PREPARATION AND HYDROLYSIS OF 3-ALKOXY-5-AMINO-4-6-DICYANO-1,8,8-TRIMETHYL-2-AZABICYCLO[2.2.2]OCTA-2,5-DIENES

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Abstract ---Solid base catalyzed condensation reaction of acetone with malononitrile in alcohol gave 3-alkoxy-5-amino-4,6-dicyano-1,8,8-trimethyl-2-azabicyclo[2.2.2]octa-2,5-dienes. The 2-aza bridge of the compound was cleaved hydrolytically in dilute hydrochloric acid to give 6-carbomethoxy-2,6-dicyano-3,5,5-trimethylcyclohex-2-enone. The compound was further decarbomethoxylated in this conditions to give 2,6-dicyano-3,5,5-trimethylcyclohex-2-enone of which crystal structure was determined by X-Ray diffraction method.

Since porous inorganic materials such as alumina or silica gel are used as packing agents of column chromatography to separate structurally simillar compounds to each other, surface of the agents can interact with varing firmness and differentiate them physically. Considering these functions of the inorganic materials, we can expect that the surface of the materials plays a versatile reaction media or catalytic activity. Indeed various inorganic materials were developed and used as basic or acidic catalysts.[1] We attended Ando's work[2] and found a condensation reaction of acetone with malononitrile catalyzed by alumina coated with KF or K_2CO_3 to give a series of bridged compounds, previously.[3] In aqueous solution KF-alumina or K_2CO_3-Al_2O_3 performed a complex condensation reaction of acetone with malononitrile on the surface of these catalysts to give a series of polycyano-2-azabicyclo[2.2.2]octa-2,5-dienes(**1**) or its potassium salt(**1-K**) as shown in Figure 1, respectively.

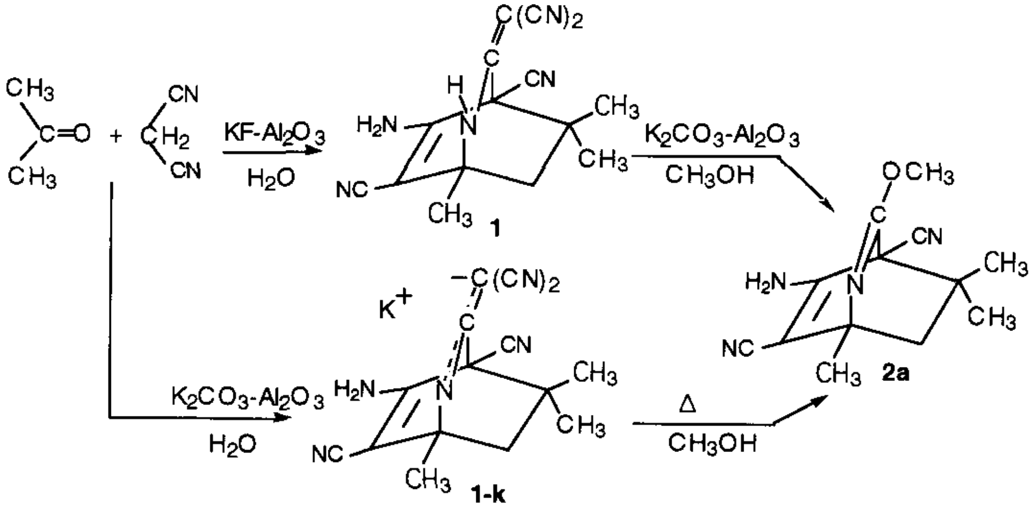
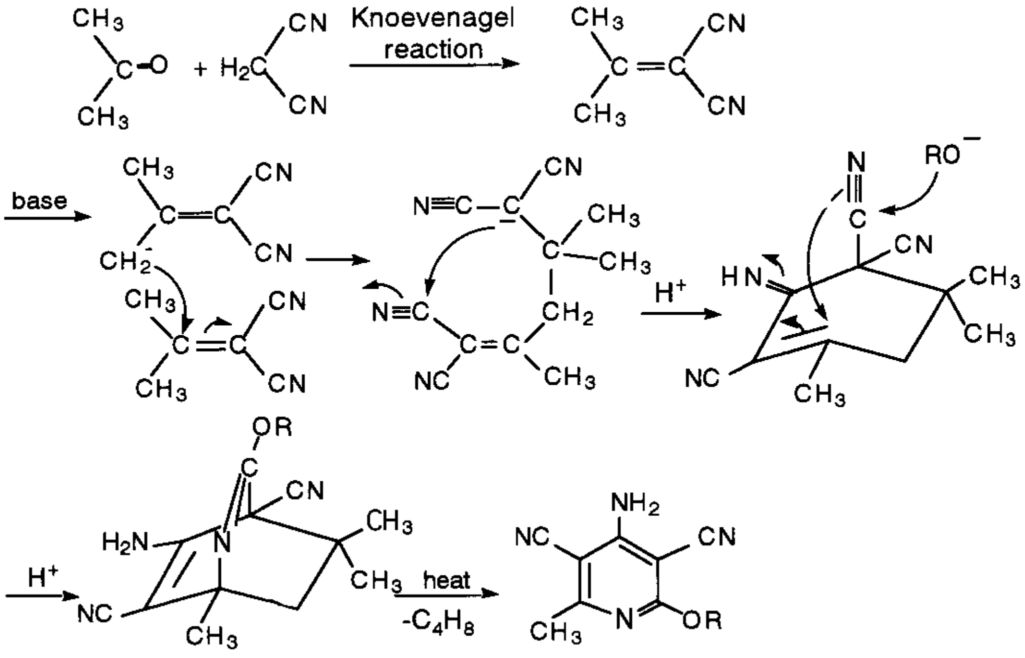


