4-Diethylamino-2,6-di-*tert*-butylpyridine

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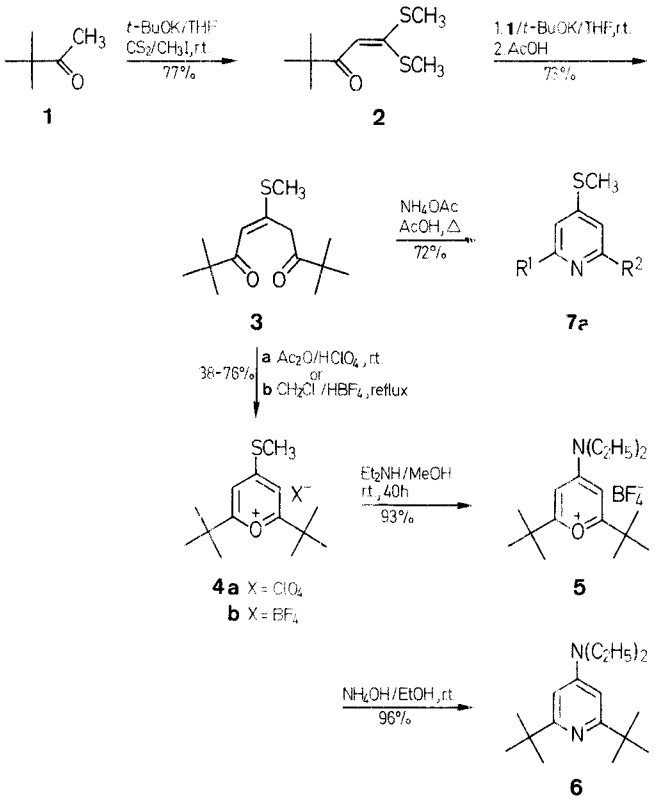
4-Diethylamino-2,6-di-*tert*-butylpyridine is prepared in satisfactory yield by a seven-step sequence starting from pinacolone and using readily available reagents. An acylketene dithioacetal, a 2-ene-1,5-dione, and pyrylium salts are intermediates in this sequence.

2,6-Di-*tert*-butylpyridines continue to be of interest due to their unusual basicities,[1] their decreased base strength being attributed to steric inhibition of solvation. Introduction of a 4-dimethylamino substituent into a pyridine ring results in enhanced basicity, and 4-dimethylaminopyridine (DMAP) is an excellent transacylation catalyst.[2] Our recently developed[3] α-oxoketene dithioacetal route to pyridines suggested a simple synthesis of 4-diethylamino-2,6-di-*tert*-butylpyridine (**6**) whose basic/nucleophilic characteristics would be of special interest.



Conversion of methyl *tert*-butyl ketone (**1**) into the α-oxoketene dithioacetal[4] **2** occurred readily with potassium *tert*-butoxide, carbon disulfide, and iodomethane in tetrahydrofuran and reaction of **2** with the potassium enolate of **1** (obtained with potassium *tert*-butoxide/tetrahydrofuran at room temperature) gave 2,2,8,8-tetramethyl-5-methylthio-4-nonen-1,5-dione (**3**) in 73% yield.[5] The pyrylium tetrafluoroborate **4a** (X = BF_4), obtained by treating **3** with perchloric acid/acetic anhydride to give **4b** (X = ClO_4) and then HBF_4, reacted readily with diethylamine in methanol at room temperature giving pyrylium salt **5** (X = BF_4) in 93% yield. Conversion of **5** into the pyridine **6** also occurred in high yield (96%) when **5** was treated with conc. aqueous ammonia in ethanol, initially at 0 °C and then at room temperature.[6] This route to 4-disubstituted aminopyridines complements effectively that utilizing the cycloaddition of 1,3-oxazin-6-ones with ketene *N,O*-acetals,[7] and also that of 1,2,4-triazines with the latter reagent.[8]

The physical characteristics of the pyrylium salts **4b** and **5** (X = BF_4) are of special interest. The salt **4b** was, as expected, insoluble in anhydrous ether; however, the salt **5** crystallized from ether. The 3,5-protons in **4b** (δ = 7.51) underwent a significant upfield shift in **5** (δ = 6.64) with only a slight change in the *t*-butyl singlet from δ = 1.48 in **4b** to δ = 1.41 in **5**. A similar upfield shift of the 3,5-protons in **7a** ($R^1 = R^2$ = *tert*-butyl) (δ = 7.18) to δ = 6.38 in **6** also occurred.

