Indian Journal of Chemistry
Vol. 58B, September 2019, pp. 1037-1041

Synthesis of dihydro-1,4-thiazine from α-keto spiro-thiazolidine

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Received 28 March 2018; accepted (revised) 5 March 2019

The reaction of α-bromocycloalkanone with 2-aminoethanthiol leads to the regioselective formation of spirothiazolidin-2-one with the oxo-group migrating to the original position occupied by the halogen atom. The reaction of 1-thia-4-azaspiro[4.5]alkan-6-one with bromine, iodine, copper (II) salts, acid or base gives dihydro-1,4-thiazine derivatives in moderate yields. Moreover, the treatment of the spiro-thiazolidine derivatives on silica gel under microwave gives the 1,4-thiazine compound.

Keywords: 1,4-Thiazine compounds, spiro-thiazolidine derivatives, microwave irradiation, intramolecular reaction

Thiazine a N, S-heterocyclic compound having four carbon atoms and one nitrogen and sulfur atom at various positions in the six-member ring. 1,4-Thazine derivatives represent one of the most important classes of organic molecules[1]. 1,4-Thiazine ring is one of such heterocycles and is known to play an important role in pigments, dyestuffs, and biologically active substances. Among these, 1,4-thazine-3-carboxylic acid derivatives are antibacterial activity[2], 1,4-benzothazines are anticancer activities[3]. Mah and Lee reported that thermal and acid catalyzed rearrangements of 1,3-thiazolidine sulfoxides to dihydro-1,4-thiazines[4]. Lee *et al*. reported that 1,3-thazolidines were converted to dihydro-1, 4-thiazines by chlorinolysis through the unisolable chlorosulfonium salt and sulfenyl chloride[5]. However, these methods were low yields for cycloalkane derivatives. Parai *et al*. reported 3,4-dihydro-2*H*-benzo[*b*][1,4]thazine derivatives were synthesized *via* a copper catalyzed intermolecular *N*-aryl amination reaction on substituted 2-(2-bromophenylthio)-ethanamines[6]. Pratap *et al*. reported that one pot method has been developed for the synthesis of 1,4-benzothiazines by allowing the condensation of 2-aminobenzenethiols and 1,3-dicarbonyls using baker's yeast[7]. Baghernejad *et al*. reported that $KHSO_4$ efficiently catalyzes the condensation of α-aminophenols and 2-bromo-1-aryl-ethanols to yield 3-aryl-2*H*-benzo[1,4]thiazines in good yields[8]. Recently, Zhao *et al*. reported that an efficient one-pot tandem method for the synthesis of pyridazino[4,5-*b*][1,4]thiazine-diones *via* Smiles rearrangement was development[9]. More recently, Nagaraju *et al*. reported that synthesis of α-hydroxyimino-β-oxodithioesters were transformed to 1,4-thiazine-3-ones *via* cascade reaction[10]. In the previous paper, we reported that condensation of 2α-bromo-3-oxo steroids or α-bromocycloalkanone with 2-aminoethanethiol gives spiro[steroid-3,2'-thiazolidin]-2-ones or 1-thia-4-azaspiro[4.5]alkan-6-ones in good yield, respectively[11]. So, we tried to introduce the useful materials from these 1,4-thiazolidine derivatives. In this report, 1,4-thiazolidine derivatives were further transformed to 1,4-thazine derivatives *via* intramolecular reaction under mild reaction conditions.

Results and Discussion

In the previous paper, we reported that the reaction of α-halo cycloalkanones with 2-aminoethanthiol gives the corresponding spiro-thiazolidine derivatives. We explored reaction of spiro-thiazolidine derivatives (**1a**-**4a**) with bromine. Dichloromethane was used as solvent dissolving bromine or iodine. In the case of 1-thia-4-azaspiro[4,5]nonan-6-one (**1a**), 1-thia-4-azaspiro[4,5]decan-6-one (**2a**), 1-thia-4-aza-8-*tert*-butylspiro[4,5]decan-6-one (**2a'**), 1-thia-4-azaspiro [4,5]uncan-6-one (**3a**), 1-thia-4-azaspiro[4,5]dodecan-6-one (**4a**), or the product, 5-oxo-3,4,6,7-tetrahydrocyclopenta-1,4-thiazine (**1b**), 5-oxo-2,3,4, 6,7,8-hexahydrocyclohexa-1,4-thiazine (**2b**), 5-oxo-7-

