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Behaviors of N-(Substituted thio)phthalimides, N-(Substituted thio)succinimides, and N-(Substituted thio)isatins toward Some Nucleophiles[1]

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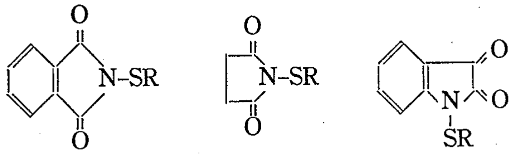
New compounds of N-(substituted thio)isatins (III) were synthesized and reactions with several nucleophiles were examined in comparison with the reaction using N-(substituted thio)phthalimides (I) and N-(substituted thio)succinimides (II): All of I, II, and III reacted with organometallic compounds, cyanide ion, and trichloromethyl carbanion to give sulfides (IV), thiocyanates (V), and trichloromethyl sulfides (VI) respectively. Different from I and II, however, the reaction of III with amines afforded 3-amino-1-substituted thio-3-hydroxy-2-oxo-indoles (X), with no formation of any sulfenamides anticipated.

The utility of N-(substituted thio)phthalimides (I) and N-(substituted thio)succinimides (II) as efficient sulfenylation reagents has been adequately demonstrated in the past few years, and it is known that they undergo displacement of phthalimide or succinimide when treated with a variety of nucleophiles: thiols,[3-5] hydrodisulfides,[4] alkoxides,[6] amines,[7,8] arenesulfinates,[9] active methylene compounds,[10,11] and enamines[12,13] result in the formation of disulfides, trisulfides, sulfenates, sulfenamides, sulfenylated active methylene compounds, and sulfenylated enamines. We newly examined the reactions with cyanide ion, trichloromethyl carbanion, and organometallic compounds in the present studies. Moreover, we found that newly synthesized N-(substituted thio)isatins (III) were useful as a novel sulfenylation reagent and investigated the reactions with several nucleophiles. Isatin is known to undergo the nucleophilic attack on the carbonyl carbon atom at the 3-position by amines and by Grignard reagents to afford 3-imino-2-oxo-indoles[14] and 3-substituted 3-hydroxy-2-oxo-indoles,[14] respectively. Therefore, the reactivities of the carbonyl group in III toward nucleophiles are of interest.



I II III

Chart 1

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[1] A part of this paper has been reported in a preliminary form; see M. Furukawa, T. Suda, and S. Hayashi, *Chem. Lett.*, **1974**, 881.

[2] Location: *5-1, Oe-hon-machi, Kumamoto, 862, Japan.*

[3] K.S. Boustany and A.B. Sullivan, *Tetrahedron Letters*, **1970**, 3547.

[4] D.N. Harpp, D.K. Ash, T.G. Back, J.G. Gleason, B.A. Orwig, W.F. VanHorn, and J.P. Snyder, *Tetrahedron Letters*, **1970**, 3551.

[5] D.N. Harpp and T.G. Back, *J. Org. Chem.*, **36**, 3828 (1971).

[6] D.H.R. Barton, G. Page, and D.A. Widdowson, *Chem. Commun.*, **1970**, 1466.

[7] K.S. Boustany, *Chimia*, **1970**, 396.

[8] D.N. Harpp and T.G. Back, *Tetrahedron Letters*, **1971**, 4953.

[9] Y. Abe and J. Tsurugi, *Chem. Lett.*, **1972**, 441.

[10] T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Letters*, **1970**, 5115.

[11] T. Kumamoto, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, **45**, 866 (1972).

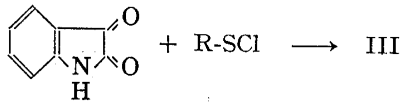
[12] M. Furukawa, Y. Kojima, S. Tsuiji, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2738 (1972).

[13] M. Furukawa, Y. Kojima, Y. Okahara, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 262 (1974).

[14] P.L. Julian, E.W. Meyer, andH.C. Printy, "Heterocyclic Compounds," ed. by,. R.C. Elderfield, Wiley, New York, London, 1960, Vol. 3, p. 218.