The pyridine **6** readily formed a crystalline hydrochloride on reaction with dry hydrogen chloride in absolute ethanol. With methyl iodide in boiling methanol, however, it did not undergo methylation, giving instead the corresponding hydroiodide of **6**, a behavior analogous to 2,6-di-*tert*-butylpyridine. This should be contrasted with the reaction of 2,6-di-*tert*-butyl-4-alkylpyridines which with methyl fluorosulfate at 180 °C at atmospheric pressure gave the corresponding *N*-methyl compound.[9] Although compound **6** was effective in converting an α-bromoketone into the corresponding enone,[10] it offered no advantages over TED, DBU, or DBN bases.[11]

Using potentiometric titration,[12] 3-methylpyridine was found to have a pK_{aH_2O} of 5.59 and a $pK_{a'}$ in 2-methoxyethanol/water of 3.63 (Δ = 1.90); similarly, 4-dimethylaminopyridine had a pK_{aH_2O} of 9.22 and in 2-methoxyethanol/water the $pK_{a'}$ was 7.70 (Δ = 1.52). Due to its insolubility in water, the $pK_{a'}$ of **6** was determined in 2-methoxyethanol/water (80:20) and found to be 7.45. Thus, the pK_a of **6** is 8.9–9.3, a value consistent with the base-strengthening effect of the 4-diethylamino substituent.

Other pyridine derivatives containing either a 2-*tert*-butyl group or 2,6-di-*tert*-butyl groups were prepared by a variation of the above procedure which involves direct reaction of diketone **3** with ammonium acetate in hot acetic acid[3]. Our recent procedure for displacement of the 4-methylthio substituent with alkyl or aryl Grignard reagents and *bis*-(triphenylphosphine)nickel dichloride[13] thus greatly extends the potential variety of substituents which can be introduced into the pyridine ring of derivatives such as those shown in the Table.

4,4-Dimethyl-1,1-bis(methylthio)-1-penten-3-one (2):
A 250 mL three-necked flask fitted with stirrer, reflux condenser, pressure-equalizing dropping funnel, and nitrogen inlet is purged with nitrogen and, while under a positive pressure, is charged with potassium *tert*-butoxide (11.2 g, 0.10 mol), anhydrous THF (150 mL), and pinacolone (**1**; 5.0 g, 0.05 mol). After 15 min, carbon disulfide (3.8 g, 0.05 mol)

Table. Some 2,6-Disubstituted 4-(Methylthio)pyridines[a] **7** Prepared

Compound	R^1	R^2	Yield (%)	b.p. (°C/Torr) or m.p. (°C)	MS[b] *m/e* (%)
7a	*t*-C_4H_9	*t*-C_4H_9	72	63/0.001	237 (44)
7b	*t*-C_4H_9	4-$CH_3OC_6H_4$	95	54–55	287 (100)
7c	4-$((CH_3)_2N)C_6H_4$	4-$((CH_3)_2N)C_6H_4$	26	158–160	363 (100)

[a] All gave satisfactory analytical data: C, H, N ±0.4%.

[b] Corresponds to M + 1 using chemical ionization.

is added dropwise, taking caution not to allow the mixture to heat up excessively. Iodomethane (14.2 g, 0.10 mol) is added in a similar fashion, and the mixture stirred at room temperature for 10 h. The resultant pink heterogeneous mixture is poured onto ice (~ 500 g), diluted to 600 mL with H_2O, and set aside. After 4 h, the resultant orange precipitate is collected by filtration; yield: 4.2 g. Chloroform extraction of the filtrate gives an additional 3.6 g. Recrystallization from hexane affords golden plates; yield: 7.8 g (77%); m.p. 59–60 °C (Lit.[4] m.p. 59–60 °C).

IR (KBr): ν = 1630 (CO) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 6.30 (s, 1 H, vinyl); 2.46 (s, 6 H, $2SCH_3$); 1.19 [s, 9 H, $C(CH_3)_3$].

2,2,8,8-Tetramethyl-5-methylthio-4-nonene-1,5-dione (3):
Methyl *tert*-butyl ketone (pinacolone, **1**; 2.5 g, 0.02 mol) in anhydrous THF (100 mL) is stirred vigorously with potassium *tert*-butoxide (5.5 g, 0.05 mol) at room temperature for 1 h and to the resultant orange-colored mixture is added 5,5-bis(methylthio)-2,2-dimethyl-4-penten-3-one (**2**; 5.0 g, 0.02 mol). Stirring is continued for 16 h and the orange crystalline solid is then separated. This solid (1.6 g, 93%) is added to glacial AcOH (40 mL), followed by ice (~ 50 g), and the resultant mixture is extracted with $CHCl_3$ (3 × 10 mL). The extract is washed with H_2O (10 mL), dried (Na_2SO_4), and evaporated to give a brown oil which on trituration with hexane crystallizes. The product crystallizes from hexane as colorless microneedles; yield: 0.2 g (3%); m.p. 109–111 °C.

