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A Synthetic Application of Methylthioacetonitrile. I. A Synthesis of *cis*- and *trans*-β-Arylacrylonitriles, β,γ-Unsaturated Nitriles and Carbonyl Compounds

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The Knoevenagel condensation of methylthioacetonitrile with carbonyl compounds such as benzaldehyde, cyclopentanone, phenylacetone, was examined to give the corresponding α-methylthio unsaturated nitriles. Desulfurization of β-aryl-α-methylthioacrylonitriles (**5a**—**f**) with Raney Nickel afforded *cis*-β-arylacrylonitriles (**6a**—**f**). Reduction of **5a**—**c** with sodium borohydride gave α-methylthiophenylpropionitriles (**7a**—**c**), which were converted to *trans*-cinnamonitriles (**9a**—**c**). α-Methylthio-α,β-unsaturated nitriles (**11a**—**d**) were lead to α-ethyl-α-methylthio-β,γ-unsaturated nitriles (**12a**—**d**). Furthermore, the α-methylthiophenylpropionitrile (**7b**) was converted to 4-methoxybenzyl methyl ketone.

Keywords——Knoevenagel condensation; methylthioacetonitrile; β-arylacrylonitrile; *cis*-cinnamonitrile; *trans*-cinnamonitrile; β,γ-unsaturated nitrile

Because of their wide applicability in synthetic organic chemistry, the chemistry of cyanide, especially α,β-unsaturated and β,γ-unsaturated nitriles, has evoked a great interest.[2] Recently, attention was also paid to phenylthioacetonitrile and related compounds (**1**)[3] and (**2**),[4] which could easily manipulated acyl anion equivalents yielding (**3**) as illustrated in Chart 1.

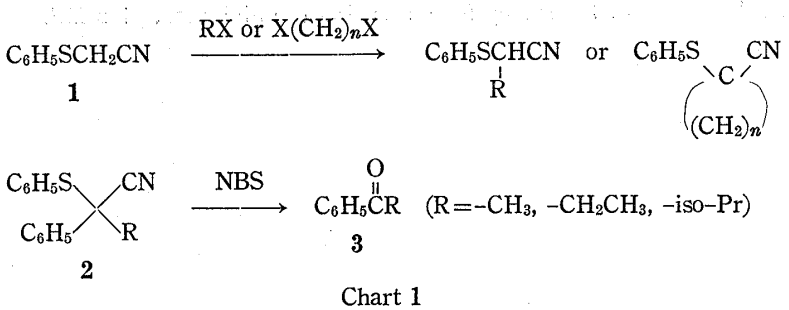

Chart 1

In connection with a study of synthetic utility of methylthioacetonitrile[5] as an acyl equivalent, we have investigated a stereo-selective synthesis of *cis*- and *trans*-β-arylacrylonitriles through β-aryl-α-methylthioacrylonitriles, obtained by the Knoevenagel condensation of arylaldehydes with methylthioacetonitrile. These results were described in this paper. We also wish to refer to a synthesis of β,γ-unsaturated nitriles and a synthetic utility of S–C–CN system as a source of carbonyl compounds.

The Knoevenagel condensation of benzaldehyde (**4a**) with methylthioacetonitrile in tetrahydrofuran (THF) in the presence of Triton B gave α-methylthiocinnamonitrile (**5a**) as

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2) "The Chemistry of the Cyano Group," ed., by Z. Rappoport, John Wiley and Sons (London, New York, Sydney, Tront), 1970.
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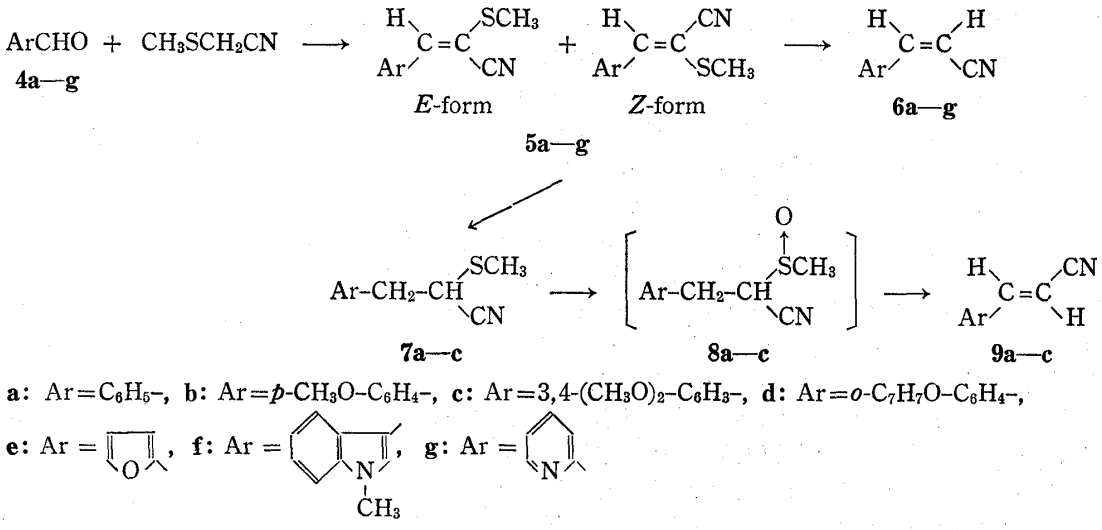

