Keten *SS*-Acetals.‡ Part 10.[1] Reaction of α-Oxoketen *SS*-Acetals with *N*-Alkylcyanoacetamides: a New General Method for Substituted and Fused 2,7-Dialkyl-8-amino-5-cyano-2,7-naphthyridine-1,6(2*H*,7*H*)-diones

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The reaction of α-oxoketen *SS*-acetals (1a—j) with *N*-methyl- and *N*-ethyl-cyanoacetamide (2a and b) in the presence of sodium isopropoxide gives good yields of 2,7-naphthyridine derivatives (4a—j) and (4k—r) respectively, which are shown to be formed through further reaction of intermediate *N*-alkylpyridones (3a—r) with anions of either (2a or b). The α-cyanoketen *SS*-acetals (9a—c), however, gave the corresponding 6-aminopyridones (10a—f) under similar conditions, whereas cyclic keten *SS*-acetals (11a and b) yielded the respective fused naphthyridines (12a—d) in excellent yields. Keten *SS*-acetals (15a and b) also react smoothly with (2a and b) to afford novel naphthonaphthyridone derivatives (16a—d) in good yields; the corresponding benzocycloheptanonaphthyridines (16e and f) were similarly obtained under identical conditions by the reaction of (15c) with (2a and b) respectively. α-Alkyl-α-oxoketen *SS*-acetals (17a—d), however, gave poor yields of pyridones (18a—e) on prolonged refluxing with either (2a or b).

In the preceding paper,[1] we described a general method for the preparation of a variety of substituted and fused 4-alkylthio-3-cyano-2(1*H*)-pyridones by the reaction of α-oxoketen *SS*-acetals with cyanoacetamide in the presence of sodium isopropoxide. The ease with which this reaction proceeds and the excellent yields of the products obtained prompted us to extend this reaction for the preparation of hitherto unknown *N*-alkyl-4-alkylthio-3-cyano-2(1*H*)-pyridones (3a—r) by the reaction of (1a—j) with *N*-alkylcyanoacetamides (2a and b). However, when (1a—j) were treated with either (2a or b), the expected pyridones (3a—r) were not obtained, though the final products isolated were shown to be formed through the intermediacy of (3a—r).

RESULTS AND DISCUSSION

Keten *SS*-acetal (1a) reacted with one equiv. of (2a) in the presence of sodium isopropoxide in refluxing propan-2-ol to give a product in 38% yield, which was characterized as 8-amino-5-cyano-2,7-dimethyl-3-phenyl-2,7-naphthyridine-1,6(2*H*,7*H*)-dione (4a) by spectral and analytical data. Thus compound (4a) showed *m/e* 306 (M^+, $C_{17}H_{14}N_4O_2$), $\nu_{max.}$ 3 400, 3 280, 3 200 (NH_2 free and bonded), 2 193 (CN), 1 650, 1 630, and 1 600 cm^{-1} (C=O and NH_2), $\lambda_{max.}$ 247 (log ε 4.19), 284 (4.64), 324 (3.90), and 362 nm (3.99). Further support for structure (4a) was obtained from the n.m.r. spectrum (CF_3CO_2H), which indicated the absence of signal due to the methylthio group, while on the other hand, singlets due to two *N*-methyl groups were present at δ 3.07 (3 H) and 3.33 (3 H). The presence of a sharp singlet at δ 6.27 (1 H, 4-H) and a multiplet at 7.09 (5 H, ArH) further confirmed the structure (4a). The reaction of (1a) with (2b) similarly yielded the corresponding 2,7-diethyl derivative (4k) (Scheme 1), the identity of which was also established by spectral and analytical data, *m/e* 334 (M^+), $\nu_{max.}$ 3 410, 3 314, 3 225 (NH_2 free and bonded), 2 198 (CN), 1 650, 1 638, and 1 618 cm^{-1} (C=O and NH_2), $\lambda_{max.}$ 250 (log ε 4.12), 287 (4.45), 325 (3.90), and 362 nm (4.03), δ 0.80 (3 H, t, NCH_2CH_3), 1.05 (3 H, t, NCH_2CH_3), 3.65 (2 H, q, NCH_2CH_3), 4.00 (2 H, q, NCH_2CH_3), 6.23 (1 H, s, 4-H), and 7.03 (5 H, m, ArH).

