

SUPPORTING INFORMATION

for

“Synthesis of Aryl and Heteroaryl Substituted 3-Benzylxy-isothiazoles via Suzuki and Negishi Cross-Coupling Reactions”

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General experimental section

Et_2O was distilled and stored over Na , THF was distilled from $\text{Na}/\text{benzophenone}$ under N_2 , EtOH was dried and distilled, ZnX_2 was flame-dried in vacuo , and $\text{Pd}(\text{PPh}_3)_4$ was freshly prepared,¹ whereas $n\text{-BuLi}$ ² and PhMgCl ³ were titrated prior to use. All solvents used in water sensitive reactions were stored over 3\AA or 4\AA molecular sieves. Air and water sensitive reactions were performed under N_2 using syringe-septum technique. Column chromatography (CC) was performed using silica gel (0,063–0,200mm), whereas silica gel (0,035–0,070mm) was used for flash chromatography (FC). Melting points were determined in open capillaries and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using CDCl_3 as solvent and TMS or CDCl_3 as internal standards. GCMS analyses were performed using electron ionization.

Attempted Negishi cross-coupling reactions using **1** to generate the nucleophile

Generation of the nucleophile: $n\text{-BuLi}$ (0.42 mL, 1.44 M, 0.60 mmol) in hexane was added to a solution of diisopropylamine (85 μL , 0.60 mmol) in Et_2O (2.5 mL) at $-78\text{ }^\circ\text{C}$ while stirring. After 20 min a solution of **1** (103 mg, 0.54 mmol) in Et_2O (2.0 mL) was slowly added drop-wise and the reaction was allowed to stir at $-78\text{ }^\circ\text{C}$ for 15 min before carefully dried ZnX_2 (5.43 mmol) was added. Stirring was continued at $-78\text{ }^\circ\text{C}$ for 15 min, and the reaction was allowed to warm to rt over 2 h.

In order to investigate the Negishi cross-coupling reaction in other solvents the exchange of solvents was made after the attempted transmetalation. While using THF or $\text{THF}/\text{Et}_2\text{O}$ as solvent the appropriate amount of THF was added, and the mixture evaporated until 2.5 mL of solvent was left. This was repeated until the desired mixture was obtained.

Negishi cross-coupling reaction: the appropriate electrophile (0.60 mmol) in THF (0.1 mL), palladium catalyst (0.03 mmol), phosphine ligand (0.09 mmol), and cosolvent (1.4 mL) were added and the reaction was stirred at the reaction temperature for 15 h.

Table 1. Reagents and conditions used in various combinations in Negishi cross-coupling reactions using **1** to generate the nucleophile.

ZnX_2	Electrophile	Solvent	Co-solvent	Palladium catalyst	Phosphine ligand	Reaction temperature
ZnCl_2	Iodobenzene	Et_2O	None	$\text{Pd}(\text{PPh}_3)_4$	None	rt
ZnBr_2	2-Bromopyridine	THF	DMF	$\text{Pd}_2(\text{dba})_3$	PPh_3	$35\text{ }^\circ\text{C}$
		$\text{Et}_2\text{O}/\text{THF}$		$\text{PdCl}_2(\text{PPh}_3)_2$	$\text{P}(\text{o-tolyl})_3$	$50\text{ }^\circ\text{C}$
				$\text{Pd}(\text{OAc})_2$	$\text{P}(2\text{-furyl})_3$	
					$\text{P}(\text{cy})_2\text{bp}$	

dba: dibenzylidene acetone, cy: cyclohexyl, bp: *m*-biphenyl

Attempted Negishi cross-coupling reactions using **2** to generate the nucleophile

Generation of the nucleophile by direct insertion of zinc: 1,2-dibromoethane (2 drops) was added to a suspension of Zn dust (145 mg, 2.22 mmol) in solvent 1 (0.5 mL). The resulting mixture was heated until evolution of ethylene gas, and the reaction was allowed to reach rt. This was repeated twice. TMSCl was added and the reaction was stirred for 30 min at rt. **2** (102 mg, 0.32 mmol) in solvent 1 (0.1 mL) was added drop-wise and the reaction was stirred for 2 h at rt.

Negishi cross-coupling reaction: the appropriate electrophile (0.35 mmol) in solvent 2 (0.1 mL), palladium catalyst (0.018 mmol), and phosphine ligand (0.053 mmol) were added, and the reaction heated to the desired reaction temperature for 15 h.