Compounds III were readily synthesized by the treatment of isatin with an equimolar quantity of alkane or arenesulfenyl chlorides in dimethylformamide (DMF) in the presence of triethylamine in fairly good yields. The structure of III was established by the elemental analyses, by disappearance of the NH absorption of isatin in the infrared (IR) spectra, and by the mass spectra in which the corresponding molecular ion peak was obtained as an abundant peak. The results are summarized in Table I.

Table I. N-(Substituted thio) isatins (III)



R	Reaction Temp. (°C)	Yield (%)	mp (°C)	Formula	Analyses (%) Calcd. (Found) C	H	N
C_6H_5	r.t.	82	129—130	$C_{14}H_9O_2NS$	65.40 (65.61)	3.45 (3.43)	5.51 (5.51)
m-$CH_3C_6H_4$	43	83	121—122	$C_{15}H_{11}O_2NS$	66.91 (67.18)	4.12 (4.51)	5.20 (5.17)
o-$NO_2C_6H_4$	r.t.	80	240—241	$C_{14}H_8O_4N_2S$	56.01 (55.86)	2.69 (2.93)	9.33 (9.69)
p-ClC_6H_4	50	80	193—194	$C_{14}H_8O_2NSCl$	58.45 (57.90)	2.78 (2.95)	4.85 (4.97)
$C_6H_5CH_2$	50	73	110—111	$C_{15}H_{11}O_2NS$	66.91 (66.94)	4.12 (4.45)	5.20 (5.66)

r.t.: room temperature

When I, II, or III was heated with an excess of alkyl or phenylmagnesium bromide in benzene under reflux, the corresponding symmetrical or unsymmetrical sulfides (IV) were obtained in 45—65% yields in all cases. The compounds I, II, and III were also allowed to react with alkyl or phenyllithium under the similar conditions to give IV in the similar yields, though slightly increased yields of IV, 55—75% yields, were observed in the case of III.

$$\text{I, II, or III} \xrightarrow[\text{or R'Li}]{\text{R'MgBr}} \text{R-S-R'}$$

IV: $R = C_6H_5,\ CH_3C_6H_4,\ C_6H_5CH_2$
$R' = CH_3,\ C_2H_5,\ n\text{-}C_4H_9,\ C_6H_5,\ C_6H_5CH_2CH_2$

Chart 2

The reaction of I, II, or III with sodium cyanide was successfully carried out by treating in a two-phase solvent, chloroform-water, at room temperature to give thiocyanates (V) in good yields similar in all cases. The structure of V was confirmed by exhibiting the SCN absorption near 2140 cm^{-1} in the IR spectra, and by the agreement of the melting point or the boiling point with that in literatures.[15-18] These results are summarized in Table II.

Direct introduction of a thiocyano group into aromatic compounds is possible only with very reactive substrates such as amines and phenols, utilizing thiocyanogen as the effective reagent.[19] Thiocyanation of aromatic compounds, in which electron withdrawing groups are substituted, is generally difficult.[19] As can be seen in Table II, *o*-nitrophenylthiocyanate

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15) H.R. Snyder and T.C. Speck, *J. Am. Chem. Soc.*, **61**, 668 (1939).
16) H. Rheinboldt and E. Giesbrecht, *J. Am. Chem. Soc.*, **71**, 1740 (1949).
17) R. Rhiemschneider, F. Wojahn, and G. Orlick, *J. Am. Chem. Soc.*, **73**, 5905 (1951).
18) F.G. Bordwell and P.J. Boutan, *J. Am. Chem. Soc.*, **78**, 854 (1956).
19) J.L. Wood, "Organic Reactions," John Wiley and Sons, Inc., New York, 1946, Vol. 3, p. 240.

