  Bull. Chem. Soc. Jpn., 60, 609—612 (1987)

A Formylcarbonium Ion Synthon. Synthesis of 3-Thio-Substituted 2-Amino Acids and Thio-Substituted Enamines from 2-Acyloxyacrylonitriles[1)]

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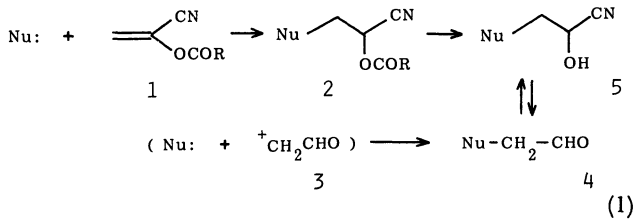
(Received May 26, 1986)

The utilization of 2-acyloxy-3-phenylthiopropionitriles (**2**) which were prepared by the Michael addition of thiophenol to 2-acyloxyacrylonitriles (CH_2=C(CN)OCOR), as a formylcarbonium ion synthon, was demonstrated by the transformation of **2** into *S*-phenylcysteine and 2-phenylthio enamines.

2-Acyloxyacrylonitriles (**1**) are useful equivalents of ketenes utilizable as dienophiles,[2)] carbene acceptors and 1,3-dipolarophiles.[3)] Structures of **1** also tell us that they can be used as Michael acceptors to give **2**-substituted acetaldehyde cyanohydrins **5** which are equivalents of the corresponding **2**-substituted aldehydes **4**. In this regard, we have investigated the addition of thiols to **1** and verified that **1** can play a role of formylcarbonium ion synthon **3** (Eq. 1) as being demonstrated in the conversion of the adduct to 3-thio-2-amino acids, such as *S*-phenylcysteine, and also to 2-phenylthio enamines.

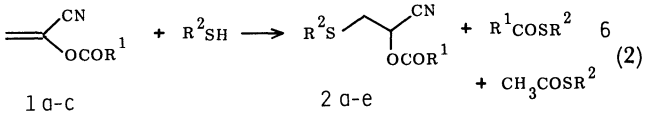


(1)

Results and Discussion

The polar addition of thiophenol to 2-benzoyloxyacrylonitrile (**1a**) in methanol at 0 °C in the presence of benzyltrimethylammonium hydroxide (Triton B, 40% in MeOH) gave 2-benzoyloxy-3-phenylthiopropionitrile.[4)] Results are summarized in Table 1 (see Eq. 2). Displacement at the carbonyl group also took place concomitantly besides the desired Michael addition. This side reaction, however, can be minimized by changing the acyloxy group: among three esters examined (benzoate **1a**, pivalate **1b**, and acetate **1c**), benzoate **1a** apparently favors the Michael addition more than the other esters.[5)] In addition, the phenyl group of **1a** may also suppress the displacement and eventually adduct **2a** predominates.[6)] The difference between **1b** and **1c** may be due to the steric effect of the *t*-butyl group that retards the displacement at the carbonyl group.

Free radical addition of thiophenol to **1c** under high-dilution conditions also yielded adduct **2c** in a better yield (55%) when pentane was the solvent. In cyclohexane, side reactions were suppressed and the isolation of **2c** was easier.

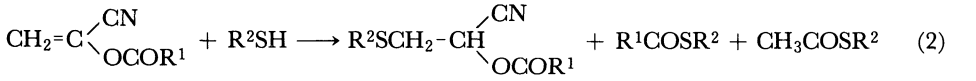


(2)

a, R^1 = Ph; **b**, R^1 = *t*-Bu; **c**, R^1 = CH_3
R^2 = Ph (**a**, **b**, **c**), R^2 = Et (**d**, **e**)

Adducts **2** were transformed effectively by the reaction with amines into 2-amino-3-phenylthiopropionitriles (**7**) (see Table 2 and Eq. 3) which are common intermediates for the synthesis of both title compounds. Pyrrolidine reacted with **2** exothermically and a diluent (ether) was required to control the reaction. Diethylamine reacted slowly at an ambient

Table 1. Reaction of 2-Acyloxyacrylonitrile (**1**) with Thiols



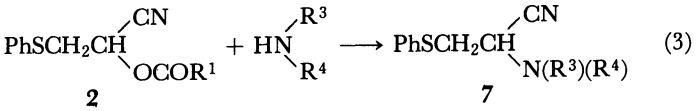
(2)

