Pergamon

Tetrahedron Vol. 51, No. 5, pp. 1337-1344, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01020-X

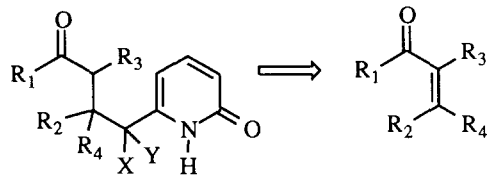
Conjugate Addition Reactions of Metallated Alkyl Pyridines. A Direct Route to 6-Substituted Pyridones

George A. Kraus* Danette R. Vines and John H. Malpert

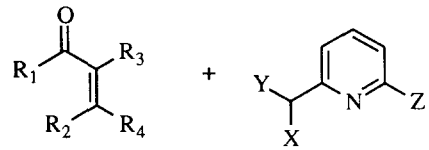
Department of Chemistry, Iowa State University, Ames, IA 50011

Abstract: The conjugate addition of metallated alkylpyridines to enones followed by RaNi deprotection affords 6-substituted pyridones.

Recently, we required a direct synthesis of 6-substituted pyridones such as **1**. A direct route to these compounds would be the conjugate addition of a side-chain metallated pyridine with an α,β-unsaturated ketone. Although the aldol[1], alkylation[2] and acylation[3] reactions of the anion of 2-methyl pyridine and related compounds have been well documented, the use of these anions as donors in conjugate addition reactions has no precedent. Cyclohexenone (**2a**), l-carvone (**2b**), 3-penten-2-one (**3a**) and methyl vinyl ketone (**3b**) and pyridines **4a-e** were chosen to explore this pathway.



1

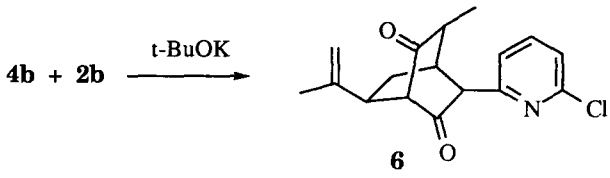


4a: X=Y=H, Z=Cl
4b: X=H, Y=CO_2Me, Z=Cl
4c: X=Y=SMe, Z=Cl
4d: X=Y=SMe, Z=OMe
4e: X=Y=SMe, Z=OCH_2Ph

Pyridine **4a** was deprotonated using lithium diisopropylamide (LDA) in THF at 0 °C.[4] The resulting anion was treated at -78 °C with l-carvone to afford alcohol **5** in 84% yield. No product resulting from 1,4-addition was observed. In recent years, many reaction conditions which provide 1,4-addition products using cuprates or higher order cuprates have been described.[5] Unfortunately, as the results in Table 1 indicate, the addition of CuCN or CuCN-HMPA did not change the regioselectivity of the addition reaction.

We next varied the acidity of the Michael donor by introducing anion-stabilizing groups. Reaction of the anion of **4a** with carbon dioxide followed by DCC-mediated esterification with methanol gave ester **4b** in 34%

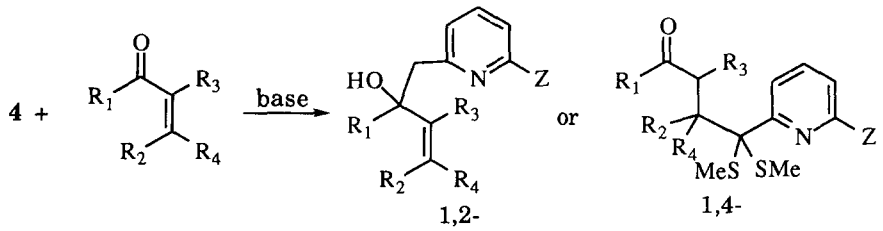
yield. Although the lithium anion was not reactive, the potassium anion, formed with potassium tert-butoxide at 0 °C, provided the unexpected bicyclic adduct **6**.



