1,3-Dipolar Cycloaddition of Methyl 3-(1-Imidazolyl)acrylate and Related Compounds

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The 1,3-dipolar cycloaddition reaction of 1-vinylimidazole and β-(1-imidazolyl)-α,β-unsaturated carboxylic esters with *N*,α-diphenylnitrone and acetonitrile oxide was carried out and compared with those of β-pyrrolidinyl- and β-phenyl-α,β-unsaturated carboxylic esters. The imidazolyl moiety bonded to olefinic double bond was suggested to have properties intermediate to pyrrolidinyl and phenyl groups.

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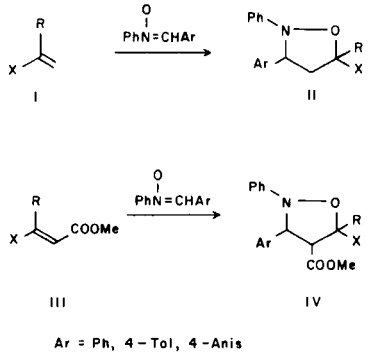
Since imidazole is regarded as an amine having aromaticity, *N*-vinylimidazole (I-d) is considered to be the analogue of both styrene and enamines. Similarly β-(1-imidazolyl)-α,β-unsaturated carbonyl compounds should be the analogues of β-phenyl- and β-amino-α,β-unsaturated carbonyl compounds.

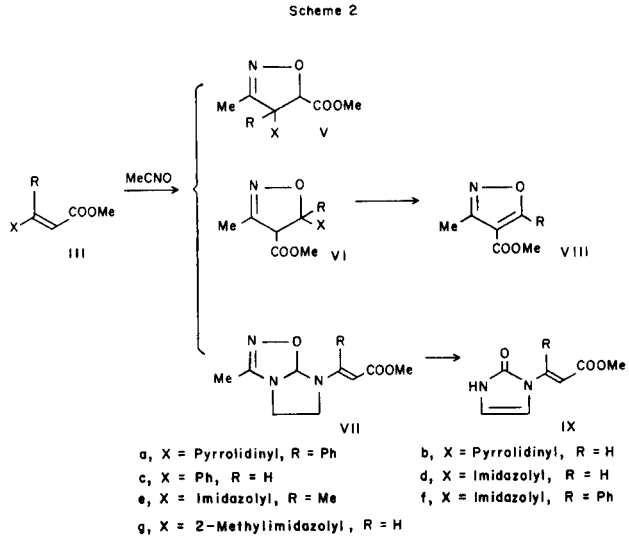
Recently, we have investigated the preparation and the nucleophilic reaction of β-(1-imidazolyl)-α,β-unsaturated carbonyl compounds [1-6]. As the results, β-(1-imidazolyl)-α,β-unsaturated carbonyl compounds exhibited the properties of conjugated carbonyl compounds having a very good leaving group. Moreover, β-(1-imidazolyl)-α,β-unsaturated carbonyl compounds showed the intermediate properties between β-phenyl- and β-amino-α,β-unsaturated carbonyl compounds in the nucleophilic reactions.

In the literature, it is widely reported that styrenes, enamines and methyl α,β-unsaturated carboxylic esters are useful 1,3-dipolarophiles [7]. For this reason, methyl 3-(1-imidazolyl)acrylate (III-d) and I-d are expected to be good 1,3-dipolarophiles. Houk and others reported that both steric and electronic factors were important to the regioselectivity of 1,3-dipolar cycloaddition of an unsymmetrical dipolarophile [8]. Therefore 1,3-dipolar cycloaddition of I-d and III-d will give the very important information on their chemical properties and electronic structure.

Scheme 1



Scheme 2



As a 1,3-dipole compound, the most remarkable features of *N*,α-diphenylnitrone are the convenience in preparation and purification but some steric effect exists in the cycloaddition. On the other hand, acetonitrile oxide shows less steric effect and convenience in product analysis in spite of the poor handling in preparation and purification.

Table 1

The 1,3-Dipolar Cycloaddition with Nitrones

Substrate	X [a]	Ar [a]	Conditions Temperature °C	Time hours	Product	Yield (%)	Ref
I-a	Py	Ph	60	1	II-a	48	9
I-c	Ph	Ph	60	40	II-c	82	10
I-d	Im	Ph	130	48	II-d	62	
I-d	Im	Tol	130	48	II-d	58	
I-d	Im	Anis	130	48	II-d	50	
III-b	Py	Ph	80	48	no reaction		
III-c	Ph	Ph	80	48	IV-c	70	11
III-d	Im	Ph	130	60	IV-d	39	

[a] Py = 1-Pyrrolidinyl, Im = 1-Imidazolyl, Tol = 4-Methylphenyl, Anis = 4-Methoxyphenyl.

