Reactivities of 3-(1-Azolyl)-2-alken-1-ones and the Related Compounds With Pyrrolidine

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From the rate constants of the reaction with pyrrolidine, the reactivities of 3-(1-azolyl)-2-alken-1-ones with nucleophiles were evaluated to be rather high. Especially the reactivities of the quaternary salts of 3-(1-imidazolyl)-2-alken-1-ones were nearly equal to those of 3-chloro-2-alken-1-ones. In conclusion, 3-(1-imidazolyl)-2-alken-1-ones satisfied the practical requirements for the starting materials of the synthesis of 3-hetero-substituted 2-alken-1-ones.

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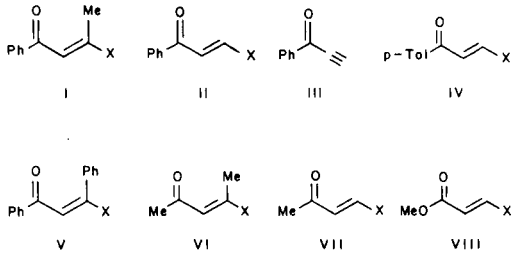
Recently, we have investigated the preparation and the reactions of 3-(1-imidazolyl)-2-alken-1-ones as the vinylogues of 1-acylimidazoles which were extensively investigated for the acylation of amines, alcohols and thiols [1]. 3-(1-Imidazolyl)-2-alken-1-ones were easily prepared from 2-alkyn-1-ones, 3-halo-2-alken-1-ones, and 2,3-dibromoalkan-1-ones by the treatment with imidazole in the presence of triethylamine [2,3]. The purification of the compounds of this series was accomplished by the recrystallization of the reaction mixture, and 3-(1-imidazolyl)-2-alken-1-ones could be stored over a year. In spite of possessing high stability in a weakly acidic or neutral solution, the imidazolyl group of 3-(1-imidazolyl)-2-alken-1-ones was rapidly replaced by nucleophiles under the basic conditions to afford 3-hetero-substituted 2-alken-1-ones [4,5]. This nucleophilic replacement reaction was accelerated by the pretreatment with methyl iodide to form the quaternary salts of 3-(1-imidazolyl)-2-alken-1-ones. Moreover, 3-(1-azolyl)-2-alken-1-ones, which bonded with various azole groups such as pyrazoles and benzimidazole on the alkenone system instead of imidazole, exhibited the similar characteristics in preparation and nucleophilic reactions [6]. Considering these facts, 3-(1-imidazolyl)-2-alken-1-ones and their related compounds satisfied the practical requirements for the synthetic purposes, especially for the synthesis of 3-hetero-substituted 2-alken-1-ones.

In order to clarify the limitation of the nucleophilic replacement reaction, the dominant factors for the replacement reaction should be elucidated by the quantitative investigation of the reactivity of 3-(1-azolyl)-2-alken-1-ones and the related compounds against the nucleophiles. Furthermore, the synthetic utility of 3-(1-azolyl)-2-alken-1-ones might be elucidated by the comparison of its nucleophilic reactivity with that of 3-chloro-2-alken-1-ones, which were the substrates generally utilized for the synthesis of 3-hetero-substituted 2-alken-1-ones.



a, 1-Imidazolyl
b, 3-Methyl-1-imidazolium
c, 2-Methyl-1-imidazolyl
d, 1-Benzimidazolyl
e, 1-Pyrazolyl
f, 3-Methyl-1-pyrazolyl
g, 3,5-Dimethyl-1-pyrazolyl
h, Cl
i, Br
j, OMe
k, SEt
m, Ethylsulfinyl
n, 1-Pyrrolidinyl

Results and Discussion.

Although various nucleophiles were available for the replacement reaction of 3-(1-azolyl)-2-alken-1-ones, pyrrolidine was chosen as the nucleophile for the evaluation of the

