THE REGIOSELECTIVE PREPARATION OF 1-ALKEN-3-ONES BY THE REACTION OF 3-(1-IMIDAZOLYL)-2-ALKEN-1-ONES WITH ORGANOMETALLIC COMPOUNDS

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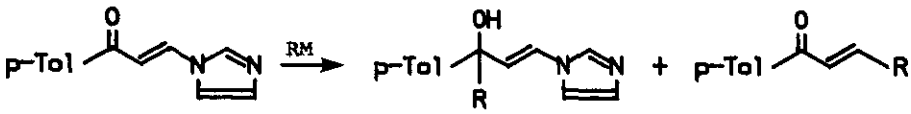
Abstract - 3-(1-Imidazolyl)-2-alken-1-ones, having substituent on the C-3 carbon, reacted with organometallic compounds to afford 3-(1-imidazolyl)-2-alken-1-ols. By the treatment of the products with sulfuric acid, 1-alken-3-ones, which were the positional isomers of the Michael addition products, was obtained regioselectively in good yields under mild conditions. Sodium borohydride reduction was also investigated.

Recently, we have investigated the preparation and the nucleophilic reactions of 3-(1-imidazolyl)-2-alken-1-ones. 3-(1-Imidazolyl)-2-alken-1-ones were easily prepared from 3-chloro-2-alken-1-ones, conjugated ynones and 2,3-dibromoalkan-1-ones with imidazole in the presence of triethylamine.[1] On the reaction of 3-(1-imidazolyl)-2-alken-1-ones with nucleophiles such as amines, alcohols and mercaptanes, 3-hetero-substituted 2-alken-1-ones could be obtained regioselectively in good yields under mild conditions.[1c,2] Furthermore, we have reported that in the reaction with organometallic compounds, 3-(1-imidazolyl)-2-alken-1-ones (1) having no substituent on the C-3 carbon gave two products 2 (1,2-adduct) and 3 (1,4-adduct) in comparable yields (Scheme 1).[3]

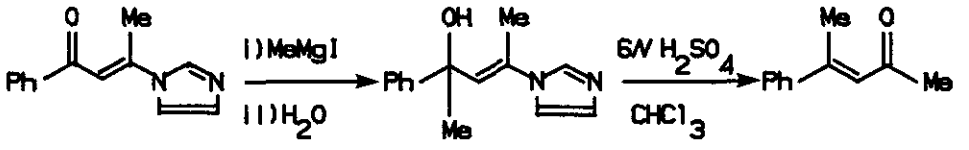


1 2 (1,2-adduct) 3 (1,4-adduct)

Scheme 1

Generally, the introduction of a substituent such as a methyl group on the C-3 carbon should raise the steric hindrance, and the nucleophilic attack on the C-3 carbon should be blocked to inhibit the formation of 1,4-adducts. For example, ethylmagnesium bromide attacked on C-3 carbon of 1,3-diphenyl-2-propene-1-one to give the 1,4-adduct in 94% yield, while the reaction with 1,3-diphenyl-3-phenyl-2-propen-1-one gave the 1,4-adduct in 44% yield.[4] Therefore, it is expected that 3-(1-imidazolyl)-2-alken-1-ones, having a substituent on the C-3 carbon, would afford 3-(1-imidazolyl)-2-alken-1-ols (1,2-adduct) regioselectively in the reaction with organometallic compounds.