Table 2

The 1,3-Dipolar Cycloaddition with Acetonitrile Oxide

Substrate		Conditions		Products (Yield, %)	Ref
	X [a]	Temperature °C	Time hours		
III-b	Py	80	0.5	VIII (85)	12
III-c	Ph	rt	16	V-c (9) + VI-c (36)	13
III-d	Im	130	3	IX-d (7)	
III-e	Im	130	3	IX-e (23)	
III-f	Im	130	3	IX-f (11)	
III-g	MeIm	130	3	VIII (27)	

[a] Py = 1-Pyrrolidinyl, Im = 1-Imidazolyl, MeIm = 2-Methyl-1-imidazolyl.

Although many 1,3-dipole compounds are available, *N*,α-diphenylnitrone and acetonitrile oxide are therefore suitable for studying the chemical behaviors of imidazole derivatives. Here, we examined the 1,3-dipolar cycloaddition of 1-vinylimidazole (I-d), methyl 3-(1-imidazolyl)acrylate (III-d), -crotonoate (III-e) and -cinnamate (III-f) with *N*,α-diphenylnitrone and acetonitrile oxide.

When I-d was heated with *N*,α-diphenylnitrone in benzene, the 1,3-dipolar cycloaddition product was formed in moderate yield. From the ir and nmr spectral data and elemental analysis, the product was found to be 5-(1-imidazolyl)-2,3-diphenylisoxazolidine (II-d, Ar = Ph) and no other product was detected. Compared with 1-phenyl-1-(1-pyrrolidinyl)ethylene (I-a) and styrene (I-c), the 1,3-dipolar cycloaddition of I-d proceeded slowly. However, the regioselectivity of the reaction was analogous to those of I-a and I-c. Similarly, α-(*p*-tolyl)- and α-(*p*-anisyl)-*N*-phenylnitrone were treated with I-d to afford 1,3-dipolar cycloaddition products, II-d (Ar = Tol) and II-d (Ar = Anis), respectively. The yields are summarized in Table 1.

Although it was reported that the reaction of *N*,α-diphenylnitrone with methyl cinnamate (III-c) gave the cycloaddition product (IV-c) in good yield [11], methyl 3-(1-pyrrolidinyl)acrylate (III-b) could not give any product by the treatment with *N*,α-diphenylnitrone. In the case of methyl 3-(1-imidazolyl)acrylate (III-d), the cycloaddition product was formed relatively slowly in the reaction with *N*,α-diphenylnitrone. From the spectral and elemental analysis, the product was deduced to be methyl 5-(1-imidazolyl)-2,3-diphenylisoxazolidinecarboxylate (IV-d, Ar = Ph). This cycloadition occurred with the same regioselectivity as in the case of III-c. These facts showed that the chemical behaviors of III-d in 1,3-dipolar cycloaddition was intermediate between those of III-b and III-c.

Next, III-d was treated with acetonitrile oxide, which was prepared from nitroethane *in situ*. From the spectral and elemental analysis, the product was found to be methyl 3-(2-oxo-2,3-dihydro-1-imidazolyl)acrylate (IX-d), and none of the expected isoxazoline or isoxazole products were isolated. Similar products were obtained in the reaction of acetonitrile oxide with methyl 3-(1-imidazolyl)crotonoate (III-e) and 3-(1-imidazolyl)cinnamate (III-f). From the fact that the oxygen atom was introduced into the C-2 position of the imidazole ring, the reaction mechanism for the formation of IX was speculated as follows. The cycloaddition of acetonitrile oxide to the relatively active C=N double bond of the imidazole ring formed the cycloadduct VII. Then the ring of VII was opened by the elimination of acetonitrile and formed IX. Further, the methyl substituent group on C-2 of imidazole should delay the cycloaddition of acetonitrile oxide on the imidazole ring. From these speculations, methyl 3-(2-methyl-1-imidazolyl)acrylate (III-g) was treated with acetonitrile oxide at 130°. By the comparison of the spectral data, the product was identified as methyl 3-methylisoxazole-4-carboxylate (VIII), which was prepared authentically from methyl 3-(1-pyrrolidinyl)acrylate (III-b) according to the method of Stork [12]. In this reaction, methyl 5-(2-methyl-1-imidazolyl)-3-methyl-2-isoxazoline-4-carboxylate (VI-g) should be the intermediate product, which was easily converted by the elimination of imidazole. By comparing this result with the fact that the regioisomeric mixture of methyl 4-phenyl-3-methyl-2-isoxazoline-5-carboxylate (V-c) and methyl 5-phenyl-3-methyl-2-iosoxazoline-4-carboxylate (VI-c) was formed by the reaction of acetonitrile oxide with methyl cinnamate (III-c), the chemical behavior of III-g was also intermediate between those of III-b and III-c.

