

A Convenient Synthesis of 3-Cyano-2-methylpyridines under Ultrasonic Irradiation

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Synopsis. Ultrasonic irradiation of α,β -unsaturated carbonyl compounds **1a–i** with acetonitrile in the presence of potassium *t*-butoxide gave 3-cyano-2-methylpyridines **2a–i** in moderate to good yields. The pyridines are produced by a Michael reaction of 3-iminobutanonitrile, an acetonitrile dimer, to the substrates **1a–i**.

Ultrasonic irradiation has gained rapidly growing recognition as an effective method for increased reaction rates and yields in organic chemistry.^{1–3)} Meyer and Chatterjea have prepared 3-cyanopyridines from α,β -unsaturated carbonyl compounds and 3-aminocrotononitrile in low yields.^{4,5)} We report here a successful synthesis of 3-cyano-2-methylpyridines from α,β -unsaturated carbonyl compounds and acetonitrile in the presence of potassium *t*-butoxide under ultrasonic irradiation.

The results of ultrasonic irradiation of α,β -unsaturated carbonyl compounds are summarized in Table 1. In order to examine the effects of ultrasonic irradiation, a few experiments were conducted. Ultrasonic irradiation and mechanical agitation of **1a** with potassium *t*-butoxide in acetonitrile afforded **2a** in 70 and 30% yields, respectively (Runs 1 and 2). Reflux and ultrasonic irradiation of **1a** with 3-aminocrotononitrile in acetonitrile gave **2a** in 72 and 34% yields,

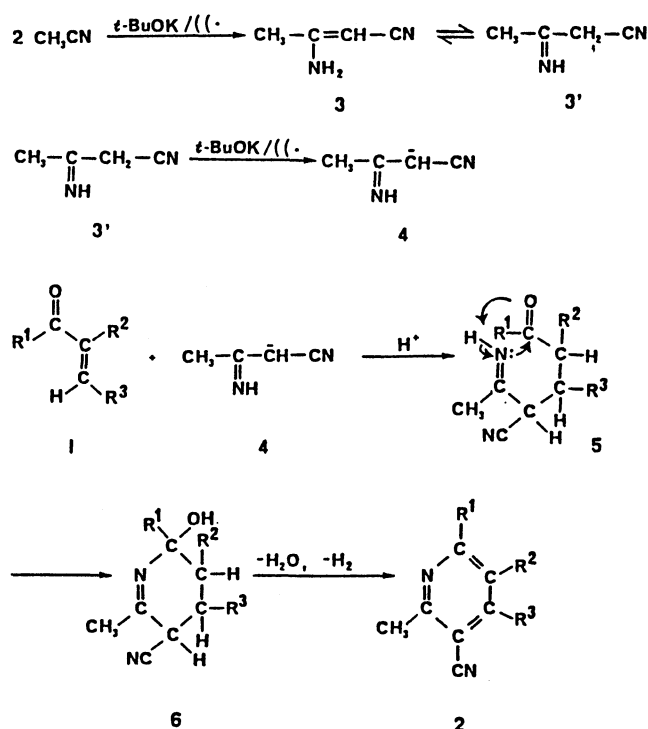
respectively (Runs 3 and 4). The results clearly show that the advantages of ultrasonic irradiation include the shorter reaction time and the higher yield for the synthesis of 3-cyano-2-methylpyridines. Other pyridines **2b–i** were also obtained in moderate to good yields (Runs 5–12). In the case of **1f**, 4-cyano-1,2,3-triphenyl-1-butanone was produced by a Michael addition of acetonitrile to **1f** (Run 9). In the case of **1g**, 2-methyl-6-phenylbenzophenone was produced by a Michael reaction of 4-oxo-4-phenyl-2-buten-1-ide to **1g** followed by protonation, intramolecular aldol condensation, and aromatization (Run 10).