Table 1

The Reaction Rate Constants of PhCO-CH=CX-Me

Compound X	λ max (log ε) nm	Reaction Rate $K(M^{-1}\cdot sec^{-1})$	Relative
Ia 1-Imidazolyl	289 (4.25)	1.30×10^{-1}	1.0
Ib 3-Methyl-1-imidazolium	248 (4.45)	2.05×10^{-1}	1.6
Ic 2-Methyl-1-imidazolyl	267 (4.23)	$1.7 \times 10^{-4}>$	0.0013>
Id 1-Benzimidazolyl	252 (4.20)	1.73×10^{-2}	0.13
Ie 1-Pyrazolyl	307 (4.33)	1.17×10^{-1}	0.90
If 3-Methyl-1-pyrazolyl	317 (4.39)	8.80×10^{-2}	0.68
Ig 3,5-Dimethyl-1-pyrazolyl	310 (4.23)	3.10×10^{-3}	0.024
Ih Cl	261 (4.29)	2.43×10^{-1}	1.9
Ii Br	266 (4.28)	3.17×10^{-1}	2.4
Ij OMe	277 (4.25)	5.17×10^{-1}	0.040
Ik SEt	330 (4.36)	$1.7 \times 10^{-4}>$	0.0013>
Im Ethylsulfinyl	260 (4.14)	1.22×10^{-1}	0.94
In 1-Pyrrolidinyl	337 (4.40)	—	—

reactivity spectroscopically by the following reasons. 1: 3-(1-Azolyl)-2-alken-1-ones gave 3-(1-pyrrolidinyl)-2-alken-1-ones without any by-product. 2: The reaction of 3-(1-azolyl)-2-alken-1-ones with pyrrolidine occurred without any catalyst. 3: The resulting 3-(1-pyrrolidinyl)-2-alken-1-ones were fairly stable. 4: The uv absorption maxima of the products appeared in a longer wave-length region with higher absorption coefficients compared with those of 3-(1-azolyl)-2-alken-1-ones. 5: The uv absorption coefficient of pyrrolidine was negligibly small. As the solvent, acetonitrile was used owing to the high solubility, the high transparence and the low nucleophilicity.

When 1-phenyl-3-(1-imidazolyl)-2-buten-1-one (Ia) was treated with an excess amount of pyrrolidine in acetonitrile, monitored by a uv absorption spectrometer at 289 and 337 nm, where the absorption maxima of Ia and 1-phenyl-3-(1-pyrrolidinyl)-2-buten-1-one (In) appeared respectively. The reaction rate derived from the increasing curve of In coincided with that from the decreasing curve of Ia. Further, the reaction rate was dependent on the concentration of pyrrolidine. These facts suggested that the rate determining step was the second order addition reaction of pyrrolidine on Ia, and that the following elimination of imidazole was a fast reaction step. Therefore, the reactivity of Ia was evaluated from the increase of the product by the pseudo first order technique. Similarly, the reaction rates of various 3-(1-azolyl)-2-alken-1-ones and their related compounds were derived and the results were summarized in the Tables 1 and 2.

When the reaction rate of 1-phenyl-3-(1-imidazolyl)-2-propen-1-one (IIa) was compared with those of 1-(4-methylphenyl)-3-(1-imidazolyl)-2-propen-1-one (IVa), 1-(1-imidazolyl)-1-buten-3-one (VIIa), and methyl 3-(1-imidazolyl)acrylate (VIIIa), the order of reactivity to pyrrolidine was given to be IIa > IVa > VIIa > VIIIa. This tendency, shown in the Table 3, was also found in the series of the superdelocalizability for nucleophiles, which is a reaction index calculated by the HMO method. This relationship showed that the reactivity was dependent on the electronic factor of 3-(1-imidazolyl)-2-alken-1-ones. Further, it is reasonably interpreted that the rate determining step was the attack of the nucleophile on the electron deficient C-3 carbon.

On the contrary, compared with the reaction rates of Ia and 1,3-diphenyl-3-(1-imidazolyl)-2-propen-1-one (Va), that of IIa was considerably large. From this fact, the large steric factor of the phenyl and methyl group was observed in the case of VIIa and 4-(1-imidazolyl)-3-penten-2-one (VIa). Moreover, in the cases of Ia, 3-(2-methyl-1-imidazolyl)- (Ic), 3-(1-pyrazolyl)- (Ie), 3-(3-methyl-1-pyrazolyl)- (If) and 3-(3,5-dimethyl-1-pyrazolyl)-1-phenyl-2-buten-1-one (Ig), the substituted methyl group on the azolyl ring retarded the replacement reaction. Especially the vicinal methyl group of Ic and Ig exhibited dramatic steric effects. The low reactivity of 3-(1-benzimidazolyl)-1-phenyl-2-buten-1-one (Id) was also explained by the steric factor of the benzimidazolyl group.

