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SYNTHESIS OF 4H-1,4-BENZOTHIAZINE DERIVATIVES THROUGH CONDENSATION OF o-AMINOTHIOPHENOL WITH α-CYANO-α-METHYLTHIOACETOPHENONES

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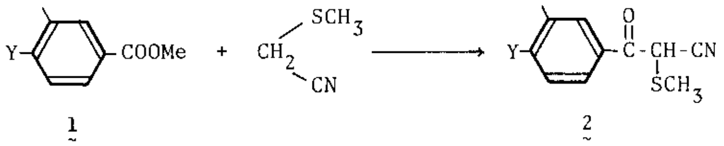
Abstract —— Condensation of methylthioacetonitrile with methyl benzoates in THF at room temperature yielded the corresponding α-cyano-α-methylthioacetophenones (2a-2e). These α-substituted acetophenones were heated with o-aminophenol in DMSO at 110 °C for 10 hr to give 2-cyano-3-phenyl-4H-1,4-benzothiazines (5a-5e).

During the investigation on the synthetic utility of sulfur-substituted active methylene compounds, methylthioacetonitrile[1] was effectively applied to the formation of cis- and trans-α,β-unsaturated nitriles and β,γ-unsaturated nitriles[2]. Furthermore, methylthioacetonitrile was easily converted to α-cyano-α-methylthioacetophenones[3] by condensation with methyl benzoates. In this paper, we wish to report the results of our studies on condensation of α-cyano-α-methylthioacetophenones with o-phenylenediamine and o-aminothiophenol.

First, α-cyano-α-methylthioacetophenones (2a-2e) were prepared by treatment of methylthioacetonitrile with NaH (1.5 eq. mole, 50 % suspension in oil) in dry THF



a: X=Y=H; b: X=Cl, Y=H; c: X=H, Y=CH_3;
d: X=H, Y=OCH_3; e: X=Y=OCH_3

Scheme 1

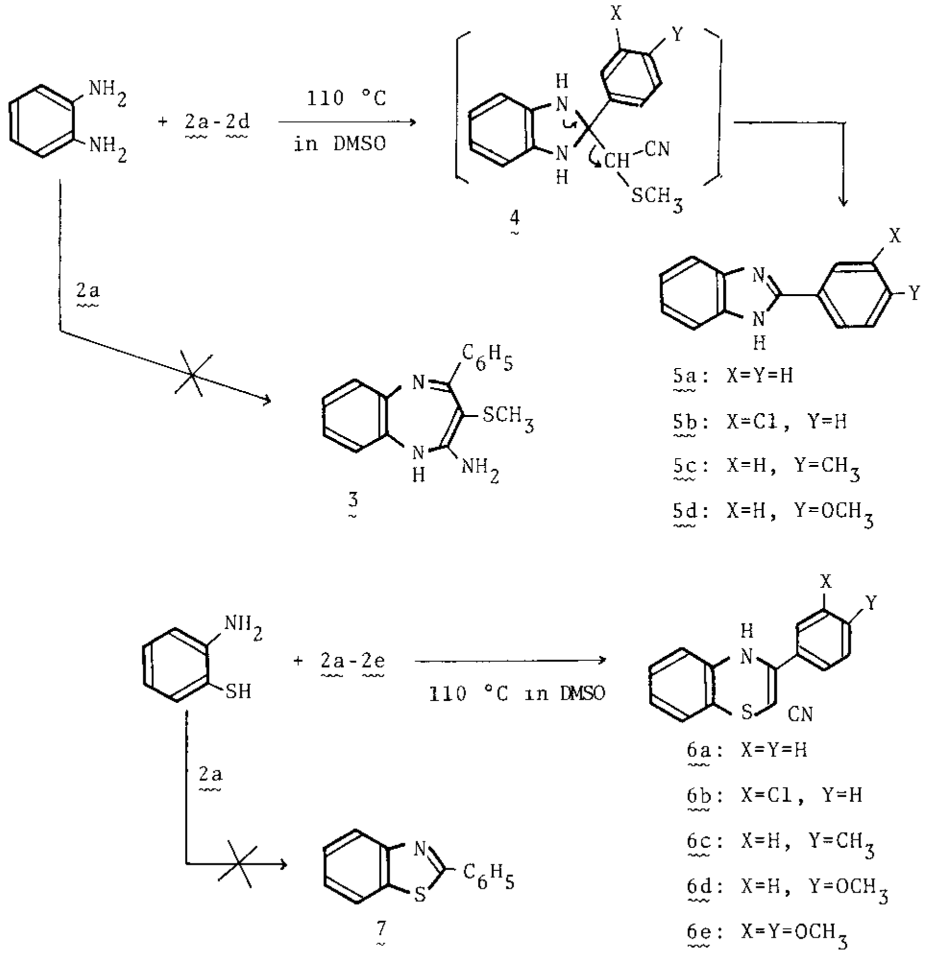
at room temperature, followed by addition of methyl benzoates (1). (Scheme 1). Physical characters were shown in the Table 1.

