SYNTHESIS OF 1,5-BENZODIAZEPINES

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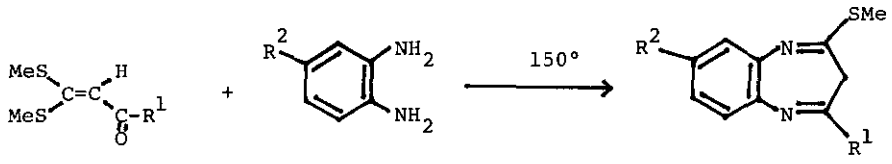
Abstract Reaction of α-oxoketene S,S-acetals (1a, b, c, d) with o-phenylenediamines gave the corresponding 1,5-benzodiazepines, 8-substituted 4-aryl-2-methylthio-3H-1,5-benzodiazepines (3a, b, c, d, e) in good yields. 2-Amino-4-aryl-8-nitro-3H-1,5-benzodiazepines (5a, b, c) were prepared by the displacement of methylthio group on compound 3b with amines (benzylamine, morpholine, 1-methylpiperazine).

Recently, Junjappa has reported a general method for the preparation of a variety of substituted and fused pyrimidine and 2-pyridone derivatives using α-oxoketene S,S-acetals.[1] In 1978, Nardi et al. reported the synthesis of 4-aryl-1,3-dihydro-2H-1,5-benzodiazepine-2-thiones by condensation of 1-aryl-3,3-dimercaptoprop-2-en-1-ones with o-phenylenediamine.[2] In general, the condensation of o-phenylenediamine with ethyl acetoacetate or ethyl benzoylacetate has been shown to yield 4-methyl- or 4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin-2-ones as the major products, together with variable quantities of N-(α-methylvinyl)- and N-(α-phenylvinyl)benzimidazol-2-ones.[3] Some these 1,5-benzodiazepines have the interesting biological properties.[4]

We have reported the synthesis of heterocyclic compounds utilizing the versatile ketenethioacetals.[5] We wish to report now further utility of α-oxoketenethioacetals in the formation of 1,5-benzodiazepine derivatives.

The condensation of 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (1a) with 4-nitro-o-phenylenediamine at 150° for 1.5 hr gave 2-methylthio-8-nitro-4-phenyl-3H-1,5-benzodiazepine (3a) which was determined by the spectroscopic data and elemental

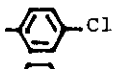
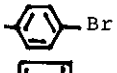
analysis. Treatment of 3a with hydrogen peroxide in acetic acid afforded 8-nitro-4-phenyl-1,3-dihydro-2H-1,5-benzodiazepin—2-one (4a), determined by Chmilenko,[6] which was identified with an authentic sample prepared by the reaction of 4-nitro-o-phenylenediamine with ethyl benzoylacetate.[4a] Similarly, other diazepines (3b, c, d, e) were prepared by the reaction of α-oxoketenethioacetals (1a, b, c, d) with o-phenylenediamine derivatives (2a, b, c) in good yields. The treatment of 3b with hydrogen peroxide gave also 1,5-benzodiazepinone (4b). Since 3 have an active methylthio group, the reaction of these compounds with amines was examined. The reaction of 3b with excess amine (benzylamine, morpholine, 1-methylpiperazine) under heating at 150° gave the corresponding displacement products (5a, b, c) of methylthio group in good yields.



1a, b, c, d

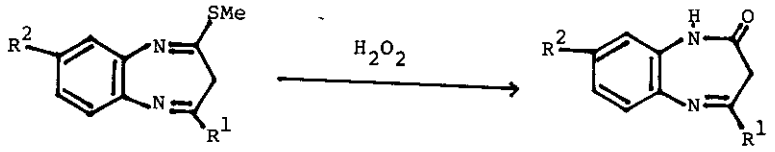
2a, b, c

3

	R^1	R^2	mp(°C)	Yield(%)
a:		NO_2	157	55
b:		NO_2	177	73
c:		NO_2	182	78
d:		Cl	141	56
e:		NO_2	222	97

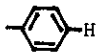
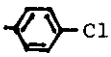
R^1: a: b: c: d: 

