The Compounds Related to 3-(1-Imidazolyl)-2-alken-1-ones. Preparation and Reactions

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Compounds related to 3-(1-imidazolyl)-2-alken-1-ones, 3-(1-imidazolyl)-2-alkenoic acid derivatives and 2-alken-1-ones having heterocycles on the C-3 carbon were prepared. The reaction of nucleophiles with these compounds was also discussed.

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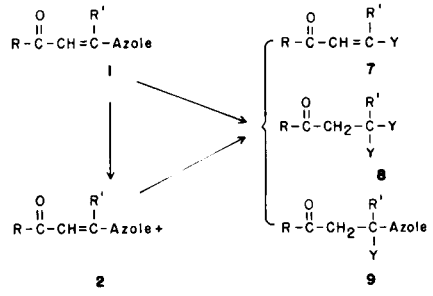
Although the *N*-acylimidazoles have been extensively studied as acylating reagents, the vinylogues of *N*-acylimidazoles, the 3-(1-imidazolyl)-2-alken-1-ones (**1**), have scarcely been studied. Previously we reported the preparation of **1** by the treatment of 3-chloro-2-alken-1-ones and 2-alkyn-1-ones with imidazole in the presence of triethylamine [1]. However, the starting materials, 3-chloro-2-alken-1-ones and 2-alkyn-1-ones, are often hard to prepare and handle. Since a new preparative method of **1** was further developed from 2,3-dibromoalkan-1-ones by the treatment with imidazole in the presence of triethylamine, 3-(1-imidazolyl)-2-alken-1-ones having various substituent groups on the enone system were conveniently prepared in good yield [2].



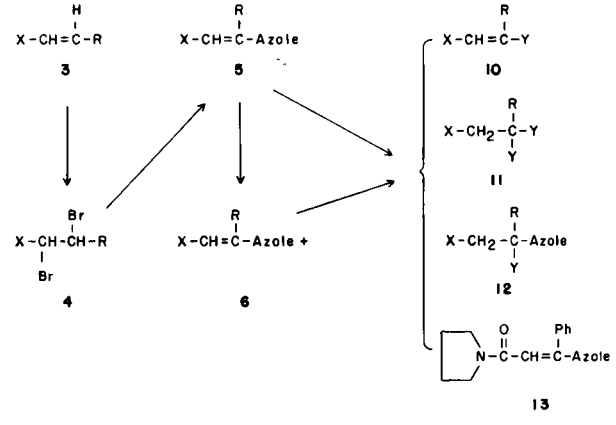
a,	R = Ph	R′ = Me	Azole = 1-Benzimidazolyl
b,	R = Ph	R′ = Me	Azole = 1-Pyrazolyl
c,	R = Ph	R′ = Me	Azole = 1-(3-Methyl)pyrazolyl
d,	R = Ph	R′ = Me	Azole = 1-(3,5-Dimethyl)pyrazolyl
e,	R = Ph	R′ = Me	Azole = 1-(1,2,4-Triazolyl)
f,	R = Ph	R′ = Me	Azole = 1-Imidazolyl
g,	R = Ph	R′ = Me	Azole = 1-(2-Methyl)imidazolyl
h,	R = Ph	R′ = Me	Azole = 1-(4-Hydroxy)pyridyl
i,	R = Me	R′ = Me	Azole = 1-Benzimidazolyl
j,	R = Me	R′ = Me	Azole = 1-Pyrazolyl
k,	R = Me	R′ = Me	Azole = 1-(3,5-Dimethyl)pyrazolyl
l,	R = Me	R′ = Me	Azole = 1-Imidazolyl
m,	R = Me	R′ = Me	Azole = 1-(2-Methyl)imidazolyl
n,	R = Me	R′ = Me	Azole = 1-(4-Methyl)imidazolyl
o,	R = Ph	R′ = Ph	Azole = 1-Imidazolyl
p,	R = Ph	R′ = H	Azole = 1-Imidazolyl
q,	R = Me	R′ = Ph	Azole = 1-Imidazolyl
r,	R = Me	R′ = H	Azole = 1-Imidazolyl
s,	R = Me	R′ = Me	Azole = 1-(3-Ethyl)imidazolium
t,	R = Me	R′ = Me	Azole = 1-(3-Phenacyl)imidazolium

Furthermore, we have investigated the reaction of **1** with nucleophiles and electrophiles. In the case of nucleophiles such as alcohols, amines, thiols and phenols, **1** gave various 3-hetero-substituted-2-alken-1-ones regioselectively by the displacement of the imidazolyl group by the nucleophiles. When **1** was treated with methyl iodide, the corresponding methiodide salts **2** of **1** were formed in good yield. The reaction of **1** with nucleophiles was activated by conversion to **2**, since the formation of the cationic molecule decreases the electron density at the C-3 carbon atom of the enone system [3,4].