TABLE II. Thiocyanates (V) from N-(Substituted thio) phthalimides (I), N-(Substituted thio) succinimides (II), and N-(Substituted thio) isatins (III)

$$\text{I, II, or III} \xrightarrow{\text{NaCN}} \underset{\text{V}}{\text{R-SCN}}$$

R	Material	Yield (%)	bp/torr or mp (℃)	IR cm^{-1} (KBr) ν SCN
C_6H_5	I	81	66—67/3 (71—73/1.5)[a]	2130
C_6H_5	II	86		
C_6H_5	III	90		
p-$CH_3C_6H_4$	I	94	79—80/3 (116—118/10)[a]	2140
p-$CH_3C_6H_4$	II	83		
m-$CH_3C_6H_4$	III	81	80/3(110—114/10)[a]	2150
o-$NO_2C_6H_4$	I	78	132—133 (131—132.5)[b]	2140
o-$NO_2C_6H_4$	II	81		
o-$NO_2C_6H_4$	III	78		
$C_6H_5CH_2$	I	78	41 (43)[c]	2130
$C_6H_5CH_2$	II	88		
$C_6H_5CH_2$	III	78		

a) reported bps[17]
b) reported mp[16]
c) reported mp[15]

possessing an electron withdrawing o-nitro group was also readily prepared in a high yield by this method. Therefore, this new procedure should provide access to a wide variety of arylthiocyanates, though the similar synthesis of thiocyanates by the S-cyanation of thiosulfates[20] is already known.

The reaction of I, II, or III with trichloromethyl carbanion was also examined. When I, II, or III was allowed to react with the trichloromethyl carbanion generated from chloroform in the presence of 50% aqueous sodium hydroxide at 40°, the corresponding trichloromethyl sulfides (VI) were successfully obtained. This reaction was moderately exothermic and resulted somewhat increased yields of VI at a lower reaction temperature (20°). Below 20°, the reaction mixture solidified and therefore the reaction was difficult to proceed. In all cases, the yield of VI was low and no difference of the yield due to the difference of these sulfenimides used was observed. The trichloromethyl carbanion is shown to be short-living species and to undergo rapid conversion to dichlorocarbene and chloride ion.[21] The formation of VI, therefore, shows that the high reaction rate for the S-trichloromethylation exceeds the rapid transformation to dichlorocarbene. Disulfides are known to react with carbanions formed from organometallic compounds to give sulfides,[22] and similarly symmetrical disulfides (VII) were allowed to react with the trichloromethyl carbanion to give VI in low yields. In the reaction with unsymmetrical alkyl aryl disulfides (VIII), only alkyl trichloromethyl sulfides were

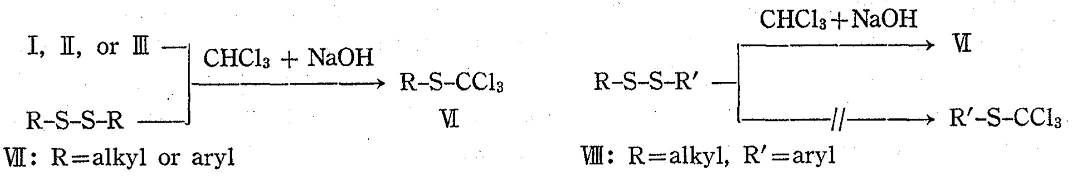

Chart 3

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20) H. Bell and S. Smiles, *J. Chem. Soc.*, **1925**, 2887.
21) W. Kirmse, "Carbene Chemistry," 2 nd ed., Academic press, New York, London, 1971.
22) A. Schönberg, A. Stephenson, H. Kaltschmitt, E. Petersen, and H. Schulten, *Chem. Ber.*, **66**, 237 (1933).

