REACTION OF KETENETHIOACETALS WITH CARBOXAMIDES

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Abstract—— Reaction of methyl 2-cyano-3,3-bis(methylthio)-acrylate (1a) with carboxamides in the presence of sodium hydride in a mixture of benzene and N,N-dimethylacetamide gave the corresponding displacement products of methylthio group, methyl 3-(N-alkyl or aryl)carbamoyl-2-cyano-3-(methylthio)-acrylates (3a,b,c,d,e,f,g,h). Refluxing of 3 in methanol gave the corresponding cyclized product, 2-alkyl or 2-aryl-5-methoxycarbonyl-6-methylthio-4(3H)-pyrimidones (4). Compound 3a was allowed to react with amine(morpholine, benzylamine, cyclohexylamine, aniline) to give 4-(substituted amino)-4(3H)-pyrimidone derivatives (6a,b,c,d).

It is now well known that ketenethioacetal derivatives easily reacted with amines and active methylene compounds and were very useful reagents for the preparation of heterocyclic compounds.[1] The reaction of ketenethioacetal derivatives with carboxamides had not been studied. We now wish to report the reaction of ketenethioacetal with various type of carboxamides and the synthesis of pyrimidine derivatives.

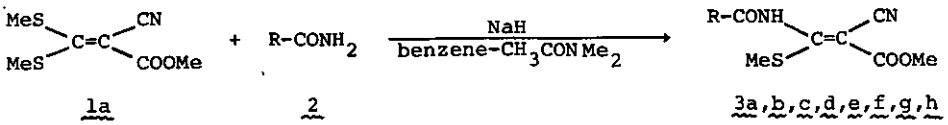
The reaction of methyl 2-cyano-3,3-bis(metylthio)acrylate (1a) with benzamide (2a) in the presence of sodium hydride in a mixture of benzene and N,N-dimethylacetamide(1:1) for 30 h at the room temperature gave methyl 3-benzamido-2-cyano-3-(methylthio)acrylate (3a), colerless needles, mp 135-137°C, in 76% yield. In the same manner, the other replacement products (3a,b,c,d,e,f,g,h) were obtained in good yields as shown in Chart 1. The above products were purified by the recrys-

tallization from benzene. When the compound 3a refluxed in methanol, cyclized product, 2-phenyl-5-methoxycarbonyl-6-methylthio-4(3H)-pyrimidone, was obtained in 90% yield. The structure of 4a was suggested by the analysis of the infrared (IR) and nuclear magnetic resonance (NMR) spectra and confirmed by comparison of its spectral data with that of authentic specimen prepared by the reaction of methyl 2-methoxycarbonyl-3,3-bis(methylthio)acrylate with benzamidine hydrochloride in the presence of sodium methylate. Similarly, the 4(3H)-pyrimidone derivatives (4a,b,c,d,e,f,g) were synthesized from the corresponding 3a,b,c,d,e,f,g in good yields as shown in Chart 2.

Moreover, reaction of 2-cyano-3,3-bis(methylthio)acrylonitrile (1b) with amides in a similar manner as described in 1a gave 2-alkyl or 2-aryl-5-cyano-6-(methylthio)-4(3H)-pyrimidones (5a,b,c,d,e,f,g) in yields as shown in Chart 3. 5-Cyano-6-methylthio-2-(phenyl and methyl)-4(3H)-pyrimidones (5a,g) were also prepared by the reaction of 1a with (benz- and acet-)amidine hydrochlorides in the presence of potassium carbonate in N,N-dimethylformamide in 80% and 92% yields, respectively.[2]

Since compounds 3 have a very active methylthio group against the nucleophiles such as amines, these compounds will become to be very useful intermediates for the preparation of heterocyclic compounds. Compound 3a easily reacted with amines (morpholine, benzylamine, cyclohexylamine, aniline) at 100°C to give 6-(substituted amino)-5-methoxycarbonyl-2-phenyl-4(3H)-pyrimidones (6a,b,c,d) in good yields. Compound 6d was refluxed in diphenyl ether to give a cyclized product, 5-hydroxy-2-phenylpyrimido[4,5-b]quinolin-4(3H)-one (7), mp > 350°C, in 85% yield. When 3a was allowed to react with morpholine at room temperature in N,N-dimethylformamide, cyclization did not proceed, resulting in the formation of replacement product (8) in 51% yield.

