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SYNTHESIS OF 1,4-DIKETONES BY MICHAEL ADDITION OF *O*-AROYLMANDELONITRILES INVOLVING REARRANGEMENT OF AROYL GROUP AND DECYANATION

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The anions derived from *O*-aroylmandelonitriles **1** reacted with Michael addition acceptors such as acrylonitrile (**7**) and methyl acrylate (**10**) to give the corresponding 1,4-diketones **12**, **13**, and **15** in moderate to good yields. Under acidic conditions, the 1,4-diketones **12**, **13**, and **15** were converted into the furans **17**, **18** and **19** in good yields.

KEY WORDS *O*-aroylmandelonitrile; anion; Michael addition; 1,4-diketone; decyanation; furan

The anions derived from mandelonitriles behave as aroyl anions,1) and *O*-aroylmandelonitriles (**1**),1e) *O*-trimethylsilylmandelonitriles (**2**),1a) and *O*-(α-ethoxyethyl)mandelonitriles (**3**)1b) can be used as aroyl anion equivalents. In connection with our studies on reactions promoted by the catalytic action of cyanide ion or the electron-accepting effect of the cyano group,2) we therefore became interested in the mandelonitriles. Further, *O*-aroylmandelonitriles (**1**) are easily prepared.

The structure of the *O*-aroylmandelonitriles **1** is similar to that of Reissert compounds **4**. It was reported that the isoquinoline Reissert compound (**4a**) reacts with acrylonitrile (**7**) to give the ketone **5** in low yield together with the pyrrole derivative **6**.3) The formation of **5** and **6** was explained in terms of Michael addition followed by rearrangement of the benzoyl group and decyanation. This result suggested that Michael addition of the anions derived from *O*-aroylmandelonitriles **1** with acrylonitrile (**7**) would give 1,4-diketones by rearrangement of the aroyl group and decyanation in the same way as Reissert compounds. 1,4-Diketones are starting compounds for preparation of five-membered heterocycles such as furans.

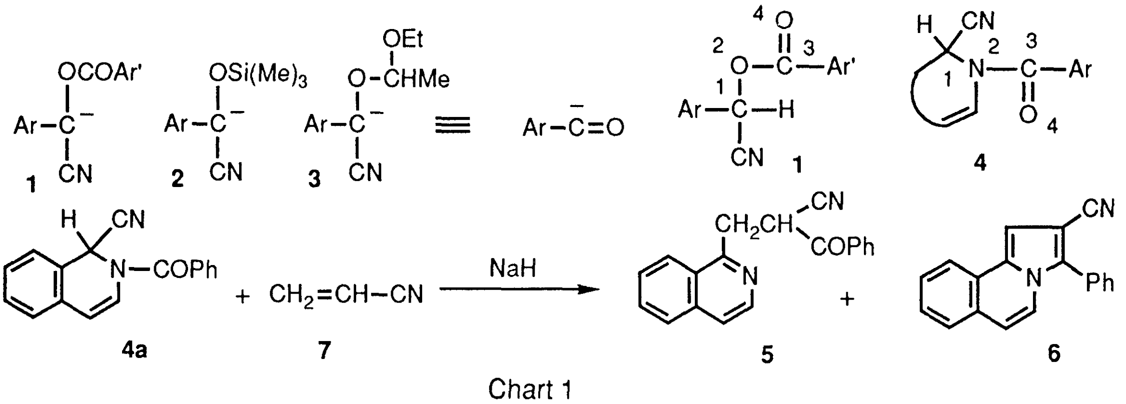

Chart 1

When *O*-benzoylmandelonitrile (**1a**) was treated with acrylonitrile (**7**) in the presence of NaNH$_2$ in DMF at room temperature for 2 h, only one product was formed.4) It was identified as 2,3-dibenzoylpropionitrile (**12a**) from the spectral data and elemental analysis.5) As assumed, the reaction appears to proceed through rearrangement of the benzoyl group and decyanation. Strong bases such as NaH and NaNH$_2$ are required to produce the anion from *O*-benzoylmandelonitrile (**1a**). DMF and DMSO were effective solvents, as shown in Chart 2.

