Keten *SS*-Acetals.‡ Part 9.[1a] Reaction of α-Oxo- and α-Cyano-keten *SS*-Acetals with Cyanoacetamide: a New General Method for Substituted and Fused 4-Alkylthio-3-cyano-2(1*H*)-pyridones and Formation of Novel Pyridones through Base-induced Rearrangements

By **R. R. Rastogi, A. Kumar,† H. Ila,† and H. Junjappa,*,† Medicinal Chemistry Division, Central Drug Research Institute, Lucknow, India**

α-Oxoketen *SS*-acetals (1a—n) react smoothly with cyanoacetamide (2) in the presence of sodium isopropoxide in refluxing propan-2-ol to give 4-alkylthio-3-cyano-2(1*H*)-pyridones (3a—n), respectively, in good to excellent yields. α-Cyanoacetals (4a—c), however, yielded corresponding 6-aminopyridones (5a—c) in relatively lower yields. Extension of this method to cyclic keten *SS*-acetals (6a—c) and (8a—c) similarly afforded good yields of fused pyridones (7a—c), benzoquinolone derivatives (9a and b), and the benzocycloheptane derivative (9c), respectively. Attempts to isolate 4-alkoxypyridones (12a and b) under varying conditions were not successful. Reaction of α-alkyl-α-oxoketen *SS*-acetals (15a—g) and (21a—c) with cyanoacetamide under similar conditions afforded novel pyridones (16a—g) and (22a—c) respectively, which are formed by initial base-induced proton migration in these acetals.

DURING the course of our studies directed towards exploring the synthetic potential of polarized keten *SS*-acetals [1] as two or three carbon fragments, we reported in a preliminary communication,[1c] that cyanoacetamide reacts with several α-oxoketen *SS*-acetals in the presence of sodium isopropoxide yielding 6-substituted and fused 3-cyano-4-methylthio-2(1*H*)-pyridones in excellent

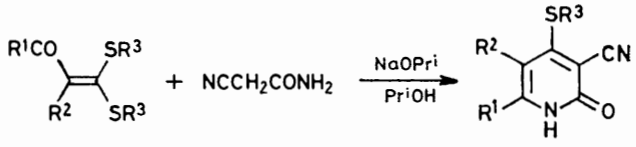
† *Present address:* Department of Chemistry, North-Eastern Hill University, Shillong 793003, Meghalaya, India.

‡ Systematic name keten dithioacetals.

[1] (*a*) Part 8, A. Kumer, H. Ila, and H. Junjappa, *J.C.S. Chem. Comm.*, 1976, 593; (*b*) S. M. S. Chauhan and H. Junjappa, *Synthesis*, 1974, 880; (*c*) R. R. Rastogi, H. Ila, and H. Junjappa, *J.C.S. Chem. Comm.*, 1975, 645; (*d*) S. M. S. Chauhan and H. Junjappa, *Synthesis*, 1975, 798; A. Kumar, H. Ila, and H. Junjappa, (*e*) *ibid.*, 1976, 324; (*f*) *J.C.S. Chem. Comm.*, 1976, 592; S. M. S. Chauhan and H. Junjappa, (*g*) *Tetrahedron*, 1976, **32**, 1779; (*h*) *ibid.*, p. 1911.

yields. The present paper describes the full details and the extension of this reaction to other keten *SS*-acetals in order to determine the scope and limitation of this method.

In a typical experiment, when (1a) was refluxed in propan-2-ol, with equimolar quantities of cyanoacetamide and $NaOPr^i$, (3a) was obtained in 82% yield. Other pyridones carrying substituted phenyl (3b—f), methyl (3g), 3-pyridyl (3h), and 4-pyridyl (3i) groups in the 6-position were similarly prepared from the respective keten *SS*-acetals (1b—i) in 65—85% overall yields (Scheme 1). Keten *SS*-acetals (1j—l), with different alkylthio groups similarly afforded the corresponding pyridones (3j—l), respectively, in excellent yields. The reaction of (1m and n) with (2) was, however, slow and required a longer reaction time to give 5-aryl-6-methylpyridones (3m and n), respectively, in relatively lower yields (48%). With the keten *SS*-acetal (1o) derived from deoxybenzoin, practically no reaction took place, even after refluxing for 12—14 h. All the pyridones (3a—n) were characterized by their spectral and analytical data given in Supplementary Publication No. SUP 22229 (13 pp.).*