1 **2** **6**

Acrylonitrile	R^1	RSH R^2	Method[a)]	Solvent	Temp °C	Time h	Product yield/%
1a	Ph	Ph	A	EtOH	20	5	**2a** 62
1a	Ph	Ph	B	EtOH	20	4	**2a** 65
1b	*t*-Bu	Ph	A	EtOH	0	7.5	**2b** 42
1b	*t*-Bu	Ph	A	MeOH	0	2.2	**2b** 41
1c	Me	Ph	A	MeOH	0	2.5	**2c** 14
1c	Me	Ph	C	Pentane	0	20	**2c** 55
1a	Ph	Et	A	MeOH	0	2.5	**2d** 25
1b	*t*-Bu	Et	A	EtOH	0	4.0	**2e** 10

a) Method A: Triton-B was used as a base. Method B: K_2CO_3 was used. Method C: Irradiation by a medium pressure Hg lamp.

Table 2. Reaction of 2-Acyloxy-3-phenylthiopropionitrile (**2**) with Amines

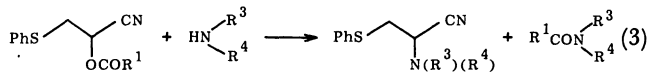


(3)

Entry	R^1	R^3	R^4	Solvent	Temp °C	Time h	Product yield/%[a]	Bp(θ_b/°C)/Torr
1	Me	$-(CH_2)_4-$		Et_2O	20	2	**7f** 88	117—125/0.04
2	Ph	$-(CH_2)_4-$		Et_2O	20	2	**7f** 71	
3	Me	Et	Et	MeOH	70	0.5	**7g** 96	115/0.02
4	*t*-Bu	Et	Et	MeOH	70	0.5	**7g** 81	
5	Me	Et	H	MeOH	70	0.5	**7h**[b]	Decomposed
6	Me	H	H	MeOH	20	2	**7i**[b]	Decomposed

a) Isolated yields. b) Not isolated but almost quantitative as determined by ^{1}H NMR analysis of the reaction mixture.

temperature without solvent but effectively in boiling methanol. Both ethylamine and ammonia reacted effectively with any compound of **2** but products were thermally too labile to be isolated by distillation. Eventually, reaction mixtures were subjected directly to the following hydrolysis. When the product mixture containing **7f** was chromatographed through a silica-gel column, 2-(phenylthio)acetaldehyde cyanohydrin (**8**, ca. 10%) was isolated, which readily reacted with diethylamine independently in methanol to give **7g** (92%). This finding is indicative of the intermediacy of **8** in the main reaction channel that leads **2** to **7**.

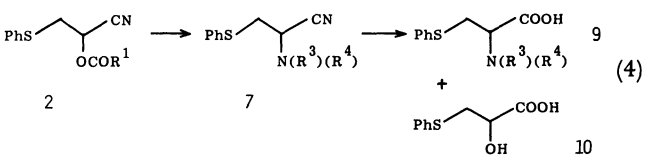


(3)

2 a-c 7 f-i

f, R^3-R^4 = $-(CH_2)_4-$; **g**, $R^3 = R^4$ = Et;
h, R^3 = Et, R^4 = H; **i**, $R^3 = R^4$ = H

The acid-catalyzed hydrolysis of **7i**[7] in aqueous HBr or H_2SO_4 gave *S*-phenylcysteine (**9**), the overall yield from **2** was 60—63% (Eq. 4). This procedure for the synthesis of **9** seems better than the reported not only in yield but also in simplicity.[8] The hydrolysis of 2-(1-pyrrolidinyl)nitrile (**7f**), however, did not give the expected amino acid, but a hydrolytic deamination took place to give 2-hydroxy-3-(phenylthio)propionic acid (**10**).[9] This is because the pyrrolidinyl group has a higher basicity than the $-NH_2$ group and hence it is protonated more easily and substituted by water.

