# The Reaction of 3-(1-Imidazolyl)-2-alken-1-ones with Nucleophiles



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Generally 3-hetero-substituted 2-alken-1-ones were prepared from 1,3-alkanediones, 3-chloro-2-alken-1-ones, or conjugated ynones. The preparation of 3-hetero-substituted 2-alken-1-ones was subjected to some limitations by these methods. By the reaction of 3-(1-imidazolyl)-2-alken-1-ones (I) and 3-(3-oxo-1-alkenyl)-1-methylimidazolium iodides (II) with nucleophiles, 3-hetero-substituted 2-alken-1-ones could be obtained regioselectively in good yield under mild conditions. These results suggested that compounds I and II were concluded to be useful intermediates for the organic synthesis.

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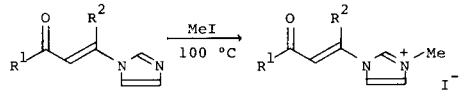
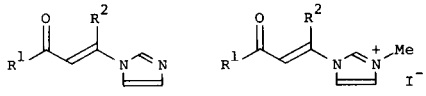
Various 3-hetero-substituted 2-alken-1-ones, such as, 3-thio-2-alken-1-ones and 3-amino-2-alken-1-ones prepared from 1,3-alkanediones or conjugated ynones, were subjected to some limitations by these methods. For example, the regioselective preparation of 3-hetero-substituted 2-alken-1-ones was sometimes impossible from 1,3-alkanediones. 3-Hetero-substituted 2-alken-1-ones could be obtained regioselectively by the Michael addition of mercaptans or amines to the conjugated ynones. However, conjugated ynones as starting material were not so easy in handling or purification. Although the conjugated ynones were prepared by acylation of acetylene (1) or by oxidation of ynols (2), the preparation of substituted ynones such as 4-(*p*-tolyl)-3-butyn-2-one was sometimes quite difficult.

We reported that 3-amino-2-alken-1-ones showed the properties of enones, enamines, and amides owing to the vinylogues of amides (3). Since imidazole is a typical heteroaromatic amine, 3-(1-imidazolyl)-2-alken-1-ones (I) are considered to be one of special 3-amino-2-alken-1-ones. Therefore, I can be expected to show the properties of enones, *N*-vinylimidazoles, and *N*-acylated imidazoles. Imidazolyl group of *N*-acylated imidazole has the characteristics of a good leaving group in the reaction with nucleophiles, because of its strong electron-withdrawing properties. Thus *N*-acylated imidazoles are extensively applicable as a useful acylating agent for amines, alcohols, carboxylic acids, and mercaptans (4). From these facts, the reaction of I was quite interesting, especially the reaction with nucleophiles. However, the paper concerning I has never been reported in the literature, except the preparation of 4-(1-imidazolyl)-3-buten-2-one (5). Recently, we reported the new synthetic methods of I from the corresponding 3-chloro-2-alken-1-ones or 2-alkyn-1-ones by the treatment with imidazole (6). Also I was succeeded to be prepared from 2,3-dibromoalkan-1-ones by the treatment with imidazole (7). According to these methods, the preparation of I having any substituent group on C-1 and C-3 positions was accomplished. Moreover, when I was treated with methyl iodide in a sealed tube, the corresponding methiodide salt, 3-(3-oxo-1-alkenyl)-1-methylimidazolium iodide (II), was obtained in good yield. (Scheme 1).




Scheme 1

Table 1 3-(1-Imidazolyl)-2-alken-1-ones (I) and Its Methiodide Salts (II)



a) $R^1 = R^2 = Me$

b) $R^1 = Ph$, $R^2 = Me$

c) $R^1 = Me$, $R^2 = Ph$

d) $R^1 = Ph$, $R^2 = Ph$

e) $R^1 = Ph$, $R^2 = p\text{-Tol}$

f) $R^1 = Ph$, $R^2 = p\text{-MeOC}_6H_4$

Table 2 Half lives of 4-(1-Imidazolyl)-3-penten-2-one (Ia) and Its Methiodide Salt (IIa) in Methanol

| Catalyst (a) | Substrate Ia | IIa |
|---|---|---|
| Sulufuric acid | <0.5 hours | ——— |
| Acetic acid | 11 hours | 16 hours |
| None | 93 hours | 11 hours |
| Triethylamine | 29 hours | 2 hours |
| Sodium Hydroxide | <0.5 hours | ——— |

(a) The concentration of catalyst was 0.1 moles/ 1.

Therefore, we examined the reaction of I and II with various nucleophiles.