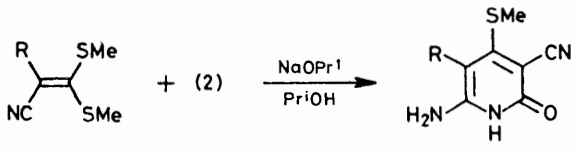


(1) (2) (3)

a; $R^1 = C_6H_5$; $R^2 = H$; $R^3 = Me$
b; $R^1 = p\text{-}MeC_6H_4$; $R^2 = H$; $R^3 = Me$
c; $R^1 = p\text{-}MeOC_6H_4$; $R^2 = H$; $R^3 = Me$
d; $R^1 = o\text{-}MeOC_6H_4$; $R^2 = H$; $R^3 = Me$
e; $R^1 = p\text{-}ClC_6H_4$; $R^2 = H$; $R^3 = Me$
f; $R^1 = p\text{-}BrC_6H_4$; $R^2 = H$; $R^3 = Me$
g; $R^1 = Me$; $R^2 = H$; $R^3 = Me$
h; R^1 = 3-pyridyl; $R^2 = H$; $R^3 = Me$
i; R^1 = 4-pyridyl; $R^2 = H$; $R^3 = Me$
j; $R^1 = C_6H_5$; $R^2 = H$; $R^3 = Me_2CH$
k; $R^1 = p\text{-}MeOC_6H_4$; $R^2 = H$; $R^3 = Et$
l; $R^1 = p\text{-}MeOC_6H_4$; $R^2 = H$; $R^3 = C_6H_5CH_2$
m; $R^1 = Me$; $R^2 = C_6H_5$; $R^3 = Me$
n; $R^1 = Me$; $R^2 = p\text{-}MeOC_6H_4$; $R^3 = Me$
o 1Q; $R^1 = R^2 = C_6H_5$; $R^3 = Me$

SCHEME 1

Reaction of α-cyanoketen *SS*-acetals (4a—d) with (2) was next examined. Thus, when (4a) was refluxed with (2) in the presence of $NaOPr^i$ in Pr^iOH, (5a) was formed in 60% yield. However, lower yields (16—20%) of (5b and c) were obtained in the case of (4b and c), respectively, while the reaction of (4d) with (2) gave an intractable polymeric mixture from which (5d) could not be isolated. Spectral and physical data for the compounds (5a—c) are described in SUP 22229.

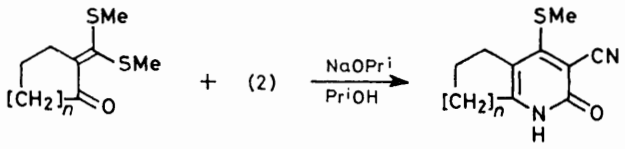


(4) (5)

a; R = CN
b; R = C_6H_5
c; R = $p\text{-}ClC_6H_4$
d; R = $p\text{-}MeOC_6H_4$

SCHEME 2

The method was next extended to cyclic keten *SS*-acetals (6a—c) and (8a—c) in order to prepare fused pyridones. Thus (6a and b) reacted smoothly with cyanoacetamide in the presence of $NaOPr^i$ to give (7a and b), respectively, in 76—77% overall yield (Scheme 3).



(6) (7)

a; n = 1
b; n = 2
c; n = 3

SCHEME 3

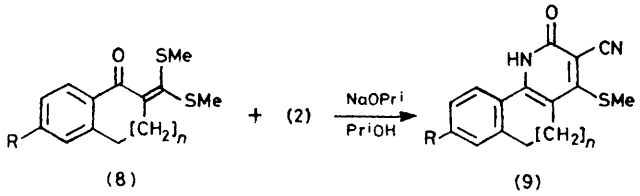
The corresponding seven-membered homologue (7) was obtained, however, in lower yields (30%), even after prolonged refluxing. The keten *SS*-acetals (8a—c) derived from the respective tetralone and benzocycloheptanone, similarly gave benzoquinolone (9a and b) and the seven-membered homologue (9c), respectively, in 43—65% overall yields. The spectral and physical properties of compounds (7a—c) and (9a—c) are described in SUP 22229. Compounds (7a and b) and (9a) have been reported to be formed in unspecified yields, either by the reaction of enamines of the respective ketones [2] with (10) or by acid catalysed cyclization of (11a—c), [3] respectively. In one of the experiments, we

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

[2] P. Eike, Ger. Offen, 1,809,467 (*Chem. Abs.*, 1970, **73**, 66,443k).