6

The reaction of the anion of **4a** with dimethyl disulfide followed by addition of a second equivalent of base and a second equivalent of dimethyl disulfide generated pyridine **4c** in 81% overall yield. Deprotonation of **4c** with n-butyl

Table 1. The Reaction of Pyridyl Anions with Enones.



1,2- 1,4-

R_1	R_2	R_3	R_4	Z	base	Product	Yield	cmpd.
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	Cl	LDA	1,2	84%	**5**
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	Cl	nBuLi, CuCN	1,2	69%	**5**
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	Cl	nBuLi, CuCN HMPA	1,2	100%	**5**
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	Cl	nBuLi, HMPA	1,4-	52%	**7**
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	Cl	nBuLi, CuI	1,4-	98%	**7**
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	OMe	nBuLi, HMPA	1,4-	61%	**8**
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	OBn	nBuLi, HMPA	1,4-	9%	**9**
$CH_2CH(C(Me)=CH_2)CH_2$		Me	H	OBn	nBuLi, CuI	1,4-	99%	**9**
$CH_2CH_2CH_2$		H	H	Cl	LDA	1,2-	64%	**10**
$CH_2CH_2CH_2$		H	H	Cl	nBuLi, CuI	1,4-	100%	**11**
Me	H	H	Me	OBn	nBuLi, CuI	1,4-	56%	**12**
Me	H	H	H	OBn	nBuLi, CuI	1,4-	100%	**13**

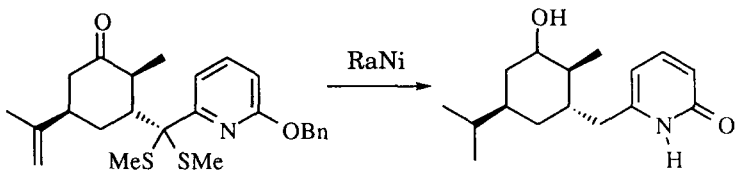
lithium and reaction with carvone provided ketone **7**. Unfortunately, we could not transform **7** into a pyridone by nucleophilic displacement of the chloride with sodium methoxide. Apparently, aldol condensations preferentially occurred.

Conjugate addition of a pyridine bearing an alkoxy group became our next objective. The reaction of **4c** with sodium methoxide in methanol[6] provided pyridine **4d** in 57% yield. Deprotonation of **4d** with n-butyl lithium and addition of HMPA followed by carvone afforded 1,4-addition product **8** in 61% yield. Attempted liberation of the pyridone using Lewis acids[7] gave complex mixtures of products. Clearly, a more labile protecting group was required.

Pyridine **4e** was readily available from **4c** by displacement of the chloride using sodium benzyloxide in benzyl alcohol. The reaction of the anion of **4e** (nBuLi, -78 °C, THF) with carvone furnished isomeric ketones **9a** and **9b** in 9% yield. The yield of **9a** and **9b** could be improved to 99% by the addition of CuI before the addition of carvone.

A parallel sequence was conducted with enones **2a**, **3a** and **3b**. The reaction of **4a** with cyclohexenone provided alcohol **10** in 64% yield. The reaction of **4e** with cyclohexenone, 3-penten-2-one and methyl vinyl ketone afforded the conjugate addition products **11** , **12** and **13** in 100% , 56% and 100% yields, respectively.

The transformation of **9a** into pyridone **12** was first attempted using TMSI. No pyridone-containing products were isolated. Attempted deprotection using catalytic hydrogenation (Pd/C, H_2) returned recovered starting material.[8] However, treatment of **9a** with freshly-prepared RaNi provided pyridone **14** in 85% yield.



9a **14**

The direct synthesis of pyridone **14** demonstrates that our conjugate addition/deprotection strategy is feasible. The two step pathway proceeds in good overall yields. Since pyridones are common structural subunits in many biologically active compounds[9], this route should have broad application.

Acknowledgement. We thank the ISU Biotechnology Committee for support of this research. DV gratefully acknowledges the receipt of a GAANN Fellowship from the Department of Chemistry at Iowa State University.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography

(sgc). The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis. All of the compounds prepared in this study were light yellow oils.