Formation of (4a) by the reaction of (1a) with (2a), can be rationalized by the initial formation of *N*-methylpyridone (3a), and its subsequent rapid reaction *in situ* with the anion of (2a), which gives (4a) as the sole product. However, all attempts to isolate (3a) from the mixture under various conditions [using lower temperatures and slowly adding the sodium salt of (2a) to a solution of (1a) in propan-2-ol] were not successful. On the other hand, improved yields of (4a) (75%) were obtained, when the reaction was carried out in the presence of two moles of (2a). Similarly, when (8) was treated with (2a) under identical conditions, in order to isolate the pyridone (3s), the product isolated was found to be identical with (4c) (by m.p., i.r., and n.m.r.). The intermediacy of (3a) was, however, established by preparing (4a) through a different route. Alkylation of pyridone (5a) with dimethyl sulphate in the presence of sodium methoxide gave a mixture of *N*- and *O*-alkyl products (3a) and (6), respectively, which were separated by column chromatography. Subsequent reaction of (3a) with one mole of (2a) in the presence of sodium isopropoxide afforded (4a) in nearly quantitative yields within 30 min. The reaction of (3a) with (2b and c) similarly afforded (4s and t), respectively, in excellent yields, which further supports the intermediacy of (3a). The structures of (4s and t) were established by spectral and analytical data given in Supplementary Publication No. SUP 22232 (20 pp.).§

The reaction of other substituted keten *SS*-acetals (1b—j) with (2a and b) under identical conditions similarly afforded (4b—j) and (4l—r), respectively, in 25—93% overall yield (Scheme 1). The spectral and physical data for the compounds (4a—r) are given in SUP 22232.

Formation of (4a) from (3a) and (2a) must involve nucleophilic displacement of the 4-alkylthio group by the anion of (2a) (Scheme 2), followed by subsequent

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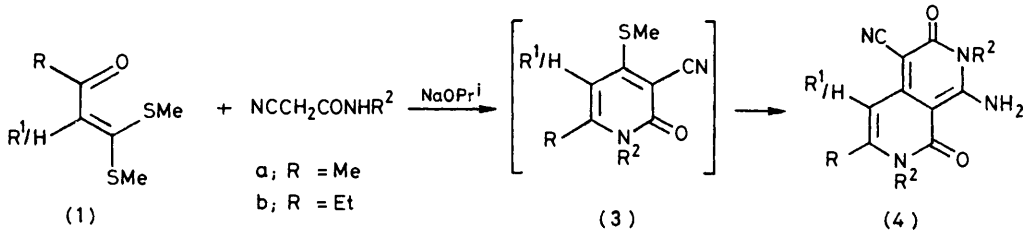
‡ Properly called keten dithioacetals.

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

[1] Part 9, R. R. Rastogi, A. Kumar, H. Ila, and H. Junjappa, preceding paper.



(1)

a; R = Me
b; R = Et

(3)

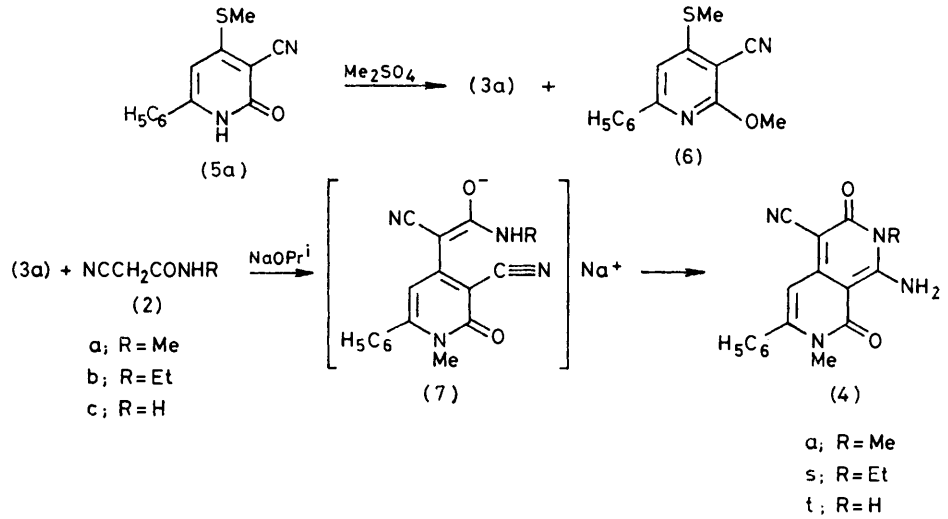
(4)