Generation of the nucleophile by transmetalation from the corresponding Grignard reagent: Mg (16 mg, 0.65 mmol) was added to a solution of **2** (190 mg, 0.60 mmol) in THF (0.25 mL). Upon initiation of the reaction, the mixture was stirred at 40 °C for 1 h and a suspension of dried ZnCl₂ (89 mg, 0.65 mmol) in THF (2 mL) was added and the reaction was stirred for 1.5 h at rt.

Negishi cross-coupling reaction: the appropriate electrophile (0.66 mmol) in solvent THF (1 mL), palladium catalyst (0.030 mmol), and phosphine ligand (0.090 mmol) were added, and the reaction heated to the desired reaction temperature for 15 h.

Table 2. Reagents and conditions used in various combinations in Negishi cross-coupling reactions using **2** to generate the nucleophile.

Electrophile	Solvent 1	Solvent 2	Palladium catalyst	Phosphine ligand	Reaction temperature
Iodobenzene	THF	None	Pd(PPh ₃) ₄	None	rt
2-Bromopyridine	DMF	THF	Pd ₂ (dba) ₃	PPh ₃	35 °C
2-Bromothiophene	DMA	DMF	PdCl ₂ (PPh ₃) ₂	P(o-tolyl) ₃	50 °C
		DMA	Pd(OAc) ₂	P(2-furyl) ₃	80°C
				P(cy) ₂ bp	

DMA: *N,N*-dimethylacetamide, dba: dibenzylidene acetone, cy: cyclohexyl, bp: *m*-biphenyl

Attempted Suzuki cross-coupling reactions using **3** as nucleophile

The palladium catalyst (0.01 mmol) was added to a solution of the appropriate electrophile (0.19 mmol) in solvent 1 (6 mL) and the suspension was stirred at rt for 15 min. The appropriate base, (1.9 mmol), **3** (0.25 mmol), and H₂O (6 mL) were added, and the reaction was stirred at the appropriate reaction temperature for 48 h.

Degassing the solvents with helium prior to reaction had no influence on the results.

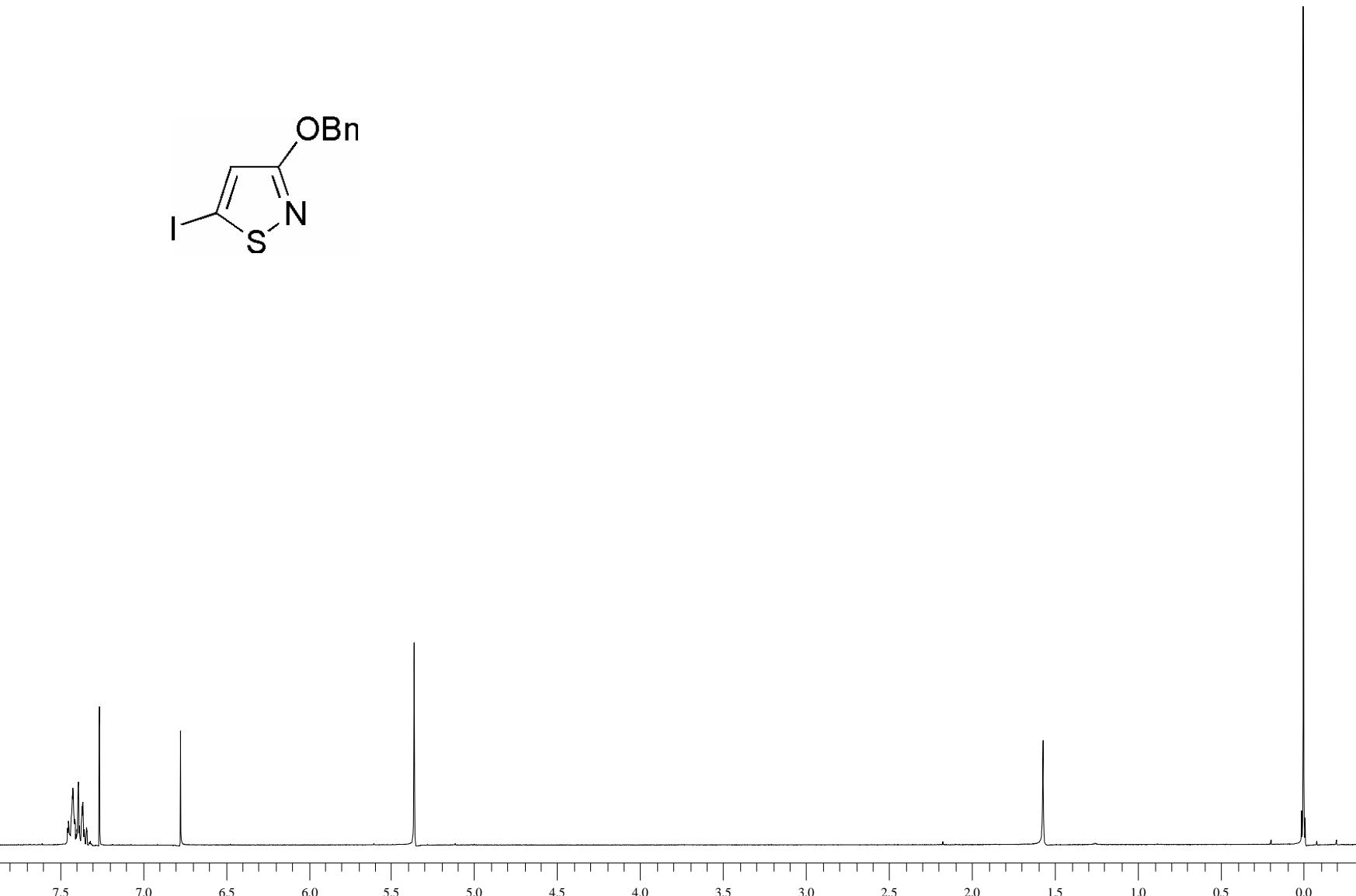
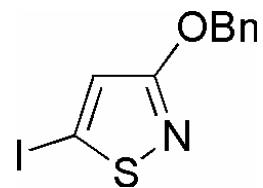
Table 3. Reagents and conditions used in various combinations in Suzuki cross-coupling reactions using **3** as nucleophile.