Methyl 6-chloropyridine-2-acetate (4b): To a solution of 6-chloro-2-picoline (0.76 g, 6 mmol) in THF (30 mL) at 0 °C was added n-BuLi (2.35 M in hexane, 6.6 mmol, 2.81 mL). The temperature was lowered to -78 °C and carbon dioxide was bubbled through the reaction mixture. The mixture was allowed to warm to 0 °C and then to rt. The mixture was quenched by the addition of 0.50 mL of trifluoroacetic acid. The mixture was diluted with THF , filtrered through a pad of Celite, and concentrated. To a solution of the crude acid in methylene chloride (0.1 M) was added 4-dimethylaminopyridine (73 mg, 0.6 mmol) and methanol (384 mg, 12 mmol). The mixture was cooled to 0 °C and dicyclohexylcarbodiimide (1.24g, 6 mmol) in methylene chloride was added. The mixture was stirred for two days at rt. The residue was purified by silica gel chromatography (hexane: AcOEt, 10:1) to give the methyl ester **4b** in 34% overall yield.

IR (film) 2951, 2254, 1740, 1559, 1471, 1340, 1268 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.63 (t, J =7.8 Hz, 1H); 7.24 (d, J= 7.5Hz, 2H); 3.88 (s, 2H); 3.72 (s, 3H); MS (CI, NH_3) m/e 186; HRMS (EI) calcd for $C_8H_8ClNO_2$ (M^+) 185.02436, found (M^+)185.02459; CMR ($CDCl_3$) δ 42.6, 51.7, 122.1, 122.3, 138.8, 150.1, 154.5, 169.8; TLC (4:1, H:EA) Rf=0.67.

2-Chloro-6-(bis-methylthiomethyl)pyridine (4c): To a stirred solution of 6- chloro-2-picoline (2 g, 15.7 mmol) in 100 mL of THF was added n-BuLi(2.38 M in hexane, 17.3 mmol, 7.3 mL) at 0 °C. The mixture was stirred for 30 min. The temperature was lowered to -78 °C and dimethyl disulfide (1.63 g, 17.3 mmol) was added and the mixture was stirred at -78 °C for 5 h. The crude mixture was poured into water and extracted with ether. The combined extracts were washed with saturated sodium chloride and dried over $MgSO_4$. The mixture was concentrated in vacuo. To a solution of the crude sulfide in THF (100 mL) was added n-BuLi (2.38 M in hexanes, 17.3 mmol, 7.3 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min. and then the temperature was lowered to 78 °C and dimethyl disulfide (1.63 g, 17.3 mmol) was added. The mixture was stirred for 5 h. The mixture was worked up as described above. The residue was purified by silica gel chromatography (30:1, H:EA) to give **4c** in 81% overall yield.

IR (film) 3399, 1617, 1558, 1405, 1171 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.66 (t, J= 7.8 Hz,1H), 7.45 (d, J= 7.8 Hz, 1H), 7.24 (d, J=7.8 Hz, 1H), 4.85 (s, 1H), 2.15 (s, 6H); MS (CI, NH_3) m/e141, 220; HRMS (EI) calcd for C_7H_7SNCl (M^+ - SMe) 171.99877, found 171.99904; CMR ($CDCl_3$) δ 14.2, 56.9, 118.7, 122.7, 139.2, 149.8, 159.8; TLC (10:1, H:EA) Rf=0.50.

2-Methoxy-6-bis-methylthiomethylpyridine (4d): Sulfide **4c** (429 mg., 2.0 mmol) was heated in a sealed tube in a sodium methoxide solution (16 mmol, 1M in methanol) for three days at 120 °C. The crude mixture was concentrated in vacuo. The crude product was taken up in water and neutralized. The aqueous solution was extracted with methylene chloride and the organic layer was dried over $MgSO_4$ to give **4d** in 57% yield.

