure gives to keto pyridazine **4** instead of **6**, since there is an equili-



Scheme 2



Scheme 3



6 **4**

Scheme 4

brium shown in Scheme 4, where the keto form **4** is in favor. Thus, **6** is formed initially by aminolysis of benzylamines, but it is rapidly converted into an equilibrium mixture that is almost all **4**. This result indicates that the 4,5-dichloropyridazin-3-one can be used as a good leaving group for various acylation reaction.

In summary, the kinetics of nucleophilic substitution reaction of 2-(*p*-substitutedbenzoyl)-4,5-dichloropyridazin-3-ones **1** with benzylamines **2** in acetonitrile at 25 °C have been studied. We proposed that aminolysis of **1** proceeds through the mechanism of formation of 4,5-dichloropyridazin-3-one based on the Hammett ρ_X, ρ_Y and Brönsted β_X values and cross-interaction constant, ρ_{XY} value. We also suggest that the 4,5-dichloropyridazin-3-one can be used as a good leaving group for various acylation reaction.

Experimental Section

Materials. 2-(*p*-Substitutedbenzoyl)-4,5-dichloropyridazin-3-ones were prepared from *p*-substitutedbenzoyl chlorides and pyridazine as described previously.[3,5-9] ^{1}H and ^{13}C NMR data were found to agree with reported results.[3,5-9] Commercial grade (> 98%). Of pyridazine (Aldrich-Gr) and *p*-substitutedbenzoyl chloride (Aldrich-Gr) were used, and Merk GR-grade (< 0.1% water) acetonitrile was used without further purification.

Kinetics. The rates for aminolysis were measured spectrophotometrically in MeCN at 25 ± 0.1 °C by following the decrease in absorbance due to disappearance of the substrate at wavelengths in the range of at ~ 260 nm. Kinetic experiments were performed using an applied photophysics DX18MV stopped-flow apparatus for fast reaction and Shimadzu UV-2401PC spectrophotometer for slow reactions.[13,17]

Product analysis. Substrate, 2-(*p*-methylbenzoyl)-4,5-dichloropyridazine-3-one was reacted with excess benzylamine with stirring for more than 15 half-lives at 25.0 °C in actonitrile, and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was treated with column chromatography (silica gel, $CHCl_3$: EtOAc = 15 : 1, v/v). Analysis of the product gave the following results.

C_6H_5(C=O)NHCH$_2$C$_6$H$_4$-CH$_3$ (*p*-Methyl-*N*-berrylbenzamide): m.p. 131 ~ 133 °C, IR (KBr), 3300 (NH), 3050 (C-H, aromatic), 2920 (C-H, CH_2), 2938 (C-H, CH_3), 1645 (C=O), 1605, 1560 (C=C, aromatic), 1520 (C=C, aromatic), ^{1}H NMR (500 MHz, $CDCl_3$), 2.22 (s, 3H), 4.40 (d, 2H, J = 6.0), 7.08 (d, 2H, J = 7.9), 7.17 (d, 2H, J = 7.9), 7.42 (t, 2H, J = 7.2), 7.47 (t, 1H, J = 7.3), 7.85 (t, 2H, J = 7.2), 8.95 (t, -NH).

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