Electrophile	Solvent 1	Solvent 2	Palladium catalyst	Base	Phosphine ligand	Reaction temperature
Iodobenzene	H ₂ O	None	Pd(PPh ₃) ₄	NEt ₃	None	rt
2-Bromopyridine	DME	H ₂ O	Pd ₂ (dba) ₃	K ₃ PO ₄	PPh ₃	35 °C
2-Bromothiophene	DMF	DME	PdCl ₂ (PPh ₃) ₂	K ₂ CO ₃	P(o-tolyl) ₃	50 °C
3-Bromothiophene	THF	DMF	Pd(OAc) ₂	KF	P(2-furyl) ₃	80°C
	Toluene	THF		NaHCO ₃	P(cy) ₂ bp	
	EtOH	Toluene		Na ₂ CO ₃		
		EtOH				

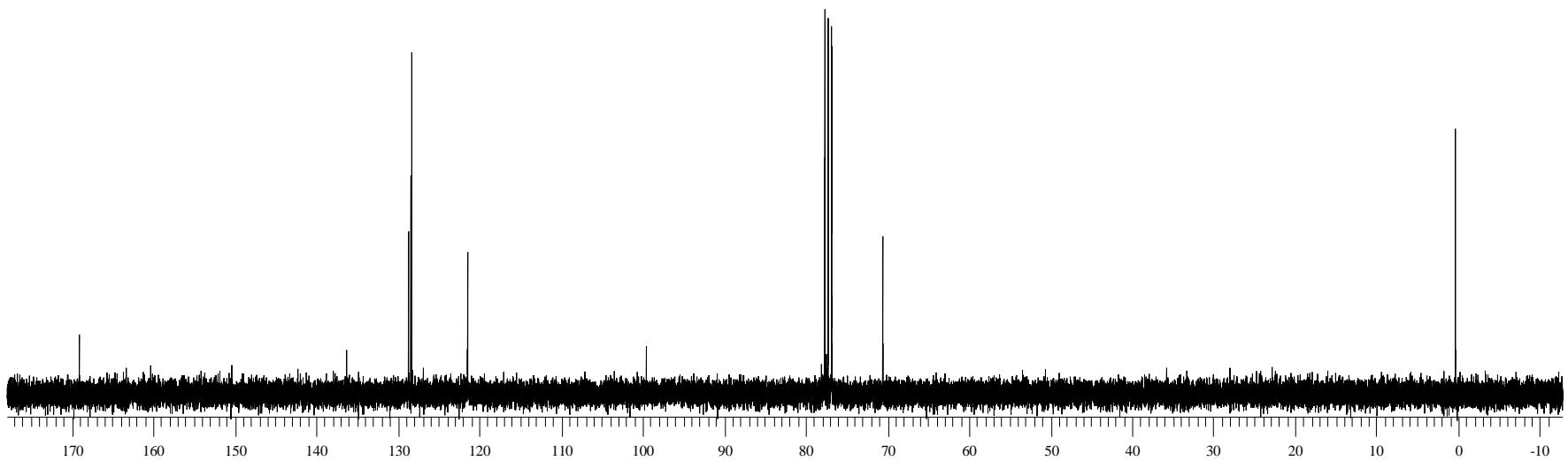
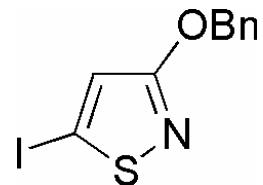
DMA: *N,N*-dimethylacetamide, dba: dibenzylidene acetone, cy: cyclohexyl, bp: *m*-biphenyl