In a previous paper, we reported that 3-(1-imidazolyl)-2-alken-1-ones exhibited the *p*Ka values of 3.0-5.0, and easily gave the quaternary salts [5]. Moreover, the nucleophilic replacement reaction was accelerated by the quaternarization of the azolyl group. Here, the degree of the activation was evaluated by the comparison of the reaction rate of the quaternary salts with those of the corresponding 3-(1-imidazolyl)-2-alken-1-ones. In the case of 1-(3-phenyl-3-oxo-1-buten-1-yl)-3-methylimidazolium iodide (Ib), the reaction rate was found to be 2.05×10^{-1} $M^{-1} \cdot sec^{-1}$, while that of Ia was 1.30×10^{-1} $M^{-1} \cdot sec^{-1}$. The ratio of these reaction rates, indicating the activating factor by the quaternization, was given to be 1.6. By the comparison with the reaction rates of 1-(3-phenyl-3-oxo-1-propen-1-yl)- (IIb), 1-(1,3-diphenyl-3-oxo-1-propen-1-yl)- (Vb), 1-(4-oxo-2-penten-2-yl)- (VIb), 1-(3-oxo-1-buten-1-yl)- (VIIb), and

Table 2

The Reaction Rate Constants of 3-(1-Imidazolyl)-2-alken-1-ones and the Related Compounds

	Compound	λ max (log ε)			Reaction Rate	
			X [a]	nm	$K(M^{-1} \cdot sec^{-1})$	Relative [b]
IIa	PhCO-CH=CX-H		Im	289 (4.33)	3.72	1.0
IIb			Im^+	248 (4.45)	3.39×10	9.1
IIh			Cl	256 (4.23)	4.11×10	11
III	PhCO-C≡CH		—	262 (4.10)	1.11×10^2	30
IVa	*p*-TolCO-CH=CX-H		Im	292 (4.43)	2.70	—
Va	PhCO-CH=CX-Ph		Im	293 (4.11)	3.58×10^{-4}	1.0
Vb			Im^+	245 (4.31)	1.48×10^{-2}	40
VIa	MeCO-CH=CX-Me		Im	274 (4.13)	8.67×10^{-3}	1.0
VIb			Im^+	246 (4.45)	1.67×10^{-2}	1.9
VIIa	Me-CO-CH=CX-H		Im	267 (4.26)	3.15×10^{-1}	1.0
VIIb			Im^+	245 (4.49)	1.97	6.2
VIIIa	MeOCO-CH=CX-H		Im	260 (4.22)	6.32×10^{-4}	1.0
VIIIb			Im^+	244 (4.47)	2.65×10^{-1}	420

[a] Im = 1-Imidazolyl, Im^+ = 3-Methyl-1-imidazolium. [b] The relative rate based on the imidazolyl derivative.

Table 3

The Reaction Rate Constants and the Superdelocalizabilities of RCO-CH=CH-Im

Compound	R	Reaction Rate $K(M^{-1}\cdot sec^{-1})$	Sr(N) [a]
IIa	Ph	3.72	2.7701
IVa	*p*-Tol	2.70	2.5606
VIIa	Me	3.15×10^{-1}	2.0609
VIIIa	MeO	6.32×10^{-1}	1.8566

[a] Sr(N) = The values of Superdelocalizability for nucleophiles at C-3 carbon.

1-(2-ethoxycarbonylvinyl)-3-methylimidazolium iodide (VIIIb), the activating factors of IIa, Va, VIa, VIIa, and VIIIa were similarly obtained and summarized in the Tables 1 and 2. The relative rates in the Tables 1 and 2 showed that the less sterically hindered 3-(1-imidazolyl)-2-alken-1-ones were much activated by the quaternization.

When the reaction rates of Ia and Ib were compared with those of 3-hetero-substituted 2-alken-1-ones, Ia and Ib were more reactive compounds for pyrrolidine than the 3-alkoxy- and 3-alkylthio-2-alken-1-ones and their sulfoxy derivatives. Further reactivity of Ib was 0.84 times as much as that of 1-phenyl-3-chloro-2-buten-1-one (Ih). Also the reactivity of IIb was nearly equal (0.82 times) to that of 1-phenyl-3-chloro-2-propen-1-one (IIh). The comparable reactivities of Ib and IIb were great values in the practical synthesis of 3-hetero-substituted 2-alken-1-ones, while the 3-chloro-2-alken-1-ones were considered to be the poor handling compounds owing to the volatile liquid with an unstability against the nucleophiles.