Table III. Trichlomethyl sulfides (VI) from N-(Substituted thio) phthalimides (I), N-(Substituted thio)succinimides (II), N-(Substituted thio) isatins (III), and Disulfides (VII or VIII)

R	Material	Yield (%)	bp/torr (°C)
C_6H_5	I	33(46)$^{a)}$	124—126/16 (86—87/0.7)$^{b)}$ mp 35.5
C_6H_5	II	34(43)$^{a)}$	
C_6H_5	III	30	
C_6H_5	VII	32(45)$^{a)}$	
$C_6H_5CH_2$	I	23(44)$^{a)}$	128—129/7 (92—94/0.1)$^{b)}$ mp 37—39
$C_6H_5CH_2$	II	39	
$C_6H_5CH_2$	III	25	
$C_6H_5CH_2$	VII	42	
p-$CH_3C_6H_4$	III	32	111—113/4
m-$CH_3C_6H_4$	III	24	90—92/3
C_2H_5	VIII	(46)$^{a)}$	65—67/23 (61—62/15)$^{b)}$
n-C_3H_7	VIII	(52)$^{a)}$	66—67/10 (70—71/12)$^{b)}$
n-C_4H_9	VIII	(52)$^{a)}$	62—63/3

a) The yield obtained by the reaction at 20°.
b) reported bps (D.H. Holsboer and A.P.M. Van der Veek, *Rec. Trav. Chim.*, **91**, 349 (1972).

obtained, any aryl trichloromethyl sulfides being not isolated. This result is similar to that of the cleavage of VIII by the cyanide ion.[23] The results are summarized in Table III.

The behaviors of III were further examined by using thiols as the nucleophile. Similarly to I and II,[3-5] III reacted with equimolar quantities of thiols in benzene under reflux to give the corresponding symmetrical or unsymmetrical disulfides (VII or VIII) in good yields. The treatment of two equimolar quantities of III with alkanedithiols under the similar condi-

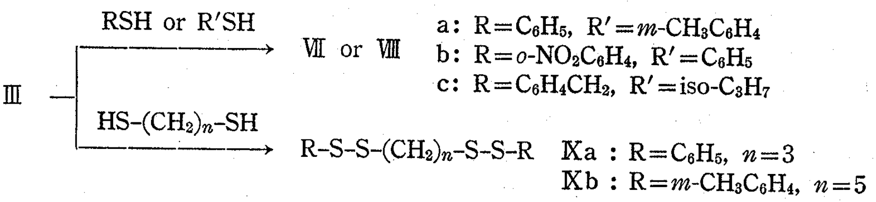

Chart 4

Table IV. Disulfides (VII, VIII, or IX) from N-(Substituted thio)-isatins (III)

Compd.	Reaction time (hr)	Yield (%)	bp/torr or mp (°C)
VII	1	91	59—60 (60—61)$^{a)}$
VIIIa	1	80	153/3 (107/0.01)$^{b)}$
VIIIb	2	73	160—162
VIIIc	3	85	114/3
IXa	1.5	87	147/2
IXb	4	79	153/2

a) reported mp (V.D. Lukashevich and M.M. Sergeeva, *Zh. Obshch. Khim.*, **19**, 1493 (1949).)
b) reported bp (D.A. Armitage and M.J. Clark, *J. Chem. Soc. Perkin I*, **1972**, 680.)

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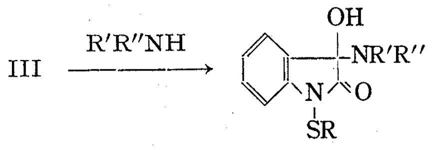
[23] R.G. Hiskey and F.I. Carroll, *J. Am. Chem. Soc.*, **83**, 4644 (1961).

tions also gave alkane-bis-disulfides (IX) in good yields. The results are summarized in Table IV.

Although the reaction of I or II with amines give the good yields of sulfenamides,[7,8] III did not afford such expected sulfenamides. When equimolar quantities of III and amines were treated in dichloromethane at room temperature, 3-amino-1-substituted thio-3-hydroxy-2-oxo-indoles (X), the addition product of amines to the carbonyl group at the 3-position in III, were obtained in moderate yields. The results are summarized in Table V.