Various *O*-aroylmandelonitriles **1a**-**f** were used in this Michael addition with acrylonitrile (**7**), and the expected 1,4-diketones **12a**-**f** were obtained in moderate to good yields. The reaction could be extended to methyl acrylate (**10**) and chalcone (**11**), and the corresponding 1,4-diketones **15a**, **15d**, and **16a** were formed in moderate yields. But, it failed to afford 1,4-diketones **14** from *O*-aroylmandelonitriles **1** and cinnamonitrile (**9**), presumably because of steric hindrance. Attempts to synthesize 1,4-diketones **12g**, **12h**, **15g**, and **15h** by the use of *O*-benzoylmandelonitriles **1g** and **1h** having not only a strong electron-withdrawing substituent but also a strong electron-donating substituent were unsuccessful. Similarly, the 1,4-diketone **12i** with an aliphatic group could not be obtained by treatment of **1i** with **7**. However, the scope and limitations of the reaction remain to be fully established.

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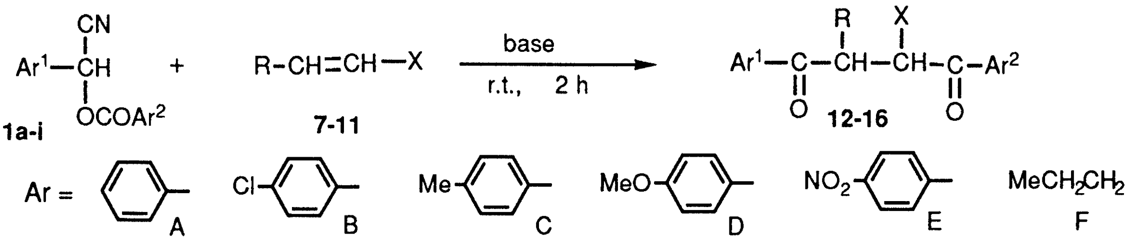


	Ar^1	Ar^2		R	X	solvent	base[1]	Yield (%) 1,4-diketone		(Recovery)
1a	A	A	**7**	H	CN	DMSO	NaH	**12a**	62	(6)
1a	A	A	**7**	H	CN	DMF	NaNH$_2$	**12a**	63	
1a	A	A	**7**	H	CN	DMF	DBU	**12a**	—	(55)
1a	A	A	**7**	H	CN	DMF	K$_2$CO$_3$	**12a**	—	(72)
1a	A	A	**7**	H	CN	THF	NaNH$_2$	**12a**	—	(85)
1a	A	A	**8**	Me	CN	DMF	NaH	**13a**	50	
1a	A	A	**10**	H	COOMe	DMF	NaNH$_2$	**15a**	84	(10)
1a	A	A	**11**	Ph	COPh	DMSO	NaH	**16a**	48	
1b	A	B	**7**	H	CN	DMF	NaNH$_2$	**12b**	41	(32)
1b	A	B	**8**	Me	CN	DMF	NaNH$_2$	**13b**	63	(19)
1b	A	B	**9**	Ph	CN	DMF	NaNH$_2$	**14b**	—	(98)
1c	A	C	**7**	H	CN	DMF	NaNH$_2$	**12c**	30	
1d	B	A	**7**	H	CN	DMF	NaNH$_2$	**12d**	55	(14)
1d	B	A	**8**	Me	CN	DMF	NaNH$_2$	**13d**	42	(24)
1d	B	A	**9**	Ph	CN	DMF	NaNH$_2$	**14d**	—	(95)
1d	B	A	**10**	H	COOMe	DMF	NaNH$_2$	**15d**	74	(8)
1e	C	A	**7**	H	CN	DMF	NaNH$_2$	**12e**	30	
1f	C	C	**7**	H	CN	DMF	NaNH$_2$	**12f**	48	
1g	D	A	**7**	H	CN	DMSO	NaH	**12g**	—	(3)[2]
1g	D	A	**10**	H	COOMe	DMF	NaNH$_2$	**15g**	—	(61)
1h	E	A	**7**	H	CN	DMF	NaNH$_2$	**12h**	—	(—)[2]
1h	E	A	**10**	H	COOMe	DMF	NaNH$_2$	**15h**	—	(—)[2]
1i	F	A	**7**	H	CN	DMF	NaNH$_2$	**12i**	—	(28)[2]

