JOC Notes

Novel Synthesis of *cis*-Nickel(II) 3-Alkylimino-3-alkyl(or aryl)thio-1-arylpropenethiolates and Their Application to the Preparation of 5-Aryl-3-(arylthio)isothiazoles

Dong Joon Lee, Bo Sung Kim, and Kyongtae Kim*

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, Korea

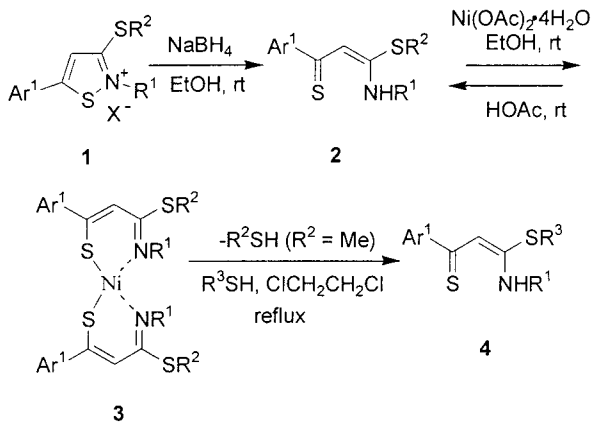
kkim@plaza.snu.ac.kr

Received June 20, 2001

Abstract: Treatment of (*E*)-3-alkylamino-3-alkylthio-1-(thioaroyl)propenes **2** with $Ni(OAc)_2 \cdot 4H_2O$ in EtOH at room temperature gave *cis*-Ni(II)-3-alkylimino-3-alkylthio-1-arylpropenethiolates **3** in excellent yields. Heating a mixture of **3** and alkyl- or arylthiols in 1,2-dichloroethane gave new ketene *S*,*N*-acetals **4** having new alkyl- or arylthio groups depending on the thiols employed. For the first time, 5-aryl-3-(arylthio)isothiazoles were prepared from **2** with an arylthio group according to a known procedure.

Among numerous isothiazole derivatives,[1] 3-alkylthioisothiazoles have attracted much attention due to their biological applications such as fungicides,[2] insect repellent,[3] and antiviral agents against enterovirus and ECHO 9.[4] Introduction of alkylthio groups for the synthesis of 3-(alkylthio)isothiazoles has been basically achieved by two different methods. The first method, which has been utilized most widely, involves nucleophilic displacement of halide ion by alkylthiolates. For instance, 4-cyano-3,5-(dimethylthio)isothiazole was prepared by treatment of 2-cyanoethylthioamide with a hydroxide base in carbon disulfide, followed by addition of iodomethane and iodine in sequence.[5] Alternatively, the reaction of the disodium salt of 4-cyano-3,5-(dimercapto)isothiazole (readily available from dicyanoethylenedithiolate and sulfur) with alkyl halides afforded 4-cyano-3,5-(dialkylthio)isothiazoles.[6] Treatment of 3,5-dichloro-4-cyanoisothiazole with sodium sulfide in the presence of iodomethane also led to the foregoing isothiazole derivatives.[4,6c] However, the latter reaction was accompanied by ring cleavage. The other method involves the thermal elimination of sulfur from 1,4,2-dithiazines, yielding 3-(methylthio)isothiazoles along with other products.[7] Of course, these methods are incompatible with the synthesis of the title compounds due to the failure to achieve S_N2 nucleophilic displacement in the case of an aryl halide. Therefore, we were interested in exploring a synthetic method for 5-aryl-3-(arylthio)isothiazoles.

SCHEME 1



During the course of our study exploring the potential synthetic utility of (*E*)-thioaroylketene *S*,*N*-acetals **2**,[8] which were prepared by treatment of 2-alkyl-3-alkylthio-5-arylisothiazolium halides **1** with $NaBH_4$ in EtOH at room temperature,[9] we found that compound **2a** (Ar^1 = Ph, $R^1 = R^2$ = Me) reacted with $Ni(OAc)_2 \cdot 4H_2O$ for 4 h in EtOH at room temperature to give a dark brown solid **3** (Scheme 1), whose structure was determined on the basis of spectroscopic and analytical data. The X-ray single-crystal structure of **3a** (Ar^1 = Ph, $R^1 = R^2$ = Me) clearly shows that two molecules of **2a** make a type of a cis square planar complex[10] by coordinating thione sulfurs and nitrogen atoms with an Ni(II) ion.