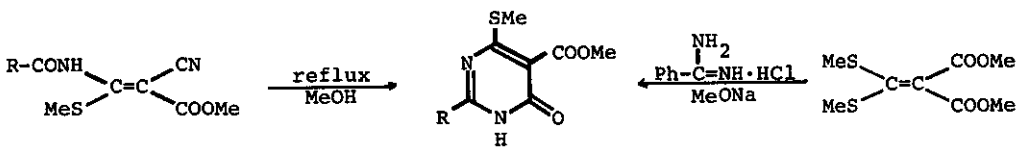
Ketenethioacetal (1a) also reacted with thioacetamide, followed by cyclization to yield 2-methyl-4-mercapto-6-methylthio-5-methoxycarbonylpyrimidine (9) which could be converted to 2-methyl-4,6-bis(methylthio)-5-methoxycarbonylpyrimidine (10) by the methylation with dimethyl sulfate in good yield.



1a 2 3a,b,c,d,e,f,g,h

Chart 1

No.	R	mp(°C)	Yield(%)
3a	C_6H_5	135-137	76
3b	p-$NO_2C_6H_4$	178-180	60
3c	p-ClC_6H_4	132	62
3d	p-$CH_3C_6H_4$	141-144	64
3e	p-$CH_3OC_6H_4$	130-132	39
3f	C_6H_5CH=CH	155	73
3g	Cl-CH_2	122-124	40
3h	CH_3	116	35



3a,b,c,d,e,f,g 4a,b,c,d,e,f,g

Chart 2

No.	R	mp(°C)	Yield(%)
4a	C_6H_5	288	90
4b	p-$NO_2C_6H_4$	265-267	96
4c	p-ClC_6H_4	255-257	94
4d	p-$CH_3C_6H_4$	270	98
4e	p-$CH_3OC_6H_4$	287	95
4f	C_6H_5CH=CH	258	91
4g	Cl-CH_2	182-184	94

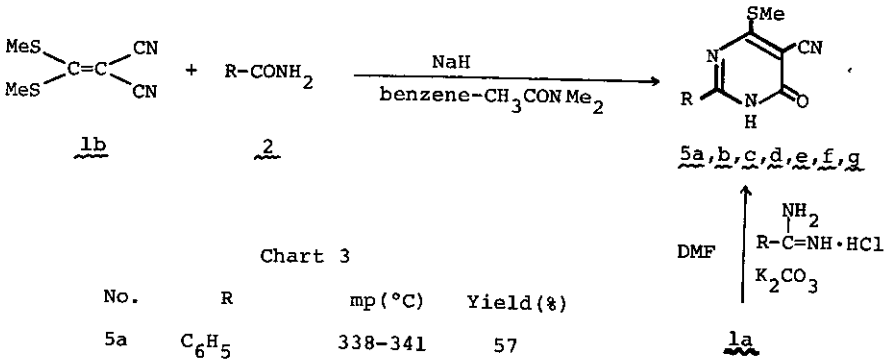


Chart 3

No.	R	mp(°C)	Yield(%)
5a	C_6H_5	338-341	57
5b	p-$NO_2C_6H_4$	335	33
5c	p-ClC_6H_4	309	28
5d	p-$CH_3C_6H_4$	315	32
5e	p-$CH_3OC_6H_4$	301	30
5f	$C_6H_5CH=CH$	354	35
5g	CH_3	307	18