IR (film) 2978, 1558, 1411, 1313, 1270; ^{1}HNMR (300 MHz, $CDCl_3$) 7.54 (t, J=7.8 Hz, 1H), 6.95 (d, J= 7.2 Hz, 1H), 6.62 (d, J=8.1 Hz, 1H), 4.81 (s, 1H), 3.93 (s, 3H), 2.17 (s, 6H); MS (CI, NH_3) m/e 137, 168, 216; HRMS (EI) calcd for $C_9H_{13}NOS_2$ (M^+) 215.04386, found (M^+) 215.04348; CMR ($CDCl_3$) δ 13.7, 52.8, 57.5, 109.0, 113.4, 138.6, 156.3, 162.8; TLC (20:1, H:EA) Rf=0.34.

2-Benzyloxy-6-bis-methylthiomethylpyridine (4e): Sulfide **4c** (7.3 mmol, 1.61 g.) was placed in *tert*-butanol (7.3 mL) . Benzyl alcohol (1.58 g, 14.6 mmol) and potassium *tert*-butoxide (1.64 g, 14.6 mmol)

were added and the mixture was heated in a sealed tube at 120 °C for two days. The mixture was concentrated in vacuo and the residue was taken up in water. The aqueous solution was neutralized by the addition of dilute HCl and extracted with methylene chloride. The combined extracts were concentrated in vacuo. The crude product was purified by silica gel chromatography (70:1, H:EA) to give **4e** in 90% yield.

IR (film) 3063, 2914, 1699, 1559, 1456, 1266, 1022 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.56 (t, J=7.5 Hz, 1H), 7.49-7.46 (m, 2H), 7.38-7.29 (m, 3H), 6.96 (d, J=7.2 Hz, 1H), 6.68 (d, J= 8.4 Hz, 1H), 5.38 (s, 2H), 4.81 (s, 1H), 2.13 (s, 6H); MS (CI, NH_3, negative ion) m/e 290; HRMS (EI) calcd for $C_{15}H_{17}NOS_2$ (M^+) 291.07516, found (M^+) 291.07547; CMR ($CDCl_3$) δ 14.0, 57.9, 67.4, 109.8, 114.0, 127.6, 128.0, 128.2, 137.2, 139.1, 156.5, 162.6; TLC (20:1, H:EA) Rf=0.40.

1-(6-Chloro-2-pyridyl)-2-methyl-5-isopropenylcyclohex-2-enol (5): To a solution of LDA (freshly prepared from n-BuLi (2.17 M in hexane; 0.74 mL, 1.6 mmol) and *N,N*-diisopropylamine (0.16 g, 1.6 mmol) in 32 mL of dry THF) was added 6- chloro-2-picoline (0.20 g, 1.6 mmol) at 0 °C. After stirring for 30 minutes, the solution was cooled to -78 °C and l-carvone (0.24 g, 1.6 mmol) in THF (2 mL) was added dropwise. The solution was stirred for 2 hours and then poured into ice water and extracted with diethyl ether (3 X 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The residue was purified by silica gel chromatography (hexane: AcOEt, 8:1) to give alcohol **5** in 84% yield.

IR(film) 3415, 3081, 2921,1645, 1550, 1408, 1183 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.59 (t, J=7.8 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.08 (d, J=7.5 Hz, 1H), 5.49-5.47 (s, 1H), 4.66 (s, 2H), 3.24 (d, J=14.4 Hz, 1H), 2.94 (d, J= 14.4 Hz, 1H), 2.44-2.27 (m, 2H), 2.19-1.89 (m, 4H), 1.76 (s, 3H), 1.65 (s, 3H) ; MS (CI, NH_3) m/e 277; HRMS (EI) calcd for $C_{16}H_{20}ClNO$ (M^+) 277.12276, found (M^+) 277.12334; CMR($CDCl_3$) δ 17.3, 20.3, 30.7, 39.6, 40.3, 44.1, 74.2, 108.9, 122.0, 123.1, 123.6, 138.2, 139.1, 148.5, 150.3, 160.0; TLC (4:1, H:EA) Rf=0.39