Alcoholysis.

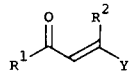
It was necessary to clarify the stability of these compounds in a solution before the investigation of the nucleophilic reactions of I and II. Although I was considerably soluble in many kinds of solvents, II was scarcely soluble

in ordinary organic solvent except alcohols. Therefore, in order to clarify the stability of I and II in methanol, 4-(1-imidazolyl)-3-penten-2-one (Ia) or its methiodide salt (IIa) was heated in methanol in the presence or absence of acids and bases. Compound Ia was fairly stable in methanol in the presence of acetic acid or triethylamine to afford 4-methoxy-3-penten-2-one (IIIa). (Table 2).

The compound IIIa which is 1,3-alkanedione enol ether, has previously prepared by *O*-methylation of 2,4-pentanedione with diazomethane (8) or methyl iodide (9). However, the products are sometimes the mixture of IIIa and 3-methyl-2,4-pentanedione, and it is very difficult to control the methylation at oxygen atom. From these results, the treatment of II with methanol in the presence of triethylamine was supposed to be applicable to the synthesis of 3-methoxy-2-alken-1-ones (III).

Similar reaction of I and II having various substituents on C-1 and C-3 positions was carried out summarized in Table 3. From Table 3, when the reaction was carried out in refluxing methanol, III was obtained in high yield without by-product. By this alcoholysis, the synthesis of 3-alkoxy-2-alken-1-ones, *i.e.*, 1,3-alkanedione enol ether, was regioselectively prepared under mild conditions.

Table 3 The Reaction of 3-(1-Imidazolyl)enones with Nucleophiles



| Product | Starting material | $R^1$ | $R^2$ | Y | Yield %,(a) |
|---|---|---|---|---|---|
| IIIa | Ia | Me | Me | OMe | 5 |
| IIIa | IIa | | | | 78 |
| IIIb | Ib | Ph | Me | OMe | 14 |
| IIIb | IIb | | | | 41 |
| IIIc | Ic | Me | Ph | OMe | rec |
| IIIc | IIc | | | | 14 |
| IVa | Ia | Me | Me | SEt | 80 |
| IVa | IIa | | | | 85 |
| IVb | Ib | Ph | Me | SEt | 73 |
| IVb | IIb | | | | 72 |
| IVc | Ic | Me | Ph | SEt | 60 |
| IVc | IIc | | | | 71 |
| Va | Ia | Me | Me | SPh | 22 |
| Va | IIa | | | | 78 |
| Vb | Ib | Ph | Me | SPh | 17 |
| Vb | IIb | | | | 96 |
| Vc | Ic | Me | Ph | SPh | rec |
| Vc | IIc | | | | 89 |
| VIa | Ia | Me | Me | NHPr | 15 |
| VIa | IIa | | | | 77 |
| VIb | Ib | Ph | Me | NHPr | 85 |
| VIb | IIb | | | | 89 |
| VIc | Ic | Me | Ph | NHPr | 15 |
| VIc | IIc | | | | 40 |
| VIIa | Ia | Me | Me | -N⟩ | 87 |
| VIIa | IIa | | | | 65 |
| VIIb | Ib | Ph | Me | -N⟩ | 26 |
| VIIb | IIb | | | | 44 |
| VIIc | Ic | Me | Ph | -N⟩ | 21 |
| VIIc | IIc | | | | 14 |
| VIIIa | Ia | Me | Me | NHPh | 75 |
| VIIIa | IIa | | | | 22 |
| VIIIb | Ib | Ph | Me | NHPh | 73 |
| VIIIb | IIb | | | | 79 |
| VIIIc | Ic | Me | Ph | NHPh | 33 |
| VIIIc | IIc | | | | trace |
| IXa | Ia | Me | Me | OTol-p | rec |
| IXa | IIa | | | | 63 |
| IXb | Ib | Ph | Me | OTol-p | rec |
| IXb | IIb | | | | 69 |
| IXc | Ic | Me | Ph | OTol-p | rec |
| IXc | IIc | | | | 50 |

(a) The yields of compounds III - V and IX were determined by glc. The yields of compounds VI - VIII were determined by lpc.

Reaction with Mercaptans.