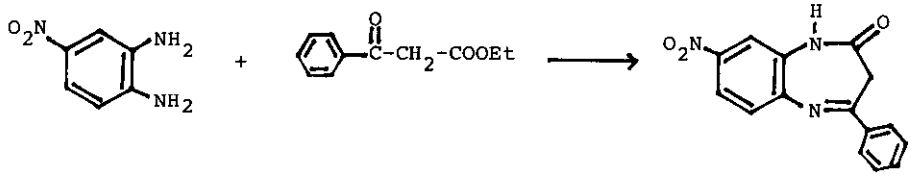
R^2: a: NO_2 b: Br c: Cl



3a, b

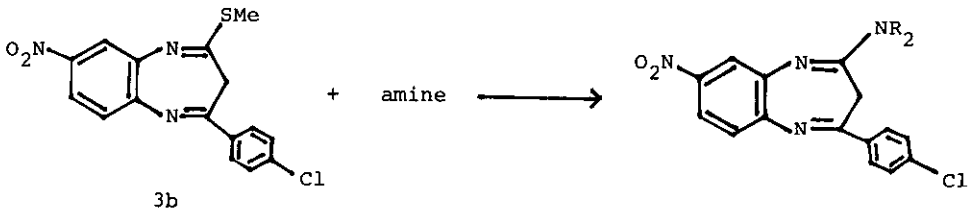
4a, b

	R^1	R^2	mp(°C)	Yield(%)
a:		NO_2	239	44
b:		NO_2	250	44



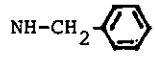
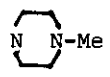
2a

4a



3b

5a, b, c

	NR_2	mp(°C)	Yield(%)
a:		223	43
b:		233	90
c:		211	58

Spectral data of 8-substituted 4-aryl-2-methylthio-3H-1,5-benzodiazepines

3a: yellow needles, UVλ_{max}^{EtOH}nm(log ε): 234(4.26), 279(4.46), 340(4.12). IRν_{max}^{KBr}cm^{-1}: 1600(-C=N-), 1500, 1330(NO_2). NMR($CDCl_3$)δ:2.50(3H, s, SMe), 3.46(2H, s, 3-CH_2-), 7.48-7.60(3H, m, 3′,4′,5′-H), 7.62(1H, d, J=8 Hz, 6-H), 8.08-8.24(2H, m, 2′,6′-H), 8.09(1H, dd, J=2, 8 Hz, 7-H), 8.35(1H, d, J=2 Hz, 9-H).

3b: brown needles, UVλ_{max}^{EtOH}nm(log ε): 236(4.28), 282(4.49), 336(4.15). IRν_{max}^{KBr}cm^{-1}: 1600(-C=N-), 1500, 1340(NO_2). NMR($CDCl_3$)δ: 2.47(3H, s, SMe), 3.41(2H, s, 3-CH_2-) 7.48(2H, d, J=9 Hz, 3′,5′-H), 7.57(1H, d, J=8 Hz, 6-H), 8.05(1H, dd, J=2, 8 Hz, 7-H), 8.07(2H, d, J=9 Hz, 2′,6′-H), 8.32(1H, d, J=2 Hz, 9-H).

3c: brown crystals, UVλ_{max}^{EtOH}nm: 236, 283, 334; λ_{min}^{EtOH}nm: 218, 244.(insufficient solubility). IRν_{max}^{KBr}cm^{-1}: 1600(-C=N-), 1500, 1340(NO_2). NMR($CDCl_3$)δ: 2.47(3H, s, SMe), 3.44(2H, s, 3-CH_2-), 7.58(2H, d, J=9 Hz, 3′,5′-H), 7.66(1H, d, J=8 Hz, 6-H), 8.00(2H, d, J=9 Hz, 2′, 6′-H), 8.08(1H, dd, J=2, 8 Hz, 7-H), 8.32(1H, d, J=2 Hz, 9-H).

3d: pale yellow needles, UVλ_{max}^{EtOH}nm(log ε): 270(4.57), 340(3.84). IRν_{max}^{KBr}cm^{-1}: 1600(-C=N-). NMR($CDCl_3$)δ: 2.46(3H, s, SMe), 3.36(2H, s, 3-CH_2-), 7.22-7.50 (5H, m, 6, 7, 9-H, 3′, 5′-H), 8.04(2H, d, J=9 Hz, 2′, 6′-H).

3e: brown needles, UVλ_{max}^{EtOH}nm(log ε): 281(4.35), 364(4.23). IRν_{max}^{KBr}cm^{-1}: 1590(-C=N-), 1500, 1320(NO_2). NMR(DMSO-D_6)δ: 2.47(3H, s, SMe), 3.70(2H, s, 3-CH_2-), 7.30 (1H, m, 4′-H), 7.61(1H, d, J=8 Hz, 6-H), 7.95-8.22(4H, m, 7, 9-H, 3′, 5′-H).

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