From these facts, it was decided that it would be interesting to investigate the preparation and the reaction of various compounds related to **1** such as 3-(1-imidazolyl)-2-alkenoic acid derivatives. Also investigation concerning the enones having various heterocycles at the C-3 carbon was undertaken.

Results and Discussion.

Preparation of 3-(1-Imidazolyl)-2-alkenoic Acid Derivatives.



a,	R = Ph	X = COOMe	Azole = 1-Imidazolyl
b,	R = H	X = COOMe	Azole = 1-Imidazolyl
c,	R = Me	X = COOMe	Azole = 1-Imidazolyl
d,	R = Ph	X = CN	Azole = 1-Imidazolyl
e,	R = H	X = CN	Azole = 1-Imidazolyl
f,	R = Me	X = CN	Azole = 1-Imidazolyl
g,	R = COOMe	X = COOMe	Azole = 1-Imidazolyl

Table 1

Yields, Melting Points and Elemental Analyses of **5**

Compound	R	X	Yield (%)	Mp (°C)	Found (%) C	H	N	Calcd. (%) C	H	N
5a	Ph	COOMe	73	102-103	68.19	5.29	12.24	68.40	5.29	12.27
5b	H	COOMe	26	121-122	55.07	5.29	18.38	55.25	5.29	18.41
5c	Me	COOMe	43	88-89	57.85	6.08	16.83	57.82	6.06	16.85
5d	Ph	CN	46	107-108	73.79	4.61	21.54	73.82	4.64	21.52
5e	H	CN	15	113-115	60.37	4.15	35.14	60.49	4.23	35.27
5f	Me	CN	22	79-80	63.01	5.28	31.74	63.14	5.29	31.55
5g	COOMe	COOMe	29	80-81	51.48	4.70	13.31	51.42	4.79	13.32

Table 2

IR and NMR Spectra of **5**

Compound	Configuration	IR (cm^{-1})	NMR (δ)
5a	E	1720, 1635	3.67, 6.26, 6.96, 7.20, 7.3-7.6, 7.64
5b	E	1705, 1645	3.80, 6.08, 7.19, 7.27, 7.81, 7.94
5c	E	1700, 1640	2.18, 3.71, 6.03, 7.10, 7.28, 7.92
5d	E	2210, 1615	5.60, 7.2-7.6, 7.81
5e	E + Z	2215, 1645	5.18, 5.73, 7.2-8.1
5f	E	2215, 1625	2.56, 5.56, 7.18, 7.30, 7.92
5g	E	1735, 1715, 1635	3.80, 3.99, 6.17, 7.20, 7.76

According to the newly developed method, methyl 3-phenyl-2,3-dibromopropionate (**4a**) was easily prepared from methyl cinnamate (**3a**) by the addition of bromine. Compound **4a** was then treated with imidazole in the presence of triethylamine. After the usual work up, methyl 3-(1-imidazolyl)cinnamate (**5a**) was obtained in 73% yield based on **3a**. Similarly, methyl acrylate (**3b**), methyl crotonate (**3c**), cinnamonitrile (**3d**), acrylonitrile (**3e**), and crotononitrile (**3f**) were converted into the corresponding 3-(1-imidazolyl) derivatives as summarized in Table 1. From the spectral data summarized in Table 2, these compounds all had the E-configuration except **5e**. In the case of either dimethyl fumarate (**3g**) or maleate (**3h**), the product was found to be 2-(1-imidazolyl)fumarate (**5g**).

Preparation of 2-Alken-1-ones having Heterocycles.

The reaction of various heterocycles other than imidazole such as pyrrole, indole, pyrazole, triazole, benzimidazole, 2-pyridone and 4-pyridone with 3-chloro-2-alken-1-ones and 2,3-dibromoalken-1-ones were examined. Enones were obtained when heterocycles having p*K*a′ [5] values larger than 2 were used. That is, 3-(1-pyrazolyl)-, 3-(1-benzimidazolyl)-, and 3-[1-(4-oxopyridyl)]-2-alken-1-ones were prepared in good yield. When 1,2,4-triazole was treated with 1-phenyl-3-chloro-2-buten-1-one the product was not 3-(4-triazolyl)- compound, but 3-(1-triazolyl)-1-phenyl-2-buten-1-one (**1e**). However, the heterocycles possessing p*K*a′ values less than 2 such as pyrrole, indole and 2-pyridone, did not react at all to give any expected product. The yields and the elemental analyses of these products are summarized in Table 3.