Chart 2

Table I. β-Aryl-α-methylthioacrylonitriles (**5a—g**)

Compound	Reaction time (hr)	bp (°C) (mmHg)	Yield (%)	NMR ($CDCl_3$) δ SCH_3[a]	MS *m/e* (M^+)	Formula	Analysis (%) Calcd. (Found) C	H	N
5a	1	135—137 (2 mmHg)	75	2.45 2.52	175	$C_{10}H_9NS$	68.56 (68.83)	5.18 (5.06)	8.00 (8.29)
5b	1	165—167 (2 mmHg)	75	2.43 2.50	205	$C_{11}H_{11}NOS$	64.38 (64.65)	5.40 (5.17)	6.83 (6.58)
5c	3	182—196 (2 mmHg)	85	2.42 2.50	235	$C_{12}H_{13}NO_2S$	61.27 (61.51)	5.57 (5.84)	5.96 (6.17)
5d[b]	3		92	2.33 2.37	281	$C_{17}H_{15}NOS$			
5e	1/6	100—103 (1 mmHg)	82	2.45 2.55	165	C_8H_7NOS	58.18 (58.49)	4.27 (4.16)	8.48 (8.72)
5f[b]	0.5		96	2.44 2.60	228	$C_{13}H_{12}N_2S$			
5g[b]	0.5		81	2.40 2.47	176	$C_9H_8N_2S$			

a) Two signals due to SCH_3 were observed because of a mixture of *E*- and *Z*-form.
b) Boiling point was not determined.

Table II. *cis*-β-Arylacrylonitriles (**6a—f**)[a]

Starting material	Product	Reaction time (hr)	Yield (%)	NMR ($CDCl_3$) δ α-H (d, J=Hz)	MS *m/e* (M^+)
5a	**6a**	16	67	5.30 (J=12 Hz)	129
5b	**6b**	16	90	5.15 (J=12 Hz)	159
5c	**6c**	14	83	5.20 (J=12 Hz)	189
5d	**6d**	14	81	5.30 (J=12 Hz)	235
5e	**6e**	36	97	5.22 (J=12 Hz)	119
5f	**6f**	12	70	4.98 (J=12 Hz)	182
5g[b]	**6g**	16	0		

a) All compounds were obtained as an oil.
b) Any desired product was not obtained.

a mixture of *E*- and *Z*-form in 75% yield. Desulfurization of **5a** with Raney nickel in ethanol under reflux afforded *cis*-cinnamonitrile (**6a**)[6,7,8] contaminating with the *trans*-isomer (**9a**)[6,7,9] in a ratio of 96: 4.[10] Column chromatography of this mixture on silica gel using benzene as an eluant yielded **6a** in a pure state. Similarly, *cis*-β-arylacrylonitriles (**6b—f**) were obtained from the corresponding arylaldehydes (**4b—f**) through desulfurization of the Knoevenagel condensation products (**5b—f**), respectively, in good yield. Any desired product was not obtained by desulfurization of **5g**. These are summarized in Chart 2, Table I and Table II. In order to prove that both of *E*-**5a** and *Z*-**5a** were converted to **6a**, both of separated *E*-**5a** and *Z*-**5a** in a pure state[11] were subjected to desulfurization with Raney nickel. The former gave **6a** without formation of *trans*-cinnamonitrile (**9a**) and the latter also gave **6a** accompanying with formation of **9a** in a ratio of 85: 15.[10]