Conclusion.

By the determination of the rate constant in the reaction with pyrrolidine, the reactivities of 3-(1-azolyl)-2-alken-1-ones and their related compounds in the nucleophilic replacement reaction were evaluated. As the results, the reactivity was dependent on the electronic and especially on the steric factors. On the other hand, the quaternization of the azolyl group promoted the reactivity of 3-(1-azolyl)-2-alken-1-ones. Moreover, the reactivity of the quaternary salts was nearly equal to those of 3-chloro-2-alken-1-ones, which were previously used as the starting compounds for the synthesis of 3-hetero-substituted 2-alken-1-ones. These facts suggested that 3-(1-imidazolyl)-2-alken-1-ones satisfied the practical requirements for the starting materials of the synthesis of 3-hetero-substituted 2-alken-1-ones.

EXPERIMENTAL

Materials.

3-Hetero-substituted 2-alken-1-ones were prepared by the ordinary procedure and purified by distillation. The compounds of 3-(1-azolyl)-2-alken-1-ones and the related compounds were prepared by the method reported in the previous papers. The spectral data and elemental analytical data of the newly prepared compounds were described below.

1-Phenyl-3-(1-imidazolyl)-2-propen-1-one (IIa).

Compound IIa had mp 157-158°; ir: 1665, 1600; nmr: δ 6.95 (d, 1H, J = 14 Hz), 7.00 (s, 1H), 7.15 (s, 1H), 7.2-7.5 (m, 3H), 7.6-7.9 (m, 3H), 7.81 (d, 1H, J = 14 Hz).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.65; H, 5.12; N, 14.10.

1-(3-Phenyl-3-oxo-1-propen-1-yl)-3-methylimidazolium Iodide (IIb).

Compound IIb has mp 202.5-203.5°; ir: 1675, 1615, 1575, 1540; nmr: δ 4.00 (s, 3H), 7.4-7.7 (m, 5H), 7.9-8.3 (m, 5H).

Anal. Calcd. for $C_{13}H_{13}IN_2O$: C, 45.90; H, 3.85; N, 8.23. Found: C, 45.87; H, 3.86; N, 8.23.

1-(1,3-Diphenyl-3-oxo-1-propen-1-yl)-3-methylimidazolium Iodide (Vb).

Compound Vb had mp 153-154°; ir: 1660, 1610, 1590, 1570, 1545; nmr: δ 4.07 (s, 3H), 7.3-8.2 (m, 13H), 9.38 (s, 1H).

Anal. Calcd. for $C_{19}H_{17}IN_2O$: C, 54.82; H, 4.11; N, 6.72. Found; C, 54.81; H, 4.01; N, 6.72.

1-(1-Imidazolyl)-1-buten-3-one (VIIa).

Compound VIIa had mp 118-119°; ir: 1670, 1640; nmr: δ 2.29 (s, 3H), 6.40 (d, 1H, J = 14 Hz), 7.20 (s, 1H), 7.27 (s, 1H), 7.83 (s, 1H), 7.85 (d, 1H, J = 14 Hz).

Anal. Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.86; H, 5.88; N, 20.55.

1-(3-Oxo-1-buten-1-yl)-3-methylimidazolium Iodide (VIIb).

Compound VIIb had mp 180-181°; ir: 1690, 1645, 1580, 1550; nmr: δ 2.50 (s, 3H), 4.11 (s, 3H), 6.80 (d, 1H, J = 15 Hz), 7.4-7.6 (m, 2H), 8.0 (m, 1H), 8.03 (d, 1H, J = 15 Hz).

Anal. Calcd. for $C_8H_{11}IN_2O$: C, 34.55; H, 3.98; N, 10.07. Found: C, 34.50; H, 3.94; N, 10.01.

The Measurement of the Reaction Rate Constants.

The substrate and pyrrolidine were dissolved individually in acetonitrile (dried over calcium hydride and distilled). The solutions were mixed in a cell of the uv spectrometer (Shimadzu UV-365 UV-VIS-NIR Recording Spectrometer). The change of absorbance at λ max of the product was displayed at 20° with time. From the increase in absorbance, the reaction rate constants were elucidated by the pseudo first order technique.

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