2-Methyl-5-isopropenyl-3-[(6-chloro-2-pyridyl)bis-methylthiomethyl] cyclohexanone(7): To a stirred solution of **4c** (143 mg, 0.65 mmol) in THF (5 mL) was added n-BuLi (0.30 mL, 0.65 mmol) at -78 °C under an Ar atm. The mixture was stirred for 1 hour. Cuprous iodide (63 mg, 0.33 mmol) was then added and the mixture stirred for an additional hour at -78 °C. Then l-carvone (50 mg, 0.33 mmol) in 0.1 mL of THF was added slowly at -78 °C and the mixture was stirred at -78 °C for 3 h. The reaction mixture was quenched by the addition of H_2O and allowed to reach rt. The precipitate was filtered and the crude mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by silica gel chromatography (hexane:AcOEt, 30:1) to give **7** (98% yield).

IR(film) 2915, 2872, 1708, 1558, 1427 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.82 (d, J=7.5 Hz, 1H), 7.67 (t, J=7.5 Hz, 1H), 7.22 (d, J=7.8 Hz, 1H), 4.81(s, 1H), 4.77 (s, 1H), 2.94-2.81 (m, 1H), 2.46-1.83 (m,6H), 2.03 (s, 3H), 1.93 (s, 3H), 1.78 (s, 3H), 0.61 (d, 3H); MS (CI, NH_3) m/e 322, 370, 387; HRMS (EI) calcd for $C_{18}H_{24}ClNOS_2$ (M^+) 369.09879, found (M^+) 369.09782; CMR ($CDCl_3$) δ 12.8, 13.6, 20.6, 28.1, 42.1, 44.5, 47.6, 48.2, 71.3, 110.1, 122.1, 122.8, 138.5, 147.0, 149.7, 160.4, 213.2; TLC (4:1, H:EA) Rf=0.57

2- Methyl-5-isopropenyl-3[(6-methoxy-2-pyridyl)bis-methylthiomethyl] cyclohexanone (8): To a stirred solution of **4d** (67 mg, 0.31 mmol) in 3 mL of THF was added n-BuLi (0.16 mL, 0.34 mmol) at -78 °C. The solution was stirred for 1 hour at -78 °C and then the temperature was raised to 0 °C and HMPA (0.06 mL, 0.34 mmol) was added. The temperature was lowered to -78 °C and l-carvone (51 mg, 0.34 mmol)

was added dropwise. The reaction mixture was stirred at -78 °C for 3 h. The reaction mixture was quenched by the addition of water and allowed to reach rt. The aqueous solution was extracted with Et_2O, washed successively with H_2O and brine, and dried ($MgSO_4$). Silica gel chromatography (70:1, H:EA) of the residue afforded **8** in 61% yield.

IR (film) 2924, 1711, 1587, 1466, 1263, 1020 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.58 (t, J=7.5 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 6.61 (d, J=8.1 Hz, 1H), 4.83-4.71 (m, 2H), 3.93 (s, 3H), 2.99-2.88 (m, 1H), 2.50-1.22 (m, 6H), 2.02 (s, 3H), 1.92 (s, 3H), 1.78 (s,3H), 0.91 (d, J= 7.2 Hz, 3H); MS (CI, NH_3) m/e 208, 320, 366; HRMS (EI) calcd for $C_{19}H_{27}NO_2S_2$ (M^+) 365.14832, found (M^+) 365.14842; CMR ($CDCl_3$) δ 18.4, 20.5, 28.4, 42.1, 44.6, 47.6, 48.2, 53.5, 72.5, 109.3, 109.9, 116.4, 123.0, 127.1, 138.5, 147.1, 156.4, 162.8, 213.6; TLC (7:1, H:EA) Rf=0.71

2-Methyl-5-isopropenyl-3[(6-benzyloxy-2-pyridyl)bis-methylthiomethyl] cyclohexanone (9): This compound was prepared following the procedure for the preparation of **7**. The product was purified by silica gel chromatography (30:1, H:EA) to give **9a** and **9b**.(a 4:1 ratio of **9a**:**9b** was obtained).