On the other hand, reduction of **5a** with sodium borohydride in methanol yielded α-methylthio-β-phenylpropiononitrile (**7a**) in quantitative yield. The nitrile (**7a**) was also obtained by benzylation of methylthioacetonitrile in dimethylsulfoxide (DMSO) with benzyl chloride in the presence of potassium hydroxide. Oxidation of **7a** with *m*-chloroperbenzoic acid in methylene chloride under ice-cooling, followed by the thermal decomposition of the sulfoxide (**8a**) in toluene under reflux for 10 hr resulted in formation of *trans*-cinnamonitrile (**9a**)[6,7,9] in good yield. In a similar fassion, *trans*-4-methoxycinnamonitrile (**9b**)[9] and *trans*-3,4-dimethoxycinnamonitrile (**9c**) were obtained from **5b** and **5c**, respectively, as shown in Chart 2, Table III and Table IV.

Table III. α-Methylthiophenylpropionitriles (7a—c)

Starting material	Product	Yield (%)	bp (°C) (mm Hg)	NMR ($CDCl_3$) δ SCH_3	MS *m/e* (M^+)	Formula	Analysis (%) Calcd. (Found) C	H	N
5a	**7a**	95	115—116 (1 mmHg)	2.27	177	$C_{10}H_{11}NS$	67.78 (67.58)	6.26 (6.65)	7.91 (7.58)
5b	**7b**	95	115—120 (1 mmHg)	2.22	207	$C_{11}H_{13}NOS$	63.75 (63.62)	6.32 (6.33)	6.76 (6.77)
5c	**7c**	92	160—161 (2 mmHg)	2.23	237	$C_{12}H_{15}NO_2S$	61.27 (61.54)	5.57 (5.53)	5.96 (6.02)

Table IV. *trans*-Cinnamonitriles (9a—c)

Compound	Yield (%)[a]	MS *m/e* (M^+)	NMR ($CDCl_3$) δ α-H (d, J=Hz)	bp or mp	lit. bp or mp
9a	90	129	5.76 (J=16 Hz)	bp 120—125 (10 mmHg)	bp 150 (30 mmHg)[6]
9b	85	159	5.59 (J=16 Hz)	bp 145—146 (1 mmHg)	mp 62—63[9]
9c[b]	83	173	5.76 (J=16 Hz)	mp 84—85 (hexane)	

a) Calculated from **7a—c**.
b) *Anal.* Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.40; N, 6.83. Found: C, 69.65; H, 5.68; N, 6.96.

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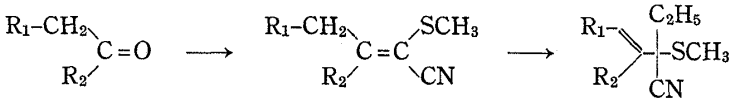
10) The ratio of *cis*/*trans* isomers was determined by the intensity of the signals due to α-proton observed in its NMR ($CDCl_3$) spectrum.
11) Separation of E-5a and Z-5a was carried out by preparative TLC on silica gel 60 PF_{254} using benzene-hexane (1: 1) as an eluant.

Condensation of cyclopentanone (**10a**) with methylthioacetonitrile in THF in the presence of Triton B under reflux afforded the desired α,β-unsaturated nitrile (**11a**) in 95% yield. In a similar fassion, cyclohexanone (**10b**), acetophenone (**10c**) and phenylacetone (**10d**) were subjected to conversion to the corresponding α,β-unsaturated nitriles (**11b—d**), respectively. These α-methylthio-α,β-unsaturated nitriles (**11a—d**) were found to be effectively applied for the formation of α-alkyl-α-methylthio-β,γ-unsaturated nitriles. The addition of *n*-butyllithium to a solution of **11a** in THF at −78° resulted in lithiation of **11a**. Quenching of this solution with ethyl iodide afforded the α-ethyl-α-methylthio-β,γ-unsaturated nitrile (**12a**) as expected. Similarly, β,γ-unsaturated nitriles (**12b—d**) were also obtained from **11b—d**, respectively. The result of analyses and physical constants of these products were listed in Table V and Table VI.