In conclusion, the imidazolyl moiety bonded to olefinic double bond shows properties analogous to the phenyl and pyrrolidinyl group in the 1,3-dipolar cycloaddition reaction. Further, β-(1-imidazolyl)-α,β-unsaturated carboxylic esters seems to have the electronic structure intermediate between those of β-amino- and β-phenyl-α,β-unsaturated carboxylic esters.

EXPERIMENTAL

Materials.

According to the method reported in previous papers [2-3], methyl 3-(1-imidazolyl)acrylate (III-d), 3-(1-imidazolyl)crotonoate (III-e) and 3-(1-imidazolyl)cinnamate (III-f) were prepared. Also methyl 3-(2-methyl-1-imidazolyl)acrylate (III-g) was similarly prepared from methyl acrylate and 2-methylimidazole.

Methyl 3-(2-Methyl-1-imidazolyl)acrylate (III-g).

This compound had mp 91-92° (from benzene-hexane), yield 15% as the mixture of *E* and *Z* isomers; ir; 1720, 1650; nmr: δ 2.22 and 2.93 (s, 3H), 3.67 and 3.71 (s, 3H), 5.7-7.8 (m, 4H).

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.06; N, 16.85. Found: C, 57.44; H, 6.09; N, 16.77.

1,3-Dipolar Cycloaddition with Nitrones.

The mixture of 1,3-dipolarophile (1.2 mmoles) and nitrone (1.0 mmoles) in benzene (20 ml) was heated for 25 hours at 130° in a sealed tube. The reaction mixture was diluted with dichloromethane, washed with water and dried over anhydrous magnesium sulfate. After removal

of the solvent, the residue was chromatographed on silica gel with hexane-ethyl acetate mixture (1:4).

5-(1-Imidazolyl)-2,3-diphenylisoxazolidine (II-d, Ar = Ph).

This compound had mp 121-122° (from benzene-hexane), yield 62%; ir 1595; pmr: δ 2.5-2.8 (m, 1H), 3.1-3.5 (m, 1H), 4.65 (d-d, 1H, J = 8.6, 7.1 Hz), 6.07 (d-d, 1H, J = 7.6, 4.2 Hz), 6.9-7.4 (m, 12H), 7.66 (s, 1H); cmr: δ 46.20 (t), 69.15 (d), 83.43 (d), 117.00 (d), 123.58 (d), 126.50 (d), 127.87 (d), 128.59 (d), 128.90 (d), 129.87 (d), 136.00 (d), 139.12 (s), 148.82 (s).

Anal. Calcd. for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.42; H, 5.97; N, 14.15.

5-(1-Imidazolyl)-3-(4-methylphenyl)-2-phenylisoxazolidine (II-d, Ar = Tol).

This compound had mp 167-168° (from benzene-hexane), yield 58%; ir: 1590, 1485; pmr: δ 2.34 (s, 3H), 2.5-2.8 (m, 1H), 3.1-3.5 (m, 1H), 4.61 (t, 1H, J = 7.8 Hz), 6.10 (d-d, 1H, J = 7.8, 4.4 Hz), 6.8-7.4 (m, 11H), 7.71 (s, 1H); cmr: δ 21.05 (q), 46.49 (t), 69.15 (d), 83.47 (d), 117.05 (d), 117.25 (d), 123.63 (d), 126.50 (d), 128.59 (d), 129.67 (d), 129.82 (d), 136.00 (s), 136.00 (d), 137.71 (s), 148.92 (s).

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.72; H, 6.27; N, 13.76. Found: C, 74.82; H, 6.27; N, 13.64.

5-(1-Imidazolyl)-3-(4-methoxyphenyl)-3-phenylisoxazolidine (II-d, Ar = Anis).