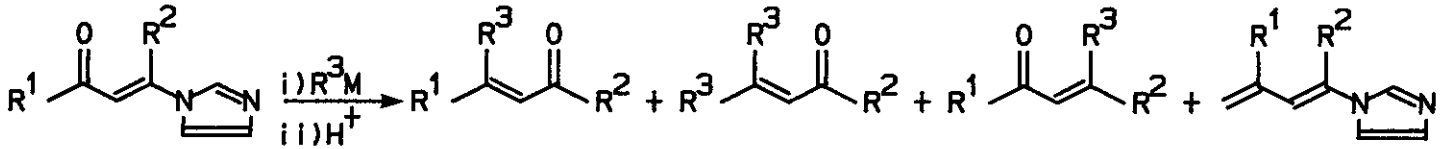
When 3-(1-imidazolyl)-1-phenyl-2-buten-1-one (**4c**) was treated with five equivalent amounts of methylmagnesium iodide, 3-(1-imidazolyl)-1-phenyl-2-buten-1-ol (**5c**) was obtained quantitatively. The ^{1}H-NMR spectrum of **5c** exhibited signals at δ 2.01 (3H, d, J=1Hz) and 6.05 ppm (1H, q, J=1Hz) with an allylic coupling between the C-1 methyl protons and C-2 proton, and the IR absorption band appeared at 3120 cm^{-1} due to the hydroxyl group. Since the imidazolyl group is a well-known good leaving group, 3-(1-imidazolyl)-2-alken-1-ols should give 1-alken-3-ones through the allylic shift of hydroxy group and the elimination of imidazolyl group by an acid catalyst. By the treatment of **5c** with 6N sulfuric acid in chloroform for 5 h under reflux, 4-phenyl-3-pentene-2-one (**6c**) was actually yielded overall in 91% yield from **4c**, which was identified by gas chromatography with an authentic sample. As a result, the introduction of steric hindrance around the C-3 carbon caused the attack on the carbonyl carbon and no trace of the Michael addition product could be detected (Scheme 2).



4c **5c** **6c**

Scheme 2

Similarly, the reaction of various 3-(1-imidazolyl)-2-alken-1-ones (**4a-d**) with methylmagnesium iodide was investigated. The products were found to be 2-alken-1-ol derivatives (**5a-d**). The crude compounds (**5a-d**) were directly converted with 6N sulfuric acid into 1-alken-3-ones (**6a-d**). On the reaction with methylmagnesium iodide, the 1,1-disubstituted-2-alken-1-ol derivatives were obtained



4 6 (1,2-add.) 7 (1,2-add.) 8 (1,4-add.) 9 (1,2-add.)

Yield (%)

4 \ R^3M			MeMgI (R^3=Me)				MeLi (R^3=Me)		$NaBH_4$ (R^3=H)		PhMgBr
	R^1	R^2	6	7	8	9	6	8	6	8	9
4a	Me	Me	33	–	0	0	–	–	–	–	–
4b	Me	Ph	28	–	a)	14	39	a)	85[b)]	0	65[c)]
4c	Ph	Me	91	–	0	0	41	a)	51	0	–
4d	Ph	Ph	0	–	0	32	–	–	98	0	–
4e	MeO	Me	0	52	0	0	–	–	–	–	–
4f	MeO	Ph	0	20	a)	14[d)]	–	–	–	–	–

a) trace ; b) yield of allyl alcohol derivative (5);
c) R^1=Ph ; d) R^1=Me.

Table 1

in 80% yield from 3-(1-imidazolyl)-2-alkenoic esters (**4e**, and **4f**).