t-butyl-2,3,4,6,7,8-hexahydrocyclohexa-1,4-thiazine (**2b'**), 5-oxo-2,3,4,6,7,8,9-hexahydrocyclohepta-1, 4-thiazine (**3b**) or 5-oxo-2,3,4,6,7,8,9-hexahydrocycloocta-1,4-thiazine (**4b**) was obtained, respectively. These results are shown in Table I (Scheme I). The reaction of **2a** with bromine proceeded at RT with in 6 h, giving **2b** in good yield (96%, Table I, Entry 3). On the other hand, use of **4a** gave low yield (9%) and long time (200 h) (Table I, entry 7). Cycloalkanone presumed to have greater strain such as 5-membred ring and 8-membredring took long reaction time.

Bromine is not easy for a material to handle. Therefore, we investigated reaction of spiro-thiazolidine **2a** using some reagents and solvents. These results are shown in Table II (Scheme II). From these results, it was found that the reaction of **2a** with copper (II) acetate in acetic acid for 6 h at RT gave **2b** in 74% yield (Table II, entry 3 and 4). In addition, the reaction of **2a** using copper (II) chloride in acetone or methanol afforded **2b** in 74% yield (Table II, entry 8 and 9). Moreover, it was found that **2a** using copper (II) chloride afforded **2b** in good yield. However, other reagents and solvents (Table II, entry 1, 6, 11, 12, 13, 14, 17, 19 and 20) were no reacted.

Table I — Reaction of α-keto spiro-thazolizine with halogen in CH_2Cl_2

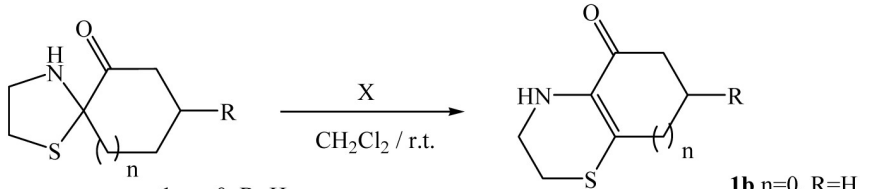
Entry	Compd	X	Equiv	Time (h)	Product	Yield (%)[a]
1	**1a**	Br_2	1.0	168	**1b**	89
2	**2a**	Br_2	0.5	7	**2b**	51
3	**2a**	Br_2	1.0	7	**2b**	96
4	**2a**	I_2	1.0	20	**2b**	66
5	**2a′**	Br_2	1.0	30	**2b′**	96
6	**3a**	Br_2	1.0	24	**3b**	92
7	**4a**	Br_2	1.0	200	**4b**	9

Reaction condition: substrate (0.5 mmol) and methylene chloride (10 mL) were employed.
[a]Yields were determined form the peark area of ^{1}H NMR.

Table II — Reaction of α-keto spiro-thazolizine (**2a**) with some reagents

Entry	Reagent (mol. equiv)	Solvent	Time (h)	Yield (%)[a]
1	$PdCl_2$ (1.0)	Acetone	22	-
2	Cu $(OCl_4)_2$ (1.0)	MeOH	22	42
3	Cu $(OAc)_2$ (0.5)	AcOH	6	74
4	Cu $(OAc)_2$ (1.0)	AcOH	6	74
5	Cu $(OAc)_2$ (1.0)	MeOH	6	12
6	Cu $(OAc)_2$ (1.0)	Acetone	6	-
7	$CuCl_2$ (0.5)	Acetone	6	16
8	$CuCl_2$ (1.0)	Acetone	6	74
9	$CuCl_2$ (1.0)	MeOH	6	74
10	$CuCl_2$ (1.0)	AcOH	6	74
11	CAN (III) (1.0)	MeOH	48	23
12	CAN (III) (1.0)	Acetone	48	-
13	Ce $(OTF)_4$ (1.0)	Acetone	19	-
14	Bf_3 (1.0)	Acetone	19	-
15	$PdCl_2$(1.0) *m*-CPBA (1.0)	CH_2Cl_2	20	13
16	*t*-BuOK (1.0) KO_2 (2.0)	Benzene	20	23
17	Et_3N (1.0) KO_2 (2.0)	Benzene	20	-
18	*t*-BuOK (1.0) hν	MeOH	20	11
19	Et_3N (1.0) hν	MeOH	20	-
20	CAN (IV) (1.0) hν	MeOH	20	-