1) DBU; 1,8-Diazabicyclo[5,4,0]-7-undecene. 2) Separation of the reaction products was not easy.

Chart 2

The proposed reaction pathway is illustrated in Chart 3. Michael addition proceeds between the anion derived from *O*-benzoylmandelonitrile (**1a**) and acrylonitrile (**7**) to give the intermediate (a). Then, rearrangement of the benzoyl group with decyanation results in the formation of the 1,4-diketone **12a**. The reaction process is similar to that of the Reissert compound **4a**. We considered that the rearrangement of the aroyl group proceeds through intramolecular reaction by formation of the intermediate (b) having a five-membered ring. To clarify the reaction pathway, cross-reaction was carried out. When a mixture of *O*-benzoylmandelonitrile (**1a**) and *O*-(*p*-toluoyl)-*p*-methylmandelonitrile (**1f**) was treated with acrylonitrile (**7**) in DMF, only 2,3-dibenzoylpropionitrile (**12a**) and 2,3-di(*p*-toluoyl)propionitrile (**12f**) were obtained. Formation of the cross-reaction products **12c** and **12e** could not be detected by HPLC analysis based on the retention times of authentic samples.[6] This result proves that the rearrangement of the aroyl group proceeds intramolecularly, as shown in Chart 3.

1,4-Diketones are useful compounds in organic synthesis. It has been reported that five-membered heterocycles such as furans can be synthesized by ring-closure of these compounds.[7] This led us to synthesize

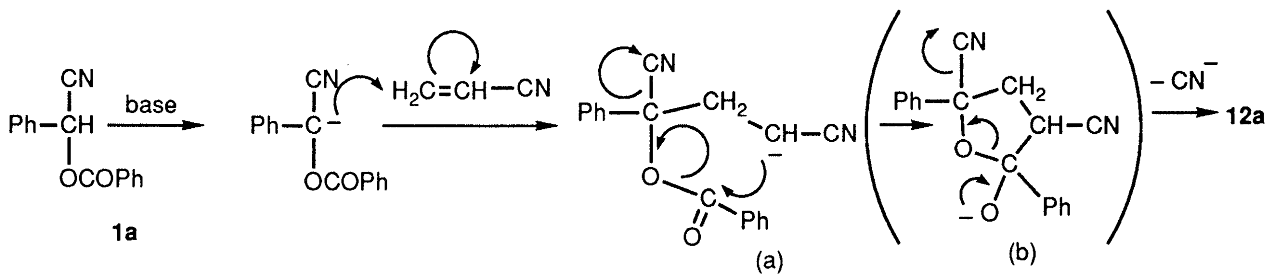
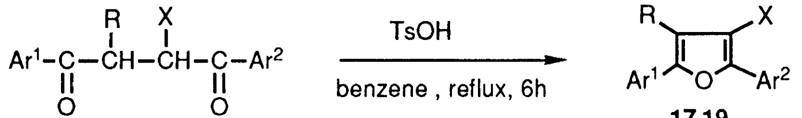


