An Improved Synthesis of 3-(1-Imidazolyl)-2-alkenoic Acid Derivatives and Related Compounds

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The preparative method of 3-(1-imidazolyl)-2-alkenoic acid derivatives and the related compounds was improved by the use of strong bases such as sodium hydride in DMF. By this improved method, the preparation of 2-substituted 3-(1-imidazolyl)-2-alkenoic acid derivatives was accomplished in good yields.

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As the vinylogues of *N*-acylimidazoles and one of the 3-amino-2-en-1-ones having the heteroaromatic ring, we have investigated the preparative methods [1-5] and the chemical behaviors of 3-(1-imidazolyl)-2-alken-1-ones and the related compounds [3-11]. Four preparative methods enabled to give 3-(1-imidazolyl)-2-alken-1-ones and the 3-(1-imidazolyl)-2-alkenoic acid derivatives having the various substituents such as alkyl and aryl groups on C-1 and C-3 positions. In the treatment of 2,3-dibromoalkan-1-ones with imidazole in the presence of triethylamine, the dehydrobromination firstly proceeded to give 2-bromo-2-alken-1-ones, which converted into 3-(1-imidazolyl)-2-alken-1-ones through addition-elimination reaction. However, in the case of 2-substituted 2,3-dibromoalkan-1-ones, the dehydrobromination reaction did not proceed at all by the action of triethylamine owing to the lack of active methine proton. Therefore, the preparation of 2-substituted 3-(1-imidazolyl)-2-alken-1-ones and the related compounds still remained. Actually by the treatment with imidazole in the presence of triethylamine, methyl 2-methyl-2,3-dibromopropanoate (**IIa**) did not give any trace of *E*- or *Z*-isomer of methyl 3-(1-imidazolyl)-methacrylate (**IIIa** or **IVa**).

In general, an inactive alkyl halide can be dehydrohalogenated by strong bases such as sodium hydride and potassium *t*-butoxide. Also imidazolyl anion, which was easily formed from imidazole by the treatment with strong bases such as sodium hydride and potassium *t*-butoxide, should be much more active nucleophiles. Therefore, we undertook the preparation of 2-substituted 3-(1-imidazolyl)-2-alkenoic acid derivatives **III** and related compounds from 2-substituted 2,3-dibromoalkanoic acid derivatives **II** by the dehydrobromination or the substitution reaction under forced conditions using strong bases.

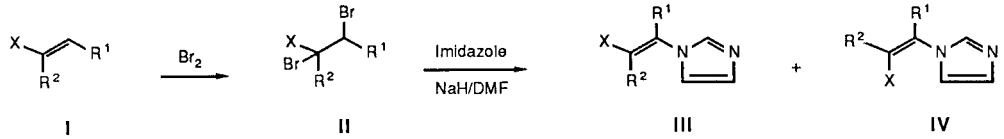
Actually, methyl methacrylate (**Ia**) was brominated to give **IIa**, which was treated with the imidazolyl anion in the presence of sodium hydride in DMF. From the spectral data and the elemental analysis, the product was shown to be **IIIa**, and traces of the *Z*-isomer **IVa** could not be detected. In the cases of methacrylonitrile (**Ie**) and acrylonitrile (**If**), the products were found to be an *E*- and

Table 1

Yields of R^1-CX=C(R^2)-$C_3H_3N_2$ **III** and **IV**

Product	Configuration	R^1	R^2	X	Yield NEt_3 [a]	Yield NaH [b]
IIIa	E	H	Me	COOMe	0	65
IIIb	E	H	H	COOMe	26	15
IIIc	E	Me	H	COOEt	43	76
IIId	E	Me	Me	COOMe	–	34
IIIe + IVe	E+Z	H	Me	CN	–	51
IIIf + IVf	E+Z	H	H	CN	15	60
IIIg	E	Me	H	CN	22	62
IIIh	E	H	Me	COPh	–	20

[a] Reaction was catalyzed by triethylamine [4]. [b] Reaction was catalyzed by sodium hydride.



