

SYNTHESIS OF 1,5-BENZODIAZEPINES

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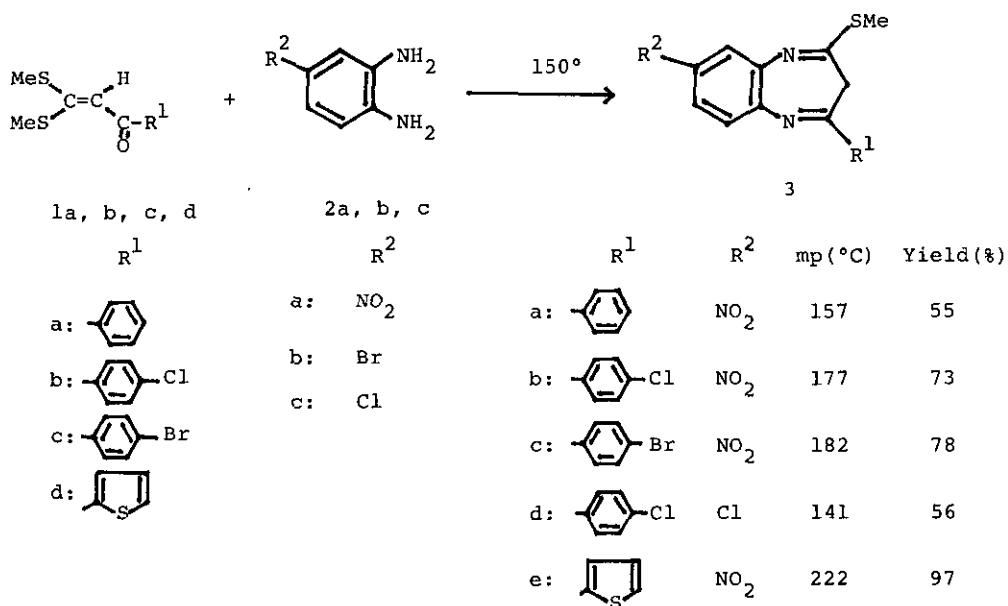
Abstract Reaction of α -oxoketene S,S-acetals (1a, b, c, d) with *o*-phenylenediamines gave the corresponding 1,5-benzodiazepines, 8-substituted 4-aryl-2-methylthio-3H-1,5-benzodiazepines (3a, b, c, d, e) in good yields. 2-Amino-4-aryl-8-nitro-3H-1,5-benzodiazepines (5a, b, c) were prepared by the displacement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

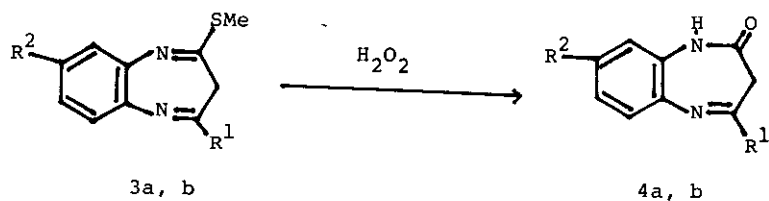
Recently, Junjappa has reported a general method for the preparation of a variety of substituted and fused pyrimidine and 2-pyridone derivatives using α -oxoketene S,S-acetals.¹⁾ In 1978, Nardi et al. reported the synthesis of 4-aryl-1,3-dihydro-2H-1,5-benzodiazepine-2-thiones by condensation of 1-aryl-3,3-dimercaptoprop-2-en-1-ones 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.

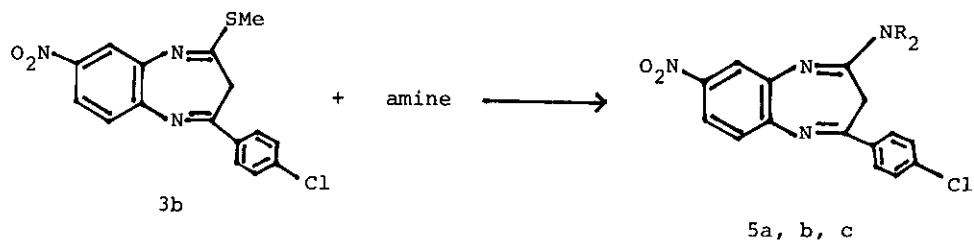
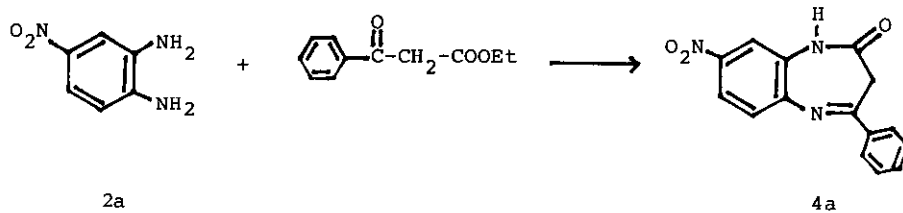
The condensation of 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (1a) with 4-nitro-*o*-phenylenediamine at 150° for 1.5 hr gave 2-methylthio-8-nitro-4-phenyl-3H-1,5-benzodiazepine (3a) which was determined by the spectroscopic data and elemental

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.





	R ¹	R ²	mp(°C)	Yield(%)
a:		NO ₂	239	44
b:		NO ₂	250	44



	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, $UV\lambda_{\max}^{EtOH}$ nm(log ϵ): 234(4.26), 279(4.46), 340(4.12). $IR\nu_{\max}^{KBr}$ 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, $UV\lambda_{\max}^{EtOH}$ nm(log ϵ): 236(4.28), 282(4.49), 336(4.15). $IR\nu_{\max}^{KBr}$ 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, $UV\lambda_{\max}^{EtOH}$ nm: 236, 283, 334; λ_{\min}^{EtOH} nm: 218, 244. (insufficient solubility). $IR\nu_{\max}^{KBr}$ 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, $UV\lambda_{\max}^{EtOH}$ nm(log ϵ): 270(4.57), 340(3.84). $IR\nu_{\max}^{KBr}$ 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, $UV\lambda_{\max}^{EtOH}$ nm(log ϵ): 281(4.35), 364(4.23). $IR\nu_{\max}^{KBr}$ 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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