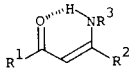
Thiolate anion was only produced in the presence of triethylamine because of p*K*a value of methanol (15.7), ethyl mercaptan (12.0), and thiophenol (7.8). Therefore, triethylamine was suitable as a catalyst for the generation of thiolate anion. Further, methanolysis was negligible at this condition (at room temperature for 2 hours) because of half life of I and II in methanolysis. In the reaction with ethyl mercaptan, I and II gave 3-ethylthio-2-alken-1-ones (IV) selectively in good yield. (Table 3). Although 3-phenylthio-2-alken-1-ones (V) were synthesized in poor yield from I, compound V was obtained in high yield from II.

In this reaction, thiolate anion attacked the C-3 position (1,4-addition) and no stereoselectivity was observed. The structure of IV and V was determined by comparison of the reported spectral data (10).

Reaction with Amines.

We examined the reaction of I and II with propylamine as a primary aliphatic amine, pyrrolidine as a secondary aliphatic amine, and aniline as an aromatic amine. The reaction was carried out in methanol at room temperature to give 3-amino-2-alken-1-ones (Table 3). The resulting 3-amino-2-alken-1-ones were identified by the comparison of the reported spectral data (11,12). In the reaction with

propylamine and aniline, the product was found to be only *Z*-form, while the product was only *E*-form in the reaction with pyrrolidine. It was well known that *N*-unsubstituted or *N*-monosubstituted 3-amino-2-alken-1-ones were easily isomerized into *Z*-form by hydrogen bonding between hydrogen atom of amine group and carbonyl oxygen (13) (Scheme 2). From these results, 3-amino-2-alken-1-ones were obtained easily and regioselectively by the use of this reaction.

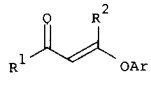


Scheme 2

Reaction with Phenols.

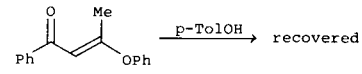
The mixture of compound I, *p*-cresol, and triethylamine in methanol was stirred for 2 hours at room temperature. However, the starting materials, *i.e.*, compound I were recovered. By the reaction of compound II under the same conditions, 3-(*p*-methyl)phenoxy-2-alken-1-ones (IX) were obtained in good yield (Table 3). Further we examined the reaction of compound II with a variety of substituted phenols (Table 4).

Table 4 Yields of 3-Phenoxy-2-alken-1-ones



| Product | $R^1$ | $R^2$ | Ar | Yield(%) |
|---|---|---|---|---|
| IXa | Me | Me | p-Tol | 63 |
| IXb | Ph | Me | p-Tol | 69 |
| Xb | Ph | Me | Ph | 64 |
| XIb | Ph | Me | p-$MeOC_6H_4$ | 62 |
| XIIb | Ph | Me | p-$ClC_6H_4$ | 71 |
| VIIIb | Ph | Me | p-$NCC_6H_4$ | 46 |
| XIVb | Ph | Me | ß-Naphth | 36 |
| IXc | Me | Ph | p-Tol | 50 |
| Xc | Me | Ph | Ph | 34 |
| IXd | Ph | Ph | p-Tol | 52 |
| Xd | Ph | Ph | Ph | 63 |
| IXe | Ph | p-Tol | p-Tol | 73 |
| Xe | Ph | p-Tol | Ph | 61 |
| XIe | Ph | p-Tol | p-$MeOC_6H_4$ | 83 |
| IXf | Ph | p-$MeOC_6H_4$ | p-Tol | 84 |

The structure of compounds IX-XIV was determined by spectral data and elemental analysis. 4-Phenyl-4-phenoxy-3-buten-2-one (Xc) and 1,3-diphenyl-3-phenoxy-2-propen-1-one (Xd) were identified by the comparison with the reported melting points (14). In these reactions, aryloxy anion attacked at C-3 position (1,4-addition). Therefore, 3-aryloxy-2-alken-1-ones having a variety of substituents could be prepared by the reaction of compound II with phenols.



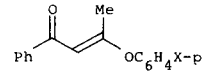
Scheme 3

Further, we studied the substituent effect of phenols. The relative rates of the *pseudo* first order reaction were measured by partial rate factor method using a large excess amount of phenoxy anions (Table 5). By the treatment of 1-phenyl-3-phenoxy-2-buten-1-one with *p*-cresol, the starting material was recovered quantitatively (Scheme 3). From this fact, the exchange reaction of phenoxy groups has not occurred.

The relative rate was correlated to Hammet's $\sigma$ value ($\rho$ = -1.02). From these results, the reaction rate was accelerated by an increase of nucleophilicity of phenols, and the rate determining step was speculated to be an attack of phenols of C-3 position and elimination of 1-methylimidazole was fast.

By the reaction of compound II with phenols, the preparation of 3-aryloxy-2-alken-1-ones, which was quite difficult, became easy.