$C_{14}H_{24}O_2S$	calc.	C 65.67	H 9.45
(256.3)	found	65.71	9.47

MS: *m/e* = 256 (6%, M^+).

IR (KBr): ν = 1691, 1640 (CO) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 6.21 (s, 1 H, vinyl); 4.08 (s, 2 H, CH_2); 2.36 (s, 3 H, SCH_3); 1.19 [s, 9 H, $C(CH_3)_3$].

2,6-Di-*tert*-butyl-4-(methylthio)pyrylium Perchlorate (4a):
The enedione **3** (0.6 g, 0.002 mol), Ac_2O (10 mL), and perchloric acid (0.2 g, 0.002 mol, 70%) are stirred together at room temperature for 2.5 h. Dilution with anhydrous Et_2O (10 mL) gives a colorless product which crystallizes from Ac_2O/Et_2O as clear, colorless needles; yield: 0.30 g (38%); m.p. 152–153 °C.

$C_{14}H_{23}ClO_5S$	calc.	49.62	H 6.85
(338.8)	found	49.72	6.89

MS: *m/e* = 239 (26%, M^+).

^{1}H-NMR ($CDCl_3$): δ = 7.42 (s, 2 H, H-3, H-5); 2.89 (s, 3 H, SCH_3); 1.44 [s, 18 H, $C(CH_3)_3$].

2,6-Di-*tert*-butyl-4-(methylthio)pyrylium Tetrafluoroborate (4b):
The enedione **3** (0.6 g, 0.002 mol), 50% aqueous HBF_4 (90 mL), and CH_2Cl_2 (20 mL) are stirred together at reflux temperature for 5 h. The aqueous layer is extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers are dried (Na_2SO_4) and evaporated and the residue is recrystallized from acetone/Et_2O to afford colorless microneedles of **4b**; yield: 0.6 g (76%); m.p. 112–114 °C.

$C_{14}H_{23}BF_4OS$	calc.	C 51.54	H 7.12
(326.1)	found	51.48	7.13

MS: *m/e* = 239 (12%, M^+).

^{1}H-NMR ($CDCl_3$): δ = 7.51 (s, 2 H, H-3, H-5); 2.91 (s, 3 H, SCH_3); 1.48 [s, 18 H, $C(CH_3)_3$].

4-Diethylamino-2,6-di-*tert*-butylpyrylium Tetrafluoroborate (5; X = BF_4):
The pyrylium salt **4b** (7.0 g, 0.02 mol), anhydrous MeOH (100 mL), and diethylamine (4.7 g, 0.065 mol) are stirred at room temperature for 40 h. Removal of the solvent leaves an orange oil that solidifies. Recrystallization from Et_2O affords the salt **5** as colorless microneedles; yield: 7.37 g (93%); m.p. 113–115 °C.

$C_{17}H_{30}BF_4NO$	calc.	C 58.12	H 8.63	N 3.99
(353.2)	found	58.21	8.66	3.95

MS: *m/e* = 264 (56%, M^+).

^{1}H-NMR ($CDCl_3$): δ = 6.64 (s, 2 H, H-3, H-5); 3.80 (q, 4 H, NCH_2CH_3, J = 7.2 Hz); 1.41 [s, 18 H, $C(CH_3)_3$]; 1.39 (t, 6 H, NCH_2CH_3, J = 7.2 Hz).

4-Diethylamino-2,6-di-*tert*-butylpyridine (6):
A solution of the pyrylium salt **5**, X = BF_4 (1.0 g, 0.003 mol) in EtOH (30 mL, 95%) is added dropwise with stirring to concentrated aqueous NH_3 (30 mL) cooled in an ice-water bath. The mixture is then stirred at room temperature for 12 h, and the separated product **6** collected. It crystallizes from ethanol as colorless needles; yield: 0.72 g (96%); m.p. 48–50 °C.

$C_{17}H_{30}N_2$	calc.	C 77.78	H 11.54	N 10.67
(262.4)	found	77.78	11.55	10.67

MS: *m/e* = 163 (100%, $M^+ + 1$)

^{1}H-NMR ($CDCl_3$): δ = 6.36 (s, 2 H, H-3, H-5); 3.39 (q, 4 H, NCH_2CH_3, J = 7.2 Hz); 1.46 [s, 18 H, $C(CH_3)_3$]; 1.20 (t, 6 H, NCH_2CH_3, J = 7.2 Hz).