Figure 1. Formation of 2-azabicyclo[2.2.2]octa-2,5-diene derivatives

Here we report a strong catalytic activity of K_2CO_3-Al_2O_3 in alcohols. The solid promoted a condensation reaction at room temperature to give 3-alkoxy derivatives(**2**) in the same mechanistic manner with that of methoxide as described previously.[4] The results of condensation reaction with K_2CO_3-Al_2O_3 were listed in Table 1 and possible mechanism was proposed in Figure 2. Thus alkoxide ion which is assumed to be formed on the surface of alumina attacks a cyano group of dimeric compound and imino anion add to conjugated double bond. Yields of the products varied according to the length of alkyl chain of alcohol. In butanol, only tarry compound was formed. We could not even isolate butoxy analogue. In isopropanol was obtained only the potassium salt(**1-K**) in moderate yield. These results showed the surfase of K_2CO_3-Al_2O_3 was strong base comparable to alkoxide ion.

Table 1. Condensation Reaction in Alcohol.

Alcohol	Products		Yields (%)
methanol	R=CH_3	**2a**	77
ethanol	R=CH_2CH_3	**2b**	35
isopropanol	potassium salt of **1**	**1-K**	57
butanol	tar	——	——



2a R= $-CH_3$
2b R= $-CH_2CH_3$

3a R= $-CH_3$
3b R= $-CH_2CH_3$

Figure 2. A possible mechanism for the condensation reaction

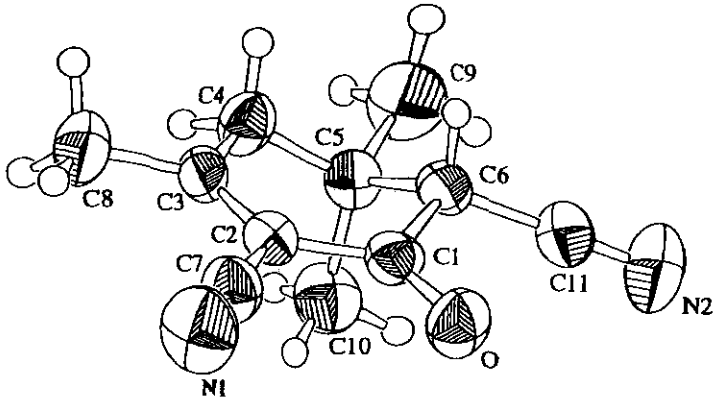


Figure 3. An ORTEP drawing of **5a**.

The condensation product(**2a**) could be hydrolyzed in acidic conditions to give 6-carbomethoxy-2,6-dicyano-3,5,5-trimethylcyclohex-2-enone(**4a**) which was decarbomethoxylated finally to give 2,6-dicyano-3,5,5-trimethylcyclohex-2-enone(**5a**). A reaction mechanism to give **5a** was shown in Figure 3. The crystal structure of final product(**5a**) was determined by X-Ray diffraction method. An ORTEP drawing of **5a** was shown in Figure 4.