a; $R = C_6H_5$
b; $R = p\text{-}MeC_6H_4$
c; $R = p\text{-}MeOC_6H_4$
d; $R = o\text{-}MeOC_6H_4$
e; $R = p\text{-}ClC_6H_4$
f; $R = p\text{-}BrC_6H_4$
g; R = Me
h; R = 4-pyridyl
i; $R = Me; R^1 = C_6H_5$
j; $R = Me; R^1 = p\text{-}MeOC_6H_4$

a; $R = C_6H_5; R^2 = Me$
b; $R = p\text{-}MeC_6H_4; R^2 = Me$
c; $R = p\text{-}MeOC_6H_4; R^2 = Me$
d; $R = o\text{-}MeOC_6H_4; R^2 = Me$
e; $R = p\text{-}ClC_6H_4; R^2 = Me$
f; $R = p\text{-}BrC_6H_4; R^2 = Me$
g; $R = Me; R^2 = Me$
h; R = 4-pyridyl; $R^2 = Me$
i; $R = Me; R^1 = C_6H_5; R^2 = Me$
j; $R = Me; R^1 = p\text{-}MeOC_6H_4; R^2 = Me$

k; $R = C_6H_5; R^2 = Et$
l; $R = p\text{-}MeC_6H_4; R^2 = Et$
m; $R = p\text{-}MeOC_6H_4; R^2 = Et$
n; $R = o\text{-}MeOC_6H_4; R^2 = Et$
o; $R = p\text{-}ClC_6H_4; R^2 = Et$
p; $R = p\text{-}BrC_6H_4; R^2 = Et$
q; R = Me; $R^2 = Et$
r; R = 4-pyridyl; $R^2 = Et$

SCHEME 1



(5a)

(6)

(2)

a; R = Me
b; R = Et
c; R = H

(7)

(4)

a; R = Me
s; R = Et
t; R = H

(8)

(2a)

(3s)

(4c)

SCHEME 2

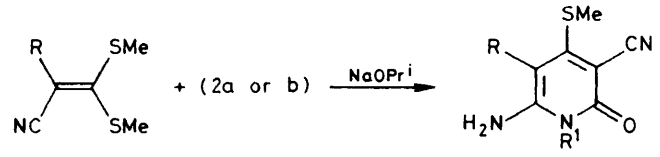
ready intramolecular cyclization of the 4-amidomethyl intermediate (7a) to afford (4a) in good yields. The presence of a 3-cyano group in (3a) enhances the electrophilicity of the pyridone ring, thus facilitating nucleophilic displacement by the anion of (2a) at the 4-position. Substituted nicotinonitrile derivatives with 4-acylmethyl or related side chains are known to undergo ready interaction with neighbouring 3-cyano groups to give 2,7-naphthyridine derivatives under various conditions.[2] 2,7-Naphthyridine derivatives have also been reported[3]

[2] (*a*) W. W. Paudler and T. J. Kress, *Adv. Heterocyclic Chem.*, 1970, **11**, 155; (*b*) J. M. Bobbitt and R. E. Doolittle, *J. Org. Chem.*, 1964, **29**, 2298; (*c*) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1965, **87**, 5198; (*d*) D. J. Sheffield and K. R. H. Woolridge, *J. Chem. Soc.* (*C*), 1972, 2506; (*e*) E. Wenkert, K. D. Dave, R. G. Lewis, and P. W. Sprague, *J. Amer. Chem. Soc.*, 1967, **89**, 6741; (*f*) E. Wenkert, E. B. Spitzner, and R. L. Webb, *Austral. J. Chem.*, 1972, **25**, 433 and references therein.