This compound had mp 121-122° (from benzene-hexane), yield 48%; ir: 1605, 1590, 1580, 1505; pmr: δ 2.4-2.8 (m, 1H), 3.1-3.5 (m, 1H), 3.75 (s, 3H), 4.55 (t, 1H, J = 8.0 Hz), 6.06 (d-d, 1H, J = 7.5, 4.0 Hz), 6.7-7.4 (m, 1H), 7.68 (s, 1H); cmr: δ 46.26 (t), 55.02 (q), 68.95 (d), 83.33 (d), 114.22 (d), 116.95 (d), 117.25 (d), 123.63 (d), 127.77 (d), 128.50 (d), 129.82 (d), 130.64 (s), 135.95 (d), 148.82 (s), 159.10 (s).

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.00; H, 5.95; N, 13.07. Found: C, 71.27; H, 5.99; N, 12.87.

Methyl 5-(1-Imidazolyl)-2,3-diphenylisoxazolidine-4-carboxylate (IV-d, Ar = Ph).

This compound was obtained in a yield of 39%, ir: 1740, 1600; pmr: δ 3.68 (s, 3H), 3.85 (d-d, 1H, J = 8.0, 4.0 Hz), 4.88 (d, 1H, J = 8.0 Hz), 6.40 (d, 1H, J = 4.0 Hz), 6.9-7.7 (m, 12H), 7.87 (s, 1H); cmr: δ 52.43 (q), 64.41 (d), 72.33 (d), 85.07 (d), 116.48 (d), 118.01 (d), 124.23 (d), 126.75 (d), 128.11 (d), 128.28 (d), 128.63 (d), 129.81 (d), 135.62 (d), 136.85 (s), 147.25 (s), 169.02 (s).

Anal. Calcd. for $C_{20}H_{19}N_3O_3 \cdot 0.5H_2O$ [14]: C, 67.01; H, 5.64; N, 11.73. Found: C, 67.35; H, 5.47; N, 11.49.

The 1,3-Dipolar Cycloaddition with Acetonitrile Oxide.

1,3-Dipolarophile (10 mmoles) in chloroform (10 ml) was added to the chloroform solution of acetonitrile oxide, which was prepared *in situ* from nitroethane (14 mmoles) and phosphoryl chloride (10 mmoles) in the presence of triethylamine (2.5 ml). The mixture was heated for 3 hours at 130° in a sealed tube. After the chloroform solution was washed with water and dried over anhydrous magnesium sulfate, the solvent was removed. The residue was chromatographed on silica gel with the mixture of chloroform-acetone-ethanol (100:20:4). The fraction of cycloadduct was recrystallized.

Methyl 3-(2-Oxo-2,3-dihydro-1-imidazolyl)acrylate (IX-d).

This compound had mp 188-190° (from ethanol), yield 7%; pmr: δ 3.8 (s, 3H), 5.83 (d, 1H, J = 14.0 Hz), 6.5-6.7 (m, 2H), 7.98 (d, 1H, J = 14.0 Hz).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.79; N, 16.65. Found: C, 49.67; H, 4.80; N, 16.38.

Methyl 3-(2-Oxo-2,3-dihydro-1-imidazolyl)crotonoate (IX-e).

This compound had mp 170-171.5° (from benzene-hexane), yield 23%; ir: 3160, 1730, 1620; pmr: δ 2.62 (d, 3H, J = 1.0 Hz), 3.73 (s, 3H), 6.4-6.5 (m, 2H), 6.74 (q, 1H, J = 1.0 Hz), 10.80 (s, 1H); cmr: δ 16.44 (q), 51.12 (q), 106.74 (d), 109.02 (d), 110.02 (d), 148.54 (s), 153.70 (s), 167.73 (s).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.37. Found: C, 52.86; H, 5.55; N, 15.23.

Methyl 3-(2-Oxo-2,3-dihydro-2-imidazolyl)cinnamate (IX-f).

This compound had mp 206-207° (from ethanol), yield 11%; ir: 3110, 1720, 1625; pmr: δ 3.61 (s, 3H), 6.2-6.3 (m, 2H), 6.5 (m, 1H), 7.44 (s, 5H), 10.21 (s, 1H); cmr: δ 51.02 (q), 109.14 (d), 111.84 (d), 112.90 (d), 127.28 (d), 128.69 (d), 130.46 (d), 135.33 (s), 144.19 (s), 152.18 (s), 164.21 (s).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.46. Found: C, 63.76; H, 4.90; N, 11.31.

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[14] Since the oily compound IV-d (Ar = Ph) was unstable at the elevated temperature, the complete removal of the solvent was difficult without decomposition.