Table V. 3-Amino-1-substituted Thio-3-hydroxy-2-oxo-indoles (X)



X

R	R'	R''	React. time (hr)	Yield (%)	mp (°C)	Analyses % Calcd. (Found) C	H	N	IR cm⁻¹ (KBr) $\nu_{C=O}$	ν_{OH}	ν_{NH}
C_6H_5	H	C_6H_{11}	10	51	95—96	67.78 (67.41)	6.26 (6.75)	7.91 (7.85)	1635	3285	3240
m-$CH_3C_6H_4$	H	C_6H_{11}	10	70	146—147	68.46 (68.56)	6.57 (6.82)	7.76 (7.58)	1620	3285	3240
o-$NO_2C_6H_4$	H	$C_6H_5CH_2$	10	57	166—168	61.91 (61.82)	4.21 (4.53)	10.32 (10.26)	1620	3290	3250
o-$NO_2C_6H_4$	$O\genfrac{}{}{0pt}{}{\diagup CH_2CH_2}{\diagdown CH_2CH_2}$		96	58	152—153	55.81 (55.91)	4.42 (4.49)	10.82 (10.80)	1630	3275	

The structure of X was established by the elemental analyses, by the IR spectra exhibiting the absorptions assignable to OH group near 3280 cm⁻¹ and to amino group near 3240 cm⁻¹, and by the mass spectra exhibiting the strong peak of the corresponding molecular ion. Even in the use of a large excess of amines, the expected sulfenamides were not isolated. Such a difference of the reactivities of amines toward III can be explained by the S-nucleophilicity[24,25] or thiophilicity.[26] In the cases of carbanions, thiols, and cyanide ion, which possess the strong thiophilicity, the sulfenyl sulfur atom of III may be the prefered site of the nucleophilic attack. On the other hand, in the case of amines possessing the weak thiophilicity,[27] the prefered site of the nucleophilic attack would be the positive carbonyl carbon atom.

Experimental

All the melting points are uncorrected. IR spectra were measured on a JASCO IRA-1 Grating Infrared Spectrometer. Mass spectra were determined at 75 eV on a JEOL JMS-01SG Mass Spectrometer.

N-(Substituted thio)isatin (III)——General Procedure: To a solution of isatin (10 mmol) and triethylamine (10 mmol) in DMF (5 ml) was added, drop by drop, with stirring alkane or arenesulfenyl chloride (10 mmol) at the reaction temperature described in Table I. Stirring was continued for an additional 30 min and then the mixture was poured into ice water (40 ml). The yellow precipitates were collected by filtration and recrystallized from ethanol.

Reaction of N-(Substituted thio)phthalimide (I), N-(Substituted thio)succinimide (II), or N-(Substituted thio)isatin (III) with Organometallic Compounds——a) With Grignard Reagents: General Procedure: A solution of N-(substituted thio)phthalimide (15 mmol), N-(substituted thio)succinimide (15 mmol), or N-

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[24] A.J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 610 (1959).
[25] A.J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 307 (1960).
[26] P.D. Bartlett, G. Lohaus, and C.D. Weis, *J. Am. Chem. Soc.*, **80**, 5064 (1958).
[27] W.A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill, New York, 1962, p. 60.

(substituted thio) isatin (15 mmol) in dry benzene (150 ml) was added with stirring into an ethereal Grignard solution[28] prepared from alkyl or aryl bromide (30 mmol) and magnesium turnings (30 mg-atom) under a nitrogen stream. After heated for 2 hr under reflux, the mixture was poured with stirring into a saturated aqueous ammonium chloride solution containing pieces of ice. The ether–benzene layer was separated, washed with a small amount of water, dried over sodium sulfate, and evaporated. The residue was extracted with petroleum ether and the extract was evaporated and then distilled under reduced pressure to give the corresponding sulfides.

b) With Organolithium Compounds: General Procedure: A solution of N-(substituted thio)phthalimide (15 mmol), N-(substituted thio)succinimide (15 mmol), or N-(substituted thio) isatin (15 mmol) in dry benzene (150 ml) was added with stirring under a nitrogen stream into a solution of organolithium compounds[29,30] prepared from alkyl or aryl bromide (30 mmol) and lithium (30 mg-atom). After heated for 3 hr under reflux, the mixture was treated by the same procedure as described above to give sulfides.