A reasonable mechanism in these pyridine formations is shown in Scheme 1. A key compound produced during the ultrasonic irradiation was identified as 3-aminocrotononitrile (**3**), the dimer of acetonitrile. No remarkable difference in the yield of **2a** was observed (Runs 1 and 3, in Table 1), suggesting that ultrasonic irradiation is effective for the formation of 3-aminocrotononitrile (**3**) in the solution. The nitrile exists as enamino and imino tautomers (**3** and **3'**, respectively) in the acetonitrile solution. On the basis of the ¹H NMR spectrum, the proportionality ratio of the imino isomer **3'** was calculated to be ca. 30% in acetonitrile. The imino isomer **3'** is easily converted into the carbanion **4** with potassium *t*-butoxide.

Table 1. Synthesis of 3-Cyano-2-methylpyridines **2a–i** from α,β -Unsaturated Carbonyl Compounds **1a–i** with Acetonitrile in the Presence of Potassium *t*-Butoxide under Ultrasonic Irradiation

Run	Compd	Substituent			Time min	Yield ^{a)} /%
		R ¹	R ²	R ³		
1	1a	Ph	H	<i>p</i> -ClC ₆ H ₄	15	70
2	1a	Ph	H	<i>p</i> -ClC ₆ H ₄	60	30 ^{b)}
3	1a	Ph	H	<i>p</i> -ClC ₆ H ₄	15	72 ^{c)}
4	1a	Ph	H	<i>p</i> -ClC ₆ H ₄	30	34 ^{d)} , (lit ^{e)} 35)
5	1b	Ph	H	Ph	15	93
6	1c	<i>p</i> -MeOC ₆ H ₄	H	Ph	15	93
7	1d	<i>t</i> -Bu	H	Ph	30	97
8	1e	Me	H	Ph	45	66
9	1f	Ph	Ph	Ph	30	59 ^{f)}
10	1g	Ph	H	Me	5	29 ^{g)}
11	1h	Ph	Me	Ph	30	32
12	1i	H	H	Ph	30	40

a) Isolated yield. b) Mechanical agitation at room temperature. c) **1a** was irradiated with 3-aminocrotononitrile (**3**, 0.04 mmol) in the presence of potassium *t*-butoxide in acetonitrile. d) Refluxed with 3-aminocrotononitrile (**3**, 0.04 mmol) in acetonitrile. e) Reference 2. f) 4-Cyano-1,2,3-triphenyl-1-butanone and *trans*-stilbene were obtained in 10 and 13% yields, respectively. g) 2-Methyl-6-phenylbenzophenone was also obtained in a 9% yield.



Scheme 1.

There are two possibilities for the formation of pyridines. One is the condensation reaction of the carbonyl group of **1** with the amino group of **3** followed by dehydrocyclization. Another is a Michael reaction of carbanion **4**. The ultrasonic irradiation of 4-oxo-2,4-diphenyl-2-butene did not give the corresponding pyridines, because of the steric hindrance of the methyl group at the β -position. This result suggests that a Michael addition of the imino isomer **3'** plays an important role in this reaction. α,β -Unsaturated carbonyl compounds react with the carbanion **4** followed by protonation to give the adduct **5**. Since the imino group is located close to the carbonyl group in the most stable conformation, the adduct **5** is easily cyclized to give the pyridine precursor **6**. Unfortunately, these compounds were not isolated. The precursor **6** is dehydrated, and dehydrogenated to give pyridine **2**.

Experimental

General. Melting points were measured with a Yanagimoto micro melting point apparatus and uncorrected. IR and NMR spectra were recorded with Jasco A302 and JEOL GX-270 spectrometers, respectively. Mass spectra were obtained with a Shimadzu GCMS 9020-DF spectrometer. Ultrasonic irradiation was carried out with a Branson ultrasonic laboratory cleaner (45 kHz, 100W).