Table 4 provides the nmr data proving the E-configuration of the enone system.

Reaction with Alkyl Halides.

In order to estimate the reactivities of **1** and **5** with electrophiles, the p*K*a′ values of the conjugate acids **1** and **5** were measured by means of titration with base in an aqueous methanol solution listed in Table 5. The p*K*a′ values of 3-(1-imidazolyl)-, 3-(1-benzimidazolyl)- and 3-(1-triazolyl)-2-alken-1-ones and 2-alkenoic acid derivatives were all found to be larger than 2.3. In the case of 3-(1-pyrazolyl)-2-alken-1-ones, the p*K*a′ values could not be measured by this method because of its small p*K*a′ value.

Next, the compounds **1** and **5** were treated with methyl iodide. The basic compounds having p*K*a′ values larger than 2.3 gave the corresponding methiodide salts (**2** and **6**). By treatment with ethyl iodide and phenacyl bromide in an acetonitrile solution, the corresponding salts were also obtained in good yields. However, the 3-(1-pyrazolyl)-2-alken-1-ones did not give any methiodide salt even under forced conditions.

Reaction of 3-Azolyl-1-phenyl-2-buten-1-ones with Nucleophiles.

When all of the 3-(1-imidazolyl)-2-alken-1-ones and their methiodide salts were treated with nucleophiles, 3-hetero-substituted 2-alken-1-ones were obtained by Michael type addition of the nucleophile followed by elimination of imidazole. Whereupon 1-phenyl-2-buten-1-ones having various azole and azolium groups were treated with nucleophiles. The results were summarized in Table 7, comparing 1-phenyl-3-(1-imidazolyl)-2-buten-1-one (**1f**) with its methiodide salt (**2f**). In all cases, the replacement of the imidazolyl group with nulceophiles occurred similar to what occurred with **1** and **2**. However, in the case of 1-pyr-

Table 3

Yields, Melting Points and Elemental Analyses of **1**

	Compound R	Azole [a]	Yield (%)	Mp (Bp) (°C)	Found (%) C	H	N	Calcd. (%) C	H	N
1a	Ph	BenzIm	54	71-72	77.92	5.37	10.69	77.84	5.37	10.67
1b	Ph	Pyra	46	77-78	73.40	5.62	13.07	73.57	5.70	13.20
1c	Ph	3-Me-Pyra	65	74-75	74.31	6.18	12.42	74.31	6.23	12.38
1d	Ph	3,5-Me-Pyra	39	(170/3)	74.91	6.75	11.77	74.97	6.71	11.65
1e	Ph	1,2,4-Triaz	31	87-88	67.55	5.18	19.66	67.59	5.19	19.70
1f	Ph	Im	70	60-65						
1g	Ph	2-Me-Im	35	112-113	74.17	6.24	12.34	74.31	6.23	12.38
1h	Ph	4-HO-Pyri [b]	36	122-124	70.17	5.82	5.44	70.02	5.88	5.44
1i	Me	BenzIm	56	108-109	72.14	6.05	14.07	71.97	6.04	13.99
1j	Me	Pyra	16	44-45	63.87	6.66	18.73	63.98	6.71	18.65
1k	Me	3,5-Me-Pyra	44	(140/3)	67.28	7.95	15.95	67.38	7.91	15.71
1l	Me	Im	53	80-81						
1m	Me	2-Me-Im	50	61-62	65.49	7.34	17.04	65.83	7.36	17.06
1n	Me	4-Me-Im	81	62-64	65.54	7.38	17.00	65.83	7.36	17.06

[a] BenzIm: Benzimidazolyl, Pyra: Pyrazolyl, Triaz: Triazolyl, Im: Imidazolyl, Pyri: Pyridyl. [b] The molecular formula of **1h** was $C_{15}H_{13}NO_2 \cdot H_2O$.

Table 4

NMR Spectral Data of **1**

Compound	NMR (δ)
1a	2.83, 7.1-8.2, 8.23
1b	2.80, 6.50, 7.3-8.2
1c	2.31, 2.74, 6.22, 7.3-8.2
1d	2.22, 2.38, 2.72, 5.98, 6.93, 7.3-7.6, 7.8-8.1
1e	2.77, 7.4-8.0, 7.77, 8.08, 8.58
1f	2.74, 7.10, 7.4-8.1, 7.23
1g	2.51, 2.59, 6.89, 7.02, 7.3-7.7, 7.8-8.1
1h	2.63, 6.40, 6.95, 7.4-8.1
1i	2.32, 2.73, 6.56, 7.2-7.9, 8.17
1j	2.26, 2.72, 6.55, 7.18, 7.79, 8.00
1k	2.19, 2.22, 2.33, 2.61, 5.94, 6.23
1l	2.32, 2.69, 6.43, 7.18, 7.39, 7.90
1m	2.25, 2.39, 2.50, 6.28, 6.88, 7.00
1n	2.26, 2.29, 2.65, 6.38, 7.06, 7.88

azolyl derivatives, the reaction ceased at the Michael type addition step to afford 3-hetero-substituted 1-phenyl-3-(1-pyrazolyl)butan-1-ones (**9**).

