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An NMR Study on a Pseudo-Intramolecular Transacylation of α-Aryl-β-keto Ester

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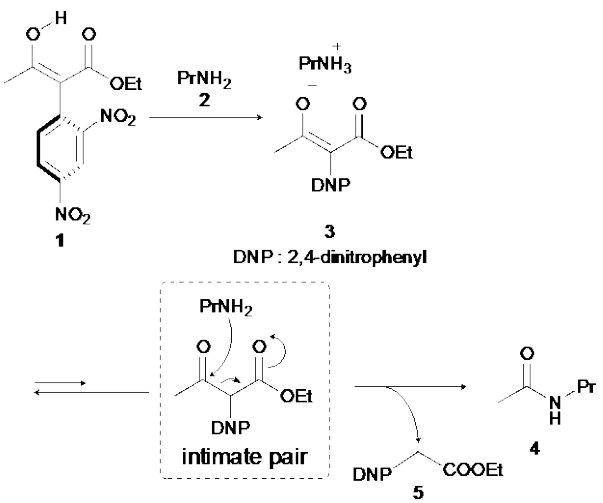
The pseudo-intramolecular reaction efficiently proceeds like an intramolecular manner although it is actually an intermolecular reaction. We obtained valuable insights by monitoring the reaction by ^{1}H NMR.

The development of a highly efficient reaction is one of significant subjects from the standpoint of green chemistry, which diminishes both wastes of resources and energy. In general, an intramolecular reaction proceeds more efficiently than an intermolecular reaction because of higher collision frequency between reaction sites. In other words, the increase of the collision frequency of reactants results in the improvement of the reaction efficiency even in an intermolecular process. Indeed, the use of reaction fields such as micelles and microcapsules enables reactions to undergo easily by increasing opportunity of reactants to encounter.[1] Such great success implies that efficient intermolecular reactions are promisingly achieved if the collision frequency of reactants can be increased even in the absence of a reaction field.

Recently, we have demonstrated a highly effective method called pseudo-intramolecular reactions.[2,3] The reactions proceed under mild conditions without any reaction fields, additives and troublesome manipulations, by which vicinally functionalized 1,4-dihydropyridines, 1,2-diazepines, and diazabicyclic compounds have been readily synthesized.[2]

The transacylation is another instance of the pseudo-intramolecular process (Scheme 1).[3a] The α-arylation of a β-keto ester increase the acidity of the hydrogen of the active methylene[4] because the aryl group stabilizes its enol form.[5] As a result, the ammonium salt **3** is easily formed upon treatment with the amine **2**. When a small amount of the amine is liberated under equilibrium, the nucleophilic amine and electrophilic keto ester locate close to each other, which is referred to an intimate pair. The spatial nearness of the reagents enables an efficient nucleophilic substitution to transfer the acyl group from the keto ester **1** to the amine **2** under mild conditions. The steric congestion around the reaction site also prevents the approach of other molecules to depress side reactions consequently.[3] Indeed, the efficient progress of the reaction is easily monitored by ^{1}H NMR. Just after the addition of equimolar amount of the amine **2** to a solution of the α-aryl-β-keto ester **1** in $CDCl_3$, the formation of the ammonium enolate **3** is confirmed by the immediate disappearance of the signal assigned to the enol hydrogen. With decreasing the signals of the salt, the signals of the transacylated products **4** and **5** increase without the formation of any by-product detectable to achieve quantitative conversion.



Scheme 1 A mechanism for the pseudo-intramolecular transacylation

The above feature of the pseudo-intramolecular process enables the chemoselective and regioselective acylation to proceed without any modification of the substrate such as the protection of another

functionality. Furthermore, this reaction also enables us to facilely synthesize unsymmetrical malonic acid derivatives by use of an α-arylated acetonedicarboxylate.[3] Hence, the present transacylation is a promising method for the synthesis of polyfunctionalized compounds. However, for applying the method to further elaborate syntheses, it is necessary to obtain further insights about the concept "the pseudo-intramolecular process". If the reaction proceeds in a pseudo-intramolecular process, the reaction order is considered to be close to first because reactants have already encountered in the intimate pair. From this viewpoint, we studied the correlation between the reaction rate and the polarity of the reaction medium/ the concentration of the substrates by monitoring the progress of the reaction with ^{1}H NMR. In addition, we evaluated the reaction order on the basis of the results.