Chart 3



12, 13, 15

17-19

	Ar¹	Ar²	R	X	Yield (%)	
12a	A	A	H	CN	**17a**	78
12b	A	B	H	CN	**17b**	62
13b	A	B	Me	CN	**18b**	85
13d	B	A	Me	CN	**18d**	84
15a	A	A	H	COOMe	**19a**	46

Chart 4

several furans by use of the 1,4-diketones obtained in this study. In refluxing benzene under acidic conditions, 2,3-dibenzoylpropionitrile (**12a**) was converted into 2,5-diphenyl-3-furancarbonitrile (**17a**) in good yield.[8] The furans **17b, 18b, 18d,** and **19a** were obtained by similar treatments of the 1,4-diketones **12b, 13b, 13d** and **15a**. This is of interest, since a number of furans found in nature have biological activities.[9]

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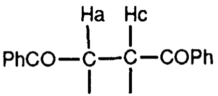
3) *a*) Giridhar V., McEwen W. E., *J. Heterocycl. Chem.*, **8**, 121-123 (1971); *b*) Uff B. C., Budhram R. S., *Synthesis*, **1978**, 206; *c*) Uff B. C., Budhram R. S., Consterdine M. F., Hicks J. K., Slingsby B. P., Pemblington J. A., *J. Chem. Soc., Perkin 1*, **1977**, 2018-2022.
4) A typical procedure: Sodium amide (86 mg, 2.2 mmol) was slowly added to a mixture of *O*--benzoylmandelonitrile (**1a**, 474 mg, 2 mmol) and acrylonitrile (**7**, 212 mg, 4 mmol) in 10 ml of DMF, and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was poured into 100 ml of H_2O, neutralized with AcOH, and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with benzene to give 1,3-dibenzoylpropionitrile (**12a**, 332 mg, 63%), colorless needles (hexane), mp 65-66°C.
5) **12a**: *Anal.* Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.68; H, 4.81; N, 5.31. IR (KBr) cm^{-1}: 2236 (CN), 1678 (CO). ^1H-NMR ($CDCl_3$) δ (ppm): 3.53 (1H, q, Ha, *J*ab = 19.8, *J*ac = 9.6), 4.07 (1H, q, Hb, *J*ba = 19.8, *J*bc = 6.0), 5.00 (1H, q, Hc, *J*cb = 6.0, *J*ac = 9.6), 7.13-7.63 (6H, m, aromatic H), 7.80-8.17 (4H, m, aromatic H).

   $$\mathrm{PhCO-\underset{Hb}{\overset{Ha}{C}}-\underset{CN}{\overset{Hc}{C}}-COPh}$$
6) HPLC conditions: Column; Develosil Packed Column (DEVELOSIL C8-5), 4.6×250 mm. Flow; 1.0 ml/min. Solvent; acetonitrile / H_2O (7:3). Detector; UV 240 nm. The chromatogram of the cross-reaction mixture was compared with that of authentic samples based on the retention times. The retention times of the authentic samples were as follows; **12a** (8.04 min), **12c** (9.69 min), **12e** (9.71 min), and **12f** (11.93 min).
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8) A typical procedure: A mixture of 1,4-dibenzoylpropionitrile (**12a**, 418 mg, 1.56 mmol) and a catalytic amount of *p*-toluenesulfonic acid (50 mg, 0.29 mmol) in 30 ml of benzene was refluxed for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on SiO_2 with benzene. The first fraction gave 2,5-diphenyl-3-furancarbonitrile (**17a**, 298 mg, 78%), colorless needles (hexane), mp 117-118 °C. *Anal.* Calcd for $C_{17}H_{11}NO$: C, 83.25; H, 4.52; N, 5.71. Found: C, 83.25; H, 4.33; N, 5.65. IR (KBr) cm^{-1}: 2222 (CN). ^1H-NMR ($CDCl_3$) δ (ppm): 6.80 (1H, s, furan C^4-H), 7.23-7.83 (8H, m, aromatic H), 7.84-8.20 (2H, m, aromatic H).
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