10a—d **11a—d** **12a—d**

a: R_1-R_2=-$(CH_2)_3$-; **b**: R_1—R_2=-$(CH_2)_4$-; **c**: R_1=H,R_2=C_6H_5-; **d**: R_1=C_6H_5-, R_2=CH_3-

Chart 3

Table V. α-Methylthio-α,β-unsaturated Nitriles (**11a—d**)

Starting material	Product	Yield (%)	bp (°C) (mmHg)	NMR ($CDCl_3$) δ SCH_3	MS *m/e* (M^+)	Formula	Analysis (%) Calcd. (Found) C	H	N
Cyclopentanone	**11a**	95	95—97 (2 mmHg)	2.33	153	$C_8H_{11}NS$	62.70 (62.71)	7.24 (7.10)	9.14 (9.08)
Cyclohexanone	**11b**	88	102—108 (2 mmHg)	2.37	167	$C_9H_{13}NS$	64.62 (64.48)	7.83 (7.84)	8.37 (8.37)
Acetophenone	**11c**	30	120—125 (2 mmHg)	2.27	189	$C_{11}H_{11}NS$	69.80 (69.72)	5.86 (5.89)	7.40 (7.17)
Phenylacetone	**11d**	65	105—136 (2 mmHg)	1.83 1.99[a]	203	$C_{12}H_{13}NS$	70.92 (70.65)	6.45 (6.68)	6.89 (6.64)

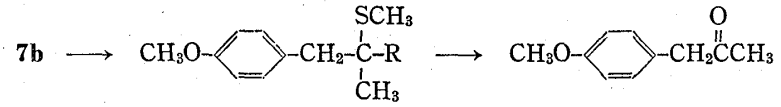
a) Two signals due to SCH_3 were observed because of a mixture of *E*- and *Z*-form.

Table VI. α-Ethyl-α-methylthio-β,γ-unsaturated Nitriles (**12a—d**)

Starting material	Product	Yield (%)	bp (°C) (mmHg)	NMR ($CDCl_3$) δ SCH_3 and γ-H	MS *m/e* (M^+)	Formula	Analysis (%) Calcd. (Found) C	H	N
11a	**12a**	85	100—106 (2 mmHg)	2.07 5.96	187	$C_{10}H_{15}NS$	66.28 (66.42)	8.34 (8.59)	7.73 (7.51)
11b	**12b**	82	104—108 (2 mmHg)	2.05 6.05	195	$C_{11}H_{17}NS$	67.66 (67.38)	8.78 (8.55)	7.17 (7.43)
11c	**12c**	58.7	130—136 (2 mmHg)	2.25 5.33, 5.64	217	$C_{13}H_{15}NS$	71.84 (71.57)	6.96 (7.25)	6.45 (6.21)
11d	**12d**	60	129—142 (2 mmHg)	1.83 6.85	231	$C_{14}H_{17}NS$	72.70 (72.93)	7.41 (7.68)	6.06 (5.90)

Finally, conversion of S–C–CN system to carbonyl group was investigated. Since direct conversion of **12a—d** to the corresponding α,β-unsaturated ethyl ketones was not successful under the conditions reported by Makosza,[4] formation of carbonyl compounds through S–C–CO_2H from S–C–CN was examined. Methylation of **7b** with methyl iodide in DMSO in

the presence of potassium hydroxide, followed by hydrolysis of α-methyl-α-methylthio-4-methoxyphenylpropionitrile (**13**) afforded α-methyl-α-methylthio-4-methoxyphenylpropionic acid (**14**), which was easily converted to 4-methoxybenzyl methyl ketone (**15**)[12] by treatment with N-bromosuccinimide under the conditions reported by Trost.[13]



13: R=CN
14: R=COOH

15

Chart 4

Thus, methylthioacetonitrile would be useful not only for the formation of α,β-unsaturated nitriles but also for the preparation of potential intermediates leading to carbonyl compounds.

Experimental[14]

Condensation of Methylthioacetonitrile with Carbonyl Compounds (Preparation of 5a—g and 11a—d); General Procedure——To a stirred solution of a carbonyl compound (5 g) and methylthioacetonitrile (1.2 eq.) in THF (100 ml) was slowly added 40% methanolic solution of Triton B (1.2 eq.) under ice-cooling. After stirring had been continued for 3 hr at the same temperature, the mixture was extracted with benzene. For the preparation of **11a—d**, after the addition of Triton B, the mixture was stirred for 3 hr under reflux. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The remaining residue was purified by distillation (See Table I and Table V).

General Procedure of Preparation of *cis*-β-Arylacrylonitriles (6a—f)——A mixture of 0.5 g of **5**, 5 ml of Raney Ni and 100 ml of EtOH was refluxed. After removal of Ni the solvent was evaporated. The remaining residue was chromatographed on silica gel (7 g) using benzene as an eluant. Removal of the solvent (50 ml) gave **6** in 65—85% yield (See Table II).