9a (trans isomer)

IR (film) 2915, 1708, 1574, 1441 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.59 (t, J= 7.8 Hz, 1H), 7.50-7.23 (m, 6H), 6.67 (d, J=8.4 Hz, 1H), 5.39 (AB quartet, J=12.3 Hz, 2H), 4.79 (s, 1H), 4.76 (s, 1H), 2.93-2.91 (m,1H) ,2.46-1.71 (m, 6H), 2.01 (s, 3H), 1.89 (s, 3H), 1.76 (s, 3H), 0.73 (d, J= 7.2 Hz, 3H); MS (CI, NH_3) m/e 382, 396, 442; HRMS (EI) calcd for $C_{25}H_{31}NO_2S_2$ (M^+) 441.17962, found (M^+) 441.18043; CMR ($CDCl_3$) δ 12.8, 13.5, 20.5, 28.1, 40.0, 42.1, 44.8, 47.6, 48.3, 67.6, 72.8, 109.5, 110.0, 118.8, 127.7, 128.0, 128.3, 137.3, 138.7, 147.2, 156.5, 161.7, 219.6; TLC (30:1, H:EA) Anal. calcd for $C_{25}H_{31}NO_2S_2$: C, 67.99; H, 7.07; N, 3.17; O, 7.25. Found: C, 67.35; H, 7.12; N, 2.90; O, 8.40. Rf=0.25.

9b (cis isomer)

IR (film) 3086, 1708, 1574, 1442 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.57 (t, J=7.8 Hz, 1H), 7.49-7.25 (m, 6H), 6.67 (d, J=7.8 Hz, 1H), 5.41 (s, 2H), 4.91 (s,1H), 4.70 (s, 1H), 2.91-2.89(m,1H), 2.70(m,1H), 2.52-2.42 (m, 4H), 2.02-1.98(m,1H), 1.95 (s, 3H), 1.88 (s, 3H), 1.80 (s, 3H), 0.69 (d, J=7.2 Hz, 3H); MS (CI, NH_3) m/e 396, 442; HRMS (EI) calcd for $C_{25}H_{31}NO_2S_2$ (M^+) 441.17962, found (M^+) 441.17953; CMR ($CDCl_3$) δ 12.5, 13.2, 22.3, 24.5, 31.1, 40.0, 40.7, 42.7, 48.0, 67.5, 72.7, 108.4, 112.9, 116.7, 127.8, 127.9, 128.3, 137.5, 138.8, 146.4, 158.8, 161.6, 214.2; TLC (30:1, H:EA) Rf=0.10

1-(6-Chloro-2-pyridyl)cyclohex-2-enol (10): To a solution of LDA (freshly prepared from n-BuLi (2.17 M in hexane; 0.74 mL, 1.6 mmol) and *N,N*-diisopropylamine (0.16 g, 1.6 mmol) in 32 mL of dry THF) was added 6- chloro-2-picoline at 0 °C (0.20 g, 1.6 mmol). After stirring for 30 minutes, the solution was cooled to -78 °C and 2- cyclohexene-1-one (0.15 g, 1.6 mmol) in THF (2 mL) was added dropwise. The solution was stirred for 2 h. and then poured into ice water and extracted with diethyl ether (3 X 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The residue was purified by silica gel chromatography (hexane: AcOEt, 8:1) to give the allylic alcohol **10** in 64% yield.