Solvation is one of crucial factors affecting the reactivity of an intermolecular process, because two solvated substrates diminish collision frequency.[6] As a result, the rate of an intermolecular process changes depending on the polarity of the reaction medium. On the other hand, reaction sites close to each other should less influenced by the polarity of the solvent in the case of an intramolecular process.[7] With the characteristics of intermolecular and intramolecular process in mind, we hypothesized that the rate of the pseudo-intramolecular process would not be influenced by the polarity of the solvent even though it is actually an intermolecular process. In order to confirm this hypothesis, we monitored the transacylation by ^{1}H NMR using six kinds of deuterated solvents (acetonitrile-d_3, THF-d_8, benzene-d_6, chloroform-d, methanol-d_4, and acetone-d_6) (Figure 1), of which the dielectric constants (ε_r) and dipole moments (μ) are shown in Table 1.[8]

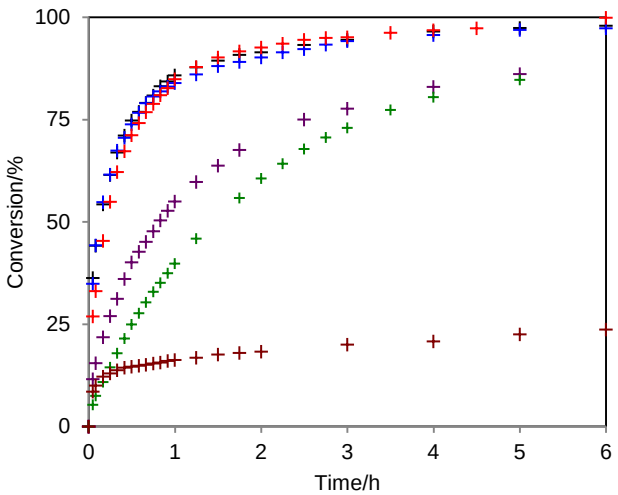


Fig. 1 Time/conversion curves for **3** in different solvents. Acetonitrile (+), THF (+), benzene (+), chloroform (+), methanol (+), and acetone (+). The reaction conducted at 30 °C using a 0.06 M solution.

Table 1 Rate constant k and relative rate constant k_{rel} with solvent parameters.

Solvent	ε_r	μ/D	k/mol^{-1}	k_{rel}
Acetonitrile	37.5	3.4	5.57×10^{-4}	1.0
THF	7.6	1.7	5.46×10^{-4}	0.99
Benzene	2.3	0	5.50×10^{-4}	1.0
Chloroform	4.8	1.2	1.77×10^{-4}	0.32
Methanol	32.6	1.7	1.18×10^{-4}	0.21
Acetone	20.7	2.7	5.60×10^{-6}	0.010

The progress of the transacylation was monitored by ^{1}H NMR at intervals of several minutes (hours). Because no signal was observed other than those of the ammonium salt **3**, the transacylated products **4** and 2,4-dinitrophenylacetate **5**, the reaction rate can be discussed on the basis of the conversion of **3**. When acetone-d_6, methanol-d_4, and chloroform-d were used, reactivities exhibited different from each other, probably due to the interaction of the solvent with the amine **2**, which would arise from an electrophilic moiety[9,10] or a hydroxy group to form a hydrogen bond. Contrary to this, when benzene-d_6, THF-d_8, and acetonitrile-d_3 were used as the solvent, the transacylations underwent with the same reaction rate. It is noteworthy that the reaction rates in the latter three solvents were almost the same despite their extremely different polarity. This result strongly indicates that the transacylation was not affected by the polarity of the solvent, as we hypothesized.

Next, the effect of the concentration of the reaction mixture was studied in a similar way with changing the concentration in a range from 0.24 to 0.015 M (Figure 2 and Table 2). Although the reaction rate varied depending on the concentration, it became almost the same in highly diluted solutions. In the case of an intermolecular process, the reaction rate considerably becomes slower with dilution of the reaction mixture. Thus, the results well support that the reaction is a pseudo-intramolecular process.

