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

Katsuyoshi SHIBATA,* Katsuyoshi URANO, and Masaki MATSUI
Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-11
(Received September 18, 1987)

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.

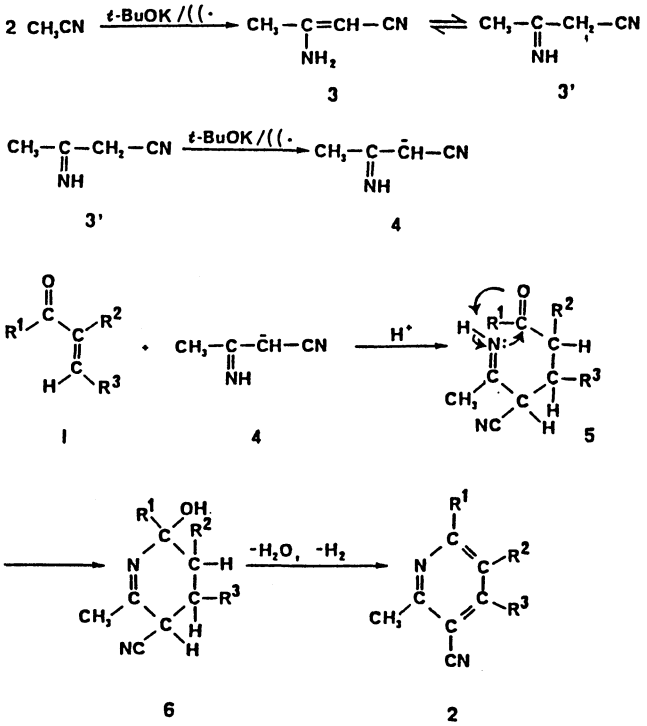
The results of ultrasonic irradiation of α,β-unsaturated carbonyl compounds are summarized in Table 1. In order to examine the effects of ultrasonic irradiation, a few experiments were conducted. Ultrasonic irradiation and mechanical agitation of **1a** with potassium *t*-butoxide in acetonitrile afforded **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 ^{1}H 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	Yield[a]/%
		R^1	R^2	R^3	min	**2**
1	**1a**	Ph	H	*p*-ClC_6H_4	15	70
2	**1a**	Ph	H	*p*-ClC_6H_4	60	30[b]
3	**1a**	Ph	H	*p*-ClC_6H_4	15	72[c]
4	**1a**	Ph	H	*p*-ClC_6H_4	30	34[d],(lit[e] 35)
5	**1b**	Ph	H	Ph	15	93
6	**1c**	*p*-$MeOC_6H_4$	H	Ph	15	93
7	**1d**	*t*-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 (lit[6] 114.0—115.0 °C). **1b**: mp 56.0—57.0 °C (lit[7] 55.0—57.0 °C). **1c**: mp 106.5—108.0 (lit[8] 105—106 °C). **1d**: mp 42.0 °C (lit[9] 45.0 °C). **1f**: mp 99.0—100.0 °C (lit[10] 100 °C). **1h**: bp 180 °C (267 Pa) (lit[11] 167 °C (80 Pa)).

Preparation of 3-Cyano-2-methylpyridines. A dry acetonitrile suspension (50 cm^3) 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 cm^3) saturated with sodium chloride, the reaction mixture was extracted with ether (20 cm^3×2). 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 (lit[5] 173 °C); IR (KBr) 2215 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.92 (3H, s) and 7.4—8.1 (10H, m). **2b**: Mp 121.5—122.5 °C (lit[5] 115—116 °C); IR (KBr) 2240 cm^{-1}; ^1H NMR ($CDCl_3$) 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 ($CDCl_3$) δ=2.89 (3H, s), 3.92 (3H, s), and 7.0—8.1 (10H, m). Found: *m/z* 300.1290. Calcd for $C_{20}H_{16}N_2O$: M, 300.1264. **2d**: Mp 89.0—90.5 °C; IR (KBr) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.38 (9H, s), 2.82 (3H, s), and 7.3—7.6 (6H, m). Found: *m/z* 250.1407. Calcd for $C_{17}H_{18}N_2$: M, 250.1471. **2e**: Mp 109.0—110.0 °C (lit[5] 105—106 °C); IR (KBr) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) 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 ($CDCl_3$) δ=2.93 (3H, s) and 6.8—7.3 (15H, m). Found: *m/z* 346.1550. Calcd for $C_{25}H_{18}N_2$: M, 346.1471. **2g**: Mp 74.0—76.5 °C; IR (KBr) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.53 (3H, s), 2.78 (3H, s), and 7.5—8.0 (10H, m). Found: *m/z* 208.1058. Calcd for $C_{14}H_{12}N_2$: M, 208.1002. **2h**: Mp 116.0—116.5 °C; IR (KBr) 2240 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.08 (3H, s), 2.83 (3H, s), and 7.2—7.8 (10H, m). Found: *m/z* 284.1296. Calcd for $C_{20}H_{16}N_2$: M, 284.1315. **2i**: Mp 98.5—99.5 °C; IR (KBr) 2240 cm^{-1}; ^1H NMR ($CDCl_3$) 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 $C_{13}H_{10}N_2$: H, M, 194.0845.

The authors wish to express their thanks to Messrs. Katsuaki Shiratsuchi and Shozo Onishi of Shimadzu Corporation for the measurement of the mass spectra.

References

1) S. Raucher and P. Klein, *J. Org. Chem.*, **46**, 3558 (1981).
2) J. Yamawaki,S. Sumi, T. Ando, and T. Hanafusa, *Chem. Lett.*, **1983**, 379.
3) J. Einhorn and J. L. Luche, *J. Org. Chem.*, **52**, 4124, (1987).
4) E. V. Meyer, *J. Prakt. Chem.*, **78**, 497 (1908).
5) J. N. Chatterjea, *J. Indian Chem. Soc.*, **29**, 323 (1952); J. N. Chatterjea and K. Prasad, *J. Sci. Industr. Res.*, **14B**, 383 (1955).
6) H. H. Szmant and A. J. Basso, *J. Am. Chem. Soc.*, **74**, 4397 (1952).
7) E. P. Kohler and H. M. Chadwell, *Org. Synth.*, Coll. Vol. I, 78 (1941).
8) H Staudinger and N. Kon, *Justus Liebigs Ann. Chem.*, **384**, 123 (1911).
9) G. A. Hill and G. M. Bramann, *Org. Synth.*, Coll. Vol. I, 81 (1941).
10) E. Knoevenagel and R. Weissgerber, *Chem. Ber.*, **26**, 441 (1893).
11) C. A. Kingsbury, D. Draney, A. Sopchik, W. Rissler, and D. Durham, *J. Org. Chem.*, **41**, 3863 (1976).