[3] (*a*) L. Birkofer and C. Kaiser, *Chem. Ber.*, 1957, **90**, 2933; (*b*) F. Krohnke, K. Ellegast, and E. Bertram, *Annalen*, 1956, **600**, 198.

to be formed by the base induced condensation of acetone or acetophenone with *N*-methylnicotinamide salt followed by subsequent cyclization of the initially formed 4-acylmethyl-*N*-methyl-1,4-dihydronicotinamide adduct. Thus the cyclization of (7a) to (4a) is not very unusual. However, the replacement of the 4-alkylthio group by an active methylene compound in (3a), appears to be of potential synthetic importance, as it provides scope for introducing a carbon side chain in the 4-position of a pyridone ring.[4] Work on this is under investigation.

The reaction of α-cyanoketen *SS*-acetals (9a—c) with (2a and b) was next examined. When (9a) was refluxed with one or two moles of (2a) in the presence of sodium isopropoxide, the product obtained was characterized as 6-amino-3-cyano-*N*-methyl-4-methylthio-2-(1*H*)-pyridone (10a). Thus the presence of an electron-donating 6-amino function in (10a) diminishes the electrophilicity of the pyridone ring, with the result that further attack on (10a) by the anion of *N*-alkylcyanoacetamide is prevented. The pyridones (10b—f) (Scheme 3) were similarly obtained in 46—68% overall yield by the reaction of the respective keten *SS*-acetals (9a—c) with either (2a or b). Spectral and physical data are in SNP 22232.



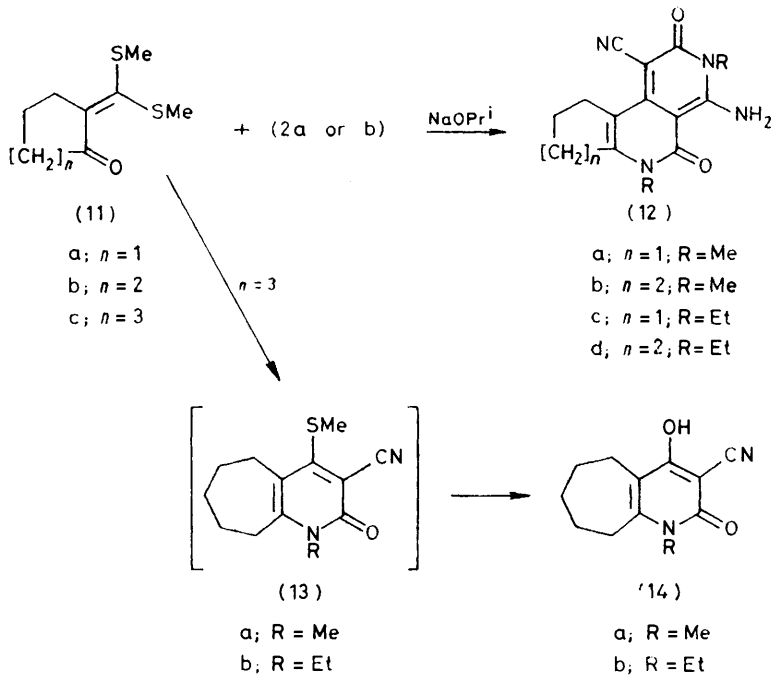
(9)

a; R = C_6H_5
b; R = *p*-ClC_6H_4
c; R = CN

(10)

a; R = C_6H_5; R^1 = Me
b; R = *p*-ClC_6H_4; R^1 = Me
c; R = CN; R^1 = Me
d; R = C_6H_5; R^1 = Et
e; R = *p*-ClC_6H_4; R^1 = Et
f; R = CN; R^1 = Et

SCHEME 3



(11)

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

(12)

a; *n* = 1; R = Me
b; *n* = 2; R = Me
c; *n* = 1; R = Et
d; *n* = 2; R = Et

(13)

a; R = Me
b; R = Et

(14)

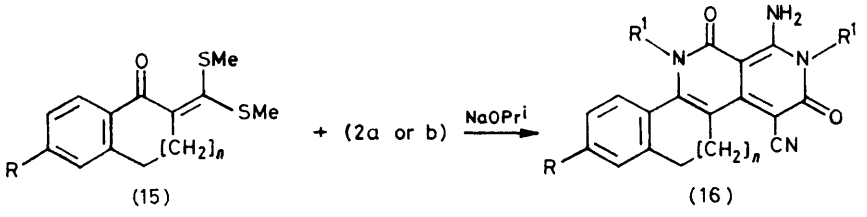
a; R = Me
b; R = Et

SCHEME 4

Treatment of cyclic keten *SS*-acetals (11a and b) with either (2a or b) in the presence of sodium isopropoxide yielded the corresponding 3,4-fused 2,7-naphthyridine derivatives (12a—d), respectively, in 71—80% overall yields (Scheme 4). The physical and spectral data (SUP 22232) for (12a—d) were in agreement with the