Similarly, the reactions with other thioaroylketene *S*,*N*-acetals **2b**−**g** under the same conditions gave nickel complexes **3b**−**g** in good to excellent yields (Table 1).

Compounds **3** are stable toward bases such as alkylamines, i.e., *i*-$PrNH_2$ and (*n*-$Bu)_2NH$, and aqueous KOH, whereas decomplexation occurs in HOAc to give **2**.

(1) (a) Pain, D. L.; Peart, B. J.; Wooldridge, K. R. H. *In Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 6, pp 131−175. (b) Chapman, R. F.; Peart, B. J. *In Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 319−372.

(2) (a) Merck, A.-G. Netherlands Pat. 6, 703, 832, 1967; *Chem. Abstr.* **1968**, *69*, 96708. (b) Merck, A.-G. Netherlands Pat. 6, 808, 400, 1968; *Chem. Abstr.* **1969**, *71*, 124429.

(3) Caton, M. P. L.; Slack, R. *J. Chem. Soc. C* **1968**, 1402−1404.

(4) (a) Cutri, C. C. C.; Garozzo, A.; Siracusa, M. A.; Sarvá, M. C.; Tempera, G.; Geremia, E.; Pinizzotto, M. R.; Guerrera, F. *Bioorg. Med. Chem.* **1998**, *6*, 2271−2280. (b) Cutri, C. C. C.; Garozzo, A.; Siracusa, M. A.; Sarvá, M. C.; Castro, A.; Geremia, E.; Pinizzotto, M. R.; Guerrera, F. *Bioorg. Med. Chem.* **1999**, *7*, 225−230.

(5) Gewald, K. *Chem. Ber.* **1968**, *101*, 383−390.

(6) (a) Hatchard, W. R. *J. Org. Chem.* **1963**, *28*, 2163−2164. (b) Söderbäck, E. *Acta Chem. Scand.* **1963**, *17*, 362−376. (c) Hatchard, W. R. *J. Org. Chem.* **1964**, *29*, 660−665. (d) Gewald, K. *J. Prakt. Chem.* **1966**, *31*, 214−218. (e) Wooldridge, K. R. H. *In Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1972; Vol. 14, pp 1−41. (f) Hoyer, G. A.; von Manfred Kless, M. *Tetrahedron Lett.* **1969**, 4265−4268. (g) Poite, J. C.; Julien, J.; Vincent, E. J.; Roggero, J. *Bull. Soc. Chim. Fr.* **1972**, *6*, 2296−2299. (h) Gewald, K.; Radke, W.; Hain, U. *J. Prakt. Chem.* **1980**, *322*, 1021−1031.

(7) Fanghänel, E. *Z. Chem.* **1965**, *5*, 386.

(8) Kim, B.; Kim, K. *J. Org. Chem.* **2000**, *65*, 3690−3699.

(9) Kim, S. H.; Kim, K.; Kim, K.; Kim, J.; Kim, J. H. *J. Heterocycl. Chem.* **1993**, *30*, 929−938.

(10) Selected bond angles (deg) and bond lengths (Å) of **3a**: N(1)−Ni−N(1)#1 92.8(2), N(1)−Ni−S(2)#1 161.9(9), N(1)#1−Ni−S(2)#1 95.15-(8), N(1)−Ni−S(2) 161.93(9), S(2)#1−Ni−S(2) 82.05(5), Ni−N(1) 1.936-(3), Ni−N(1)#1 1.936(3), Ni−S(2)#1 2.1602(10), Ni−S(2) 2.1602(10).

10.1021/jo010631r CCC: $22.00
Published on Web 06/21/2002

TABLE 1. Synthesis of Complexes 3 by Reaction between (*E*)-3-Alkylamino-3-alkylthio-1-(thioaroyl)-propenes 2 and $Ni(OAc)_2 \cdot 4H_2O$ in EtOH at Room Temperature

substrate	Ar^1	R^1	R^2	product	time (h)	yield[a] (%)
2a	Ph	Me	Me	**3a**	4	92
2b	Ph	Me	*i*-Pr	**3b**	4	91
2c	Ph	Et	Me	**3c**	3	86
2d	Ph	Et	*n*-Pr	**3d**	4	87
2e	3-$MeOC_6H_4$	Me	Me	**3e**	4	92
2f	4-ClC_6H_4	Me	Me	**3f**	4	90
2g	4-$MeOC_6H_4$	Et	Me	**3g**	4	96

[a] Isolated yields.