- (1) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
- (2) Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755-3756.
- (3) Lin, H.-S.; Paquette, L. A. *Synth. Comm.* **1994**, *24*, 2503-2506.

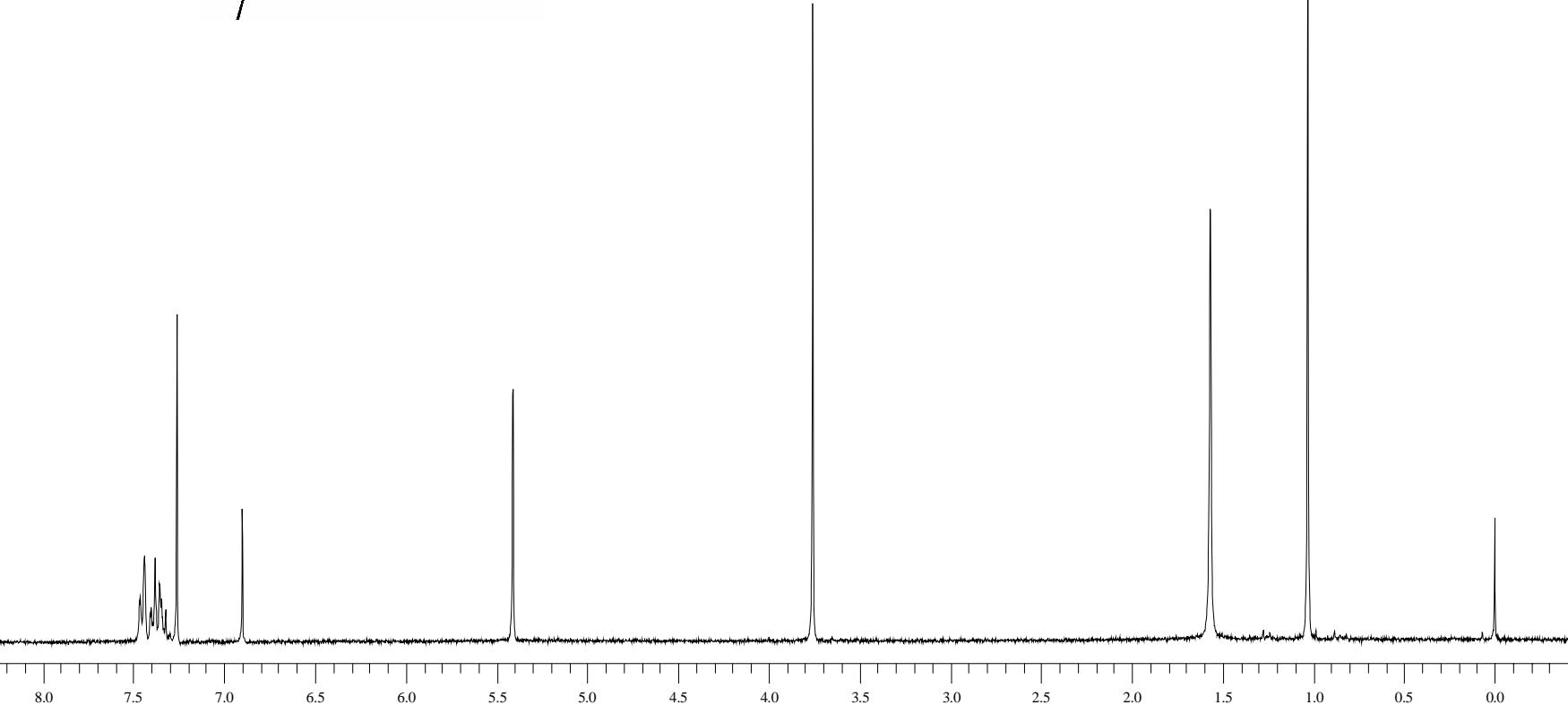
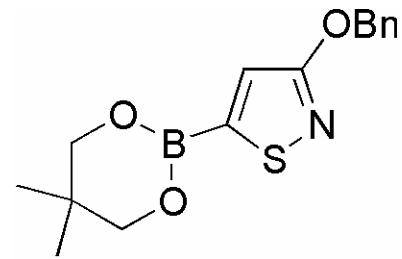
3-Benzylxy-5-iodoisothiazole, **2**