4-Diethylamino-2,6-di-tert-butylpyridine Hydrochloride (**6** · HCl) crystallizes from acetone/Et_2O as colorless needles; yield: 98%; m.p. 184 °C.

$C_{17}H_{31}ClN_2$	calc.	C 68.30	H 10.47	N 9.37
(298.4)	found	68.35	10.47	9.35

MS: *m/e* = 263 (100%, $M^+ + 1$).

IR (KBr): ν = 3680, 3210 (NH); 1600 (N^+H) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 6.49 (s, 2 H, H-3, H-5); 3.60 (q, 4 H, NCH_2CH_3, J = 7.2 Hz; 1.69 [s, 18 H, $C(CH_3)_3$]; 1.32 (t, 6 H, NCH_2CH_3, J = 7.2 Hz).

4-Diethylamino-2,6-di-tert-butylpyridine Hydroiodide (**6** · HI) crystallizes from acetone/Et_2O as colorless needles; yield: 59%; m.p. 184–186 °C.

$C_{17}H_{31}IN_2$	calc.	C 52.30	H 8.02	N 7.18
(390.3)	found	52.51	8.00	7.16

MS: *m/e* = 263 (100%, $M^+ + 1$).

^{1}H-NMR ($CDCl_3$): δ = 6.10 (s, 2 H, H-3, H-5); 3.70 (q, 4 H, NCH_2CH_3, J = 7.2 Hz); 1.65 [s, 18 H, $C(CH_3)_3$]; 1.38 (t, 6 H, NCH_2CH_3, J = 7.2 Hz).

2,6-Disubstituted 4-(Methylthio)pyridines (7); Typical Procedure:
Potassium *tert*-butoxide (5.5 g, 0.05 mol), anhydrous THF (100 mL), and methyl *tert*-butyl ketone (**1**; 2.5 g, 0.02 mol) are stirred at room temperature for 1 h; then, 4,4-dimethyl-1,1-bis(methylthio)-1-penten-3-one (**2**; 5.0 g, 0.02 mol) is added. Stirring is continued for 16 h and NH_4OAc (7.6 g, 0.10 mol) and glacial AcOH (75 mL) are added and the THF is distilled off. The cooled mixture is poured onto ice, (~ 250 g, diluted to 400 mL with H_2O, and the aqueous solution is extracted with $CHCl_3$ (3 × 20 mL). The $CHCl_3$ extract is washed with Na_2CO_3 solution (10 mL) and dried (Na_2SO_4). Removal of the solvent leaves a yellow oil which is distilled under reduced pressure to give *2,6-di-tert-butyl-4-(methylthio)pyridine* (**7a**) as a colorless oil; yield: 4.16 g (72%); b.p. 63 °C/0.001 Torr.

$C_{14}H_{23}NS$	calc.	C 70.81	H 9.78	N 5.90
(237.3)	found	70.79	9.80	5.81

MS: *m/e* = 237 (44%, M^+).

^{1}H-NMR ($CDCl_3$): δ = 7.18 (s, 2 H, H-3, H-5); 2.74 (s, 3 H, SCH_3); 1.61 [s, 18 H, $C(CH_3)_3$].

1,1-Bis(methylthio)-3-oxo-3-(4-dimethylaminophenyl)propene [α-(4-Dimethylaminobenzoyl)ketene Dimethyl Dithioacetal]:
Potassium *tert*-butoxide (6.9 g, 0.06 mol) in anhydrous THF (150 mL) is treated dropwise with a solution of 4-(dimethylamino)acetophenone (5.0 g, 0.03 mol) in THF (50 mL). Carbon disulfide (2.3 g, 0.03 mol) is then added in a similar fashion and the resultant heterogeneous orange mixture is treated with methyl iodide (8.7 g, 0.06 mol). After stirring at room temperature for 10 h, the heterogeneous tan mixture is poured onto ice (~ 600 g), diluted to 1000 mL with H_2O, and set aside overnight. The separated brown material crystallized from methanol as golden needles; yield: 1.64 g (66%); m.p. 120–122 °C.

$C_{13}H_{17}NOS_2$	calc.	C 58.38	H 6.42	N 5.24
(267.3)	found	58.34	6.43	5.20

MS: *m/e* = 267 (48%, M^+).

IR (KBr): ν = 1600 (CO) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 7.90 (d, 2 H_{arom}, J = 9.0 Hz); 6.79 (s, 1 H_{vinyl}); 6.67 (d, 2 H_{arom}, J = 9.0 Hz); 3.01 (s, 6 H, 2 NCH_3); 2.51 (s, 3 H, SCH_3); 2.49 (s, 3 H, SCH_3).

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