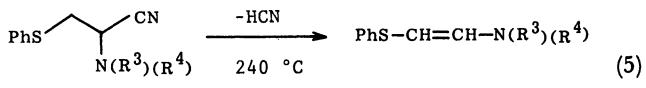


(4)

2 7 9 10

In addition to the synthesis of 3-substituted 2-amino acids such as **9**, amino nitriles **7** exhibited an interesting behavior which can be synthetically utilizable to the preparation of thio-substituted enamines. We found that, in general, propionitriles **7** are thermally labile and unable to be isolated or purified by distillation.[10] We thought this deserves to be explored and the pyrolysis of **7** was independently investigated.[11]

When a benzene solution of **7f** was heated at 240 °C, 1-phenylthio-2-(1-pyrrolidinyl)ethene (**11f**) was obtained as a mixture of cis and trans isomers in 83% yield (conversion 71%) (Eq. 5). Analogously **7g** gave the diethylamino enamine **11g**. The same pyrolytic behaviors of both **7f** and **7g** were also observed in their VPC analysis when the injection temperatures were above 200 °C. It is noteworthy that the cyano group is the most preferable leaving group to the other potentially removable ones (phenylthio and amino group).



(5)

7 f, g 11 f, g

To summarize, 2-acyloxy-substituted acrylonitriles (**1**) have been proved to be a viable formylcarbonium ion synthon and they seem to provide us with easy access to several 2-substituted aldehyde derivatives.

Experimental

General Procedures. Boiling points are uncorrected. ^{1}H NMR spectra (chemical shifts are given in δ units in $CDCl_3$ solution) were recorded on Varian T-60A and IR spectra on JASCO IRA-1 spectrometers. Elemental Analyses were performed by Microanalysis Center of Kyoto University. Mass spectra including exact mass analyses were measured on a Hitachi M-80A mass spectrometer, and VPC anal ysis on Shimadzu GC-4CIT gas chromatograph (glass column; 10% Apiezon L on Chromosorb unless otherwise noted).

2-Acyloxyacrylonitriles (1). 2-Benzoyloxy- (**1a**), 2-pivaloyloxy- (**1b**), and 2-acetoxyacrylonitrile (**1c**) were synthesized from the corresponding acyl chlorides and acetyl cyanide according to our previous study.[12] Spectroscopic data of **1b** (for **1a**, **1c**, and **1d**, see Ref. 12) are as follows. ^{1}H NMR 1.27 (s, 9H), 5.65 (dX2, 2H, J=2.0 Hz). IR (liq film) 2960 (m), 1760 (s), 1630 (m), 1095 (s) cm^{-1}. $P^+(m/z)$ 153 (M^+).

Preparation of 3-Thio-substituted 2-Acyloxypropio-

Table 3. Spectroscopic Data of Products **2** and **7**

	^{1}H NMR[a,b]						IR cm^{-1}	P$^+$
	CH_2	CH	R^1	R^2	R^3	R^4	(liq film)	(m/z)
2a	3.47(d) J=6.6	5.64(t)	7—8(m)		—	—	1730, 1260, 1100	283(M^+)
2b	3.26(d) J=7	5.32(t)	1.15(s)	7.4(m)	—	—	1740, 1280, 1100	263(M^+)
2c	3.35(d) J=7	5.40(t)	2.03(s)	7.4(m)			1750, 1375, 1210, 1030	221(M^+)
2d	3.06(d) J=6.6	5.67(t)	7.5—8.2 (m)	1.30(t), 2.73(q) J=7	—	—	1740, 1270, 1100 720	174(M^+—EtS(61))
2e	2.93(d) J=6.6	5.36(t)	1.23(s)	1.26(t) 2.65(q) J=7	—	—		
7f	3.18 (ABX) J=13.0, 8.6, 6.8	3.85 (ABX) J=8.6, 6.8	—	—	1.8(m) 2.6(m)		2950, 2800, 1480, 1440, 740, 685	232(M^+) 205(M^+—HCN(27))
7g	3.20 (ABX) J=13.0, 9.2, 7.0	3.75 (ABX) J=9.2, 7.0	—	—	1.03(t) 2.5(q) J=7.0		2960, 2800, 1480, 1440, 740, 680	234(M^+) 207(M^+—HCN(27))
7h	3.20(m)	3.60(br m)	—	—	1.10(t) 2.8(m) J=7.8	1.5(m)	2980, 1485, 1445, 1030, 745, 695	
7i	3.17(br d) J=6.6	3.78(br t)	—	—	2.0(br s)			

a) Chemical shifts are in δ units and J values in Hz. b) Chemical shifts of Ph groups of **7** are abbreviated.

nitriles (2). Method A: To a mixture of acrylonitrile **1** (4 mmol) and thiol (R=Ph or Et, 5 to 6 mmol) in a solvent (MeOH, EtOH, *t*-BuOH, or Et_2O) was added a 40% MeOH solution of benzyltrimethylammonium hydroxide (Triton B, 40—80 μL) or K_2CO_3 (4 mmol). After stirring for a period at a desired temperature, the reaction mixture was extracted by a mixture of Et_2O and water, and the ethereal solution was dried ($MgSO_4$). Product **2** was separated after a silica-gel column chromatography.