[4] E. Wenkert, C. J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Amer. Chem. Soc.*, 1976, **98**, 3645 and references therein.

assigned structures. The reaction of the corresponding seven-membered acetal (11c) with either (2a or b), however, gave different products, which were characterized as *N*-alkyl-3-cyano-4-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepteno[*b*]pyridin-2(1*H*)-ones (14a and b) respectively. These products (14a and b) must have been most cases the starting materials were recovered when the reaction was worked up after 1 h. However, when (17a) and (2a) were refluxed for 8—10 h in the presence of two equiv. of sodium isopropoxide, the rearranged product (18a) was obtained in 16% yield. The pyridones (18b—e) were similarly formed in 16—19% overall



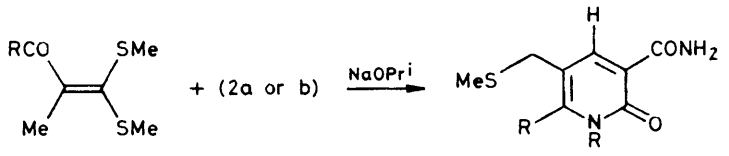
(15)

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

(16)

a; R = H; *n* = 1; R¹ = Me
b; R = MeO; *n* = 1; R¹ = Me
c; R = H; *n* = 2; R¹ = Me
d; R = H; *n* = 1; R¹ = Et
e; R = MeO; *n* = 1; R¹ = Et
f; R = H; *n* = 2; R¹ = Et

SCHEME 5



(17)

a; R = *p*-MeC$_6$H$_4$
b; R = *p*-MeC$_6$H$_4$
c; R = *p*-ClC$_6$H$_4$
d; R = *p*-BrC$_6$H$_4$

(18)

a; R = *p*-MeC$_6$H$_4$; R¹ = Me
b; R = *p*-MeOC$_6$H$_4$; R¹ = Me
c; R = *p*-ClC$_6$H$_4$; R¹ = Me
d; R = *p*-BrC$_6$H$_4$; R¹ = Me
e; R = *p*-MeC$_6$H$_4$; R¹ = Et

SCHEME 6

formed through base induced hydrolysis of (13a and b), respectively, during work-up of the reaction mixtures. The physical and spectral data are in SUP 22232. When the cyclic keten *SS*-acetals (15a and b), derived from the respective tetralones, were treated with (2a and b) under similar conditions, the corresponding naphthonaphthyridine derivatives (16a and b) and (16d and e) were obtained in 80—90% overall yield (Scheme 5). Similar treatment of (15c) with (2a and b) afforded the corresponding naphthyridines (16c and f) in good yield. Spectral and physical data are in SUP 22232.

From the examples discussed, it is apparent that the reaction of *N*-alkylcyanoacetamide with keten *SS*-acetals affords a ready one-step entry to a variety of novel substituted and fused 2,7-naphthyridine derivatives. The scope of this reaction for the preparation of 8-alkyl- and 8-aryl-2,7-naphthyridine derivatives by using α-acyl- or aroyl-*N*-alkylcyanoacetamide is under investigation.

The reaction of α-methyl-α-oxoketen *SS*-acetals (17a—d) with (2a and b) was found to be very slow and in yields (Scheme 6). The structures were confirmed by spectral and analytical data (SUP 22232).

EXPERIMENTAL

See Part 9 [1] for general details.

Starting Materials.—Keten *SS*-acetals were prepared by the reported method by the condensation of the respective ketones or nitriles with carbon disulphide in the presence of equimolar quantities of sodium t-butoxide or sodium hydride followed by subsequent treatment with methyl iodide.[1] *N*-Methyl- (2a) and *N*-ethyl-cyanoacetamide (2b) were prepared by the condensation of ethyl cyanoacetate with methyl- and ethyl-amine respectively at lower temperatures.