TABLE 2. Synthesis of Ketene *S,N*-Acetels 4 by Reaction between Complexes 3 and R^3SH in Refluxing 1,2-Dichloroethane

complex	R^1	R^3	product	time (h)	yield[a] (%)
3a	Me	*n*-Pr	**4a**	8	78
3a	Me	Allyl	**4b**	8	66
3a	Me	Ph	**4c**	12	62
3a	Me	4-$MeOC_6H_4$	**4d**	12	51
3a	Me	4-MeC_6H_4	**4e**	10	69
3a	Me	4-BrC_6H_4	**4f**	9	70
3a	Me	2-$MeOC_6H_4$	**4g**	48	22
3a	Me	2-ClC_6H_4	**4h**	10	50
3a	Me	2-BrC_6H_4	**4i**	12	43
3a	Me	2-naphthyl	**4j**	12	30
3c	Et	Ph	**4k**	10	64
3f	Me	Ph	**4l**	12	63
3f	Me	2-BrC_6H_4	**4m**	12	43
3g	Et	Ph	**4n**	12	60
3g	Et	2-BrC_6H_4	**4o**	12	38

[a] Isolated yields.

Interestingly, treatment of **3** (Ar^1 = Ph, R^1 = alkyl, R^2 = Me) with alkanethiols as well as arenethiols in 1,2-dichloroethane at reflux gave new ketene *S,N*-acetals **4** in which the R^2S group of **3** is replaced by either a new alkylthio group (**4a**−**b**) or arylthio group (**4c**−**o**) depending on the thiols employed. Reaction times and product yields are summarized in Table 2.

The replacement of the R^2S group by other alkylthio groups by this method appears to be a convenient alternative to the direct reduction of the corresponding compounds **1**, which are synthesized from cinnamic acid derivatives[8] by a multistep sequence. Moreover, this methodology is useful for preparing thioaroylketene *S,N*-acetals bearing an arylthio group, which have been hitherto inaccessible.

Since compounds **4c**−**o** were in hand, 3-arylthio-isothiazoles **6** were synthesized according to a known procedure[11] (Scheme 2). Reaction times and yields of compounds **5** and **6** are summarized in Table 3.

In summary, we have developed a synthetic method for 3-alkylamino-1-aryl-3-(arylthio)propenethiones **4** utilizing an Ni(II) complex **3**. 3-Arylthio-5-phenylisothiazoles can be readily prepared starting from **4** using a two-step procedure.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solution containing Me_4Si as an internal standard unless otherwise stated. *J* values are given in hertz. IR spectra were obtained in KBr or as thin films on KBr plates. GC-MS spectra were obtained by electron impact at 70 eV from the National Center for Inter-University Research Facilities, Seoul National University. Elemental analyses were carried out by the Korea Basic Science Research Institute. Column chromatography was performed using silica gel (70−230 mesh, ASTM). Melting points are uncorrected. Thioaroylketene *S,N*-acetals **2** were prepared by a documented procedure.[9] Reagent-grade 1,2-dichloroethane was used without further purification.

SCHEME 2

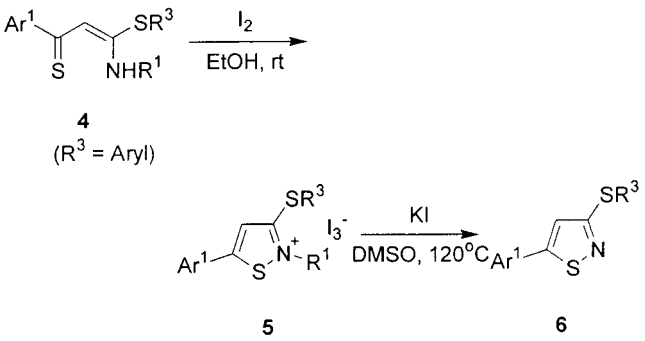


TABLE 3. Synthesis of 3-(Arylthio)isothiazoles 6 by Reaction of Compounds 4 with I_2 in EtOH at Room Temperature to Give Isothiazolium Triiodides 5 Followed by Treatment with KI at 120 °C in DMSO

substrate	time (min)	compd	yield[a] (%)	time (h)	compd	yield[a] (%)
4c	30	**5c**	80	4	**6c**	76
4d	30	**5d**	90	5	**6d**	92
4e	30	**5e**	87	5	**6e**	91
4f	30	**5f**	75	5	**6f**	86
4g	30	**5g**	63	5	**6g**	87
4h	30	**5h**	69	3	**6h**	67
4i	30	**5i**	85	4	**6i**	84
4j	30	**5j**	85	4	**6j**	85
4l	30	**5l**	86	4	**6l**	86
4m	30	**5m**	79	4	**6m**	79
4n	30	**5n**	88	4	**6n**	74
4o	30	**5o**	70	4	**6o**	74

[a] Isolated yields.