Method B: Sodium metal (0.5 g, 20 mmol) was slowly added to a solution of PhSH (9.0 g, 90 mmol) and the mixture was warmed at 40 °C until sodium dissolved. The solution was cooled at −7 °C, **1c** (2.24 g, 20 mmol) was added, and the mixture was stirred for 1.5 h. The workup procedure was analogous to that of Method A.

Method C: In a photolysis apparatus equipped with a Pyrex filter and a medium pressure mercury lamp, a diluted pentane solution (200 mL) of PhSH (7.0 g) was charged and to which, under irradiation, a mixture of **1c** (3.9 g, 35 mmol) and PhSH (7.0 g) was added slowly over 2 h. After 20 h, **1c** disappeared. Adduct **2c** was isolated by a vacuum distillation. Bp 115—125 °C/1.5 mmHg (1 mmHg=133.3 Pa). Yield 55%.

Results are summarized in Table 1 and the spectroscopic data for **2** in Table 3. Exact mass of **2a**: Found, 283.0670. Calcd for $C_{16}H_{13}NO_2S$, 283.0667. **2b**: Found, 263.0978. Calcd for $C_{14}H_{17}NO_2S$, 263.0981. **2c**: Found, 221.0512. Calcd for $C_{11}H_{11}NO_2S$, 221.0511. Anal. of **2d**: Found: C, 61.53; H, 5.62; N, 5.93%. Calcd for $C_{12}H_{13}O_2NS$: C, 61.25; H, 5.57; N, 5.95%.

2-Amino-3-phenylthiopropionitriles (7). 2-Acyloxy-3-phenylthiopropionitrile (2, 1 mmol) in a solvent (Et_2O or MeOH) was mixed with an excess amount of amine (pyrrolidine, Et_2NH, 30% MeOH solution of $EtNH_2$, or NH_3 in MeOH; 3 to 20 equivalents), and the total mixture was stirred at an ambient temperature or 70 °C. 2-Amino-substituted 3-phenylthiopropionitriles (**7**) were obtained by distillation except the reactions with $EtNH_2$ and NH_3. In the latter cases products were thermally too labile to be distilled and, therefore, used directly in subsequent reactions. Results are listed in Table 2 and the spectroscopic data for **7** in Table 3.

Exact Mass of 7f: Found, 232.1038. Calcd for $C_{13}H_{16}N_2S$, 232.1036. Exact mass of the fragment peak corresponding to **11f**: Found, 205.0904. Calcd for $C_{12}H_{15}NS$, 205.0927. **7g**: Found, 234.1186. Calcd for $C_{13}H_{18}N_2S$, 234.1192. Exact mass of the fragment peak corresponding to **11g**: Found, 207.1065. Calcd for $C_{12}H_{17}NS$, 207.1083.

Acid-Hydrolysis of 2-Amino-3-phenylthiopropionitrile (7i). Nitrile **7i** (1.1 mmol) prepared quantitatively from **2c** and aqueous ammonia by the above procedure, but not isolated, was mixed with 0.2 mL of concd H_2SO_4 and 2 mL of water. The mixture was warmed at 120 °C for 24 h, cooled down to 20 °C, 2 mL of water was added, and neutralized by 28% aqueous ammonia to pH 8, After a small amount of charcoal was added, the solution was filtered, slightly acidified by diluted H_2SO_4 to pH 5, and cooled in dark to separate

S-phenylcysteine **9** in 63—70% yields. ^{1}H NMR 3.70 (br d, 2H, J=6.0 Hz), 4.50 (br q or t, 1H), 7.5 (m, 3H), 7.4 (m, 5H), 11.5 (s). IR (KBr) 2800 (broad), 1600 (s), 1500 (m), 1400 (s), 1360 (s), 720 (m) cm^{-1}.