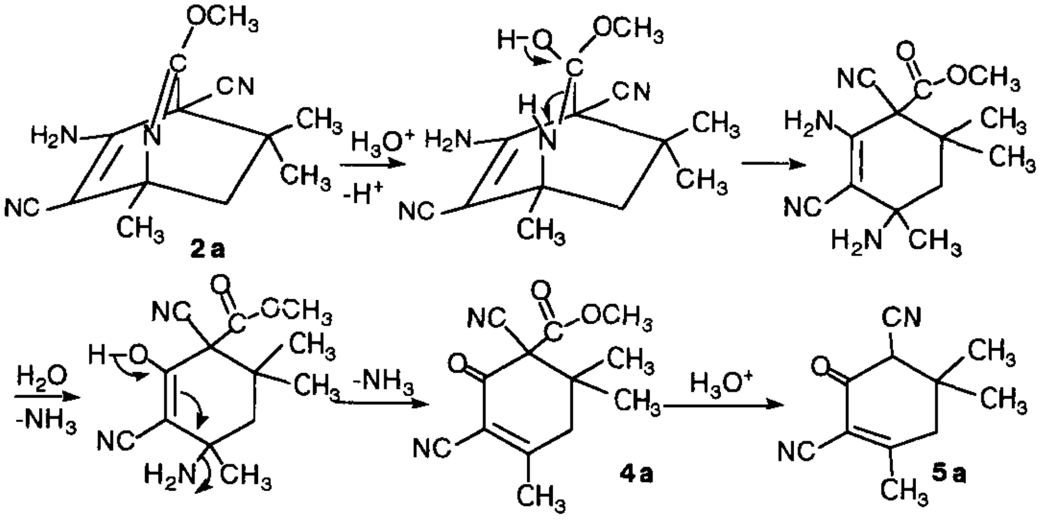


Figure 4. A mechanism for the hydrolysis reaction

The methoxy substituted compound(**2a**) was also *formed* by *refluxing* **1-K** *in methanol* for 48 h which was detected by TLC[3] and identified by IR. We assumed that potassium salt(**1-K**) promoted a self catalyzed substitution reaction. In this reaction, the potassium salt(**1-K**) was converted to neutral compound(**1**) once and methoxide ion added to conjugated double bond in Michael reaction manner and malononitrile left. Indeed, **2a** was also formed directly from **1** in methanol in the presence of K_2CO_3-Al_2O_3 as shown in Figure 1.

EXPERIMENTAL

Since we did not report preparation of the solid catalyst, K_2CO_3-Al_2O_3, previously, preparative method of K_2CO_3-Al_2O_3 was described in detail here. Aluminium oxide 90 (Merck)(30 g) was suspended in a solution of K_2CO_3(48 g) in H_2O(200 mL). Water was removed with a evaporator. The white solid was dried under reduced pressure with an aspirator at 100 ℃ for 12 h.

Typical preparative procedure of 5-amino-4,6-dicyano-3-methoxy-1,8,8-trimethyl-2-azabicyclo[2.2.2]octa-2,6-diene(2a): A mixture of acetone(5.8 g, 0.1 mol) and malononitrile(6.6 g, 0.1 mol), and K_2CO_3-Al_2O_3(14.6 g) in methanol(400 mL) was stirred at rt for 24 h. Same isolating procedure with **1**[3] was accomplished as follows. Yellow solid was filtered and rinsed throughly with hot methanol. Washing methanol and filtrate were condensed together and the crude product was recrystallized from methanol. **2a:** Yield:77 % mp: 200-202℃. Since **2a** was described previously,[4] only spectral data were reported here. IR (KBr): ν=3430, 3120, 2960, 2190, 1670, 1300 cm^{-1}. ^1H NMR(DMSO-d_6) δ=6.86(2H, br s, NH_2), 3.71(3H, s, OCH_3),1.53(3H, s, CH_3), 1.52(1H, d, J=12), 1.37 (1H, d, J=12), 1.06 and 1.05(6H, 2CH_3). ^{13}C NMR(DMSO-d_6) δ=164.96, 156.17, 117.26, 114.52, 79.02, 59.77, 56.64, 55.80, 49.39, 43.34, 28.47, 26.40, 25.14.