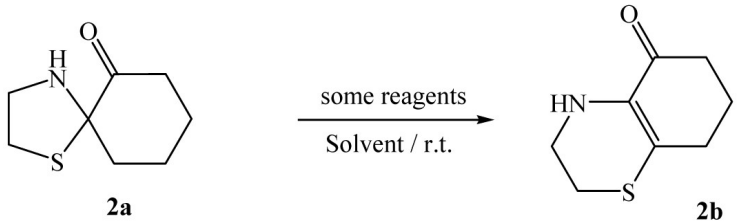
Reaction condition: Substrate (0.25 mmol), reagent (0.25-0.50 mmol) and solvent (5 mL) were employed. a) Determined by GLC analysis using *n*-dodecane as internal standard.



1a n=0, R=H
2a n=1, R=H
2a' n=1, R=*t*-Bu
3a n=2, R=H
4a n=3, R=H

1b n=0, R=H
2b n=1, R=H
2b' n=1, R=*t*-Bu
3b n=2, R=H
4b n=3, R=H

Scheme I — Reaction of α-keto spiro-thiazolidine with halogen in CH_2Cl_2



2a **2b**

Scheme II — Reaction of α-keto spiro-thiazolidine (**2a**) with some reagents

We then extended this reaction to other spiro-thiazolidine derivatives **1a, 2a and 2a'**. These results are shown in Table III (Scheme III). The reaction of spiro-thiazolidine derivatives (**1a**-**2a'**) using copper (II) salts in all the case the corresponding 1,4-thiazine derivatives (**1b**-**2b'**) were obtained. Treatment of **2a** with copper (II) acetate in acetic acid or copper (II) chloride in acetone gave the corresponding **2b** in 74% yield (Table III, entry 3 and 4). However, treatment of spiro-thiazolidine derivatives **1a** and **2a'** with copper (II) acetate in acetic acid or copper (II) chloride in acetone afforded 1,4-thiazine derivatives **1b** and **2b'** in low yields (10-52%, Table III, entry 1, 2, 5, 6).

The reaction of spiro-thiazolidine **2a** with acid or base was investigated. These results are shown in Table IV (Scheme IV). In the case of 2 mol. eq NaOH in MeOH-H_2O (9:1), **2b** was obtained in 74% yield (Table IV, entry 2). Reaction of compound **2a** with triethylamine in methanol, HCl in methanol-H_2O (9:1), at reflux temperatute did not proceed (Table IV, entry 7, 8, 9, 10 and 11).

Spiro-thiazolidine derivatives **1a, 2a and 2a'** proceeding in the presence of NaOH in methanol-H_2O (9:1) yielded the 1,4-thiazine derivatives **1b**, **2b** and **2b'** in 40-74% yields. These results are shown in Table V (Scheme V).

The microwave irradiation method is known as powerful tool for preparation of various organic compounds. In the previous paper, we reported that reaction of α-bromo ketone under microwave irradiation gives the pyrazine and quinoxaline derivatives in good yields[12]. The reaction affords a clean and convenient synthetic method for pyrazine and quinoxaline derivatives. The treatment of the spiro-thiazolidine derivatives **2a** and **2a'** on silica gel under microwave gave the 1,4-thiazine compound **2b** and **2b'**. These results are shown in Table VI

