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THE SYNTHESIS AND TAUTOMERIZATION OF KETENE AMINALS WITH BENZIMIDAZOLINE RING

Zhi-Tang Huang* and Mei-Xiang Wang
Institute of Chemistry, Academia Sinica, Beijing, China

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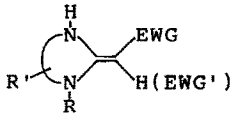
Abstract--The first isolation of benzimidazoline ring substituted ketene aminals 7a-c and/or their amidine tautomers 7'b-d, which were synthesized by the reactions: (1) benzoyl substituted ketene mercaptals 3 with N-methyl-o-phenylenediamine 4, and (2) 1,2-dimethylbenzimidazole 5 with ethyl benzoates 6, were disclosed. The tautomeric equilibrium between 7 and 7', along with benzothiazoline and benzoxazoline ring substituted ketene N,S-acetals 8 and 8' and ketene N,O-acetals 9 and 9', were discussed.

INTRODUCTION

A great development has been achieved in all respects of enamine chemistry, since the first reported by Stork et al.[1-3] Enamine chemistry has become an important part of organic chemistry.[4] Heterocyclic ketene aminals 1, or 1,1-enediamines, are the member of enamine with some intriguing properties. Due to the incorporation of electron-donating ability of nitrogen atom and electron-withdrawing ability of EWG groups, the conjugated double bond in the structure is highly polarized. It results in the increase of the length of double bond[5-7] and the electron density on the α-carbon.[8,9] The nucleophilicity of α-carbon is always stronger than that of nitrogen atom, but the secondary amino moiety of the molecule can also participate in the reaction. Therefore, heterocyclic ketene aminals can serve as di-nucleophiles, and much attention has been given to their nucleophilic substitution and addition reactions, and a wide variety of fused heterocycles has been synthesized through these and cyclocondensation reaction sequences.[10-27]



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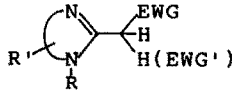

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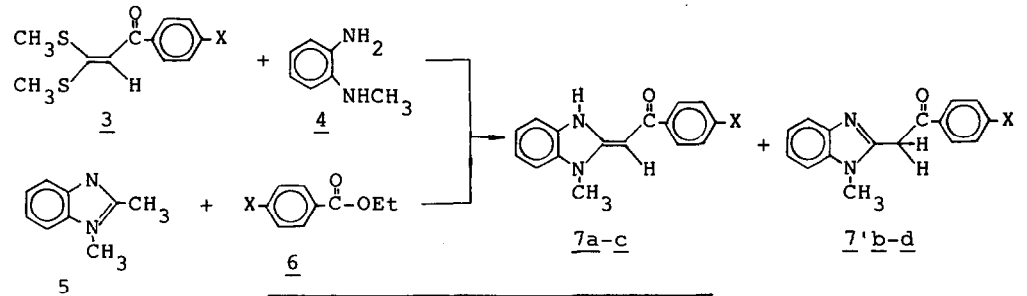
EWG, EWG' = NO_2, COR, COAr, CO_2R, CN, ----

Enamine with secondary amino group would tautomerize to its imine isomer and the tautomeric equilibrium between them has been studied.[28-31] Like their enamine analogues, heterocyclic ketene aminals 1 may coexist with their amidine form 2. Although many researches on their structural characteristics have been reported, it is surprising to us that the investigation on the tautomeric problems of 1 and 2 is very rare, and was only briefly mentioned on one paper.[32] The observations of tautomeric equilibrium of acyclic ketene aminals and benzothiazoline and benzoxazoline ring substituted ketene N,S-, and N,O-acetals have been recently reported by us.[33-35] Because of the significance of exploring the novel synthetic method and interpreting the reaction mechanism, we embarked on the synthesis of benzimidazoline ring substituted ketene aminals and study of their tautomerism. Here we wish to report these results.

RESULTS AND DISCUSSION

1-Methyl-2-(benzoylmethylene)benzimidazoline (7b) has been synthesized in literatures,[32,36,37] but the yield is very low. Now, 1-methyl-2-(aroylmethylene)benzimidazolines 7a-d were synthesized by the reaction of benzoyl substituted mercaptals 3 with N-methyl-o-phenylenediamine 4. The reaction is easily monitored by the bubbling of methanethiol. In order to avoid both the unpleasant methanethiol released and relatively inconvenient preparation of reactants 3 and 4, we explored the reaction of 1,2-dimethylbenzimidazole 5 with ethyl benzoates 6. In the presence of excess of sodium hydride, the reaction afforded desired products 7a,b in moderate yields, but the yield of 7c was low due to the weaker electrophilicity of 6c. The reaction conditions and yields are listed in Table 1.