[3] P. Eike, Ger. Offen, 1,811,973 (*Chem. Abs.*, 1970, **73**, 559,789).

treated the morpholinoenamine of cyclohexanone with (10) under the reported conditions,[2] and (7b) was isolated



(8) (9)

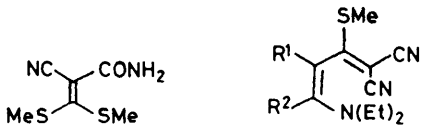
a ; R = H; n = 1
b ; R = MeO; n = 1
c ; R = H; n = 2

SCHEME 4

in very poor yields (m.p., i.r., n.m.r. spectra similar to our compound). Thus, our method is definitely superior because of the simpler conditions and stable starting materials in comparison with the moisture sensitive enamines and (11a—c).

When (1a) was refluxed with (2) in the presence of two equiv. of sodium ethoxide in ethanol, an inseparable mixture of (3a) and (12b) (in a 9 : 1 ratio, characterized by n.m.r.) was always obtained. Our efforts to improve the yield of (12b) by prolonging the reaction time of (1a) with sodium ethoxide, while simultaneously slowing down the addition of cyanoacetamide, failed; similar experiments in the case of the reaction of (1a) with guanidine gave the corresponding alkoxypyrimidines in excellent yields.[1g] These results can best be explained on the basis of the weak nucleophilicity of guanidine in comparison with cyanoacetamide carbanion towards *SS*-acetals (1). While guanidine could react with the *OS*-acetal (13) faster than with the *SS*-acetal (1a), the cyanoacetamide carbanion could react with both (1a) and (13) competitively thus yielding a mixture of 4-methylthio- (3a) and 4-alkoxy-pyridines (12a and b).*

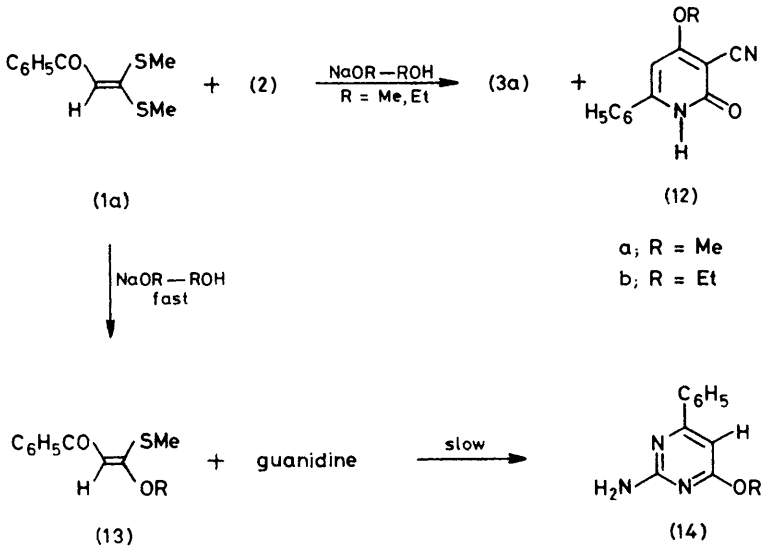
The reaction of cyanoacetamide with keten *SS*-acetals (15a—g), in which the α-proton is replaced by a methyl group, was next examined. Thus, when a mixture of (15a) and (2) was refluxed in the presence of two moles of sodium isopropoxide for 4 h, the product