IR (film) 3410, 2935, 1587, 1558, 1441, 1171 cm^{-1}; HNMR (300 MHz, $CDCl_3$) 7.58 (t, J= 7.8 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.10 (d, J=7.2 Hz, 1H), 5.82-5.76 (m, 1H), 5.55 (d, J=9.9 Hz, 1H), 4.36 (s, 1H), 3.74-3.70 (m, 1H), 3.55-3.15 (m, 1H), 2.96 (AB quartet, J= 11.1 Hz, 2H), 2.37-1.18 (m, 4H); MS (EI) m/e 79.1, 97.1, 129.0, 177.0, 204.1, 223.1; HRMS (EI) calcd for $C_{12}H_{14}ClNO$ (M^+) 223.07639, found (M^+)

223.07602; CMR ($CDCl_3$) δ 18.8, 24.9, 35.8, 47.8, 69.5, 121.8, 126.1, 129.3, 131.7, 138.8, 149.9, 159.6; TLC (5:1 H:EA) Rf=0.19

3-[(6-Chloro-2-pyridyl)bis-methylthiomethyl]cyclohexanone (11): To a stirred solution of **4c** (200 mg, 0.91 mmol) in THF (8 mL) was added n-BuLi (2.22 M in hexane, 0.41 mL, 0.91 mmol) at -78 °C under an Ar atm. The mixture was stirred for 1 h. Cuprous iodide (87 mg, 0.45 mmol) was then added and the mixture stirred for an additional hour at -78 °C. Then, 2-cyclohexene-1-one (43 mg, 0.45 mmol) in 0.5 mL of THF was added slowly at -78 °C and the mixture was stirred at -78 °C for 3 h. The reaction mixture was quenched by the addition of H_2O and allowed to reach rt. The precipitate was filtered and the crude mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by silica gel chromatography (hexane:AcOEt, 25:1) to give the ketone **11** in 100% yield.

IR (film) 2916, 1699, 1574, 1553, 1423, 1136 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$) 7.78 (d, J=7.8 Hz, 1H), 7.66 (t, J= 7.8 Hz, 1H), 7.24 (t, J=7.8 Hz, 1H), 2.66-2.08 (m,5 H) ,2.04 (s, 3 H), 1.97 (s, 3 H), 1.66-1.28(m, 4H); MS (CI, NH_3) m/e 268, 316, 333; CMR ($CDCl_3$) δ 13.2, 13.5, 24.8, 27.8, 41.0, 44.3, 47.7, 71.8, 121.7, 122.9, 138.7, 150.2, 159.9, 210.7; TLC (2:1, H:EA) Rf =0.49.

4-[(6-Benzyloxy-2-pyridyl)bis-methylthiomethyl]-2-pentanone (12):
This compound was prepared following the procedure for the preparation of **7**. The product was purified by silica gel chromatography (40:1, then 10:1 H:EA) to give **12**

12: NMR ($CDCl_3$) δ 7.59 (t, J=7.8 Hz, 1 H), 7.50 (d, J=7.2 Hz, 2 H), 7.43 (d, 7.5 Hz, 1 H), 7.29-7.38 (m, 3 H), 6.69 (d, 8.1 Hz, 1 H), 5.44 (AB quartet, J_1=12.6, J_2=12.3, 2 H), 3.19 (dd, J_1=17.7 Hz, J_2=1.8 Hz, 1 H), 2.79-2.90 (m, 1 H), 2.03 (s, 3 H), 2.00 (s, 3 H), 1.95 (s, 3 H), .984 (d, 6.6 Hz, 3 H). IR (film) cm^{-1} 2917, 1715, 1575, 1456, 1311, 1258, 989. MS: m/e 91, 225, 280, 328, 376. HRMS: m/e for $C_{20}H_{25}O_2S_2N$ calcd. 375.13267 measured 375.13314. CMR ($CDCl_3$) δ 12.8, 13.3, 16.6, 30.6, 37.2, 47.6, 67.5, 73.9, 109.4, 116.5, 127.7, 127.9, 128.3, 137.5, 138.7, 156.0, 161.9, 207.8. TLC (10:1 H:EA) Rf=0.52.