Table III — Reaction of α-keto spiro-thazolizine with copper salts

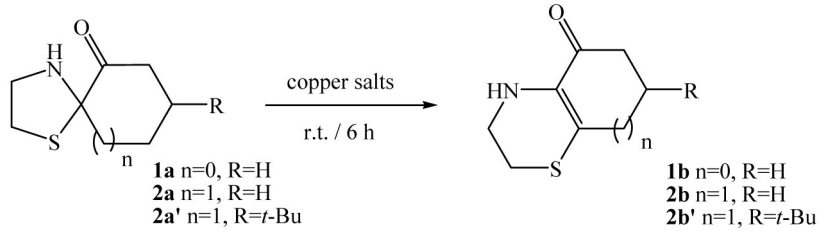
Entry	Compd	Solvent	Temp (°C)	Time	Yield (%)[a]
1	**1a**	Cu $(OAc)_2$ (1.0)	AcOH	**1b**	10
2	**1a**	$CuCl_2$ (1.0)	Acetone	**1b**	22
3	**2a**	Cu $(OAc)_2$ (1.0)	AcOH	**2b**	74
4	**2a**	$CuCl_2$ (1.0)	Acetone	**2b**	74
5	**2a′**	Cu $(OAc)_2$ (1.0)	AcOH	**2b′**	52
6	**2a′**	$CuCl_2$ (1.0)	Acetone	**2b′**	36

Reaction condition: Substrate (0.25 mmol) copper salt (0.125-0.25 mmol) and solvent (5 mL) were employed for 6h. (a) Determined by GLC analysis using *n*-dodecane as internal standard.

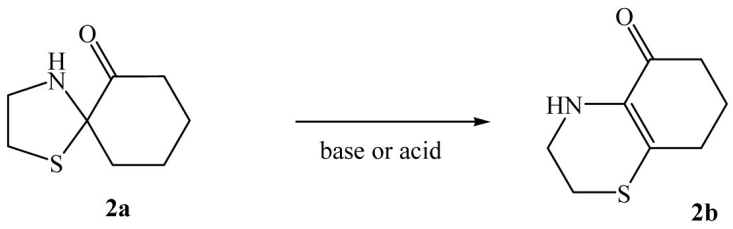
Table IV — Reaction of α-keto spiro-thazolizine (2a) with some base or acid

Entry	Reagent (mol. equiv)	Solvent	Temp (°C)	Time	Yield (%)[a]
1	NaOH (1.0)	MeOH-H_2O (9:1)	reflux	7 days	42
2	NaOH (2.0)	MeOH-H_2O (9:1)	reflux	6 h	74
3	*t*-BuOK (1.0)	MeOH	reflux	6 h	64
4	*t*-BuOK (2.0)	MeOH	reflux	6 h	67
5	KOH (1.0)	MeOH-H_2O (9:1)	reflux	6 h	24
6	KOH (2.0)	MeOH-H_2O (9:1)	reflux	6 h	54
7	Et_3N (1.0)	MeOH	reflux	6 h	−
8	Et_3N (2.0)	MeOH	reflux	6 h	−
9	HCl (0.5)	MeOH-H_2O (9:1)	reflux	6 h	−
10	HCl (1.0)	MeOH-H_2O (9:1)	reflux	6 h	−
11	HCl (2.0)	MeOH-H_2O (9:1)	reflux	6 h	−

Reaction condition: Substrate (0.25 mmol), reagent (0.125-0.50 mmol) and solvent (5 mL) were employed. a) Determined by GLC analysis using *n*-dodecane as internal standard



Scheme III — Reaction of α-keto spiro-thiazolidine with copper salts



Scheme IV — Reaction of α-keto spiro-thiazolidine (**2a**) with some base or acid

(Scheme VI). However, reaction of compound **1a** and **3a** did not proceed (Table VI, entry 1 and 8). It was found that the use of microwave affords shortening the reaction time in comparison with usual conditions.

In conclusion, it was found that 1,4-thiazine derivatives could be synthesized directly from the corresponding spiro-thiazolidine derivatives in moderate to good yields.

Table V — Reaction of α-keto spiro-thazolizine (**2a**) with NaOH

Entry	Compd	Reagent (mol. equiv)	Solvent	Product	Yield (%)[a]
1	**1a**	NaOH (2.0)	MeOH-H_2O (9:1)	**1b**	40
2	**2a**	NaOH (2.0)	MeOH-H_2O (9:1)	**2b**	74
3	**2a′**	NaOH (2.0)	MeOH-H_2O (9:1)	**2b′**	40

Reaction condition: Substrate (0.25 mmol), reagent (0.50 mmol) and solvent (5 mL) were employed for 6 h under reflux. (a) Determined by GLC analysis using n-dodecane as internal standard.

