A New Route to 3*H*-1,5-Benzodiazepines and Heterocylic Ketene Aminals from Benzoyl Substituted Ketene Dithioacetals and Diamines

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Heterocyclic ketene aminals **5** or 3*H*-1,5-benzodiazepines **4** were obtained from the reaction of benzoyl substituted ketene dithioacetals **1** with various diamines **2**. The mechansim of formation of these two different products are discussed.

Heterocyclic ketene aminals have received much attention in recent years due to their interesting structural characteristics and synthetic potential. A wide variety of complicated heterocyclic compounds has been successfully synthesized from these intermediates.[1-9]

In our ongoing study on the structure and reaction of heterocyclic ketene aminals, we required benzimidazoline ring substituted ketene aminals **6**. The reaction of ketene dithioacetals with diamines is a general preparative method for ketene aminals, therefore, we envisioned that the reaction between ketene dithioacetals **1a–d** and *o*-phenylenediamine (**2c**) would give the desired products **6**. Surprisingly, 3*H*-1,5-benzodiazepines **4** were obtained instead of the expected compounds **6**. This fact made us aware of the necessity of examining the general methodology of the synthesis of heterocyclic ketene aminals from ketene dithioacetals and diamines. In order to understand the mechanism of the reaction, a series of reactions between benzoyl substituted ketene dithioacetals with diamines were investigated.

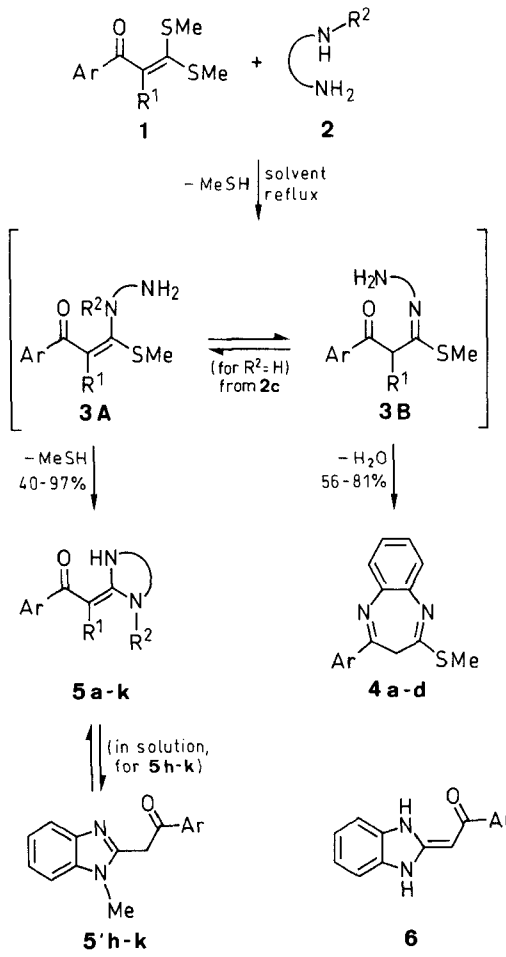
Ketene dithioacetals **1** reacted with diamine **2a,b** to yield the heterocyclic ketene aminals **5a–f**. Benzimidazoline ring substituted ketene aminal **5g** was also isolated from the reaction of **1e** with *o*-phenylenediamine (**2c**). It is noticeable that *N*-methyl-*o*-phenylenediamine (**2d**) reacted with **1a–d** to afford the corresponding benzimidazoline ring substituted ketene aminals **5h–k** and/or their imine tautomers **5'h–k**, while its analogue *o*-phenylenediamine (**2c**) gave the fused seven-membered ring products **4a–d**.

The reaction conditions and the spectroscopic data of the products are listed in Tables 1 and 2, respectively. The structures of the products were confirmed by elemental analyses and spectroscopic data. The bathochromic shift of the carbonyl group of **5** is due to conjugation of the carbonyl group with the double bond and the nitrogen atoms. The spectral data show that **5h–k** are in equilibrium with their tautomer **5'h–k** in solution; details about the tautomerization of **5h–k** will be published elsewhere.[10] The configurations of **5b,d,f** and **h–k** were determined based on the presence of an intramolecular hydrogen bond observed in these compounds as indicated by the downfield shift of the nitrogen proton in the ^{1}H NMR spectra. These data show that compounds **5b,d** and **h–k** exist in *E*-configuration while **5f** has the *Z*-configuration.

The results mentioned above reveal that ketene dithioacetals having two electron-withdrawing groups reacted with both aliphatic and aromatic diamines to give heterocyclic ketene aminals. The products from the reaction of one aroyl substituted ketene dithioacetals are dependent on the type of amine used. When aliphatic diamines and *N*-methyl-*o*-phenylenediamine are used, the reaction products are heterocyclic ketene aminals, but 3*H*-1,5-benzodiazepines are obtained with *o*-phenylenediamine. Based on these facts we propose a reaction mechanism involving an enamine–imine tautomeric intermediate as shown in the Scheme.