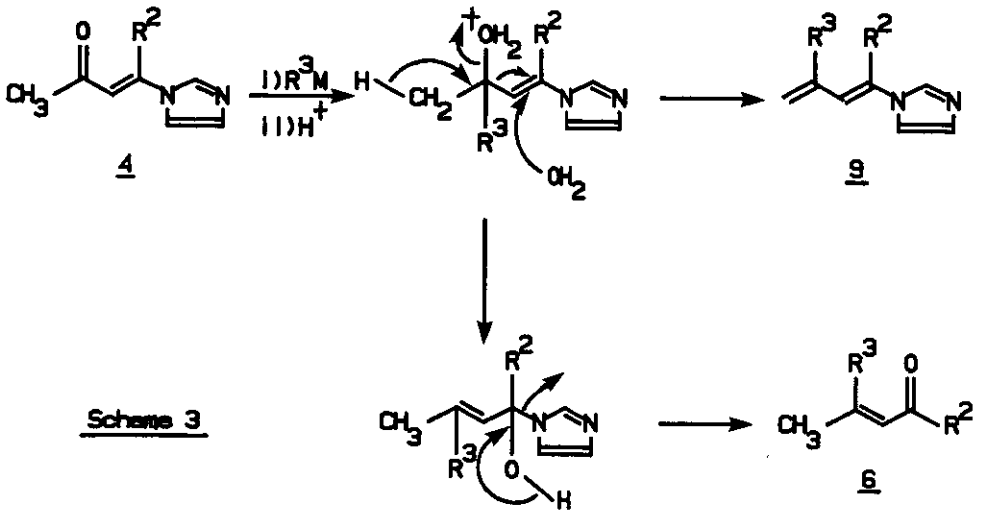
On the reaction of 3-(1-imidazolyl)-2-alken-1-ones (**4b**, and **4c**) with methyllithium followed by the treatment with sulfuric acid, no remarkable increase in the yield of the 1-alken-3-one could be observed.

When compounds (**4a-d**) were treated with sodium borohydride, 2-alken-1-ol derivatives (**5**) were obtained quantitatively, which were converted into 1-alken-3-ones (**6**) by the treatment with 6N sulfuric acid. The yields of **6** were summarized in Table 1. The products (**6a-d**, **7e-f**, and **8a-d**) were confirmed with authentic compounds[5] by gas chromatography and ^{1}H-NMR spectra.

In the case of phenyl group substituted on the C-3 carbon (**4b**, **4d**,and **4f**), the 2-alken-1-ones (**6**) were obtained in poor yield on the reaction with sulfuric acid. Instead of **6**, imidazolyl derivatives were predominantly isolated. In the ^{13}C-NMR spectra, a triplet peak at about 120 ppm was observed, and the IR spectra exhibited an absorption at 900 cm^{-1} attributable to the terminal olefin group. Moreover, the IR spectra exhibited absorption at 1600 and 1650 cm^{-1} attributable to the conjugated diene. From these data, the products were assigned to be 4-(1-imidazolyl)-1,3-butadiene derivatives (**9**), which was supported by the high resolution mass spectra.

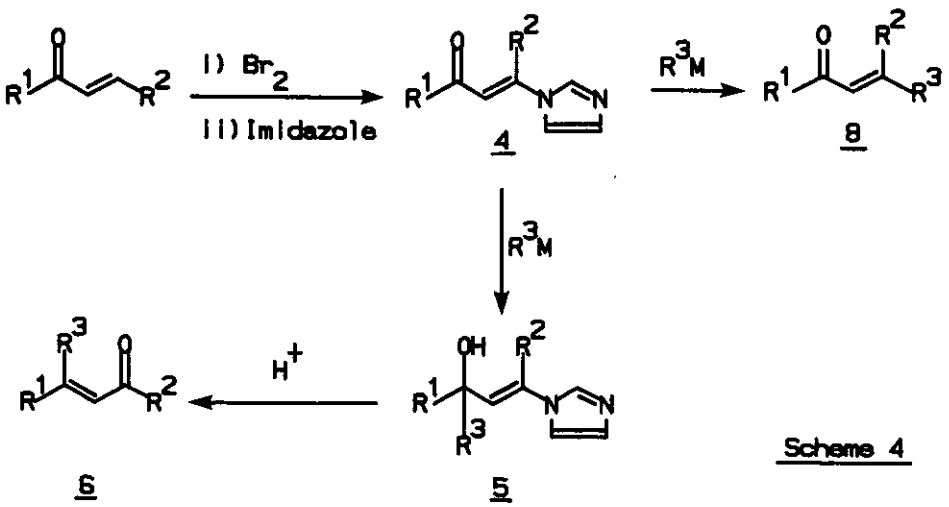
These reactions are explained in Scheme 3. The introduction of substituent on the C-3 carbon caused the remarkable steric hindrance. By the steric hindrance around the C-3 carbon, the Michael addition reaction was disturbed and nucleophilic attack of organometallic compounds was regioselectively controlled to carbonyl carbon. That is, 3-(1-imidazolyl)-2-alken-1-ols (**5**) were predominantly obtained in the first step. In the second step, which was the treatment with sulfuric acid, the hydroxyl group was dehydrated accompanied by allylic rearrangement, and finally water molecule attacked on the C-3 carbon accompanying the elimination of imidazole. As a whole, 2-alken-1-ol (**5**) was converted into 1-alken-3-one (**6**) with the transference of olefinic double bond. In the case of phenyl group as substituent on the C-3 carbon, the highly sterically hindered C-3 carbon could not accept the attack of the final water molecule. Thereby, the butadiene derivatives (**9**) were formed by dehydration.