Nucleophilic Reaction of 3-(1-Imidazolyl)-2-alkenoic Acid Derivatives.

The nucleophilic reactions of methyl 3-(1-imidazolyl)-cinnamate (**5a**), acrylate (**5b**), crotonate (**5c**), and their methiodide salts were carried out. Also the corresponding nitriles were treated with nucleophiles. From the results listed in Table 8 and 9, the reactivities of these compounds seemed to be lower than that of the enones. Especially, in the case of thiols, the elimination of imidazole was retarded by the change of the ketone to an ester or nitrile group. Moreover, when methyl 3-(1-imidazolyl)cinnamate (**5a**) was treated with pyrrolidine, 3-(1-imidazolyl)cinnamic acid

Table 5

The p*Ka'* Values of **1**, **5** and Related Heterocycles [c]

Compound	p*Ka'*	Reference	Compound	p*Ka'*	Reference
Imidazole	7.05	[a]	2-Methylimidazole	7.85	[a]
1-Acetylimidazole	3.60	[a]	4-Methylimidazole	7.51	[a]
1-Vinylimidazole	5.14		Benzimidazole	5.4	[a]
1o	4.15		**1a**	2.80	
1f	4.05		3,5-Dimethylpyrazole	4.38	[a]
1p	3.50		3-Methylpyrazole	3.56	[a]
1q	4.43		4-Pyridone	3.27	[a]
1l	4.18		Pyrazole	2.48	[a]
1r	3.60		**1b**	2.2 >	
5a	4.41		1,2,4-Triazole	2.30	[a]
5b	4.18		**1e**	2.35	
5c	3.59		2-Pyridone	0.75	[a]
			Pyrrole	−0.27	[b]
			Indole	−2.4	[a]

[a] Referred in ref [5]. [b] Referred in ref [6]. [c] The p*Ka'* refers to the dissociation constant of the conjugated acid of each compound.

Table 6

Yields, Melting Points and Elemental Analyses of **2** and **6**

	Compound R	Compound X	Azolium [a]	Yield (%)	Mp (°C)	Found (%) C	Found (%) H	Found (%) N	Calcd. (%) [b] C	Calcd. (%) [b] H	Calcd. (%) [b] N
2a	Me	Bz	3-Me-BenzIm+	72	208-209	52.71	4.20	6.59	52.31	4.39	6.77
2b	Me	Bz	2-Me-Pyra+	0							
2e	Me	Bz	4-Me-1,2,4-Triaz+	70	170-172	43.03	4.31	11.70	42.87	4.15	11.54
2s	Me	Ac	3-Et-Im+	66	184-185	39.12	4.93	9.12	39.23	4.93	9.15
2t	Me	Ac	3-($BzCH_2$)−Im+	77	102-105	52.38	5.23	7.67	52.32	5.22	7.63
6a	Ph	COOMe	3-Me-Im+	87	204-206	45.41	4.06	7.62	45.42	4.08	7.56
6b	H	COOMe	3-Me-Im+	80	211-212	32.66	3.77	9.51	32.67	3.77	9.52
6c	Me	COOMe	3-Me-Im+	89	163-164	34.94	4.17	9.07	35.08	4.25	9.09
6d	Ph	CN	3-Me-Im+	79	266-268	46.25	3.57	12.48	46.31	3.58	12.46
6f	Me	CN	3-Me-Im+	75	190-191	34.83	3.67	15.17	34.92	3.66	15.27

[a] BenzIm+: Benzimidazolium, Pyra+: Pyrazolium, Triaz+: Triazolium, Im+: Imidazolium. [b] The molecular formulas of **2a**, **2e** and **2t** were $C_{18}H_{17}N_2OI \cdot 0.5H_2O$, $C_{13}H_{14}N_3OI \cdot 0.5H_2O$ and $C_{16}H_{17}N_2O_2Br \cdot H_2O$, respectively.

