A Convenient Synthesis of 3-Amino-4-cyano-1,5,5-trimethylcyclohexa-1,3-diene and its Derivatives

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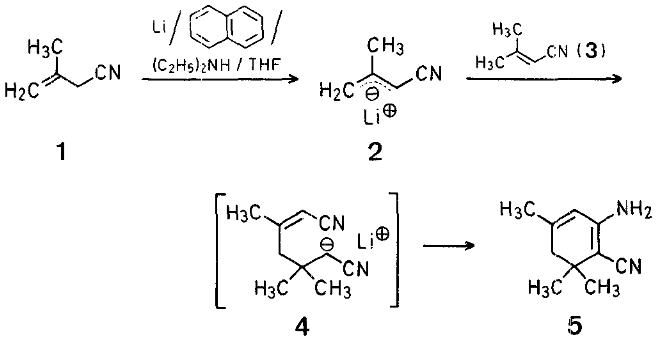
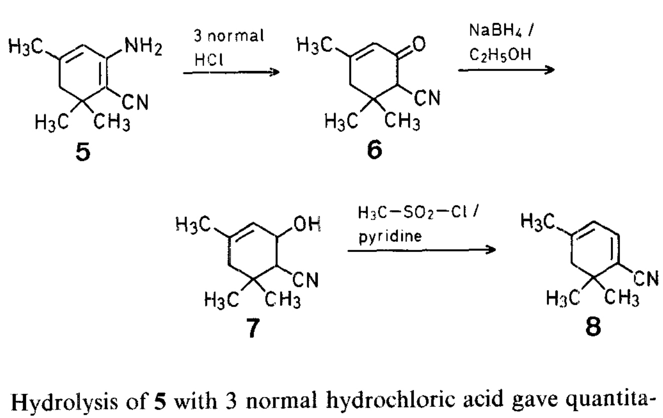
Lithiated nitriles are useful intermediates for the synthesis of a variety of organic compounds[1] and it has been recognized that terpenoids bearing a nitrile group may have wide utility in fragrances[2]. Recently, we reported that the base-initiated self-dimerization of 3-methyl-3-butenenitrile gave the cyclodimer selectively[3]. In this report we describe a convenient synthesis of 3-amino-4-cyano-1,5,5-trimethylcyclohexa-1,3-diene (**5**), having the ferulol skeleton[4], from the reaction of lithiated 3-methyl-3-butenenitrile (**2**) with 3-methyl-2-butenenitrile (**3**), and its conversion to 4-cyano-1,5,5-trimethylcyclohexa-1,3-diene (**8**).



3-Methyl-3-butenenitrile (**1**) was treated with lithium naphthalene/diethylamine in tetrahydrofuran, and the resultant lithiated derivative **2** was allowed to react with 3-methyl-2-butenenitrile (**3**) to give selectively **5** in 85% isolated yield. This reaction was also examined with other bases, of which lithium diisopropylamide and lithium diethylamide, prepared *in situ* from *n*-butyllithium and the corresponding dialkylamines, were effective and the yields of **5** were 81 and 77%, respectively. The reaction of 3-methyl-2-butenenitrile (**3**) with lithium diethylamide was also examined, however, the yield of **5** was low (37% after 19 h at 25 °C) and a considerable amount of polymer was obtained.



Hydrolysis of **5** with 3 normal hydrochloric acid gave quantitatively 4-cyano-3-oxo-1,5,5-trimethylcyclohexene (**6**), which was reduced by sodium borohydride in ethanol to afford 4-cyano-3-hydroxy-1,5,5-trimethylcyclohexene (**7**) in 73% yield. Compound **7** was dehydrated with methanesulfonyl chloride/pyridine in ether to give 4-cyano-1,5,5-trimethylcyclohexa-1,3-diene (**8**) in 53% yield.

All the compounds were characterized by ^{1}H-N.M.R., I.R., mass spectral, and microanalytical data.

3-Amino-4-cyano-1,5,5-trimethylcyclohexa-1,3-diene (5):

Method A: Lithium naphthalene/diethylamine: To a stirred solution of naphthalene (1.8 g, 14 mmol) in tetrahydrofuran (20 ml) is added at room temperature (25 °C) lithium (0.1 g) in small pieces. After 1 h of stirring, the resultant lithium naphthalene solution is cooled at 0 °C and diethylamine (1.0 g, 14 mmol) is added dropwise. The mixture is stirred for 30 min, and then a solution of **1** (1.0 g, 12 mmol) in tetrahydrofuran (8 ml) is added dropwise. After 30 min of stirring, a solution of **3** (1.0 g, 12 mmol) in tetrahydrofuran (8 ml) is added dropwise and the mixture is stirred for 1 h. Then the reaction mixture is warmed to room temperature and stirred for 3 h. The reaction mixture is cooled again at 0 °C, and quenched by addition of ethanol (2 ml). After evaporation of the solvents, ether (50 ml) is added, the ether layer is washed with brine, dried

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with anhydrous magnesium sulfate, and evaporated to give the crude product which is chromatographed (alumina, *n*-hexane/ether) to afford pure **5**; yield: 1.69 g (85%); m.p. 97–98 °C.

$C_{10}H_{14}N_2$	calc.	C 74.03	H 8.70	N 17.27
(162.2)	found	74.23	8.85	17.36

M.S.: $m/e = 162$ (M^+).