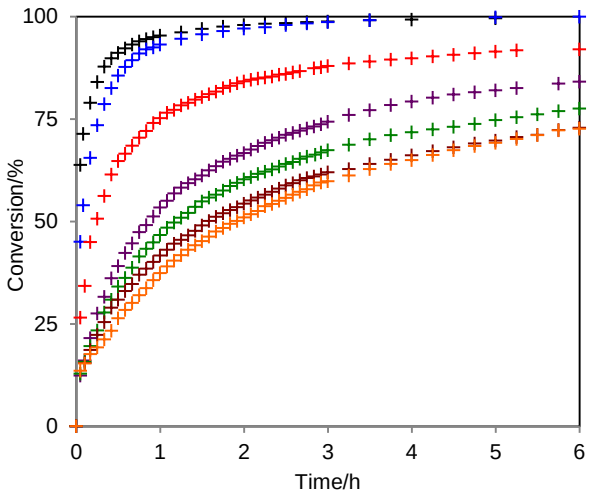


Fig. 2 Time/conversion curves for **3** under various concentrations. 0.24 (+), 0.12 (+), 0.06 (+), 0.03 (+), 0.025 (+), 0.02 (+), and 0.015 (+) M. The reaction conducted at 30 °C using benzene-d_6 as a solvent.

Table 2 % conversions of **3** monitored at hourly intervals at at intervals 30 °C using benzene-d_6, at differing concentrations of **3**.

Concentration/M	Conversion/%			
	1 h	2 h	3 h	4 h
0.24	96	98	99	100
0.12	94	98	99	100
0.06	76	85	88	90
0.03	54	67	75	80
0.025	47	61	68	72
0.02	42	55	62	67
0.015	38	51	60	65

In order to obtain insight furthermore, the reaction order *n* of the reaction, carried out in a different concentration, was calculated using Equation 1, where *k* is the rate constant, *A* is the concentration of the ammonium enolate **3**, and *t* is the reaction time.[11] The calculated value *n* of each reaction is between first and second (Table 3). Because the quantitative formation of the ammonium salt **3** was confirmed just after the addition of the amine **2** to a solution of the keto ester **1**, the higher reaction order caused by the intermolecular reaction between two intimate pairs as shown in Figure 3.

$$\frac{1}{n-1}\left(\frac{1}{[A]^{n-1}} - \frac{1}{[A]_0^{n-1}}\right) = kt \qquad \text{Eq. (1)}$$

Table 3 Reaction orders measured for reaction in benzene-d_6.

Concentration/M	Reaction order
0.24	1.8
0.12	1.6
0.06	1.6
0.03	1.6
0.015	1.4

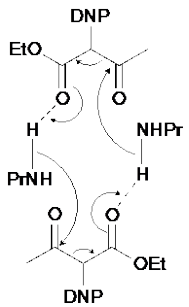


Fig. 3 A plausible reaction between two intimate pairs.

These results imply that the first order reaction and the second order reaction proceed in the present system. Consequently, the pseudo-intramolecular process is concluded to be fundamentally a first order reaction.

In summary, the present transacylation was monitored by ^{1}H NMR to give insights; 1) the reaction rate was not affected by the polarity of a solvent, 2) the reaction efficiently proceeded even in a highly diluted solvents, 3) the reaction order was lower than second order. These results reveal that the transacylation proceeds like an intramolecular process rather than an intermolecular process. The information will be helpful for designing highly efficient and environmentally benign synthetic protocols for polyfunctionalized compounds.

Notes and references

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Electronic Supplementary Information (ESI) available: Monitoring the transacylation by ^{1}H NMR by using benzene-d_6 as a solvent and NMR data of compounds **1**, **4**, and **5**. NMR study of the reaction of the propylamine **2** and equimolar amount of acetone in benzene-d_6. See DOI: 10.1039/c000000x/

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10 When equimolar amount of acetone was added to a solution of the propylamine **2** in benzene-d_6, small signals were observed in the lower field, which were assigned to the propylammonium group derived from the addition of **2** to the carbonyl group (see ESI). In acetone solution, larger amount of the adduct should be formed.

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