Table 7

Nucleophilic Reaction of **1** and **2**

Substrate	Nucleophile	Yield (%) **7**	**8**	**9**
1a	EtSH	22	8	
	PhSH	70		
	MeONa	46	24	
	Pyrrolidine	70		
2a	EtSH	45	15	
	PhSH	30		
	MeONa	34		
	MeOH	25		
1b	EtSH			75
	PhSH			80
	MeONa	56		
	Pyrrolidine	77		
1d	EtSH		10	54
	PhSH	26		
	MeONa	46	25	
	Pyrrolidine	70		
1e	EtSH	10	12	
	PhSH	82		
	MeONa	46	21	
	Pyrrolidine	78		
2e	EtSH	27	9	
	PhSH	33		
	MeONa	17	7	
	MeOH	8		
	p-Tol-OH	10		
1f	EtSH	73		
	PhSH	22		
	MeONa	14		
	Pyrrolidine	26		
2f	EtSH	72		
	PhSH	96		
	MeONa	41		
	Pyrrolidine	44		

Table 8

Nucleophilic Reaction of **5** and **6**

Substrate	Nucleophile	Yield (%) **10**	**11**	**12**	**13**
5c	EtSH			65	
	PhSH			80	
	MeONa	71			
	Pyrrolidine	42			
6c	EtSH	79			
	PhSH	42			
	Pyrrolidine	27			
5b	EtSH			74	
	PhSH			70	
	Pyrrolidine	50			
6b	EtSH	46	23		
	PhSH		69		
	Pyrrolidine	65			
5a	EtSH			76	
	PhSH			27	
	MeONa	21			
	Pyrrolidine	17			31
6a	EtSH	79			
	PhSH	83			
	MeONa	21			

pyrrolidinylamide (**13**) was formed in 31% yield as well as methyl 3-(1-pyrrolidinyl)cinnamate (**10a**). This fact showed that the nucleophilic reaction was governed by the steric hindrance on the C-3 carbon.

Conclusion.

By the previously reported methods, various compounds related to 3-(1-imidazolyl)-2-alken-1-ones were prepared. In the case of heterocycles having the p*Ka'* values larger than 2.3, the corresponding 3-azolyl-2-alken-1-ones were prepared. The reaction with methyl idodide proceeded with 3-(1-imidazolyl)-, 3-(1-triazolyl)- and 3-(1-benzimidazolyl) derivatives. These compounds were treated with various nucleophiles similar to 3-(1-imidazolyl)-2-alken-1-ones.

Table 9

Nucleophilic Reaction of **5** and **6**

Substrate	Nucleophile	Yield (%)		
		10	**11**	**12**
5f	EtSH			70
	PhSH			73
	MeONa	57	10	
	Pyrrolidine	61		
6f	EtSH	71		
	PhSH	95		
	MeOH	37		
5e	EtSH	43		
	PhSH	73		
5d	EtSH			65
	PhSH	45		
6d	EtSH	72		
	PhSH	71		
	Pyrrolidine	56		

EXPERIMENTAL

General Preparation of **1** and **5**.

According to the method reported previously, compounds **5** were prepared from corresponding 2-alkenoic acid derivatives by bromination and then treatment with imidazole in the presence of triethylamine. Compounds **1** were prepared from 1-phenyl-1,3-butanedione and 2,4-pentanedione by the chlorination with carbon tetrachloride-triphenyl phosphine followed by the treatment with heterocycles in the presence of triethylamine.

General Procedure in the Reaction with Alkyl Halides.

Generally, compounds **1** and **5** were dissolved in excess amounts of methyl iodide and the solution was heated at 100° for 30 minutes in a sealed tube. The reaction mixture was concentrated and the residue was recrystallized from ethanol. In the case of ethyl iodide and phenacyl bromide, **11** and an equimolar amount of halide were dissolved in acetonitrile and refluxed for 5 hours. After concentration of the solvent, the residue was recrystallized from an ethanol-ethyl acetate mixture.

General Procedure of Nucleophilic Reaction of **1, 2, 5** and **6**.

The substrate (**1, 2, 5** or **6**) and the nucleophiles were dissolved in methanol in the presence of triethylamine, and the mixture was stirred for 2 hours at room temperature. The products were purified by silcia gel column chromatography. In the case of sodium methoxide, the substrate was dissolved in the methanol solution of sodium methoxide, and the mixture was stirred for 2 hours at room temperature.

The Measurement of p*Ka'*.

The p*Ka'* was measured by the titration of the conjugate acid of each heterocycle with sodium hydroxide in 50% aqueous methanol after addition of an equimolar amount of sulfamic acid.

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[5] The p*Ka'* refers to the dissociation constant of the conjugate acid of each heterocycle.

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