Table 5 Relative Rates of Attack of p-Substituted Phenols



| X | rel rate |
|---|---|
| MeO | 2.13 |
| Me | 1.56 |
| H | 1.00 |
| Cl | 0.59 |
| CN | 0.35 |

## EXPERIMENTAL

Melting and boiling points were uncorrected. The ir spectra were recorded on a Jasco IRA-1 infrared spectrophotometer. The $^1$H-nmr spectra were given by Hitachi R-24A type nuclear magnetic resonance spectrometer. The vpc was recorded on a Hitachi 163 gas chromatography by using SE-30. The lpc was taken on a Jasco Familic-100N micro-lpc instrument by using SIL-$C_{18}$-10 with aqueous acetonitrile.

General Procedure.

All reactions were run under an argon atmosphere. The mixture of 3-(1-imidazolyl)-2-alken-1-ones (I) [or 3-(3-oxo-1-alkenyl)-1-methylimidazolium iodide (II)] (1 mmole) and nucleophiles (methanol, ethylmercaptan, thiophenol, amines, or phenols) (10 mmoles) in methanol (7 ml) was stirred for 2 hours at room temperature in the presence of triethylamine (10 mmoles). After stirring, the reaction mixture was diluted with water and the product was extracted 3 times with dichloromethane. The organic layer was washed with aqueous sodium hydroxide and 2 times with water, and then dried over anhydrous magnesium sulfate. After removal of solvent, yield of products was measured by vpc or lpc.

The structure of compounds III-VIII and Xc,d was determined by comparison with reported spectral data and melting points.

4-(*p*-Methyl)phenoxy-3-penten-2-one (IXa).

This compound was obtained in a yield of 63%, bp 50°/$10^{-3}$ mm Hg;

nmr (deuteriochloroform): δ 2.02 (3H, s), 2.37 (3H, s), 2.45 (3H, s), 5.33 (1H, s), 6.92 (2H, d, J = 8.0 Hz), 7.23 (2H, d, J = 8.0 Hz); ir (liquid film): ν max 1610, 1680 $cm^{-1}$.

*Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.81; H, 7.45.

1-Phenyl-3-(*p*-methyl)phenoxy-2-buten-1-one (IXb).

This compound was obtained in a yield of 69%, mp 67°; nmr (deuteriochloroform): δ 2.37 (3H, s), 2.58 (3H, s), 6.09 (1H, s), 6.9-7.8 (9H, m); ir (potassium bromide): ν max 1650 $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.77; H, 6.35.

4-Phenyl-4-(*p*-methyl)phenoxy-3-buten-2-one (IXc).

This compound was obtained in a yield of 50% and was the mixture of *E*- and *Z*-isomer (*E*:*Z* = 2:1), bp 80°/$10^{-3}$ mm Hg; nmr (deuteriochloroform): *E*-isomer, 2.22 (3H, s), 2.41 (3H, s), 6.23 (1H, s), 6.7-7.7 (9H, m); *Z*-isomer, 1.91 (3H, s), 2.36 (3H, s), 5.53 (1H, s), 6.7-7.7 (9H, m); ir (liquid film): ν max 1620, 1675 $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.90; H, 6.43.

1,3-Diphenyl-3-(*p*-methyl)phenoxy-2-propen-1-one (IXd).

This compound was obtained in a yield of 52% and was the mixture of *E*- and *Z*-isomer, bp 140°/$10^{-3}$ mm Hg; nmr (deuteriochloroform): δ 2.19 (1.8H, s), 2.36 (1.2H, s), 6.14 (0.4H, s), 6.7-8.1 (14.6H, m); ir (liquid film): ν max 1600, 1655 $cm^{-1}$.

*Anal.* Calcd. for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.90; H, 5.75.

1-Phenyl-3-(*p*-tolyl)-3-(*p*-methyl)phenoxy-2-propen-1-one (IXe).

This compound was obtained in a yield of 73% and was the mixture of *E*- and *Z*-isomer, mp 131-132°; nmr (deuteriochloroform): 2.14 (1.5H, s), 2.28 (4.5H, s), 6.13 (0.5H, s), 6.7-8.0 (13.5H, m); ir (potassium bromide): ν max 1585, 1650 $cm^{-1}$.

*Anal.* Calcd. for $C_{23}H_{20}O_2$: C, 84.11; H, 6.13. Found: C, 84.01; H, 6.12.

1-Phenyl-3-(*p*-methoxy)phenyl-3-(*p*-methyl)phenoxy-2-propen-1-one (IXf).