(10) (11)

a; R¹, R² = [CH₂]₃
b; R¹, R² = [CH₂]₄
c; R¹, R² = C₆H₄[CH₂]₄

isolated was not the expected pyridone (17a), but 3-cyano-4-methylthiomethyl-6-phenyl-2(1*H*)-pyridone [spectral properties and elemental analysis, *m/e* 256 (M^+, $C_{14}H_{12}N_2OS$), $\nu_{max.}$ 2 225 (CN) 1 652 and 1 550 cm^{-1} (C=O and pyridone ring)]. Further confirmation of the structure was obtained from its n.m.r. spectrum, δ 1.98 (3 H, s, Me) and 3.50 (2 H, s, CH_2). The signal for 4-H was present at lower field (δ 8.00) than that for 5-H of (3a) (δ 6.56) due to the deshielding effect of the cyano-group.[4] The formation of (16f and g) carrying SEt and SCH_2Ph groups from (15f and g), respectively, further supported the structure of (16a). Keten *SS*-acetals (15b—e) similarly gave (16b—e), respectively, in 48—63% overall yields. The physical and spectral data (SUP 22229) for compounds (16b—g) were in conformity with the assigned structures.



(1a) (12)

a; R = Me
b; R = Et

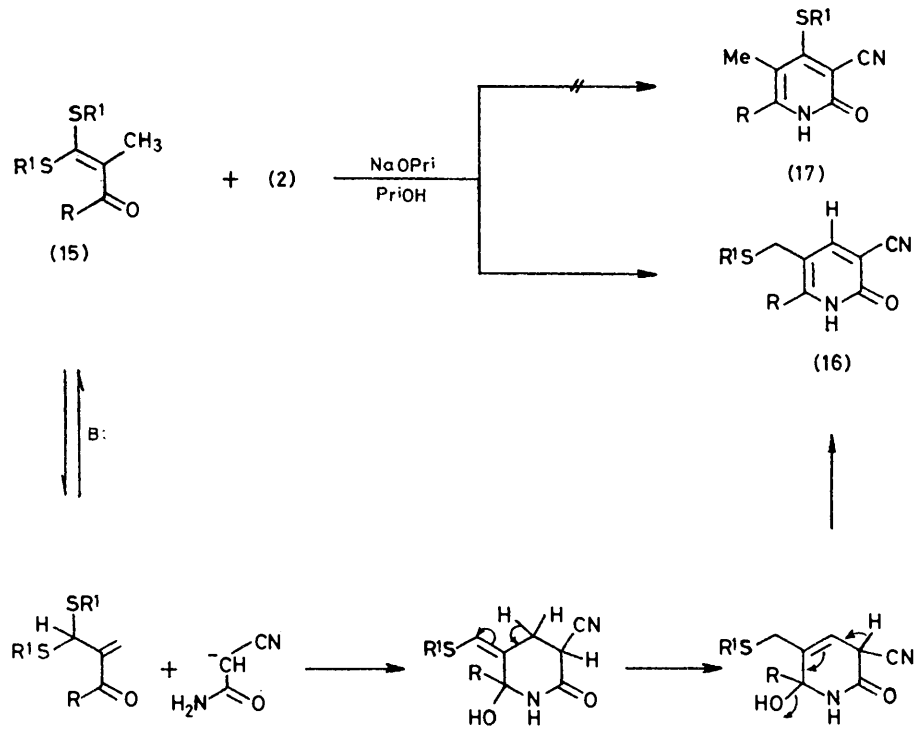
(13) (14)

SCHEME 5

* Attempted synthesis of (12b), by first refluxing (1a) with 1 mole of sodium ethoxide in ethanol for 6—7 h and subsequent addition of the sodium salt of cyanoacetamide in ethanol followed by refluxing for 1 h, resulted in the formation of a dark, intractable mixture from which (12b) could not be isolated.

[4] S. Boatman, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, 1965, **30**, 3593.

Formation of (16a—g) from (15a—g) and cyanoacetamide is analogous to the reaction of (15a—g) with guanidine in the presence of sodium ethoxide,[11] involving a common olefinic intermediates (18a—g) formed by an initial base induced 1,3-proton shift. Allylic displacement of the methylthio group in (18a—g) by cyanoacetamide carbanion followed by ring closure and proton transfer yields (16a—g) as the final products (Scheme 6).