Materials. α,β -Unsaturated carbonyl compounds **1e**, **1g**, and **1i** were available from Nakarai Chemicals Ltd. and used without further purification. The other compounds, **1a**, **1b**, **1c**, **1d**, **1f**, and **1h**, were prepared as described in the literature and their purity was checked by GLC. The melting or boiling points were as follows: **1a**: mp 114.5–115.0°C (lit⁶ 114.0–115.0°C). **1b**: mp 56.0–57.0°C (lit⁷ 55.0–57.0°C). **1c**: mp 106.5–108.0°C (lit⁸ 105–106°C). **1d**: mp 42.0°C (lit⁹ 45.0°C). **1f**: mp 99.0–100.0°C (lit¹⁰ 100°C). **1h**: bp 180°C (267 Pa) (lit¹¹ 167°C (80 Pa)).

Preparation of 3-Cyano-2-methylpyridines. A dry acetonitrile suspension (50 cm³) of potassium *t*-butoxide (100 mg) was irradiated on a water bath for 15 minutes at room temperature. α,β -Unsaturated carbonyl compounds (**1**, 0.48 mmol) was then added to the suspension, which was further irradiated. The end point of the reaction was checked by TLC. After the addition of water (50 cm³) saturated with sodium chloride, the reaction mixture was extracted with ether (20 cm³×2). The extract was dried over anhydrous sodium sulfate. The solvent was then evaporated under reduced pressure. In the cases of **1a–d**, the residue was recrystallized from ethanol. In the cases of **1e–i**, the residue was chromatographed on a silica-gel column (Wakogel C-200, hexane:chloroform=1:5). **2a**: Mp 178.0–178.5°C (lit⁵

173°C); IR (KBr) 2215 cm⁻¹; ¹H NMR (CDCl₃) δ =2.92 (3H, s) and 7.4–8.1 (10H, m). **2b**: Mp 121.5–122.5°C (lit⁵ 115–116°C); IR (KBr) 2240 cm⁻¹; ¹H NMR (CDCl₃) δ =2.92 (3H, s) and 7.5–8.0 (11H, m). **2c**: Mp 138.5–139.0°C; IR (KBr) 2220 cm⁻¹; ¹H NMR (CDCl₃) δ =2.89 (3H, s), 3.92 (3H, s), and 7.0–8.1 (10H, m). Found: *m/z* 300.1290. Calcd for C₂₀H₁₆N₂O: M, 300.1264. **2d**: Mp 89.0–90.5°C; IR (KBr) 2220 cm⁻¹; ¹H NMR (CDCl₃) δ =1.38 (9H, s), 2.82 (3H, s), and 7.3–7.6 (6H, m). Found: *m/z* 250.1407. Calcd for C₁₇H₁₈N₂: M, 250.1471. **2e**: Mp 109.0–110.0°C (lit⁵ 105–106°C); IR (KBr) 2220 cm⁻¹; ¹H NMR (CDCl₃) δ =2.63 (3H, s), 2.82 (3H, s), and 7.1–7.6 (6H, m). **2f**: Mp 180.0–181.5°C; IR (KBr) 2220 cm⁻¹; ¹H NMR (CDCl₃) δ =2.93 (3H, s) and 6.8–7.3 (15H, m). Found: *m/z* 346.1550. Calcd for C₂₅H₁₈N₂: M, 346.1471. **2g**: Mp 74.0–76.5°C; IR (KBr) 2220 cm⁻¹; ¹H NMR (CDCl₃) δ =2.53 (3H, s), 2.78 (3H, s), and 7.5–8.0 (10H, m). Found: *m/z* 208.1058. Calcd for C₁₄H₁₂N₂: M, 208.1002. **2h**: Mp 116.0–116.5°C; IR (KBr) 2240 cm⁻¹; ¹H NMR (CDCl₃) δ =2.08 (3H, s), 2.83 (3H, s), and 7.2–7.8 (10H, m). Found: *m/z* 284.1296. Calcd for C₂₀H₁₆N₂: M, 284.1315. **2i**: Mp 98.5–99.5°C; IR (KBr) 2240 cm⁻¹; ¹H NMR (CDCl₃) δ =2.87 (3H, s), 7.29 (1H, d, *J*=5.2 Hz), 7.5–8.6 (5H, m), and 8.68 (1H, d, *J*=5.2 Hz). Found: *m/z* 194.0825. Calcd for C₁₃H₁₀N₂: H, M, 194.0845.

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