According to this mechanism, one methylthio group of the ketene dithioacetals **1** is substituted by the amino reactants **2** to form intermediate **3A** at first. Intermediate **3A** could be further substituted by the other amino group to eliminate a second methylthio group to give ketene aminals **5**, or tautomerizes to the imine form **3B** with *anti*-configuration due to steric reasons; then **3B** may transform to **4** by cyclocondensation of the amino group with the carbonyl group. The outcome of the reaction is determined by the stability of the key intermediate **3A**. In the case of aliphatic diamines, the enamine form **3A** can be stabilized by either one or two electron-withdrawing groups;[11] therefore, the products with a ketene aminal structure are obtained. When *o*-phenylenediamine (**2c**) is used, **3A** is stable only when two electron-withdrawing groups are present. With one aroyl substituent, **3A** is tautomerized to the imine form due to conjugation with the aromatic ring, and 3*H*-1,5-benzodiazepine derivatives are finally obtained. However, when *N*-methyl-*o*-phenylenediamine (**2d**) is used, the first substitution is by the methylamino group, the intermediate **3A** thus formed could not tautomerize to the imine form, therefore, ketene aminals **5** are obtained in this case. This mechanism can also best interpret the results reported in the literature;[12,13] especially the reaction between ketene dithioacetals and 2-aminothiophenol[14] or 2-aminophenol[15] in the presence of sodium, and guanidine[16] or hydrazine.[17]
In conclusion, benzoyl substituted ketene dithioacetals react with diamines to give different heterocycles depending on the structure of diamines used. Thus we present a method for the synthesis of heterocyclic ketene aminals and 3*H*-1,5-benzoazepines. In addition, the mechanism provided makes the reaction predictable based on the nature of the reactants. 3*H*-1,5-Benzodiazepines **4** have been synthesized by the methylation of 1,5-benzodiazepin-2-thione,[18,19] but only obtained in the impure state as an oily product.

Melting points are uncorrected. IR spectra were obtained on a Perkin-Elmer 782 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Jeol FX-100 and Varian 400 spectrometers with TMS as internal standard. UV spectra were measured in MeOH using a Hitachi 380 spectrometer. MS were obtained using a AEI MS-50 spectrometer. Microanalyses were carried out by the Analytical Laboratory of the Institute.



3*H*-1,5-Benzodiazepines 4; General Procedure:
A mixture of ketene dithioacetals **1a–d** (2.5 mmol) and *o*-phenylenediamine (**2c**; 0.270 g, 2.5 mmol) in xylene (20 mL) was refluxed for 24 h. After removal of the solvent, the residue was chromatographed on silica gel using EtOAc/petroleum ether (bp 30–60°) (2:25) as eluent (Tables 1 and 2).

4a:
^{13}C NMR ($CDCl_3$): δ = 13.8, 39.3, 124.6, 125.6, 127.7, 128.8, 129.3, 135.5, 136.9, 139.6, 140.5, 150.7, 152.5, 156.2.

4b:
^{13}C NMR ($CDCl_3$): δ = 12.5, 38.2, 123.3, 124.2, 126.4, 126.6, 127.3, 129.4, 135.9, 138.6, 139.1, 152.7, 155.2, 163.4.

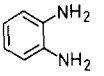
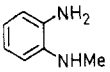
4c:
^{13}C NMR ($CDCl_3$): δ = 13.7, 21.3, 39.4, 124.5, 125.2, 127.7, 128.1, 128.7, 129.3, 134.5, 139.7, 140.9, 151.7, 153.8, 156.3

4d:
^{13}C NMR ($CDCl_3$): δ = 13.8, 39.2, 55.3, 113.9, 124.5, 125.0, 127.6, 128.5, 129.8, 148.2, 148.4, 150.7, 153.3, 156.4, 161.7.

Heterocyclic Ketene Aminals 5a–g; General Procedure:
A mixture of ketene dithioacetals **1b, e** or **f** (2 mmol) and diamines **2a–c** (2 mmol) in the appropriate solvent (20 mL, Table 1) was refluxed. The reaction was complete, when the methanethiol had ceased to bubble out. The solvent was partially removed and the product crystallized on cooling was collected by filtration (Tables 1 and 2).