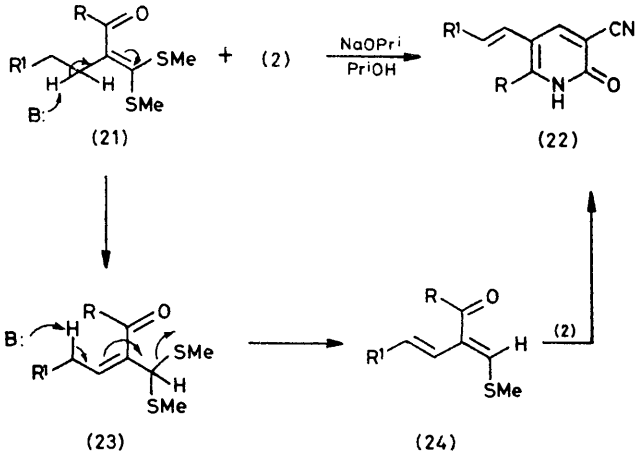


a; R = C_6H_5 ; R^1 = Me
b; R = p-MeC_6H_4 ; R^1 = Me
c; R = p-$MeOC_6H_4$; R^1 = Me
d; R = p-ClC_6H_4 ; R^1 = Me
e; R = p-BrC_6H_4 ; R^1 = Me
f; R = C_6H_5 ; R^1 = Et
g; R = C_6H_5 ; R^1 = $C_6H_5CH_2$

SCHEME 6

Reaction of homologous keten *SS*-acetals (21a—c) with (2) in the presence of sodium isopropoxide, also followed a pattern similar to that observed in the reaction of (21a—c) with guanidine in the presence of sodium ethoxide. Thus, refluxing (21a) with (2) in the presence of two equiv. of sodium isopropoxide in propan-2-ol yielded (22a) in 17% yield. Keten *SS*-acetals (21b and c) similarly afforded (22b and c), respectively. In all these cases, the reaction was found to be slow and appreciable amount of starting material was recovered even after prolonged refluxing. The structures of (22a—c) were established by their physical and spectral data (SUP 22229), *m/e* 222 (M^+ $C_{14}H_{10}N_2O$), 2 210 (CN), 1 650, and 1 550 cm^{-1} (C=O and pyridone ring). The best support for structure (22a) was obtained from the characteristic ABC pattern for the vinyl protons (δ 5.00—6.13) in the n.m.r. spectrum, together with characteristic low field singlet at δ 8.01 (4-H).

Formation of (22a—c) also involves initial base induced isomerization of (21a—c) to olefinic intermediates (23a—c) prior to the attack by (2). The ole-



a; R = C_6H_5 ; R^1 = H
b; R = p-$MeOC_6H_4$; R^1 = H
c; R = C_6H_5 ; R^1 = Me

SCHEME 7

finic intermediates (23a—c) undergo further base catalysed allylic elimination to give the respective diene intermediates (24a—c) which on subsequent reaction with (2) yield the products (22a—c). However, none of the products formed either by 1,3-allylic shift of the methylthio group or by elimination of formaldehyde dithioacetals, as observed in the reaction of guanidine with (21a), could be isolated from the mixture.

EXPERIMENTAL

M.p.s were determined on a Townson and Mercer (England) apparatus (capillary method) and are uncorrected. I.r. spectra were recorded on Perkin-Elmer 137, 177, and 337 spectrophotometers. N.m.r. spectra were obtained on a Varian A-60D spectrometer using tetramethylsilane as internal standard. Mass spectra were recorded with a Hitachi RMU-6E mass spectrometer fitted with a direct inlet system.

Starting Materials.—Keten *SS*-acetals were prepared according to the method reported earlier,[1g,5,6] by condensation of the appropriate ketone or nitrile with carbon disulphide in the presence of two equiv. of sodium t-butoxide and sodium hydride followed by subsequent treatment with alkyl halide.

3,3-*Bis*(*methylthio*)-1-(3-*pyridyl*)*prop*-2-*en*-1-*one* (1h) was obtained as pale yellow plates (ethyl acetate–hexane), yield 62%; m.p. 92—94°; $\delta_{max.}$ (KBr) 1 633 (C≡O) cm^{-1}; δ($CDCl_3$) 2.47 (3 H, s, SCH_3), 6.60 (1 H, s, H-2), 7.01 (1 H, m, pyridyl 5-H'), 7.93—8.10 (1 H, m, pyridyl 4-H), 8.41—8.66 (1 H, m, pyridyl 2- or 6-H), and 8.83—8.96 (1 H, m, pyridyl 6- or 2-H) (Found: C, 53.4; H, 4.7; N, 6.35. $C_{10}H_{11}NOS_2$ requires C, 53.35; H, 4.9; N, 6.2%).

