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Note

One-pot Synthesis of (*Z*)-Thioaurones from *N*-Methoxy-*N*-methyl 2-mercaptobenzamide and Arylethynyllithiums

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Thioaurones belong to the family of thioflavonoids and are interesting compounds due to their photoswitchable property depending upon the scale of wavelength.[1] They possess pharmacological activities such as an anticancer property[2] against human tumor cells and a liphophilic drug characteristic[3] that plays an important role in their biological action.

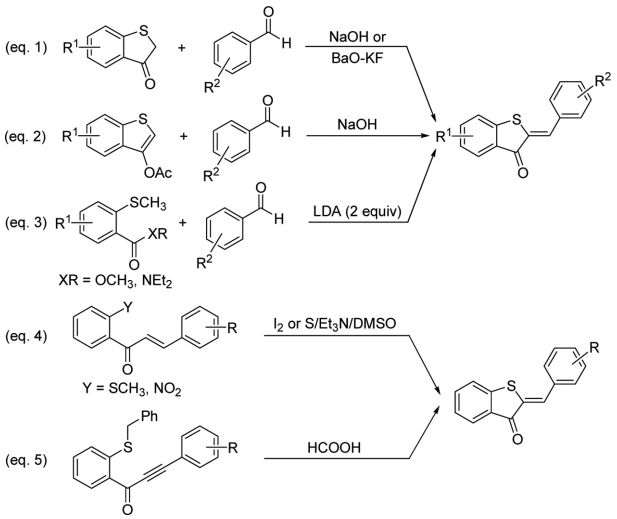
Several methods for synthesizing (*Z*)-thioaurones have been reported.[4] The base-catalyzed condensation of benzothiophen-3-ones with arylaldehydes using NaOH/*t*-BuOH[5] or BaO-KF[6] under microwave irradiation afforded (*Z*)-thioaurones (*Scheme* 1, eq. 1). Similarly, the condensation of 3-acetoxybenzothiophenes with arylaldehydes using NaOH afforded (*Z*)-thioaurones (eq. 2).[7] The intramolecular cyclization through lithiation of methyl (2-methylthio)benzoates[8] or *N*,*N*-diethyl (2-methylthio)benzamides[9] in the presence of 2.5 equiv of lithium diisopropylamide (LDA) also led to benzothiophen-3-ones *in situ*, followed by an aldol condensation with arylaldehydes to give (*Z*)-thioaurones (eq. 3).

The cyclization of 2′-methylthiochalcones using 0.5 equiv of iodine afforded (*Z*)-thioaurones with demethylation of their methylthio groups in DMSO at 150 °C, together with thioflavones as side products.[10] Furthermore, the incorporation of sulfur atoms into 2′-nitrochalcones with 5 equiv of sulfur in the presence of 5 equiv of Et_3N in DMSO and the successive nucleophilic substitution of the nitro group gave (*Z*)-thioaurones (eq. 4).[11] Recently we developed method for synthesizing (*Z*)-thioaurones through 5-*exo* cyclization of 1-(2-benzylthio)phenyl-3-phenyl-2-propyn-1-ones using formic acid in THF at 65 °C (eq. 5).[12]

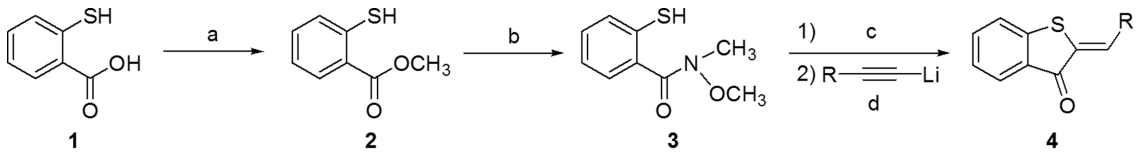
Among the methods reported for synthesizing (*Z*)-thioaurones, some suffer from lack of regioselectivity during cyclization, the use of excess reagent, and harsh conditions. As an extension of our studies on the syntheses and biological activities of thioflavonoids,[13] we report the efficient synthesis of (*Z*)-thioaurones from *N*-methoxy-*N*-methyl 2-mercaptobenzamide and arylethynyllithiums in a one-pot operation.