Table VI — Reaction of α-keto spiro-thazolizine using microwave

Entry	Compd	Temp (°C)	Time (min)	Product	Yield (%)[a]
1	**1a**	70	10	**1b**	-
2	**2a**	60	10	**2b**	46
3	**2a**	70	5	**2b**	40
4	**2a**	70	10	**2b**	73
5	**2a**	70	20	**2b**	70
6	**2a**	80	10	**2b**	60
7	**2a′**	70	10	**2b′**	53
8	**3a**	70	10	**3b**	-

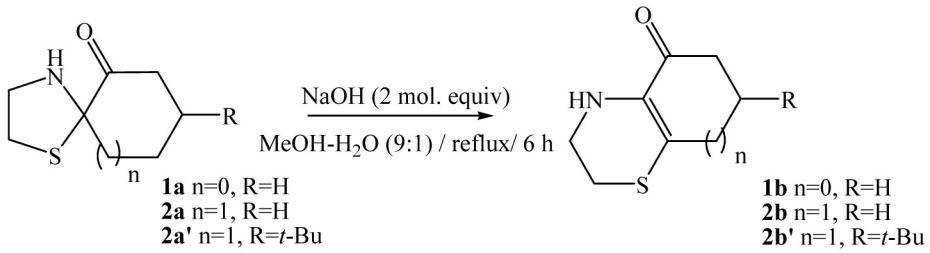
Reaction condition: Substrate (0.25 mmol) copper salt (0.125-0.25 mmol) and solvent (5 mL) were employed for 6h. (a) Determined by GLC analysis using *n*-dodecane as internal standard.

Experimental Section

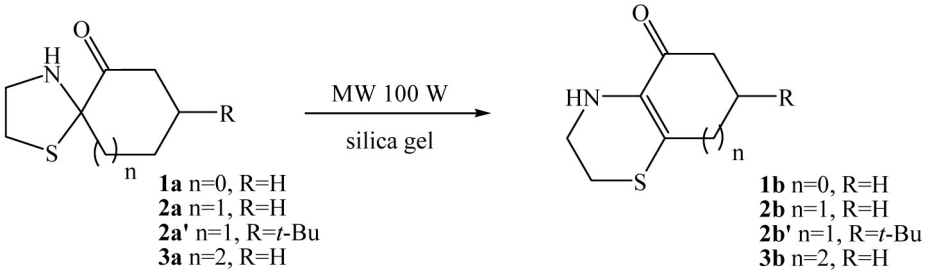
Melting points were determined with Yanagimoto apparatus, and are uncorrected. IR spectra were recorded in NaCl on a Hitachi Model 270-30 grating infrared spectrometer. GC-analysis was performed using a Shimazu GC-17A instrument with a FID detector equipped with DB1 (0.25 mm × 30m, 0.25μm) capillary column. Yields were determined by GC and used *n*-decane an internal standard. Gas chromatography/mass spectrometry analysis was Shimadzu GCMS-QP5050 (EI-MS 70 eV) using DB1 (0.25 mm × 30 m × 0.25 μm) capillary column GC; GC: GC-17A. The NMR spectral data were measured on a JEOL GSX 400 spectrometer in $CDCl_3$ with TMS as internal standard. Thin-layer chromatography (TLC) was performed on silica gel 60 F 254 (Merck). Column chromatography was performed with silica gel (230-400 mesh).

Synthesis of 1-thia-4-azaspiro[4.5]decan-6-one, 2a

Mixture of 2-bromocyclohexanone (**2**) (1 mmol) and 2-aminoethanethiol (6 mmol) in benzene (10 mL) was stirred at RT for 1 h. The solvent was removed under reduced pressure. Water was added to the residue, which was extracted with diethylether (2 × 25 mL). The ethereal solution was washed successively with saturated aq NaCl (10 mL), aq $NaHCO_3$ (10 mL), and water (10 mL), dried over Na_2SO_4, and concentrated under vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane-ether (2:1) gave 1-thia-4-azaspiro[4.5]decan-6-one (**2a**) as needles.