3,3-*Bis*(*methylthio*)-1-(4-*pyridyl*)*prop*-2-*en*-1-*one* (1i) was purified by crystallization from ethyl acetate–hexane as brownish yellow plates, m.p. 103—104°; yield 65%; $\nu_{max.}$ (KBr) 1 610 (C=O) cm^{-1}; δ($CDCl_3$) 7.68 (2 H, dd, pyridyl 3- and 5-H) and 8.53—8.68 (2 H, dd, pyridyl 2- and 6-H) (Found: C, 53.2; H, 4.7; N, 6.1%).

3,3-*Bis*(*isopropylthio*)-1-*phenylprop*-2-*en*-1-*one* (1j) was obtained as light yellow needles (benzene–hexane) in 50% yield, m.p. 90°; $\nu_{max.}$ (KBr) 1 635 (C=O) cm^{-1}; δ($CDCl_3$) 1.40 [6 H, d, $CH(CH_3)_2$], 1.42 [6 H, d, $SCH(CH_3)_2$], 3.67—3.73 [2 H, quint, $-CH(CH_3)_2$], 7.00 (1 H, s, 2-H), and 7.50—7.83 (5 H, m, ArH) (Found: C, 64.6; H, 7.45. $C_{15}H_{20}OS_2$ requires C, 64.25; H, 7.2%).

3,3-*Bis*(*ethylthio*)-1-(p-*methoxyphenyl*)*prop*-2-*en*-1-*one* (1k) was purified by crystallization from benzene–hexane, yield 78%; m.p. 65—66°, $\nu_{max.}$ (KBr) 1 639 (C=O) cm^{-1}; δ($CDCl_3$) 1.42 (3 H, t, SCH_2CH_3), 1.47 (3 H, t, SCH_2CH_3), 3.08 (2 H, q, SCH_2CH_3), 3.13 (2 H, q, SCH_2CH_3), 3.83 (3 H, s, p-$CH_3OC_6H_4$), and 6.83 (1 H, s, 2-H), 6.90—7.83 (4 H, dd, A_2B_2, ArH) (Found: C, 59.4; H, 6.3. $C_{14}H_{18}O_2S_2$ requires C, 59.55; H, 6.2%).

3,3-*Bis*(*methylthio*)-1,2-*diphenylprop*-2-*en*-1-*one* (1o) was obtained in 68% yield as light yellow plates (ethyl acetate–hexane), m.p. 108°; $\nu_{max.}$ (KBr) 1 653 (C=O) cm^{-1}; δ($CDCl_3$) 2.29 (3 H, s, SCH_3), 2.35 (3 H, s, SCH_3), 7.5—7.9 (10 H, m, ArH) (Found: C, 67.9; H, 5.2. $C_{17}H_{16}OS_2$ requires C, 68.0; H, 5.35%).

2-[*Bis*(*methylthio*)*methylene*]-2,3,4,5-*tetrahydrobenzocyclohepten*-1-*one* (8c) was crystallized from ethyl acetate–hexane as light yellow needles, yield 56%; m.p. 61°; $\nu_{max.}$ (KBr) 1 618 (C=O) cm^{-1}; δ($CDCl_3$) 2.40 (3 H, s, SCH_3), 2.43 (3 H, s, SCH_3), 1.76—2.96 (6 H, m, 3-, 4-, 5-H_2), 7.03—7.56 (3 H, m, ArH), and 7.75—7.96 (1 H, m, 9-H) (Found: C, 63.2; H, 5.9. $C_{14}H_{16}OS_2$ requires C, 63.65; H, 6.1%).