Methyl 2-mercaptobenzoate (**2**) was prepared from 2-mercaptobenzoic acid (**1**) using 20 mol% H_2SO_4 in CH_3OH at reflux according to a similar method described by Unelius *et al.*[14] (*Scheme* 2). The esterification proceeded sluggishly for 48 h at 65 °C, presumably due to the resonance and steric effect of *o*-thiol on COOH group. The usual basic work-up after evaporation of CH_3OH and purification by vacuum distillation gave **2** as a yellow liquid in 94% yield.

N-Methoxy-*N*-methyl 2-mercaptobenzamide (**3**) was prepared by the slow addition of 3 equiv of isopropylmagnesium chloride to a slurry solution of **2** and *N,O*-dimethylhydroxylamine hydrochloride for 0.5 h between -10 °C and 0 °C. The resulting *N*-methoxy-*N*-methylmagnesium chloride, generated from $CH_3(CH_3O)NH_2Cl$ and 2 equiv of *i*-PrMgCl, smoothly substituted for the methoxy group



***Scheme* 1.** General method for synthesizing (*Z*)-thioaurones.



1 2 3 4

R = C_6H_5 (**a**); 2-CH_3O-C_6H_4 (**b**); 3-Cl-C_6H_4 (**c**); 4-Br-C_6H_4 (**d**); 4-CH_3-C_6H_4 (**e**); 4-CH_3O-C_6H_4 (**f**); 3-Thienyl (**g**); 2-Pyridyl (**h**); 2-CH_3-4-CH_3O-C_6H_3 (**i**); 3,5-$(CH_3O)_2$-C_6H_3 (**j**)

***Scheme* 2.** Reagents and conditions: (a) CH_3OH, 20 mol% H_2SO_4, reflux, 48 h; (b) $CH_3(CH_3O)NH_2Cl$, 3 equiv *i*-PrMgCl, THF, -10~0 °C, 0.5 h; 1 N HCl; (c) LDA, THF, 0 °C, 10 min; (d) THF, 0 °C~rt, 2~3 h; 0.1 N HCl.

in **2**. The reaction mixture was quenched with 1 N HCl solution, followed by evaporation of THF. The usual acidic work-up and purification by silica gel column chromatography gave **3** in 84% yield.

Initially the synthesis of (*Z*)-thioaurone (**4a**) was carried out by the direct addition of 2 equiv of LDA to a mixture solution of *N*-methoxy-*N*-methyl 2-mercaptobenzamide (**3**) and phenylacetylene in THF at 0 °C, but **4a** was obtained in only 18% yield. However, (*Z*)-thioaurones (**4**) could be synthesized by the nucleophilic acyl substitution of **3** with arylethynyllithiums and the successive intramolecular cyclization. For example, the treatment of **3** with LDA in THF for 10 min at 0 °C afforded the resulting lithium thiophenolate intermediate, the *N*-methoxy-*N*-methyl group of which was then substituted by phenylethynyllithium. The successive one-pot 5-*exo* cyclization by sulfur anion in the resulting lithiothiolate alkynone produced (*Z*)-thioaurone (**4a**) by kinetic control for 2.5 h between 0 °C and room temperature in 58% yield. Upon employing this process, various (*Z*)-thioaurones (**4**) could be obtained in yields ranging from 43–66% after the usual acidic work-up and purification by silica gel column chromatography. Although (*Z*)-thioaurone was synthesized by the reaction of the magnesium thiophenolate intermediate, generated from **3** and *t*-BuMgCl, and phenylethynylmagnesium chloride for 4.5 h between 0 °C and room temperature, the yield was decreased to 35% yield.

The IR spectra of the C=O band in the synthesized (*Z*)-thioaurones appeared in the range of 1669–1683 cm^{-1} as the conjugated form. The configuration of C=C in **4** appeared to be (*Z*), judging from the value of chemical shifts of vinyl protons and the corresponding (*E*)-isomers were not obtained. The ^1H NMR spectra of vinyl protons in **4** appeared in the range of 7.85–7.97 ppm, which indicated the presence of thioaurones in the (*Z*)-form. In the case of the (*E*)-form, the vinyl proton was shifted about 0.6–0.8 ppm upfield.[9b] However, in the cases of 2′-substituted (*Z*)-thioaurones with methoxy (**4b**) and methyl (**4i**) groups, the vinyl protons appeared at 8.43 and 8.18 ppm, respectively, and the downfield shift was tentatively attributed to the anomeric "ortho effect".