When 2-alken-1-ols (**5**) were treated with 6N sulfuric acid in the presence of a small amount of sodium dodecyl sulfate (SDS), some 2-alken-1-ols gave 1-alken-3-ones in higher yield. For example, **5c** with SDS afforded **6c** in 86% yield (without SDS, 51%).



Scheme 3

In conclusion, the reaction of 3-(1-imidazolyl)-2-alken-1-ones (4) with organometallic compounds afforded only 3-(1-imidazolyl)-2-alken-1-ols (5) without any trace of the Michael addition product and the metal effect of the organometallic compound was rather small. By the treatment with sulfuric acid, 2-alken-1-ol derivatives (5) were converted into 1-alken-3-ones (6) through dehydration and hydrolysis. The resulting 1-alken-3-ones (6) were positional isomers with the 2-alken-1-ones (8) (Scheme 4).



Scheme 4

EXPERIMENTAL

The IR spectra were measured on a Jasco IRA-1 Infrared spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Hitachi R-24 and JEOL-100 spectrometer using tetramethylsilane as an internal standard. The vpc was recorded on a Shimadzu GC-4CM gas chromatography by using SE-30. High resolution mass spectra were measured on a JEOL DX-300 spectrometer.

General Procedure.

3-(1-Imidazolyl)-2-alken-1-one (4) (1 mmol) in tetrahydrofuran (5 ml) was added to an ethereal solution of organometallic compound (5 mmol). After the mixture was stirred for 1 h at room temperature, water was added to the reaction mixture and the product was extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, then the residue was treated with 6N sulfuric acid (2 ml) in chloroform (15 ml) in the presence or absence of SDS (10 mg) without purification. After reflux for 5 h, the reaction mixture was quenched with aqueous sodium hydrogen carbonate solution. The product was extracted with dichloromethane. After dryness over anhydrous magnesium sulfate, the yield of the product (6) was determined by gas chromatography. The configurations of products (E-, Z-) (6, 7, and 8) were to be found in the more stable forms.[5]

Reaction with Sodium Borohydride.

To a solution of (4) (1 mmol) in ethanol (20 ml), sodium borohydride (4 mmol) was added. After stirring for 4 h at room temperature, the reaction mixture was diluted with water, and the product was extracted with dichloromethane. After removal of the solvent, the residue was treated with 6 N sulfuric acid as noted above.

3-(1-Imidazolyl)-1-methyl-1-phenyl-2-buten-1-ol (5c).

Mp 113.5-114.5°C.

^{1}H-NMR (deuteriochroloform): δ 1.72 (s, 3H), 2.01 (d, 3H, J=1Hz), 5.03 (s, 3H), 6.05 (q, 1H, J=1Hz), 6.9-7.7 (m, 8H).

Ir (chloroform): ν max 1160, 1660, 3120 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.21. Found: C, 73.69; H, 6.96; N, 12.21.