Heterocyclic Ketene Aminals 5h–k; General Procedure:
A mixture of ketene dithioacetals **1a–d** (5 mmol) and *N*-methyl-*o*-phenylenediamine (**2d**; 0.733 g, 6 mmol) in xylene (30 mL) and DMF (5 mL) or dioxane (35 mL) was refluxed for 24 h. An additional amount of **2d** (0.4 mmol) was added and the mixture was refluxed for 24 h more. After removal of the solvent, the residue was

1	R^1	Ar
a	H	4-ClC_6H_4
b	H	Ph
c	H	4-MeC_6H_4
d	H	4-$MeOC_6H_4$
e	CN	Ph
f	CO_2Et	Ph

2	$H_2N\overset{\frown}{N}HR^2$	
a	$H_2NCH_2CH_2NH_2$	(R^2 = H)
b	$H_2NCH_2CH_2NHMe$	(R^2 = Me)
c		(R^2 = H)
d		(R^2 = Me)

4	Ar
a	4-ClC_6h_4
b	Ph
c	4-MeC_6H_4
d	4-$MeOC_6H_4$

5	R^1	Ar	$N\overset{\frown}{N}$	R^2	5,5′	R^1	Ar	$N\overset{\frown}{N}$	R^2
a	H	Ph	$-NCH_2CH_2N-$	H	**g**	CN	Ph		H
b	H	Ph	$-NCH_2CH_2N-$	Me	**h**	H	4-ClC_6H_4		Me
c	CN	Ph	$-NCH_2CH_2N-$	H	**i**	H	Ph		Me
d	CN	Ph	$-NCH_2CH_2N-$	Me	**j**	H	4-MeC_6H_4		Me
e	CO_2Et	Ph	$-NCH_2CH_2N-$	H	**k**	H	4-$MeOC_6H_4$		Me
f	CO_2Et	Ph	$-NCH_2CH_2N-$	Me					

Scheme

Table 1. Compounds **4** and **5** Prepared

Starting Materials		Product	Reaction Conditions Solvent/Time (h)	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c] or Lit. mp (°C)
Ketene Dithioacetal	Diamine					
1a	**2c**	**4a**	xylene/24 h	56	82.5–83.5	$C_{16}H_{13}ClN_2S$ (300.8)
1b	**2c**	**4b**	xylene/24 h	75	81–82	$C_{16}H_{14}N_2S$ (266.4)
1c	**2c**	**4c**	xylene/24 h	59	110–111	$C_{17}H_{16}N_2S$ (280.4)
1d	**2c**	**4d**	xylene/24 h	81	58–61	$C_{17}H_{16}N_2OS$ (296.4)
1b	**2a**	**5a**	toluene/2 h	86	207–209	208–210[20]
1b	**2b**	**5b**	toluene/6 h	72	99–100.5	98–100[20]
1e	**2a**	**5c**	EtOH/2 h	86	224.5–225.5	$C_{12}H_{11}N_3O$ (213.3)
1e	**2b**	**5d**	EtOH/2 h	85	154–155	$C_{13}H_{13}N_3O$ (227.3)
1f	**2a**	**5e**	toluene/5 h	97	120–121	$C_{14}H_{16}N_2O_3$ (260.3)
1f	**2b**	**5f**	toluene/5 h	85	82–83.5	$C_{15}H_{18}N_2O_3$ (274.3)
1e	**2c**	**5g**	DMF/5 h	70	> 320	> 325[21]
1a	**2d**	**5h**	xylene-DMF/48 h	42	125–126.5	$C_{16}H_{13}ClN_2O$ (284.8)
1b	**2d**	**5i**	dioxane/48 h	41	150–151	150–151[22]
1c	**2d**	**5j**	xylene-DMF/48 h	40	131–132	$C_{17}H_{16}N_2O$ (264.3)
1d	**2d**	**5'k**	dioxane/48 h	40	135–136	$C_{17}H_{16}N_2O_2$ (280.3)

[a] Yield of isolated product based on **1**.
[b] Solvent for recrystallization, **4a, c**: MeOH; **4b**: petroleum ether (bp 30–60 °C).
[c] Satisfactory microanalyses obtained: C ±0.28, H ±0.27, N ±0.25, S ±0.17. Exceptions: **5d, f** C +0.44, **4a** H −0.37, **4d, 5e** N −0.36.