Scheme V — Reaction of α-keto spiro-thiazolidine with NaOH



Scheme VI — Reaction of α-keto spiro-thiazolidine using microwave

Synthesis of 1,4-thiazine derivatives by halogen atom

Bromine (0.25 mmol) and thiazolidines (0.25 mmol) in dichloromethane (5 mL) was stirred at RT under closed system. The reaction mixture was extracted with ether, washed with saturated NaCl then water and concentrated under vacuum. Colum chromatography (*n*-hexane-ether 1:1) over silica gel gave the 1,4-thiazine derivatives.

Synthesis of 1,4-thiazine derivatives by copper salts

Copper salts (0.125-0.250 mmol) and thiazolidines (0.25 mmol) in acetic acid (5 mL) was stirred at RT under closed system. Neutralized (sat. $NaHCO_3$) of reaction mixture was extracted with ether, washed with saturated NaCl then water and concentrated under vacuum. Colum chromatography (*n*-hexane-ether 1:1) over silica gel gave the 1,4-thiazine derivatives.

Synthesis of 1,4-thiazine derivatives by some base or acid

Base or acid (0.125-0.500 mmol) and Thiazolidines (0.25 mmol) in MeOH (4.5 mL) or MeOH-H_2O (4.5 mL-0.5 mL) was stirred reflux under closed system. The reaction mixture was extracted with ether, washed with saturated NaCl then water and concentrated under vacuum. Column chromatography (*n*-hexane-ether 1:1) over silica gel gave the 1,4-thiazine derivatives.

Synthesis of 1,4-thiazine derivatives using microwave

α-Keto spiro-thiazolidine (0.l mmol) and silica gel (0.45 g) was irradiated using a microwave generating equipment Model (DISCOVER Lab Mate, CEM Corporation). After the irradiation was completed, the reaction mixture was extracted with diethylether and washed with saturated NaCl solution. The ethereal solution was dried over Na_2SO_4 and concentrated in vacuum.

5-Oxo-2,3,4,6,7,8-hexahydrocyclohexa-1,4-thiazine, **2b**: Pale yellow oil. IR (NaCl): 3377, 1647, 1601 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.98 (q, 2H), 2.40 (t, 2H), 2.46 (t, 2H), 3.05 (m, 2H) and 3.45 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 22.6, 28.5, 29.8, 36.9, 40.6, 126.4, 133.2 and 189.6; EI-MS (EI) *m*/*z* 169 (M^+).

5-Oxo-7-*t*-butyl-2,3,4,6,7,8-hexahydrocyclohexa-1,4-thiazine, **2b'**: Pale yellow oil. IR (NaCl): 3406, 1646, 1597 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (s, 9H), 1.87 (m, 1H), 2.20 (dd, 1H), 2.31 (d, 2H) 2.57 (dd, 1H) 3.06 (m, 2H), 3.35 (n, 1H), 3.54 (m, 1H) and 4.38 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 27.1, 28.6, 31.4, 32.2, 38.7, 40.5, 44.9, 126.3, 132.7 and 190.5; EI-MS (EI) *m*/*z* 225 (M^+).

5-Oxo-2,3,4,6,7,8,9-hexahydrocyclohepta-1,4-thiazine, **3b**: Pale yellow oil. IR (NaCl): 3374, 1637, 1586 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.77 (m, 2H), 2.48 (m, 2H), 2.62 (m, 2H), 3.06 (m, 2H) 3.39 (m, 2H) and 5.05 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 20.4, 24.5, 29.9, 32.4, 39.9, 40.2, 126.5, 135.9 and 194.3; EI-MS (EI) *m*/*z* 183 (M^+).

5-Oxo-2,3,4,6,7,8,9-hexahydrocycloocta-1,4-thiazine, **4b**: Pale yellow oil. IR (NaCl): 3406, 1646, 1597 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (s, 9H), 1.87 (m, 1H), 2.20 (dd, 1H), 2.31 (d,2H), 2.57 (dd, 1H), 3.06 (m, 2H), 3.35 (m, 1H), 3.54 (m, 1H), 4.38 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 27.1, 28.6, 31.4, 32.2, 38.7, 40.6, 45.0, 126.3, 132.7, 190.6; EI-MS (EI) *m*/*z* 225 (M^+).

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