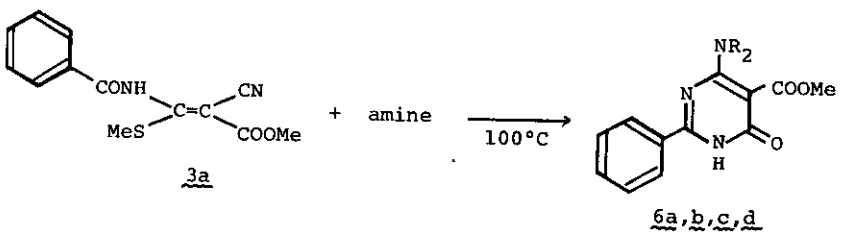
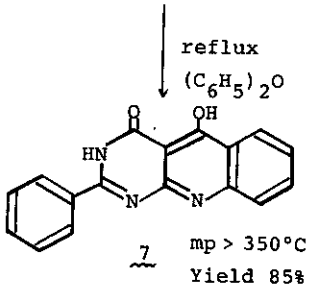
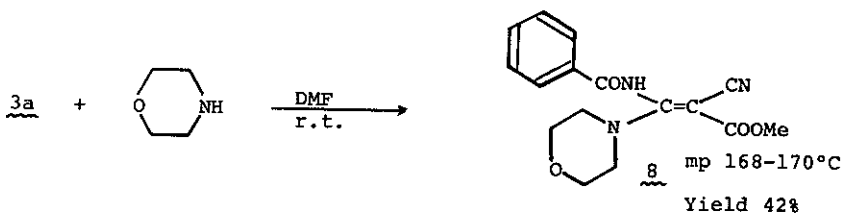
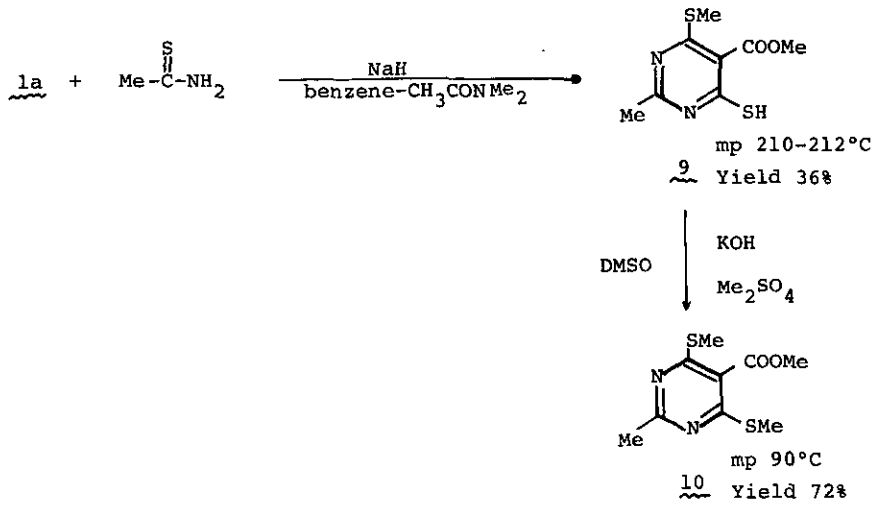


Chart 4

No.	NR_2	mp(°C)	Yield(%)
6a	$C_6H_5CH_2NH$	255-259	56
6b		230-233	42
6c		296	61
6d	C_6H_5NH	268	60







Physical Properties

3a) IRν_{max}^{KBr}cm^{-1}: 1670, 1710(C=O), 2198(C≡N). UVλ_{max}^{EtOH}nm(log ε): 242(4.42), 278(4.44) 328(4.33). NMR($CDCl_3$)δppm: 2.71(3H, s, S-CH_3), 3.84(3H, s, O-CH_3), 7.20-8.19 (5H, m, Ph-H), 12.80(1H, s, N-H).