As shown in *Table* 1, various (*Z*)-thioaurones were efficiently synthesized from *N*-methoxy-*N*-methyl 2-mercaptobenzamide and arylethynyllithiums in one-pot operation. The conversion of **3** to **4** worked well with both electron-donating (**4b**, **4e**, **4f**, **4i**, **4j**) and electron-withdrawing (**4c**, **4d**) operating on the phenyl ring of arylethynyllithiums. Furthermore, the reaction of **3** and the two heteroarylethynyllithiums containing the heteroaromatic group, 3-thienyl (**4g**) and 2-pyridyl (**4h**), proceeded well to give the corresponding (*Z*)-thioaurones in 47% and 43% yield, respectively.

In conclusion, we have described a highly regioselective method for synthesizing (*Z*)-thioaurones from *N*-methoxy-*N*-methyl 2-mercaptobenzamide and arylethynyllithiums in a one-pot procedure.

EXPERIMENTAL

General

All chemicals were purchased from Aldrich Chemical Co., Tokyo Chemical Co., and used without further purification. Tetrahydrofuran was refluxed over sodium-benzophenone ketyl under argon atmosphere and distilled prior to use. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker Avance 300 (300 MHz) spectrometer in $CDCl_3$ as a solvent. FT-IR spectra were recorded with Bruker vector 22 spectrometer. Low-resolution mass spectra were measured with Agilent Gc/Ms (6890 Gc/5933 Ms). Melting points were measured with Mel-temp II (Aldrich) and were uncorrected.

Preparation of Methyl 2-mercaptobenzoate (2)

To a solution of 2-mercaptobenzoic acid (**1**, 3.08 g, 20.0 mmol) in CH_3OH (40 mL) was added sulfuric acid (213 μL, 4.0 mmol) and the reaction mixture was refluxed for 48 h.

After evaporating the CH_3OH, the residue was dissolved in methylene chloride (30 mL) and poured into a saturated $NaHCO_3$ solution (50 mL). After extraction with methylene chloride (3×30 mL), the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by vacuum distillation using Kugelrohr apparatus to give **2** (3.16 g, 94%) as a yellow liquid. bp 90–95 °C/1.5 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 1H), 7.28–7.33 (m, 2H), 7.11–7.19 (m, 1H), 4.69 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 138.3, 132.5, 131.7, 130.9, 125.8, 124.6, 52.2; FT-IR (film) 1709 (C=O) cm^{-1}; Ms *m/z* (%) 168 (M^+, 34), 136 (100), 108 (46).

Preparation of *N*-Methoxy-*N*-methyl 2-mercaptobenzamide (3)

To a slurry solution of **2** (2.52 g, 15.0 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.61 g, 16.5 mmol) in THF, isopropylmagnesium chloride (2.0 M in THF, 24 mL, 48.0 mmol) was slowly added during 0.5 h by syringe while the temperature of the mixture was kept between -10 °C and 0 °C. After stirring for 0.5 h, the mixture was quenched with 1 N HCl solution (5 mL) and the THF was evaporated. The mixture was poured into 0.5 N HCl solution (50 mL) and extracted with methylene chloride (3×25 mL). The concentrated residue was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane as an eluent to give **3** (2.49 g, 84%). mp 59–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.7, 1.2 Hz, 1H), 7.28–7.34 (m, 1H), 7.25 (dd, J = 7.6, 1.8 Hz, 1H), 7.16–7.22 (m, 1H), 3.89 (s, 1H), 3.57 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 135.3, 131.2, 129.7, 129.0, 127.6, 125.6, 61.2, 33.5; FT-IR (KBr) 1642 (C=O) cm^{-1}; Ms *m/z* (%) 197 (M^+, 7), 165 (46), 137 (100), 109 (46).