I.R. (KBr): $\nu = 3440$; 3350; 2170; 1660 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 1.10$ (s, 6H, CH_3); 1.86 (s, 3H, CH_3); 2.04 (s, 2H, CH_2); 4.12–4.52 (br. s, 2H, NH_2); 5.5–5.7 ppm (m, 1H, =CH).

Method B: Lithium diisopropylamide: To a stirred solution of diisopropylamine (1.61 g, 16 mmol) in tetrahydrofuran (10 ml), a 15% solution of *n*-butyllithium (12 mmol) in hexane is added dropwise under nitrogen at −78 °C. The solution is stirred for 30 min and then a solution of **1** (0.81 g, 10 mmol) in tetrahydrofuran (10 ml) is added dropwise at −78 °C. After 30 min of stirring, a solution of **3** (0.81 g, 10 mmol) in tetrahydrofuran (10 ml) is added dropwise and the mixture is stirred for 1 h. Then the mixture is allowed to warm to room temperature and stirred for 3 h. Work-up as described above, and chromatography gives pure **5**; yield: 1.31 g (81%).

4-Cyano-3-oxo-1,5,5-trimethylcyclohexene (6):

3 Normal hydrochloric acid (30 ml) is added to a stirred solution of **5** (2.00 g, 12.3 mmol) in ether (10 ml) at 0–5 °C and then the mixture is stirred overnight at room temperature. The product is extracted with ether (3 x 30 ml), the ether extract is washed with sodium hydrogen carbonate, brine, and dried with anhydrous magnesium sulfate. The ether is evaporated in vacuo to give **6**; yield: 1.98 g (98%); m.p. 57–58 °C.

$C_{10}H_{13}NO$	calc.	C 73.59	H 8.03	N 8.58
(163.2)	found	73.48	7.90	8.52

M.S.: $m/e = 163$ (M^+).

I.R. (KBr): $\nu = 2225$; 1665; 1630; 880 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 1.12$ (s, 3H, CH_3); 1.23 (s, 3H, CH_3); 1.97 (s, 3H, CH_3); 2.31 (s, 2H, CH_2); 3.28 (s, 1H, CH); 5.82 ppm (br. s, 1H, =CH—).

4-Cyano-3-hydroxy-1,5,5-trimethylcyclohexene (7):

A solution of **6** (1.00 g, 6.13 mmol) in ethanol (20 ml) is slowly added to a mixture of sodium borohydride (0.70 g, 18.5 mmol) and ethanol (15 ml) at 0–5 °C. Then the reaction mixture is heated at 50–60 °C and stirred for 3 h. The solvent is removed in vacuo, the residue is extracted with ether (3 x 30 ml), the ether extracts are washed with brine, and dried with anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gives the crude **7**; yield: 0.91 g [G.L.C. (FFAP, 2.5 m, 200 °C) shows three peaks in a ratio of 5:81:14] (yield of **7** by G.L.C.: 73%). Pure **7** (main peak) is isolated by preparative G.L.C.

$C_{10}H_{15}NO$	calc.	C 72.69	H 9.15	N 8.48
(165.2)	found	72.42	9.01	8.43

M.S.: $m/e = 165$ (M^+).

I.R. (neat): $\nu = 3450$; 2225; 1675; 1060; 845 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 0.95$ (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 1.69 (s, 3H, CH_3); 1.9–2.4 (m, 2H, CH_2); 2.77 (d, 2H, $J = 5.5$ Hz, CH); 3.8–4.3 (m, 1H); 4.1–4.6 (m, 1H); 5.39 ppm (br. s, 1H, =CH—).

4-Cyano-1,5,5-trimethylcyclohexa-1,3-diene (8):

To a solution of **7** (1.83 g, 11.1 mmol), pyridine (6.40 g, 80.9 mmol), and ether (15 ml) is added dropwise methanesulfonyl chloride (8.64 g, 75.5 mmol) in ether (5 ml) at 0–5 °C. After stirring for 18 h at room temperature, the reaction mixture is quenched by addition of water (30 ml) at 0–5 °C, and neutralized by addition of sodium hydrogen carbonate solution. The products are extracted with ether (3 x 30 ml), the ether extracts are washed with copper(II) sulfate solution, brine, and dried with anhydrous magnesium sulfate. After evaporation of the solvent, the resulting liquid is chromatographed (alumina, *n*-hexane/ether) to afford **8**; yield: 0.86 g (53%). The analytical sample is purified by preparative G.L.C. (Apiezon L, 2.5 m, 142 °C).

$C_{10}H_{13}N$	calc.	C 81.58	H 8.90	N 9.52
(147.2)	found	81.45	9.08	9.33

M.S.: $m/e = 147$ (M^+).

I.R. (neat): $\nu = 2220$; 1650; 1575; 820 cm^{-1}.

^{1}H-N.M.R. (CCl_4): $\delta = 1.09$ (s, 6H, CH_3); 1.81 (br. s, 3H, CH_3); 2.07 (br. s, 2H, CH_2); 5.68 (dq, 1H, $J = 5.5$ Hz, 1.5 Hz, =CH—); 6.40 ppm (d, 1H, $J = 5.5$ Hz, 1H).

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