4-[(6-Benzyloxy-2-pyridyl)bis-methylthiomethyl]-2-butanone (13):
This compound was prepared following the procedure for the preparation of **7**. The product was purified by silica gel chromatography (30:1, H:EA) to give **13**

13: NMR ($CDCl_3$) δ 7.58 (t, J=7.8 Hz, 1 H), 7.47 (d, J=7.2 Hz, 2 H), 7.27-7.36 (m, 3 H), 7.21 (d, J=7.5 Hz, 1 H), 6.68 (d, 8.1 Hz, 1 H), 5.41 (s, 2 H), 2.37-2.48 (m, 4 H), 2.02 (s, 3 H), 1.91 (s, 6 H). IR (film) cm^{-1} 2917, 2848,1716, 1575, 1472, 1462, 719. MS: m/e 91, 266, 314, 362. HRMS: m/e for $C_{19}H_{23}O_2S_2N$ calcd. 361.11702 measured 361.11713. CMR ($CDCl_3$) δ 12.3, 30.2, 30.8, 39.3, 67.4, 109.0, 109.6, 114.5, 127.7, 127.9, 128.3, 137.6, 139.1, 157.5, 162.0, 207.9. TLC (20:1 H:EA) Rf=0.13.

2-Methyl-3-[(2-pyridone)methyl]-5-isopropyl-cyclohexanol (14): The sulfide (0.26 mmol) and Raney nickel (1 g) were boiled in 10 mL of ethanol for two hours. The crude solution was filtered carefully. The filtrate was concentrated in vacuo to afford **12**.

IR (film) 3377, 3279, 2957, 2870, 1651, 1616, 1264, 1006 cm^{-1};^{1}HNMR (300MHz, $CDCl_3$) 7.36 (t, J=6.9 Hz,1H), 6.41 (d, J= 9 Hz, 1H), 6.05 (d, J=6.9 Hz, 1H), 3.62-3.55 (m, 1H), 2.56-2.45 (m, 2H), 1.93-0.97 (m, 9H), 0.85 (d, J=6.3 Hz, 6H), 0.79 (d, J=6.9 Hz, 3H) ; MS (CI,NH_3) m/e 110, 127, 248, 264, 281; CMR ($CDCl_3$) δ 20.0, 21.2, 30.0, 32.2, 33.3, 34.0, 38.2, 39.9, 41.6, 73.0, 73.3, 108.1, 117.2, 143.1, 150.0, 166.6; TLC (10:1, EA: MeOH) Rf=0.46.

REFERENCES

1. Winterfeld, K.; Schneider, E. *Annallen*, **1953**, *581*, 66. Buchi, J.; Kracher, F.; Schmidt, G. *Helv. Chim. Acta*, **1962**, *45*, 729. Eisch, J. J.; Kovacs, C. A.; Chobe, P.; Boleslawski, M. K. *J. Org. Chem.*, **1987**, *52*, 4427.

2. Bergmann, E.; Rosenthal, W. *J. Prakt. Chem.* [2], **1932**, *135*, 267.

3. Sakamoto, M.; Abe, M.; Ishii, K. *Chem. Pharm. Bull.*, **1991**, *39*, 277. Tolstikov, G. A.; Spivak, A. Y.; Kresteleva, I. V. *Zh. Org. Khim.*, **1989**, *25*, 149.

4. The usual reagent for deprotonating alkylpyridines is n-BuLi. However, this reagent adds to **4a** to produce an alkylated pyridine.

5. Lipshutz, B. H.; Sengupta, S. *Organic Reactions* (Wiley, NY, 1992), vol. 41, p. 135-633.

6. Van Zoest, W. J.; van Hertog, H. J. *Rec. Trav. Chim. Pays-Bas*, **1974**, *93*, 166.

7. Zoltewicz, J. A.; Sale, A. A. *J. Org. Chem.*, **1970**, *35*, 3462.

8. Kozikowski, A. P.; Xia, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4116.

9. Hoffman, J. M.; Smith, A. M.; Rooney, C. S.; Fisher, T. E.; Wai, J. S.; Thomas, C. M. *J. Med. Chem.*, **1993**, *36*, 953.

(*Received in USA* 19 *July* 1994; *accepted* 14 *November* 1994)