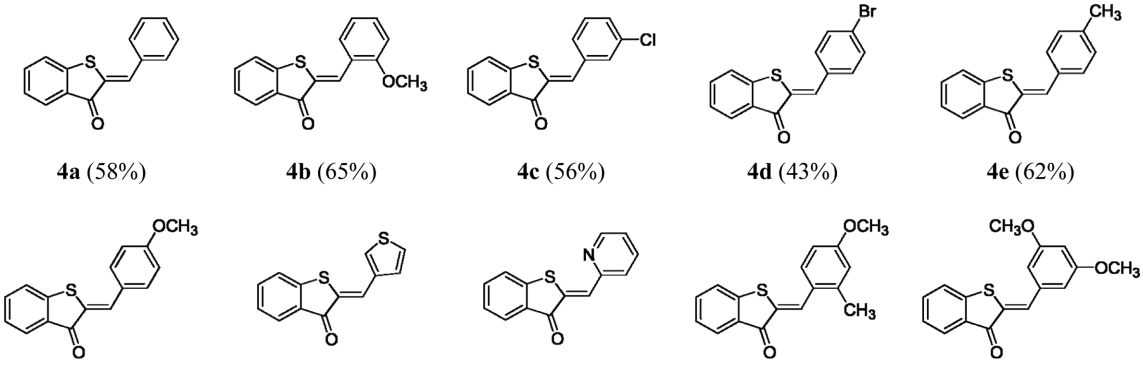
Preparation of (*Z*)-4'-Methoxythioaurone (4f)

To a solution of **3** (395 mg, 2.0 mmol) in THF (4 mL) was added LDA (1.8 M in THF, 1.1 mL, 2.0 mmol) at 0 °C and stirred for 10 min. 4-Methoxyphenylethynyllithium, prepared from 1-ethynyl-4-methoxybenzene (317 mg, 2.4 mmol) and methyllithium (1.5 M in Et_2O, 1.6 mL, 2.4 mmol) in THF (4 mL) for 15 min between 0 °C and room temperature, was added to the above solution at 0 °C. The reaction mixture was stirred for 3 h between 0 °C and room temperature and then the resulting tan-color solution was quenched with 0.1 N HCl solution (5 mL). After evaporating the THF, the mixture was poured into 0.1 N HCl solution (30 mL) and extracted with methylene chloride (3×20 mL). The concentrated residue was separated by silica gel column chromatography using EtOAc/*n*-hexane/CH_2Cl_2 (v/v/v=1/1/1) as an eluent to give **4f** (338 mg, 63%) as a yellow solid. mp 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.93 (d, J = 7.1 Hz, 1H), 7.67 (d, J = 8.7 Hz, 2H), 7.52–7.59 (m, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.24–7.31 (m, 1H), 6.99 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 161.3, 146.0, 134.9, 133.7, 133.0, 130.8, 127.8, 127.1, 126.9, 125.5, 123.9, 114.7, 55.5; FT-IR (KBr) 1669 (C=O) cm^{-1}; Ms *m/z* (%) 268 (M^+, 100), 267 (93), 237 (41).

(*Z*)-Thioaurone (4a): mp 131–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.6 Hz, 2H), 7.54–7.60 (m, 1H), 7.39–7.51 (m, 4H), 7.26–7.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 146.1, 135.3, 134.4, 133.5, 131.0, 130.5, 130.3, 130.1, 129.0, 127.1, 125.6, 123.9; FT-IR (KBr) 1675 (C=O) cm^{-1}; Ms *m/z* (%) 238 (M^+, 59), 237 (100).

(*Z*)-2'-Methoxythioaurone (4b): mp 153–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.94 (d, J = 7.1 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.46–7.60 (m, 2H), 7.36–7.44 (m, 1H), 7.24–7.32 (m, 1H), 7.06 (t, J = 7.4 Hz,

***Table* 1.** Synthesis of (*Z*)-thioaurones from **3** and arylethynyllithiums



4a (58%) **4b** (65%) **4c** (56%) **4d** (43%) **4e** (62%)

4f (63%) **4g** (47%) **4h** (43%) **4i** (66%) **4j** (45%)

1H), 6.34 (d, J = 8.2 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 159.2, 146.2, 135.1, 131.9, 130.8, 130.2, 129.9, 128.6, 127.0, 125.4, 123.9, 123.5, 120.7, 111.0, 55.6; FT-IR (KBr) 1677 (C=O) cm^{-1}; Ms *m/z* (%) 268 (M^+, 25), 237 (100).