2b: When ethanol was used instead of methanol, 3-ethoxy derivative was obtained. The product was recrystallized from ethanol. Yield:35%. mp: 231-232 ℃. Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H 7.02; N 21.69. Found: C, 65.147; H, 7.03; 21.840. IR (KBr): ν=3430, 3120, 2970, 2180, 1670, 1300, 1020 cm^{-1}. ^{1}H NMR(DMSO-d_6) δ=6.84(2H, br s, NH_2), 4.11(2H, m, OCH_2), 1.52(1H, d, J=12), 1.37 (1H, d, J=12), 1.25(3H, t, OCH_2CH_3, J=7), 1.25(3H, s, CH_3),1.06(6H, s, 2CH_3). ^{13}C NMR(DMSO-d_6) δ =163.42, 155.41, 116.53, 113.77, 78.22, 63.66, 58.90, 55.81, 48.62, 42.50, 27.59, 25.73, 24.43, 13.92.

Acidic hydrolysis of 2a. 6-Carbomethoxy-2,6-dicyano-3,5,5-trimethylcyclohex-2-enone(**4a**): A mixture of **2a**(1.14 g, 4.7 mmol), 50 mL of methanol and 50 mL of 2N HCl was refluxed for 5 h. The homogeneous solution was poured into water. The crystal precipitated was recrystallized from methanol. Yield: 0.82 g(62 %). mp:136 -138 ℃. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.18; H, 5.64; N, 11.19. MS, m/z(%); 246(16), 174. IR (KBr): ν=3440, 2980, 2240, 1730, 1690, 1610, 1380, 1250 cm^{-1}. ^{1}H NMR($CDCl_3$) δ =3.87(3H, s, OCH_3), 2.95(1H, d, J=20), 2.50(1H, d, J=20), 2.40(3H, s, CH_3), 1.45(3H, s, CH_3), 1.33(3H, s, CH_3). ^{13}C NMR($CDCl_3$) δ=180.60, 175.75, 162.86, 113.32, 112.31, 111.38, 64.89, 54.47, 44.15, 39.58, 25.60, 25.43, 24.76.

2,6-Dicyano-3,5,5-trimethylcyclohex-2-enone(**5a**): A mixture of **4**(0.8 g, 3.3 mmol), methanol (30 mL) and 2N HCl(30 mL) was refluxed for 2 days. The reaction mixture was evaporated. The residue was recrystalized from methanol. Yield: 0.55 g(90 %). mp:120 -122 ℃. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.89. Found: C, 69.92; H, 6.58; N, 14.69. MS, m/z(%); 188(69), 107. IR(KBr): ν=3440, 2970, 2880, 2240, 1680, 1610, 1380 cm^{-1}. ^1H NMR($CDCl_3$) δ=3.49(1H,CH), 2.63(2H,CH_2), 2.37(3H,CH_3), 1.32(3H,CH_3), 1.19(3H,CH_3), ^{13}C NMR($CDCl_3$) δ=182.96, 174.54, 113.80, 112.40,112.34, 51.21, 45.59, 36.43, 28.16, 24.71, 23.23.

4-Amino-3,5-dicyano-2-ethoxy-6-methylpyridine(**3b**): **2b**(0.24 g, 1.19 mmol) was heated in xylene(20 mL) for 5 h. The crystal was recrystallized from ethanol.

Yield: 0.18 g(96%). mp:230～232℃. Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.25; H, 4.99; N, 27.77. MS, m/z(%); 202(41), 174. IR (KBr): ν =3420, 3340, 3240, 2220, 1650, 1570, 1440, 1380, 1340, 1300, 1160,1020 cm^{-1}. ^1H NMR(DMSO-d_6) δ=7.58(2H,NH_2), 4.41(2H,CH_2), 2.46(3H,CH_3), 1.31(3H,CH_3), ^{13}C NMR(DMSO-d_6) δ=165.85, 165.82, 158.47, 115.16, 113.53, 87.99, 75.55, 63.28, 24.12, 14.39.

X-Ray Analysis of 5a

$C_{11}H_{12}N_2O$ F.W.=188, mp 120-122 ℃(methanol). Crystal data: a=12.184(2), b=13.104(2), c=6.704(2), V=1070.4(3) $Å^3$, orthorhombic. $P2_12_12_1$, Dx=1.168 g/cm^3, F(OOO)=400,, μ(Mo Kα)=077 cm^{-1}. The diffraction experiment was carried out using a single crystal with dimension of 0.70x0.38x0.30 mm. The diffractometer Rigaku AFC-7R was used with graphite monochromated Mo Kα radiation. The unit cell dimensions were determined 25 2θ values in the range of 38.5-40.5 degrees. In total 2240 reflections were measured and 1434 reflections were used for the calculation. The structure was solved by the direct method. The refinement of atomic parameters assuming anisotropic thermal displacement was applied for all non hydrogen atoms. All the H-atoms were found in difference Fourier map and were included in the refinement. The final R value was 0.039(Rw=0.038). The minimum and maximum peaks on the final difference Fourier map were -0.11 and 0.08 e/Å^3. All calculations were carried out using TEXSAN on the SGI Indy computer. Atomic parameters and B_{eq} of non-H atoms, bond lengths, and angles are collected in Tables 2 and 3.