4-(1-Imidazolyl)-2-methyl-3-phenyl-1,3-butadiene (9b).

Bp >200°C/10^{-3} mmHg.

^{1}H-NMR (deuteriochloroform): δ 1.51 (d, 3H, J=1Hz), 5.0-5.2 (3H, m), 6.7-7.6 (8H, m).

^{13}C-NMR (deuteriochloroform): δ 19.5 (q), 120.1 (s), 120.9 (d), 121.6 (t), 125.6 (d), 127.7 (d), 128.4 (d), 128.7 (d), 129.4 (d), 136.7 (s), 138.7 (d), 139.3 (s).

Ir (chloroform): ν max 899, 1592, 1680 cm^{-1}.

Exact mass: Calcd. for $C_{14}H_{14}N_2$: 210.1158. Found: 210.1157.

4-(1-Imidazolyl)-2,4-diphenyl-1,3-butadiene (9d).

Bp >200°C/10^{-3} mmHg.

^{1}H-nmr (deuteriochloroform): δ 5.15 (d, 1H, J=1Hz), 5.48 (s, 1H), 6.74 (t, 1H, J=1.5Hz), 6.8-7.7 (m, 13H).

^{13}C-nmr (deuteriochroloform): δ 118.5 (t), 118.6 (d), 119.9 (d), 120.9 (s), 123.8 (d), 125.7 (d), 126.2 (d), 126.5 (d), 126.9 (d), 127.9 (s), 128.2 (d), 128.8 (d), 129.2 (d), 129.5 (s), 136.8 (d), 137.1 (d), 138.0 (d), 138.1 (d), 142.9 (s).

Ir (chloroform): ν max 902, 1597, 1630 cm^{-1}.

Exact mass: Calcd. for $C_{19}H_{16}N_2$: 272.1315. Found: 272.1242.

REFERENCES AND NOTES

1. [a] C. Kashima and T. Tajima, Synthesis, 1980, 880; [b] C. Kashima, M. Shimizu, and T. Tajima, Heterocycles, 15, 961 (1981); [c] C. Kashima, T. Tajima, and Y. Omote, J. Heterocyclic Chem., 21, 171 (1984).
2. [a] C. Kashima, T. Tajima, M. Shimizu, and Y. Omote, J. Heterocyclic Chem., 19, 1325 (1982); [b] C. Kashima, Y. Konno, N. Yoshiwara, and T.Tajima, J. Heterocyclic Chem., 19, 1535 (1982); [c] C. Kashima, N. Yoshiwara, S. Shirai, and Y. Omote, Chem. Lett., 1982, 1455; [d] C. Kashima, T. Tajima, and Y. Omote, J. Heterocyclic Chem., 21, 133 (1984); [e] C. Kashima, A. Tsuzuki, and T. Tajima, J. Heterocyclic Chem., 21, 201 (1984); [f] C. Kashima, T. Tajima, C. Higuchi, and Y. Omote, J. Heterocyclic Chem., 21, 345 (1984).
3. C. Kashima, T. Tajima, and Y. Omote, Heterocycles, 20, 1811 (1983); [b] C. Kashima and Y. Omote, Heterocycles, 19, 1211 (1982).
4. E. P. Khohler, Am. Chem. J., 38, 511 (1907).

5. [a] Conaunt, and Tuttle, Org. Syn., 1, 53 (1921); [b] Georges Darzens, Compt. rend., 211, 435 (1940); [c] G. A. R. Konand, and E. A. Speight, J. Chem. Soc., 1926, 2727; [d] Wayne, and Adkins, Org. Syn., 21, 39 (1941); [e] E. P. Kohler, and Bryn Mawr Coll, Am. Chem. J., 42, 375; [f] A. Mailhe, Bull. Soc. Chim., 15, 324; [g] Kohler, and Chadwell, Org. Syn., 2, 1 (1922).

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