(*Z*)-3'-Chlorothioaurone (4c): mp 162–163 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 1H), 7.85 (s, 1H), 7.66 (s, 1H), 7.52–7.62 (m, 2H), 7.49 (d, J = 7.9 Hz, 1H), 7.34–7.44 (m, 2H), 7.24–7.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 145.8, 136.1, 135.6, 135.1, 131.6 (overlapped), 130.5, 130.2 (overlapped), 130.0, 129.0, 127.2, 125.9, 124.0; FT-IR (KBr) 1683 (C=O) cm^{-1}; Ms *m/z* (%) 274 (M^++2, 27), 273 (47), 272 (M^+, 73), 271 (100), 237 (93), 208 (14).

(*Z*)-4'-Bromothioaurone (4d): mp 168–169 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.7 Hz, 1H), 7.86 (s, 1H), 7.55–7.63 (m, 5H), 7.48–7.54 (m, 1H), 7.28–7.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.5, 145.7, 135.5, 133.2, 132.3, 132.2, 132.0, 130.9, 130.3, 127.2, 125.8, 124.6, 124.0; FT-IR (KBr) 1681 (C=O) cm^{-1}; Ms *m/z* (%) 318 (M^++2, 63), 316 (M^+, 62), 237 (100), 208 (20).

(*Z*)-4'-Methylthioaurone (4e): mp 138–139 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.89–7.93 (m, 1H), 7.51–7.62 (m, 3H), 7.45–7.51 (m, 1H), 7.23–7.31 (m, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 146.1, 140.9, 135.2, 133.8, 131.5, 131.1, 130.6, 129.9, 129.2, 127.0, 125.5, 123.9, 21.6; FT-IR (KBr) 1671 (C=O) cm^{-1}; Ms *m/z* (%) 252 (M^+, 60), 251 (69), 237 (100).

(*Z*)-2-(3-Thienylmethylene)benzo[*b*]thiophen-3(2*H*)-one (4g): mp 169–170 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.73–7.78 (m, 1H), 7.53–7.60 (m, 1H), 7.40–7.51 (m, 3H), 7.24–7.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 145.6, 136.7, 135.2, 130.9, 130.4, 129.6, 128.7, 127.0, 126.9, 126.8, 125.6, 124.0; FT-IR (KBr) 1673 (C=O) cm^{-1}; Ms *m/z* (%) 244 (M^+, 92), 243 (100), 171 (13).

(*Z*)-2-(2-Pyridylmethylene)benzo[*b*]thiophen-3(2*H*)-one (4h): mp 154–155 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, J = 4.7 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.87 (s, 1H), 7.72–7.79 (m, 1H), 7.53–7.60 (m, 2H), 7.49 (d, J = 7.9 Hz, 1H), 7.23–7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 152.9, 149.7, 149.5, 136.7, 135.5, 134.8, 130.3, 129.3, 127.6, 126.8, 125.4, 124.1, 123.2; FT-IR (KBr) 1679 (C=O) cm^{-1}; Ms *m/z* (%) 239 (M^+, 100), 238 (68), 210 (57).

(*Z*)-4'-Methoxy-2'-methylthioaurone (4i): mp 139–141 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.94 (d, J = 7.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.45–7.59 (m, 2H), 7.24–7.32 (m, 1H), 6.86 (d, J = 6.7 Hz, 1H), 6.81 (s, 1H), 3.85 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 161.0, 146.3, 142.3, 134.9, 131.1, 131.0, 130.8, 128.8, 127.0, 125.9, 125.4, 123.9, 116.6, 111.8, 55.4, 20.5; FT-IR (KBr) 1671 (C=O) cm^{-1}; Ms *m/z* (%) 282 (M^+, 75), 267 (100), 265 (73), 250 (27).

(*Z*)-3',5'-Dimethoxythioaurone (4j): mp 167–168 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 1H), 7.86 (s, 1H), 7.54–7.61 (m, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.26–7.33 (m, 1H), 6.85 (d, J = 2.2 Hz, 2H), 6.52 (t, J = 2.2 Hz, 1H), 3.85 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 161.0, 146.1, 136.0, 135.4, 133.7, 130.8, 130.4, 127.1, 125.7, 123.9, 108.7, 102.8, 55.5; FT-IR (KBr) 1674 (C=O) cm^{-1}; Ms *m/z* (%) 298 (M^+, 56), 297 (28), 267 (100), 224 (13).

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