General Procedure for the Synthesis of Ni(II) 3-Alkylamino-1-aryl-3-(arylthio)propenothiolates (3). To a solution of 3-alkylamino-3-alkylthio-1-arylpropenethiones **2** (0.193−1.49 mmol) in EtOH (5−15 mL) was added $Ni(OAc)_2 \cdot 4H_2O$ (0.097−0.746 mmol) at room temperature. The mixture was stirred for 3−6 h at room temperature by the time $Ni(OAc)_2 \cdot 4H_2O$ was completely dissolved, and a dark brown solid was precipitated out. The solid was filtered, washed with ether, and recrystallized from a mixture of CH_2Cl_2 and EtOH. Yields are given in Table 1.

General Procedure for the Synthesis of 3-Alkylamino-3-alkyl(or aryl)thio-1-arylpropenethiones (4). To a solution of **3** (0.097−0.158 mmol) in 1,2-dichloroethane (10−15 mL) was added a large excess of thiol (0.472−1.21 mmol). The mixture was heated for 8−12 h at reflux and then cooled to room temperature. To the cooled mixture was added sodium cyanide (0.097−0.158 mmol), and the mixture was stirred for an additional 20 min. Removal of the solvent in vacuo gave a residue, which was chromatographed on a silica gel (1.5 × 15 cm) with a 1:9 mixture of EtOAc and *n*-hexane as the eluent to give **4**. Yields are given in Table 2.

General Procedure for the Synthesis of 5-Aryl-3-arylthio-2-methylisothiazolium Triiodides (5). To a stirred solution of **4** (0.156−0.506 mmol) in EtOH (30 mL) was added dropwise a solution of iodine (0.6−2.1 mmol) in EtOH (20 mL) until the

(11) McKinnon, D. M.; Robak, E. A. *Can. J. Chem.* **1968**, *46*, 1855−1858.

spot corresponding to **4** disappeared on TLC (silica gel, 1:4 EtOAc:*n*-hexane). The yellow triiodide **5** formed was filtered, washed with ether, and recrystallized from a mixture of CH_2Cl_2 and EtOH. Yields are given in Table 3.

General Procdure for the Synthesis of 5-Aryl-3-(arylthio)isothiazoles (6). To a stirred solution of **5** (0.099−0.152 mmol) in DMSO (20 mL) was added KI (0.199−0.301 mmol). The mixture was heated for 3−5 h at 120 °C. Removal of the solvent in vacuo gave a residue, which was chromatographed on a silica gel (1.5 × 15 cm) with a 1:15 mixture of EtOAc and *n*-hexane as the eluent to give **6**. Yields are given in Table 3.

X-ray Structure Analysis of Compound 3a. A single crystal of **3a** was obtained from a mixture of CH_2Cl_2 and EtOAc. The data were collected using graphite-monochromated Mo Kα radiation. The structure was inferred by direct methods and subsequent Fourier maps. Refinements were carried out by full-matrix least-squares techniques. Non-hydrogen atoms were anisotropically refined. Atomic scattering factors were taken from International Tables for X-ray Crystallography, Vol. IV, 1974.[12] Atomic coordinates, bond lengths, angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.[13]

Acknowledgment. Financial support from the Brain Korea 21 program is gratefully acknowledged.

Supporting Information Available: Copies of ^{1}H NMR, IR, and elemental analyses of **2b**−**g**, **3a**−**g**, **4a**−**o**, **5c**−**j**, **5l**−**o**, **6c**−**j**, and **6l**−**o**, X-ray crystallographic data of **3a**, and an ORTEP drawing of an Ni(II) 3-methylimino-3-methylthio-1-phenylpropenethiolate (**3a**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO010631R

(12) Kynoch Press, Birmingham, England.
(13) CCDC-176866.