General Method for the Preparation of Substituted and Fused 2,7-Dialkyl-8-amino-5-cyano-2,7-naphthyridine-1,6-(2H,7H)-diones.—To a solution of sodium isopropoxide [prepared by dissolving sodium (0.46 g, 0.02 mol) in propan-2-ol (70 ml)], *N*-methyl- or *N*-ethyl-cyanoacetamide (0.02 mol) was added and the mixture was stirred for 5—10 min. The appropriate keten *SS*-acetal (0.01 mol) was then added and the mixture was refluxed for 0.5—2 h. The solvent was then distilled off under reduced pressure and the residue diluted with water. Neutralization of the diluted

mixture with a few drops of dilute HCl gave amorphous solids, which were filtered and purified by crystallization.

2,7-Naphthyridinediones (4a—t), (12a—d), and (16a—f) (SUP 22232) were prepared by the above general procedure. The reaction of (11c) with either (2a or b) under identical conditions yielded a viscous semisolid, which on trituration with hexane gave (14a and b), respectively, as colourless solids.

N-Alkyl-6-aminopyridones (10a—f) (SUP 22232) were also obtained in the same manner, by using *N*-alkylcyanoacetamide (0.011 mol). Pyridones (18a—e) (SUP 22232) were also prepared by the above general procedure by using sodium isopropoxide (0.02 mol) and *N*-alkylcyanoacetamide (0.01 mol) and refluxing the mixture for a longer time (8—10 h). The viscous semisolids obtained by work-up of the mixture were triturated with hexane and the solids obtained were purified by crystallization.

Alkylation of (5a). *Preparation of* 3-*Cyano*-N-*methyl*-4-*methylthio*-6-*phenyl*-2(1H)-*pyridone* (3a) *and* 3-*Cyano*-2-*methoxy*-4-*methylthio*-6-*phenylpyridine* (6).—To a solution of sodium methoxide [prepared by dissolving sodium (1.38 g, 0.06 mol) in absolute methanol (200 ml)], compound (5a) (12.1 g, 0.05 mol) was added and the mixture was stirred at room temperature for 10—15 min. Dry dimethyl sulphate (8.82 g, 0.07 mol) was then added and the mixture was refluxed with stirring for 3 h. Removal of the solvent and dilution of the residue with cold water gave a solid which was filtered and dried. The product was then dissolved in boiling chloroform and the solution was filtered to remove the unalkylated pyridone (5a). The filtrate was then concentrated and the solid (9.8 g) obtained was chromatographed on a silica gel column. Elution with benzene–chloroform (1 : 1) gave (6a) (3.20 g, 25%) as *needles*, m.p. 144—145°; $\nu_{max.}$ (KBr) 2 190 cm^{-1} (C≡N); δ($CDCl_3$) 2.63 (3 H, s, SCH_3), 4.10 (3 H, s, OCH_3), 7.17 (1 H, s, 5-H), 7.25—7.65 (3 H, m, ArH), and 7.90—8.15 (2 H, m, ArH) (Found: C, 65.4; H, 4.5; N, 10.85. $C_{14}H_{12}OS$ requires C, 65.6; H, 4.7; N, 10.95%). Further elution with chloroform gave (3a) (5.40 g, 42%) as a *solid*, m.p. 180°; $\nu_{max.}$ (KBr) 2 193 (C≡N) and 1 631 cm^{-1} (C=O); δ($CDCl_3$) 2.51 (3 H, s, SCH_3), 3.31 (3 H, s, NCH_3), 6.05 (1 H, s, 5-H), and 7.30—7.65 (5 H, m, ArH) (Found: C, 65.7; H, 4.3; N, 10.75. $C_{14}H_{12}N_2OS$ requires C, 65.6; H, 4.7; N, 10.95%).

Reaction of Compound (3a) *with* (2a—c). *Preparation of* (4a, s, *and* t).—To a solution of sodium isopropoxide [prepared by dissolving sodium (0.115 g, 0.005 mol) in propan-2-ol (25 ml)], (2a) (0.49 g, 0.005 mol) was added and the mixture was shaken for 5 min. *N*-Methylpyridone (3a) (1.28 g, 0.005 mol) was then added and the mixture was refluxed for 1 h. Evaporation of the solvent followed by dilution with water and subsequent neutralization with dilute HCl gave (4a) as an amorphous solid. Compounds (4s and t) were also prepared in the same manner by using (2b and c) (0.005 mol) respectively.

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