Reaction of N-(Substituted thio)phthalimide (I), N-(Substituted thio)succinimide (II), or N-(Substituted thio)isatin (III) with Sodium Cyanide——General Procedure: A solution of sodium cyanide (20 mmol) in water (30 ml) was added with vigorous stirring into a solution of N-(substituted thio)phthalimide (15 mmol), N-(substituted thio)succinimide (15 mmol), or N-(substituted thio) isatin (15 mmol) in chloroform (150 ml) at room temperature under a stream of nitrogen. Stirring was continued for an additional 1 hr. Then the chloroform layer was separated, washed with water, dried over sodium sulfate, and the chloroform was evaporated. The residue was distilled under reduced pressure to give the corresponding thiocyanates.

Reaction of N-(Substituted thio)phthalimide (I), N-(Substituted thio)succinimide (II), or N-(Substituted thio)isatin (III) with Trichloromethyl Carbanion——General Procedure: An aqueous 50% sodium hydroxide (10 ml) was added portionwise with vigorous stirring into a mixture of N-(substituted thio)phthalimide (50 mmol), N-(substituted thio)succinimide (50 mmol), or N-(substituted thio) isatin (50 mmol) in chloroform (500 ml). The reaction was slightly exothermic, and the temperature rose to more than 40°. Keeping the temperature at 40°, stirring was continued for an additional 3—4 hr. The mixture gradually turned red brown. The mixture was then diluted with water, the chloroform layer separated, and the aqueous layer extracted with chloroform. The combined chloroform solution was washed with water, dried over sodium sulfate, and the chloroform was evaporated. The residue was distilled under reduced pressure to give trichloromethyl sulfides. The same reactions were also carried out at 20° and slightly increased yields of the sulfides were obtained.

Reaction of Disulfide (VII and VIII) with Trichloromethyl Carbanion——General Procedure: Dialkyl or diaryl disulfide (50 mmol) in chloroform (500 ml) was treated with an aqueous 50% sodium hydroxide (10 ml) by the same procedure described above to give alkyl or aryl trichloromethyl sulfides.

Similarly, a chloroform solution (300 ml) of alkyl phenyl disulfide (50 mmol) was treated with an aqueous 50% sodium hydroxide (10 ml) under the same conditions to give alkyl trichloromethyl sulfides, and no trace of phenyl trichloromethyl sulfide was isolated.

Reaction of N-(Substituted thio)isatin (III) with Thiols——General Procedure: A solution of N-(substituted thio)isatin (5 mmol) and a thiol (5 mmol) in dry benzene (20 ml) was heated for 1 hr under reflux. After cooling, the precipitated isatin was filtered off and the filtrate was evaporated by distillation. The residue was purified by recrystallization or by distillation under reduced pressure to give the corresponding disulfides. In the reaction with alkane-dithiols, two equimolar quantities of N-(substituted thio) isatin were used.

Reaction of N-(Substituted thio)isatin (III) with Amines——General Procedure: A mixture of N-(substituted thio)isatin (10 mmol) and an amine (10 mmol) in dichloromethane was stirred for 10—96 hr at room temperature and then evaporated under reduced pressure. The residue was chromatographed on silica gel. Development with benzene and then recrystallization from 70% ethanol gave 3-amino-1-substituted thio-3-hydroxy-2-oxo-indoles.

Acknowledgement We wish to thank Mrs. Shiraki and Mr. Takeda for microanalyses and spectral data.

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28) H. Gilman and E.A. Zoellner, *J. Am. Chem. Soc.*, **50**, 2520 (1928).

29) H. Gilman, J.A. Bell, C.G. Brannen, M.W. Bullock, G.E. Dunn, and L.S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

30) G. Wittig, "Newer Methods of Preparative Organic Chemistry," Vol. 1, Interscience Publishers, New York, 1948, p. 571.