3,6,7,7'	a	b	c	d
X	Cl	H	CH_3	CH_3O

It is noteworthy that both ketene aminals 7 and their amidine tauto-

mers 7'were obtained in crystals from the reaction mixture. The substituent at benzoyl group play an important role in determination of their isomer formation. It gave exclusive ketene aminal 7a or amidine isomer

Table 1. Compounds 7 and 7'prepared

Compound	Preparative method*	Yield (%)	M.p. (°C)	IR (cm^{-1})
7a	A, C	42, 32	125-126.5	3440(NH), 1632(C=O), 1567, 1509
7b	B, C	41, 40	150-151 (150-152)[32,36]	3439(NH), 1632(C=O), 1575, 1513
7'b			134-134.5	1673(C=O), 1588, 1510
7c	A, C	40, 13	131-132	3439(NH), 1630(C=O), 1572, 1511
7'c			122-123	1673(C=O), 1603, 1510
7'd	B	40	135-136	1665(C=O), 1595, 1575, 1505

* method A: 3 + 4, reflux in xylene/DMF.
method B: 3 + 4, reflux in dioxane.
method C: 5 + 6.

7'd with 4-chloro or 4-methoxy substituted benzoyl group. Benzoyl and 4-methyl benzoyl substituted substrates gave both two isomers 7b,c and 7'b,c recrystallized from ethanol, and they can be easily separated mechanically. To our knowledge, it is the first example that enamine and imine tautomers are both obtained from the recrystallization mixture.

The constitution of the products was confirmed by elemental analyses and mass spectra. Infrared spectra determined from KBr tablet show great difference in 7 and 7'for their carbonyl absorption. The carbonyl absorption of 7'b-d, the colorless needles, is ranged at normal values (1665-1673 cm^{-1}), while the carbonyl absorption of the pale yellow prisms 7a-c is shifted to 1630-1632 cm^{-1}due to the conjugation of carbonyl group with double bond and nitrogen atoms. Although they gave same fragment ions in mass spectra, the most abundant ion for 7a-c was molecular ion, while 7'b-d gave aroyl fragment as base peak. In the ^{1}H-NMR spectra, two set of signals were detected, in addition to the signals of the nitrogen proton and the ethylenic proton, a methylene proton was also observed. Besides, two methyl proton signals were

recorded. These indicated that a tautomeric equilibrium between 7 and 7' exists in solution. The tautomerization of these compounds was further confirmed by the ^{13}C-NMR spectra, in which the signals corresponding to 7'a-d were presented in addition to the signals of 7a-d. The presence of the ketonic carbonyl carbon signals in the ^{13}C-NMR spectra also excluded the structure of imine-enol tautomer. In general, compounds with intramolecular hydrogen bond are more stable, and the downfield shift of the NH signal in the ^{1}H-NMR spectra suggests the compounds 7a-d in E-configuration.

The tautomeric equilibrium between 7 and 7' was studied at different temperatures and in different solvents. The ratio of 7 to 7', estimated roughly from the ^{1}H-NMR spectra, is listed in Table 2. In order to inquire on the role of the heteroatoms in the tautomerization, the results of benzothiazoline and benzoxazoline ring substituted analogues, ketene N,S-acetals[34] 8 and 8' and ketene N,O-acetals[35] 9 and 9', are also listed in Table 2.

Table 2. The ratio of 7, 8 and 9 to 7', 8' and 9'

7,8,9 7',8',9'

	solvent	temp. °C	a	b	c	d
7/7' Z = NCH_3	$CDCl_3$	25	59/41	62/38	64/36	64/36
	$CDCl_3$	50	82/18	82/18	81/19	84/16
	DMSO-d_6	25	95/5	86/14	77/23	73/27
8/8' Z = S	$CDCl_3$	25	81/19	67/33	53/47	33/67
	DMSO-d_6	25	92/8	82/18	78/22	65/35
9/9' Z = O	CCl_4	25	100/0	92/8	86/14	
	$CDCl_3$	25	67/33	50/50	44/56	
	DMSO-d_6	25	52/48		29/71	