General Procedure of Preparation of α-Methylthiophenylpropiononitriles (7a—c)——To a methanolic solution of 10 g of **5a—c** was added 10 g of $NaBH_4$ under stirring at room temperature within 0.5 hr. After stirring had been continued for 14 hr at room temperature, the solvent was evaporated and worked up as usual. The product was purified by distillation *in vacuo* (See Table III).

General Procedure of Preparation of *trans*-Cinnamonitriles (9a—c)——To a stirred solution of **7a—c** (2 g) in 50 ml of CH_2Cl_2 was added 1 equimolar amount of *m*-chloroperbenzoic acid under ice-cooling. After stirring had been continued for 3 hr at the same temperature, the mixture was washed with 5% $NaHCO_3$, H_2O, and dried over Na_2SO_4. Removal of the solvent yielded the sulfoxides (**8a—c**), which were used without purification for the following reaction. A solution of **8a—c**, thus obtained, in 30 ml of toluene was refluxed for 10 hr. Evaporation of the solvent afforded **9a—c**, which were purified by distillation or recrystallization (See Table IV).

General Procedure of Preparation of α-Ethyl-α-methylthio-β,γ-unsaturated Nitriles (12a—d)——To a stirred solution of **11a—d** (3 g) in 30 ml of THF was added a solution of *n*-BuLi (1 eq.) in hexane at −78°. After 15 min, ethyl iodide (1 eq.) was added to the mixture. The reaction mixture was allowed to stand for 1 hr at the same temperature under stirring. The mixture was treated with water and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The resulting oil was distilled *in vacuo* to give **12a—d** (See Table VI).

α-Methyl-α-methylthio-4-methoxyphenylpropionitrile (13)——To a stirred mixture of 2 g of α-methylthio-4-methoxyphenylpropionitrile (**7b**), 2 g of KOH and 20 ml of DMSO was added 1 ml of methyl iodide at room temperature. After stirring had been continued for 4 hr, the mixture was poured into 150 ml of H_2O and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give 2 g of **13**, bp 115—120° (2 mmHg). NMR ($CDCl_3$) δ: 1.48 (3H, s, CH_3), 2.25 (3H, s, SCH_3), 2.78, 3.12 (2H, each d, J=14 Hz, $ArCH_2$–), 3.73 (3H, s, OCH_3), 6.78 (2H, d, J=7 Hz, Ar–H), 7.17 (2H, d, J=7 Hz, Ar–H). MS *m/e*: 221 (M^+). *Anal.* Calcd. for $C_{12}H_{15}NOS$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.05; H, 6.93; N, 6.02.

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14) Nuclear magnetic resonance (NMR) spectra were taken with a Varian T-60 spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were measured with a Hitachi RMU-7L spectrometer.

α-Methylthio-β-phenylpropionitrile (7a)——To a stirred mixture of 2 g of methylthioacetonitrile, 2 g of KOH and 20 ml of DMSO was added 2.93 g of benzyl chloride at room temperature. After stirring had been continued for 4 hr, the mixture was poured into 150 ml of H_2O and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give 2.1 g of oil, which was identical with **7a** prepared from **5a** in all respects.

α-Methyl-α-methylthio-4-methoxyphenylpropionic Acid (14)——A mixture of 2 g of **13**, 18 ml of MeOH, 2 ml of dioxane and 2 g of KOH was refluxed for 30 hr. After removal of the solvent, the resulting residue was made acidic with 10% HCl and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give 1.9 g of **14** as colorless needles, mp 61—63° (from ether). MS *m/e*: 230 (M^+). NMR ($CDCl_3$) δ: 1.35 (3H, s, CH_3), 2.35 (3H, s, SCH_3), 2.77, 3.35 (2H, each d, J=14 Hz, $ArCH_2$–), 3.75 (3H, s, OCH_3), 6.75 (2H, d, J=7 Hz, Ar–H), 7.11 (2H, d, J=7 Hz, Ar–H). *Anal.* Calcd. for $C_{12}H_{16}O_3S$: C, 58.99; H, 6.71. Found: C, 59.74; H, 6.65.

4-Methoxybenzyl Methyl Ketone (15)——A mixture of 0.5 g of **14**, 0.17 g of $NaHCO_3$, 0.37 g of N-bromosuccinimide and 15 ml of MeOH was stirred for 3.5 hr under ice-cooling. The solvent was evaporated and the resulting residue was extracted with benzene. The extracted was washed with H_2O, dried over Na_2SO_4 and evaporated. The remaining residue was chromatographed on silica gel (3.5 g) using benzene as an eluant. Removal of the solvent (40 ml) afforded 0.3 g of **15**.[12]

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