I II III IV

a, R^1 = H, R^2 = Me, X = COOMe

b, R^1 = R^2 = H, X = COOMe

c, R^1 = Me, R^2 = H, X = COOEt

d, R^1 = R^2 = Me, X = COOMe

e, R^1 = H, R^2 = Me, X = CN

f, R^1 = R^2 = H, X = CN

g, R^1 = Me, R^2 = H, X = CN

h, R^1 = H, R^2 = Me, X = COPh

Z-mixture of 3-(1-imidazolyl)methacrylonitrile (**IIIe**) and 3-(1-imidazolyl)acrylonitrile (**IIIf**), respectively. Similarly, methyl *E*-3-(1-imidazolyl)acrylate (**IIIb**), ethyl *E*-3-(1-imidazolyl)crotonate (**IIIc**), methyl *E*-2-methyl-3-(1-imidazolyl)crotonate (**IIId**), *E*-3-(1-imidazolyl)crotononitrile (**IIIg**) and *E*-2-methyl-3-(1-imidazolyl)acrylophenone (**IIIh**) were prepared from methyl acrylate (**Ib**), ethyl crotonate (**Ic**), methyl 2-methylcrotonate (**Id**), crotononitrile (**Ig**) and 2-methylacrylophenone (**Ih**) respectively, in the yields listed in Table 1.

In conclusion, the preparation of 3-(1-imidazolyl)-2-alkenoic acid derivatives **III** and the related compounds from dibromo compounds **II** and imidazole was improved by the use of strong bases. Especially, this improved method was much useful for the preparation of 2-substituted 3-(1-imidazolyl)-2-alkenoic acid derivatives **III**.

EXPERIMENTAL

General Procedure.

To a suspension of sodium hydride (0.15 mole) in an anhydrous mixture of DMF (10 ml) and benzene (50 ml), imidazole (0.1 mole) was added. After the evolution of hydrogen ceased, the mixture was chilled in an ice-methanol bath. Then the benzene solution of 2,3-dibromo compound **II**, which was prepared by the bromine addition reaction from the corresponding 2-alkenoic acid derivative **I** (0.05 mole) in carbon tetrachloride was added slowly. After stirring overnight at room temperature, the mixture was quenched with water, and extracted with benzene. The organic layer was washed several times with water, and dried over anhydrous magnesium sulfate. The residue was chromatographed on a silica gel column with a chloroform-acetone-ethanol (100:10:2 v/v) mixture.

Methyl *E*-3-(1-Imidazolyl)methacrylate (**IIIa**).

This compound had mp 77.5-78.5° (from benzene-hexene); ir: 1710, 1640; pmr: δ 2.18 (d, 3H, J = 1.5 Hz), 3.87 (s, 3H), 7.22 (s, 1H), 7.31 (s, 1H), 7.85 (s, 1H), 7.97 (q, 1H, J = 1.5 Hz); cmr: δ 167.7 (s), 138.2 (d), 132.1 (d), 130.5 (d), 119.0 (d), 118.2 (s), 52.4 (q), 13.2 (q).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.06; N, 16.85. Found: C, 57.78; H, 6.00; N, 16.76.

Methyl *E*-2-Methyl-3-(1-imidazolyl)crotonate (**IIId**).

This compound had bp 130-140°/5 mm Hg; pmr: δ 1.80 (q, 3H, J = 1.2 Hz), 2.39 (q, 3H, J = 1.5 Hz), 3.82 (s, 3H), 6.97 (m, 1H), 7.12 (m, 1H), 7.53 (m, 1H); cmr: δ 167.8 (s), 139.8 (s), 135.8 (d), 129.0 (d), 123.9 (s), 117.9 (d), 51.5 (q), 21.4 (q), 15.0 (q).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.54. Found: C, 59.55; H, 6.84; N, 15.33.

E- and *Z*-Mixture of 3-(1-Imidazolyl)methacrylonitrile **IIIe** and **IVe**.

This compound had bp 130-140°/5 mm Hg; pmr: δ 2.09 (d, 2.2H, J = 1.5 Hz), 2.16 (d, 0.8H, J = 1.5 Hz), 7.15 (d, 1H, J = 1.0 Hz), 7.23 (m, 1H), 7.45 (m, 0.3H), 7.75 (m, 0.7H), 7.87 (s, 1H); cmr: δ 137.7 (d), 135.4 (d), 134.2 (d), 130.9 (d), 118.7 (d), 117.0 (d), 99.9 (s), 94.5 (s), 18.6 (q), 15.9 (q).

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.29; N, 31.55. Found: C, 62.89; H, 5.33; N, 31.41.

E-2-Methyl-3-(1-imidazolyl)acrylophenone (**IIIh**).

This compound had bp 100-110°/0.001 mm Hg; pmr: δ 2.27 (d, 3H, J = 1.5 Hz), 6.8-8.0 (m, 9H); cmr: δ 196.9 (s), 138.1 (d), 137.7 (s), 134.9 (d), 132.1 (d), 130.5 (d), 129.1 (d), 128.5 (d), 126.8 (s), 119.1 (d), 13.6 (q).

Anal. Calcd. for $C_{13}H_{12}N_2O$ 0.2H_2O: C, 72.32; H, 5.80; N, 12.98. Found: C, 72.32; H, 5.75; N, 13.07.

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