This compound was obtained in a yield of 84% and was the mixture of *E*- and *Z*-isomer, mp 110-111°; nmr (deuteriochloroform): δ 2.15 (2H, s), 2.31 (1H, s), 3.71 (3H, s), 6.13 (0.3H, s), 6.7-8.1 (13.7H, m); ir (potassium bromide): ν max 1600, 1650 $cm^{-1}$.

*Anal.* Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 79.99; H, 5.89.

1-Phenyl-3-phenoxy-2-buten-1-one (Xb).

This compound was obtained in a yield of 64%, bp 50°/$10^{-3}$ mm Hg; nmr (deuteriochloroform): δ 2.59 (3H, s), 6.08 (1H, s), 7.0-7.9 (10H, m); ir (liquid film): ν max 1600, 1650 $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.55; H, 5.91.

1-Phenyl-3-(*p*-tolyl)-3-phenoxy-2-propen-1-one (Xe).

This compound was obtained in a yield of 61%, mp 76-77°; nmr (deuteriochloroform): δ 3.25 (3H, s), 6.7-8.0 (15H, m); ir (potassium bromide): ν max 1610, 1655 $cm^{-1}$.

*Anal.* Calcd. for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.02; H, 5.77.

1-Phenyl-3-(*p*-methoxy)phenoxy-2-buten-1-one (XIb).

This compound was obtained in a yield of 83% and was the mixture of *E*- and *Z*-isomer, mp 84°; nmr (deuteriochloroform): δ 2.32 (3H, s), 3.63 (1.5H, s), 3.77 (1.5H, s), 6.11 (0.5H, s), 6.7-8.1 (13.5H, m); ir (potassium bromide): ν max 1615, 1665 $cm^{-1}$.

*Anal.* Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.16; H, 5.92.

1-Phenyl-3-(*p*-chloro)phenoxy-2-buten-1-one (XIIb).

This compound was obtained in a yield of 71%, mp 59-60°; nmr (deuteriochloroform): δ 2.60 (3H, s), 6.09 (1H, s), 7.0-7.9 (9H, m); ir (potassium bromide): ν max 1600, 1650 $cm^{-1}$.

*Anal.* Calcd. for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80. Found: C, 70.38; H, 4.77.

1-Phenyl-3-(*p*-tolyl)-3-(*p*-methoxy)phenoxy-2-buten-1-one (XIe).

This compound was obtained in a yield of 83% and was the mixture of *E*- and *Z*-isomer, mp 84°; nmr (deuteriochloroform): 2.32 (3H, s), 3.63 (1.5H, s), 3.77 (1.5H, s), 6.11 (0.5H, s), 6.7-8.1 (13.5H, m); ir (potassium bromide): ν max 1615, 1665 $cm^{-1}$.

*Anal.* Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.16; H, 5.92.

1-Phenyl-3-(*p*-cyano)phenoxy-2-buten-1-one (XIIIb).

This compound was obtained in a yield of 46%, mp 90-92°; nmr (deuteriochloroform): δ 2.57 (3H, d, J = 0.6 Hz), 6.20 (1H, q, J = 0.6 Hz), 7.2-7.9 (9H, m); ir (potassium bromide): 2330, 1650 $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.97; N, 5.31. Found: C, 77.51; H, 4.96; N, 5.25.

1-Phenyl-3-(β-naphthoxy)-2-buten-1-one (XIVb).

This compound was obtained in a yield of 36%, bp 100°/$10^{-3}$ mm Hg; nmr (deuteriochloroform): δ 2.63 (3H, s), 6.12 (1H, s), 7.1-8.1 (12H, m); ir (liquid film): 1600, 1660 $cm^{-1}$.

*Anal.* Calcd. for $C_{20}H_{16}O_2$: C, 80.30; H, 5.59. Found: C, 82.90; H, 5.59.

Measurement of Relative Rate in the Reaction with Phenols.

General Procedure.

The mixture of 3-(4-oxo-4-phenyl-2-buten-2-yl)-1-methylimidazolium iodide (IId) (1 mmole), phenol (12 mmoles), *p*-substituted phenols (10-15 mmoles), and triethylamine (30 mmoles) in methanol (10 ml) was stirred for 2 hours at room temperature. The reaction mixture was diluted with water and extracted 3 times with dichloromethane. The organic layer was washed with aqueous sodium hydroxide and 2 times with water, then dried over anhydrous magnesium sulfate. After removal of solvent, the ratio of two products was measured by vpc.

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