Table 2. Spectroscopic Data of Compounds **4** and **5**

Product	IR (KBr) ν (cm^{-1})	UV (MeOH) λ_{max} (nm) (log ε)	^1H NMR ($CDCl_3$)[a] δ, J (Hz)	MS m/z (%)
4a	1584, 1566, 1542	218 (3.54), 262 (3.88), 328 (3.23)	2.48 (s, 3H), 3.36 (s, 2H), 7.20–7.53 (m, 4H), 7.44 (d, 2H, J = 8.6), 8.03 (d, 2H, J = 8.6)	302 (39), 301 (21), 300 (M^+, 100), 285 (16), 267 (17), 253 (21), 228 (38), 218 (58)
4b	1583, 1564, 1540	220 (3.55), 252 (3.88), 328 (3.21)	2.47 (s, 3H), 3.42 (s, 2H), 7.18–8.16 (m, 9H)	266 (M^+, 100), 251 (18), 233 (20), 219 (59), 194 (27)
4c	1584, 1563, 1535	210 (4.10), 232 (3.96), 296 (3.88), 364 (3.14)	2.42 (s, 3H), 2.48 (s, 3H), 3.37 (s, 2H), 7.18 (d, 2H, J = 8.2), 7.20–7.52 (m, 4H), 7.97 (d, 2H, J = 8.2)	280 (M^+, 100), 265 (19), 247 (20), 233 (49), 218 (24), 208 (21)
4d	1586, 1566, 1536, 1503	224 (3.75), 274 (3.96), 324 (sh)	2.42 (s, 3H), 3.28 (s, 2H), 3.88 (s, 3H), 6.96 (d, 2H, J = 8.4), 7.16–7.56 (m, 4H), 8.08 (d, 2H, J = 8.4)	296 (M^+, 100), 281 (19), 263 (16), 249 (32), 234 (14), 224 (19)
5c	3265, 3210 (NH), 2185 (C≡N), 1600 (C=O), 1593	212 (3.61), 229 (3.67), 294 (3.68)	3.59 (s, 4H), 7.15–7.75 (m, 5H), 8.65 (s, 2H)	213 (M^+, 82), 212 (100), 136 (39), 105 (32), 77 (48)
5d	3300 (NH), 2180 (C≡N), 1593 (C=O), 1565	214 (4.07), 230 (4.11), 295 (4.16)	3.15 (s, 3H), 3.57 (s, 4H), 7.18–7.72 (m, 5H), 9.68 (s, 1H)	227 (M^+, 63), 226 (100), 150 (31), 122 (5), 105 (29), 77 (41)
5e	3350, 3290 (NH), 1650, 1640 (C=O), 1567	212 (4.04), 238 (4.19), 282 (4.06)	0.67 (t, 3H, J = 7.2), 3.76 (s, 4H), 3.81 (q, 2H, J = 7.2), 7.24–7.47 (m, 5H), 8.20 (s, 1H), 9.48 (s, 1H)	260 (M^+, 71), 259 (37), 213 (100), 183 (13), 155 (11), 111 (39), 105 (69), 77 (72)
5f	3270 (NH), 1686, 1670 (C=O), 1580	231 (4.07), 271 (4.21), 300 (3.52)	0.72 (t, 3H, J = 7.2), 3.71 (s, 4H), 3.78 (q, 2H, J = 7.2), 7.24–7.60 (m, 5H), 8.84 (s, 1H)	274 (M^+, 88), 229 (24), 227 (37), 201 (39), 105 (100), 77 (69)
5g	3225, 3122 (NH), 2195 (C≡N), 1622 (C=O), 1590	216 (4.08), 240 (4.10), 270 (3.64), 336 (4.32)	7.00–7.90 (m, 9H), 13.03 (s, 2H)	261 (M^+, 91), 260 (100), 184 (16), 156 (10), 105 (34), 77 (60)
5h	3440 (NH), 1632 (C=O), 1567, 1509	214 (4.16), 248 (4.22), 362 (4.26)	3.66 (s), 4.26 (s), 4.54 (s), 5.68 (s), 7.20–7.97 (m), 12.00 (s)	286 (34), 284 (M^+, 100), 283 (85), 258 (23), 256 (73), 173 (49), 145 (41), 139 (55)
5i	3439 (NH), 1632 (C=O), 1575, 1513	212 (4.04), 244 (3.94), 358 (3.72)	3.67 (s), 4.26 (s), 4.80 (s), 5.84 (s), 7.22–7.94 (m), 10.80 (s)	250 (M^+, 100), 249 (94), 222 (63), 173 (44), 145 (36), 105 (27), 77 (10)
5j	3439 (NH), 1630 (C=O), 1572, 1511	217 (4.15), 256 (4.22), 362 (4.06)	2.40 (s), 2.44 (s), 3.62 (s), 4.23 (s), 4.72 (s), 5.80 (s), 7.17–7.92 (m), 10.40 (s)	264 (M^+, 30), 263 (32), 236 (34), 173 (17), 145 (12), 119 (100), 91 (37)
5'k	1665 (C=O), 1595, 1573, 1505	220 (4.04), 280 (4.24), 362 (3.92)	3.67 (s), 3.84 (s), 3.86 (s, 4.24) (s), 4.68 (s), 6.04 (s), 6.85–7.98 (m), 10.64 (s)	280 (M^+, 18), 279 (15), 252 (21), 173 (7), 145 (6), 135 (100)

[a] The ^1H NMR spectra of compounds **5c, d, g** were measured in DMSO-d_6.

chromatographed on silica gel using EtOAc/petroleum ether (bp 30–60 °C) (3:7) as eluent. The product was recrystallized from EtOH. (Tables 1 and 2).

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