Acid-Hydrolysis of 2-(1-Pyrrolidinyl)-3-phenylthiopropionitrile (7f). A mixture of **7f** (0.22 g, 0.95 mmol), water (0.5 mL), and 0.5 mL of 47% HBr was heated for 24 h under refluxing conditions. After the removal of water in vacuo, the residue was washed with a mixture of water and Et_2O, and the ethereal solution was analyzed to find that it consisted of only one product. The solution was esterified in MeOH by the Fischer method to give methyl 2-hydroxy-3-(phenylthio)-propionate **12** (30%). ^{1}H NMR 3.35 (s, 1H), 3.60 (s, 3H), 3.65 (br d, 2H, J=5.0 Hz), 4.37 (t, 1 H, J=5.0 Hz), 7.5 (m, 5H). IR (liq film) 3500 (broad, m), 1750 (s), 1595 (m), 1230 (broad, m), 1100 (s), 750 (m), 700 (m) cm^{-1}.

Pyrolysis of 2-(1-Pyrrolidinyl)-3-phenylthiopropionitrile (7f): Preparation of 1-Phenylthio-2-(1-pyrrolidinyl)ethene (11). A vertically fixed Pyrex column (30 cm length×10 mm i.d.) packed with glass beads was heated at 240 °C under a N_2 stream at 50 mmHg. A benzene solution (2 mL) of **7f** (0.4 mmol) was slowly injected from the top of the column and a product mixture was collected at −70 °C. 1-Phenylthio-2-(1-pyrrolidinyl)ethene (**11f**) was formed in 82% (conversion 71%). ^{1}H NMR 1.8 (m, 4H), 2.6 (m, 4H), 4.38 (d, 1H, J=12.8 Hz), 6.83 (d, 1H, J=12.8 Hz), 7.3 (m, 5H). For the exact mass of **11f**, see Experimental section corresponding to the preparation of **7f**. The same pyrolysis procedure on **7g** gave the thio enamine **11g** in 22% yield (conversion 49%). Mass spectrum of **11g**, m/z (relative intensity): 207 (M^+, 68), 174 (26), 116 (55), 91 (49), 56 (100). Exact mass: Found, 207.1070. Calcd for $C_{12}H_{17}NS$, 207.1083.

References

1) Ketene Equivalents, No. 11. For No. 10 see Ref. 3b.

2) a) D. A. Evans, W. L. Scott, and J. K. Truesdale, *Tetrahedron Lett.*, **1972**, 121; b) A. Oku, H. Hasegawa, J. Nishimura, and T. Harada, *J. Org. Chem.*, **46**, 4152 (1981); c) A. Oku, Y. Nozaki, J. Nishimura, and T. Harada, *J. Org. Chem.*, **48**, 4374 (1983).

3) a) A. Oku, T. Yokoyama, and T. Harada, *J. Org. Chem.*, **48**, 5333 (1983); b) A. Oku, T. Yokoyama, and T. Harada, *Tetrahedron Lett.*, **24**, 4699 (1983).

4) Thiol esters **6** (benzoate, pivalate) and thiol acetate were also formed as byproducts.

5) Not only the acidity constants of the acids corresponding to the respective ester but also the NMR chemical shift of the CH_2=proton of **1** may tell the relative reactivity toward Michael addition. Thus, the observed decreasing order in δ values of CH_2 (**1a** 5.87>**1c** 5.74>**1b** 5.67) may correspond to the reactivity order in the Michael addition. So does the IR(C=O) frequency the carbonyl reactivity toward thiolate ion, and the order in frequencies (**1c** 1765>**1b** 1760>**1a** 1740 cm^{-1}) may correspond to the reactivity in the displacement at the carbonyl.

6) Alcoholic solvents (MeOH, EtOH, *t*-BuOH) are more suitable for the reaction than ethers. When potassium carbonate was used instead of Triton B in the reaction of **1a**, the yield of **2a** slightly increased from 62 to 65% while **6a** decreased from 29 to 13%.

7) The reaction mixture of **2b** and NH_3 was directly hydrolyzed without isolating the intermediate **7i** (R^3=R^4=H)

8) L. Goodman, R. M. Moss, and B. R. Baker, *J. Org. Chem.*, **23**, 1251 (1958).

9) Product **10** was isolated as the Me ester after the treatment with MeOH.

10) Nitrile **7i** was also thermally labile under a VPC condition (injection 250 °C column 220 °C).

11) It was reported that 2-amino-2,3-diphenylpropionitrile was thermally unstable and underwent a dehydrocyanation to give the corresponding enamine. C. H. Hauser, A. M. Taylor, and T. G. Ledford, *J. Am. Chem. Soc.*, **82**, 1786 (1960).

12) A. Oku and S. Arita, *Bull. Chem. Soc. Jpn.*, **52**, 3337 (1979).