Table 1. α-Cyano-α-methylthioacetophenones (2)[4]

	Yield (%)	mp °C	*m/e* (M^+)	NMR ($CDCl_3$): ppm
2a	65	40-42 (Et_2O-hexane)	191	2.22 (3H, s), 5.12 (1H, s), 7.37-7.57 (3H, m), 7.83-8.02 (2H, m)
2b	75	94-97 (Et_2O-hexane)	227 (M^++2) 225	2.27 (3H, s), 5.05 (1H, s), 7.33-7.97 (4H, m)
2c	70	124-126 (Et_2O-hexane)	205	2.23 (3H, s), 2.40 (3H, s), 5.10 (1H, s), 7.20 (2H, d, *J*=7 Hz), 7.77 (2H, d, *J*=7 Hz)
2d	73	134-136 (Et_2O-hexane)	221	2.27 (3H, s), 3.88 (3H, s), 5.10 (1H, s) 6.93 (2H, d, *J*=9 Hz), 7.92 (2H, d, *J*=9 Hz)
2e†	53	——	251	2.27 (3H, s), 5.02 (1H, s), 6.95 (1H, d, *J*=7 Hz), 7.53 (1H, d, *J*=2 Hz), 7.67 (1H, d,d, *J*=2 and 7 Hz)

† 2e was not isolated as a pure state. According to its NMR ($CDCl_3$) spectrum, it is contamintated with *ca* 10 % unidentified impurity.

Condensation of 2a with *o*-phenylenediamine was examined in the expectation that 2-amino-3-methylthio-4-phenyl-1*H*-1,5-benzodiazepine (3) might be obtained. A mixture of 2a and *o*-phenylenediamine was heated in DMSO at 110 °C for 10 hr to give 2-phenylbenzimidazole (5a), mp 285-287 °C (*lit.*[5] mp 287-288 °C), in 65 % yield. In a similar fashion, 2-(3-chlorophenyl)benzimidazole (5b[6]; 58 %), 2-(4-methylphenyl)benzimidazole (5c[7], 70 %) and 2-(4-methoxyphenyl)benzimidazole (5d[8]; 73 %) were obtained by condensation of *o*-phenylenediamine with the ketones (2b-2d), respectively[9]. In these reactions, the formation of the desired 1*H*-1,5-benzodiazepine derivatives was not observed. 2-Phenylbenzimidazoles would be derived from the intermediates (4) through elimination of methylthioacetonitrile. On the other hand, condensation of *o*-aminothiophenol with 2a under the same conditions afforded 2-cyano-3-phenyl-4*H*-1,4-benzothiazine (6a) in 75 % yield without formation of 2-phenylbenzothiazole (7). In this way, 2-cyano-3-(3-chlorophenyl)-4*H*-1,4-benzothiazine (6b), 2-cyano-3-(4-methylphenyl)-4*H*-1,4-benzothiazine (6c), 2-cyano-3-(4-methoxyphenyl)-4*H*-1,4-benzothiazine (6d) and 2-cyano-3-(3,4-dimethoxy)-4*H*-1,4-benzothiazine (6e) were yielded. (Scheme 2 and Table 2).



Scheme 2

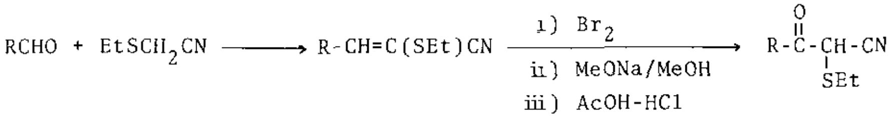
Table 2. 2-Cyano-3-phenyl-4H-1,4-benzothiazines (6)

	Yield (%)	mp °C	m/e (M$^+$)	IR (Nujol) (CN) cm^{-1}
6a	75	209-211 (acetone-Et$_2$O)	250	2170
6b	73	245-246 (acetone-Et$_2$O)	286 (M$^+$+2) 284	2170
6c	77	200-202 (acetone-Et$_2$O)	264	2170
6d	75	206-208 (CHCl$_3$-hexane)	280	2170
6e	55	215-217 (CHCl$_3$-hexane)	310	2170

Thus, 2-cyano-3-phenyl-4*H*-1,4-benzothiazine derivatives were obtained by condensation of *o*-aminothiophenol with α-cyano-α-methylthioacetophenones through elimination of methyl mercaptan.

References and Footnotes

1. R. Dijkstra and H. J. Backer, *Rec. Trav. Chim. Pays-Bas.*, **72**, 569 (1953).
2. S. Kano, T. Yokomatsu, T. Ono, S. Hibino, and S. Shibuya, *Chem. Pharm. Bull.* **26**, 1374 (1978).
3. Recently, α-cyano-α-sulfenyl ketones were prepared through the scheme outlined below: F. Pochat, *Tetrahedron Lett.*, **1979**, 19.



$$\mathrm{RCHO} + \mathrm{EtSCH_2CN} \longrightarrow \mathrm{R{-}CH{=}C(SEt)CN} \xrightarrow[\substack{\text{ii) MeONa/MeOH} \\ \text{iii) AcOH-HCl}}]{\text{i) Br}_2} \mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}\underset{\underset{SEt}{|}}{C}H{-}CN}$$

4. All new compounds gave satisfactory microanalyses and spectral data. NMR spectra were taken with a Varian T-60 spectrophotometer, mass spectra with a Hitachi RMU-7L spectrometer. Ir spectra were measured with a 215 Hitachi Grating Infrared Spectrophotometer.
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9. The structures of these 2-phenylbenzimidazoles were determined by their spectral data and comparison of their melting points with those in the literatures.

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