3c) IRν_{max}^{KBr}cm^{-1}: 1670, 1718(C=O), 2202(C≡N). UVλ_{max}^{EtOH}nm(log ε): 250(3.76), 283(3.92) 327(3.79). NMR($CDCl_3$)δppm: 2.71(3H, s, S-CH_3), 3.86(3H, s, O-CH_3), 7.52(2H, d, J=9Hz, Ph-H), 7.96(2H, d, J=9Hz, Ph-H).

3g) IRν_{max}^{KBr}cm^{-1}: 1675, 1710(C=O), 2200(C≡N). UVλ_{max}^{EtOH}nm(log ε): 295(3.80), 322(2.68) NMR($CDCl_3$)δppm: 2.65(3H, s, S-CH_3), 3.88(3H, s, O-CH_3), 4.24(2H, s, CH_2).

4a) IRν_{max}^{KBr}cm^{-1}: 1620, 1674(C=O). UVλ_{max}^{EtOH}nm(log ε): 219(*), 257(*), 306(*) NMR($CDCl_3$)δppm: 2.70(3H, s, S-CH_3), 3.99(3H, s, O-CH_3), 7.27-8.26(5H, m, Ph-H)

4c) IRν_{max}^{KBr}cm^{-1}: 1635, 1682(C=O). UVλ_{max}^{EtOH}nm(log ε): 218(4.42), 257(4.23), 310(4.51) NMR($CDCl_3$)δppm: 2.73(3H, s, S-CH_3), 4.03(3H, s, O-CH_3), 7.56(2H, d, J=8Hz, Ph-H), 8.02(2H, d, J=8Hz, Ph-H).

4g) IRν_{max}^{KBr}cm^{-1}: 1655(C=O). UVλ_{max}^{EtOH}nm(log ε): 244(2.83), 295(4.41). NMR($CDCl_3$)δppm: 2.66(3H, s, S-CH_3), 4.03(3H, s, O-CH_3), 4.63(2H, s, CH_2).

5a) IRν_{max}^{KBr}cm^{-1}: 1655(C=O), 2207(C≡N). UVλ_{max}^{EtOH}nm(log ε): 254(3.55), 300(3.32), 318 (4.32). NMR($CDCl_3$)δppm: 2.81(3H, s, S-CH_3), 7.39-8.37(5H, m, Ph-H).

6d) IRν_{max}^{KBr}cm^{-1}: 1650(C=O). UVλ_{max}^{EtOH}nm(log ε): 255(*), 263(*), 311(*). NMR($CDCl_3$)δppm: 4.04(3H, s, O-CH_3), 7.30-8.30(5H, m, Ph-H).

7) IRν_{max}^{KBr}cm^{-1}: 1678(C=O). UVλ_{max}^{EtOH}nm(log ε): 211(*), 233(*), 262(*), 270 (*), 290(*), 322(*). NMR($CDCl_3$)δppm: 8.56(1H, d, J=8Hz, Ph-H).

8) IRν_{max}^{KBr}cm^{-1}: 1708(C=O), 2197(C≡N). UVλ_{max}^{EtOH}nm(log ε): 255(3.56), 322(3.66). NMR ($CDCl_3$)δppm: 3.75(3H, s, O-CH_3), 3.20-4.10(8H, m, CH_2), 7.19-8.18(5H, m, Ph-H). 11.06(1H, s, N-H).

9) IRν_{max}^{KBr}cm^{-1}: 1730(C=O). UVλ_{max}^{EtOH}nm(log ε): 252(4.00), 279(3.43), 305(3.64), 350 (3.86). NMR($CDCl_3$)δppm: 2.69(3H, s, S-CH_3), 2.77(3H, s, C-CH_3), 4.08(3H, s, O-CH_3).

10) IRν_{max}^{KBr}cm^{-1}: 1490(C=O). UVλ_{max}^{EtOH}nm(log ε): 270(3.62), 296(4.87). NMR($CDCl_3$)δppm: 2.50(6H, s, S-CH_3), 2.59(3H, s, O-CH_3), 3.94(3H, s, C-CH_3).

* Concentration is unknown because of insufficient solubility.

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