From Table 2, it is indicated that the electron-withdrawing substituent in aroyl group favors the tautomeric equilibrium towards ketene aminal isomers in general, this is extremely supported by the fact of the exclusive isolation of 7a from the reaction mixture. This results are similar to that of the enamines.[31] In addition, the higher the temperature, the equilibrium is more favorable to ketene aminals. The

tautomeric equilibrium varied drastically in different solvents depending on different heterocycles. The ratio of 7/7' is insensitive to the different substituent on the aroyl group in $CDCl_3$. However, in DMSO-d_6, the change of this ratio depending on different substituent is obvious, and more ketene aminal isomers are existed in this solvent. For sulfur atom containing heterocycles, ketene N,S-acetals 8 exist also favorably in DMSO-d_6. On the contrary, ketene N,O-acetals 9 predominates in CCl_4.

The different preference to solvents of enamine and imine isomers of 7, 8 and 9 may be explained by the different electronegativity of the heteroatoms. The lower values of electronegativity of nitrogen and sulfur atom make the double bond of 7 and 8 more polarized due to the more electron-donating ability of these atoms. Therefore, the highly polarized molecules of enamine form of 7 and 8 may be more preferred in the more polar solvents, such as DMSO. However, for 9 with a more electronegative oxygen atom, the polarization of the double bond in enamine form is alliviated, and it led to the decrease of enamine form in polar solvent and increase of this form in nonpolar solvent, particularly in CCl_4.

EXPERIMENTAL

Melting poinls are uncorrected. Infrared spectra were obtained on FTIR-IFS-113V (Bruker) and Perkin-Elmer 782 spectrometers. ^1H and ^{13}C-NMR spectra were recorded on a Jeol FX-100 spectrometer with TMS as interal standard. UV spectra were recorded in methanol solution on a Hitachi 340 spectrometer. MS were measured with a AEI MS-50 mass spectrometer. Elemental analyses were carried out by the Analytical Laboratory of the Institute. Compounds 3 and 4 were synthesized according to the literature,[38,39] respectively.

1-Methyl-2-[(4-chlorobenzoyl)methylene]benzimidazoline (7a): (Method A)

A mixture of 3a (1292 mg, 5 mmol) and 4 (732 mg, 6 mmol) in xylene (30 ml) and DMF (5 ml) was refluxed for one day. Another small amount of 4 (50 mg) was added and the mixture was refluxed for another day. After removal of the solvent, the residue was chromatographed on silica gel using petroleum ether (30-60°C)/ethyl acetate (7/3) as eluent. After recrystallization from ethanol, 600 mg (42%) of 7a was obtained as pale yellow prisms. MS: m/z = 286 (34), 284 (M^+, 100), 283 (85), 258 (23), 256 (73), 173 (49), 145 (41), 139 (55). UV: λ_{max} (lg ε) = 214 (4.16), 248 (4.22), 362 nm (4.26). ^1H-NMR ($CDCl_3$): δ = 12.00 (s, NH), 7.20-7.97 (m), 5.68 (s, =CH-), 4.54 (s, CH_2), 4.26 (s, NCH_3), 3.66 ppm

(s, NCH_3). ^{13}C-NMR ($CDCl_3$): δ = 190.7, 187.5, 168.2, 153.4, 143.0, 141.3, 136.7, 136.2, 133.4, 132.4, 131.2, 130.3, 129.4, 129.3, 128.5, 128.0, 127.3, 124.2, 123.4, 122.8, 122.5, 114.8, 114.4, 110.4, 108.5, 39.6, 31.7, 29.3 ppm. Anal. calc. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found C, 67.45; H, 4.63; N, 9.88.

1-Methyl-2-[(benzoyl)methylene]benzimidazoline (7b) and 1-Methyl-2-[(benzoyl)methyl]benzimidazole (7'b): (Method C)