Table 2. Atomic coordinates and Beq of non-H atoms for **5a**.

Atom	x/a	y/b	z/c	*Beq*	Atom	x/a	y/b	z/c	*Beq*
O	0.3934(1)	0.0176(1)	0.7435(2)	5.20(3)	C5	0.3177(1)	0.2111(1)	0.3868(3)	3.68(3)
N1	0.6424(1)	-0.0626(1)	0.5408(3)	7.38(5)	C6	0.2890(1)	0.1134(1)	0.5051(3)	3.32(3)
N2	0.1525(1)	0.1449(1)	0.7983(3)	6.36(5)	C7	0.5721(1)	-0.0107(1)	0.4958(3)	4.68(4)
C1	0.3903(1)	0.0583(1)	0.5798(2)	3.54(3)	C8	0.5747(2)	0.0990(2)	0.1208(3)	5.23(5)
C2	0.4829(1)	0.0549(1)	0.4401(3)	3.45(3)	C9	0.2127(2)	0.2594(2)	0.3041(4)	5.69(5)
C3	0.4838(1)	0.1073(1)	0.2675(3)	3.56(3)	C10	0.3772(2)	0.2868(1)	0.5214(4)	5.10(5)
C4	0.3907(1)	0.1771(1)	0.2142(3)	4.22(4)	C11	0.2127(1)	0.1315(1)	0.6707(3)	4.31(4)

$$B_{eq}=8/3\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta$$
$$+2U_{23}bb^*cc^*\cos\alpha)$$

Table 3. Selected bond length(Å) and angles(°) and dihedral angles(°) for **5a**.

O-C1	1.220(2)	C3-C4	1.499(2)				
N1-C7	1.134(2)	C3-C8	1.485(2)				
N2-C11	1.140(2)	C4-C5	1.527(2)				
C1-C2	1.467(2)	C5-C6	1.546(2)	O-C1-C2-C3	-173.7(2)	O-C1-C2-C7	8.1(2)
C1-C6	1.515(2)	C5-C9	1.531(2)	O-C1-C6-C5	141.6(2)	O-C1-C6-C11	14.2(2)
C2-C3	1.346(2)	C5-C10	1.525(3)	C1-C2-C3-C4	3.2(2)	C1-C2-C3-C8	-176.3(2)
C2-C7	1.436(2)	C6-C11	1.468(2)	C1-C6-C5-C4	58.1(2)	C1-C6-C5-C9	176.4(2)
O-C1-C2	125.5(2)	C4-C5-C6	106.2(1)	C1-C6-C5-C10	-62.3(2)	C2-C1-C6-C5	-40.0(2)
O-C1-C6	122.1(2)	C4-C5-C9	109.5(2)	C2-C1-C6-C11	-167.4(1)	C2-C3-C4-C5	19.0(2)
C2-C1-C6	115.4(1)	C4-C5-C10	111.2(1)	C3-C2-C1-C6	7.9(2)	C3- C4-C5-C6	-47.9(2)
C1-C2-C3	122.7(1)	C6-C5-C9	109.8(1)	C3- C4-C5-C9	-166.4(2)	C3- C4-C5-C10	71.7(2)
C1-C2-C7	115.7(1)	C6-C5-C10	110.0(1)	C4-C3-C2-C7	-178.7(2)	C4-C5-C6-C11	-176.3(1)
C3-C2-C7	121.6(2)	C9-C5-C10	110.1(2)	C5-C4-C3-C8	-161.5(2)	C6-C1-C2-C7	-170.3(1)
C2-C3-C4	120.7(1)	C1-C6-C5	112.4(1)	C7-C2-C3-C8	1.8(3)	C9-C5-C6-C11	-58.0(2)
C2-C3-C8	122.5(2)	C1-C6-C11	110.1(1)	C10-C5-C6-C11	63.3(2)		
C4-C3-C8	116.8(2)	C5-C6-C11	113.4(1)				
C3-C4-C5	116.0(1)	N1-C7-C2	179.7(2)				
		N2-C11-C6	179.2(2)				

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