3,3-*Bis*(*methylthio*)-2-*methyl*-1-(p-*tolyl*)*prop*-2-*en*-1-*one* (15b) was obtained as an orange, viscous liquid after purification by distillation, b.p. 185—190° at 1 mmHg; yield 64%; $\nu_{max.}$ (film) 1 635 (C=O) cm^{-1}; δ($CDCl_3$) 2.08 (3 H, s, SCH_3), 2.18 (3 H, s, 2-CH_3), 2.35 (3 H, s, SCH_3), 2.42 (3 H, s, p-$CH_3C_6H_4$), 7.26—7.48 (2 H, m, ArH), and 7.55—7.90 (2 H, m, ArH) (Found: C, 61.6; H, 6.0. $C_{13}H_{16}OS_2$ requires C, 61.9; N, 6.4%).

3,3-*Bis*(*methylthio*)-1-(p-*chlorophenyl*)-2-*methylpropen*-2-1-*one* (15d) was purified by distillation, orange-red oil, b.p. 195—200° at 1 mmHg; yield 73%; $\nu_{max.}$ (film) 1 640 (C=O) cm^{-1}; n.m.r. ($CDCl_3$) 2.08 (3 H, s, SCH_3), 2.20 (3 H, s, 2-CH_3), 2.36 (3 H, s, SCH_3), 7.36—7.66 (2 H, m, ArH), 7.80—8.00 (2 H, m, ArH) (Found: C, 52.6; H, 3.9. $C_{12}H_{13}ClOS_2$ requires C, 52.85; H, 4.25%).

3,3-*Bis*(*methylthio*)-1-(p-*bromophenyl*)-2-*methylpropen*-2-1-*one* (15e) was obtained as a red oil on distillation, b.p. 180—185° at 1 mmHg; yield 65%; $\nu_{max.}$ (film) 1 640 (C=O) cm^{-1}; δ($CDCl_3$) 2.06 (3 H, s, SCH_3), 2.20 (3 H, s, 2-CH_3), 2.38 (3 H, s, SCH_3), 7.30—7.96 (4 H, m, ArH) (Found: C, 47.2; H, 4.6. $C_{12}H_{13}BrOS_2$ requires C, 47.5; H, 4.3%).

General Procedure for the Preparation of 4-*Alkylthio*-3-*cyano*-2(1H)-*pyridones.*—To a solution of sodium isopropoxide [prepared by dissolving sodium (0.46 g, 0.02 mol) in propan-2-ol (70 ml)], cyanoacetamide (1.68 g, 0.02 mol) was added and the mixture was shaken for 5—10 min. The appropriate keten *SS*-acetal (0.02 mol) was then added and the mixture refluxed for 0.5—8 h. Evaporation of the solvent yielded a bright yellow to orange sodium salt of the pyridone which was dissolved in water (20—25 ml) and acidified with dilute HCl (8%) to give the pyridone as an amorphous solid which was purified by crystallization.

All the pyridones (3a—n), (7a—c), (9a—c), (16a—g), and (22a—c) were prepared by the above procedure. In a few cases (7c) and (22a—c), acidification of the reaction mixture gave a viscous semisolid from which pure pyridones were obtained by trituration with hexane.

Pyridones (5a—c) were also prepared by the above general procedure except that the sodium salt obtained after evaporation of the solvent was first neutralized with glacial AcOH (3—4 ml) followed by subsequent addition of water.

In the preparation of pyridones (16a—g) and (22a—c), 2 equiv. (0.04 mol) of sodium isopropoxide were employed, giving greater yields.

Reaction of 1-*Morpholinocyclohexene with Compound* (1o).—A mixture of 1-morpholinocyclohexene (1.67 g, 0.01 mol) [7] and (10) (1.98 g, 0.01 mol) in dry dioxan (30 ml) was refluxed under nitrogen for 5 h. The mixture after evaporation of solvent and dilution with water gave a pale yellow viscous semisolid which on trituration with hexane gave (7b) (0.24 g, 11%), m.p., i.r., n.m.r. identical with those of (7b) obtained from (6b).

R. R. R. and A. K. thank the CSIR for Junior Research Fellowships.

[7/1351 *Received*, 25*th July*, 1977]

[5] A. Thuillier and J. Vialle, *Bull. Soc. chim. France*, 1959, 1398.

[6] I. Shahak and Y. Sasson, *Tetrahedron Letters*, 1973, 4207.

[7] S. Hünig, E. Lücke, and W. Brenninger, *Org. Synth.*, 1961, **41**, 65.