To a mixture of 1,2-dimethylbenzimidazole (5) (292 mg, 2 mmol) and ethyl benzoate (6b) (300mg, 2 mmol) in benzene (10 ml) and DMF (0.5 ml), an excess amount of sodium hydride (120 mg, 80% in mineral oil) was added and the mixture was refluxed for 9 hours. After cooling, water (15 ml) was added gradually and the mixture was extracted with ethyl acetate (20 ml). The organic layer was washed with water (2 x 10 ml) and sodium chloride solution (2 x 10 ml), and dried with anhydrous sodium sulfate. After removal of the solvent, 200 mg (40%) of product was obtained. Compound 7b as pale yellow prisms and 7'b as colorless needles were separated mechanically by recrystallization from ethanol. MS: 7b, m/z = 250 (M^+, 100), 249 (94), 222 (63), 173 (44), 145 (36), 105 (27), 77 (10); 7'b, m/z = 250 (M^+, 68), 249 (62), 222 (46), 173 (38), 145 (30), 105 (100), 77 (61). UV: λ_{max} (lg ε) = 212 (4.04), 244 (3.94), 358 nm (3.92). ^{1}H-NMR ($CDCl_3$): δ = 10.80 (s, NH), 7.22-7.94 (m), 5.84 (s, =CH-), 4.80 (s, CH_2), 4.26 (s, NCH_3), 3.67 ppm (s, NCH_3). ^{13}C-NMR ($CDCl_3$): δ = 192.3, 188.2, 173.3, 154.1, 137.9, 136.6, 135.3, 134.5, 133.1, 129.8, 129.1, 128.7, 128.1, 127.4, 127.3, 127.0, 126.6, 126.0, 124.0, 122.5, 122.3, 122.1, 113.9, 110.4, 108.2, 38.4, 31.6, 28.9 ppm. Anal. calc. for $C_{14}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20. Found 7b, C, 76.83; H, 5.62; N, 10.95. 7'b, C, 76.87; H, 5.54; N, 11.31.

1-Methyl-2-[(4-methylbenzoyl)methylene]benzimidazoline (7c) and 1-Methyl-2-[(4-methylbenzoyl)methyl]benzimidazole (7'c):

Compound 7c was obtained as pale yellow prisms and 7'c as colorless needles. MS: 7c, m/z = 264 (M^+, 30), 263 (32), 236 (34), 173 (17), 145 (12), 119 (100), 91 (37); 7'c, 264 (M^+, 37), 263 (40), 236 (40), 173 (18), 145 (12), 119 (100), 91 (37). UV: λ_{max} (lg ε) = 217 (4.15), 256 (4.22), 362 nm (4.06). ^{1}H-NMR ($CDCl_3$): δ = 10.40 (s, NH), 7.17-7.92 (m), 5.80 (s, =CH-), 4.72 (s, CH_2), 4.23 (s, NCH_3), 3.62 (s, NCH_3), 2.44 (s, CH_3), 2.40 ppm (s, CH_3). ^{13}C-NMR ($CDCl_3$): δ = 192.1, 188.5, 172.8, 154.3, 145.6, 142.5, 139.7, 136.6, 135.7, 134.9, 133.2, 130.3, 130.0, 129.4, 129.0, 126.9, 126.0, 124.0, 122.6, 122.2, 122.1, 118.9, 114.3, 110.4, 108.2, 38.7, 31.6, 28.7, 21.7, 21.3 ppm. Anal. calc. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.60. Found 7c, C, 77.59; H, 6.26;

N, 10.67. 7'c, C, 77.13; H, 6.01; N, 10.55.

1-Methyl-2-[(4-methoxybenzoyl)methyl]benzimidazole (7'd): (Method B)

Same as Method A, dioxane was used as reaction medium instead of xylene/DMF. Compound 7'd (40%) was obtained as colorless needles. MS: m/z = 280 (M^+, 18), 279 (15), 252 (27), 173 (7), 145 (6), 135 (100). UV: λ_{max} (lg ε) = 220 (4.04), 280 (4.24), 362 nm (3.92). ^{1}H-NMR ($CDCl_3$): δ = 10.64 (s, NH), 6.85-7.98 (m), 6.04 (s, =CH-), 4.68 (s, CH_2), 4.24 (s, NCH_3), 3.67 (s, NCH_3), 3.86 (s, OCH_3), 3.84 ppm (s, OCH_3). ^{13}C-NMR ($CDCl_3$): δ = 191.3, 188.4, 170.5, 154.9, 164.9, 163.7, 142.6, 136.7, 132.5, 131.8, 131.1, 127.8, 127.7, 127.0, 125.6, 124.1, 122.7, 122.4, 122.2, 121.7, 118.7, 114.2, 113.7, 110.5, 109.4, 55.5, 55.4, 38.5, 31.8, 30.2 ppm. Anal. calc. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 10.00. Found C, 72.78; H, 5.70; N, 10.10

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