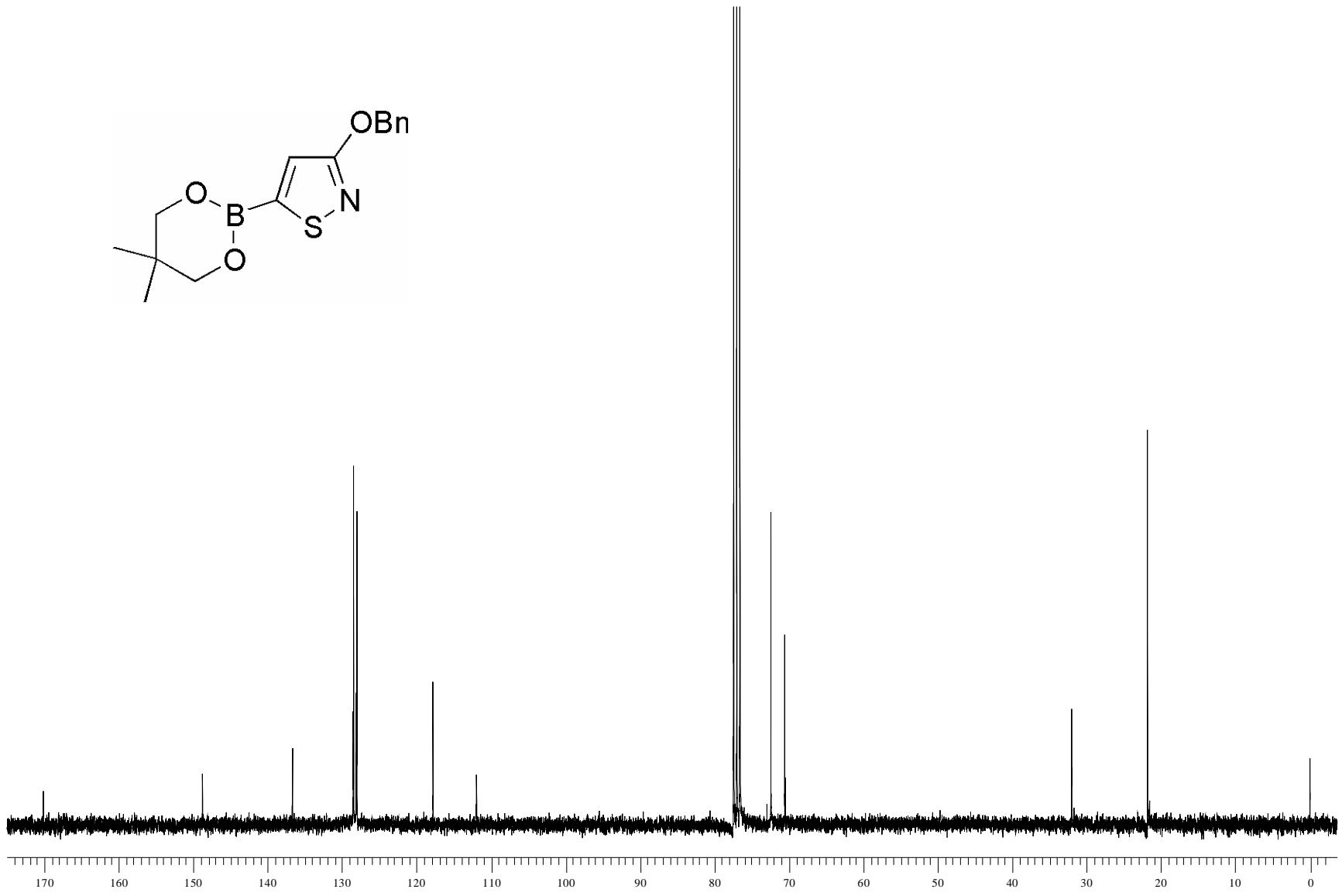
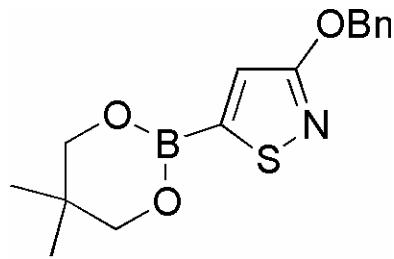
3-Benzylxy-5-iodoisothiazole, **2**



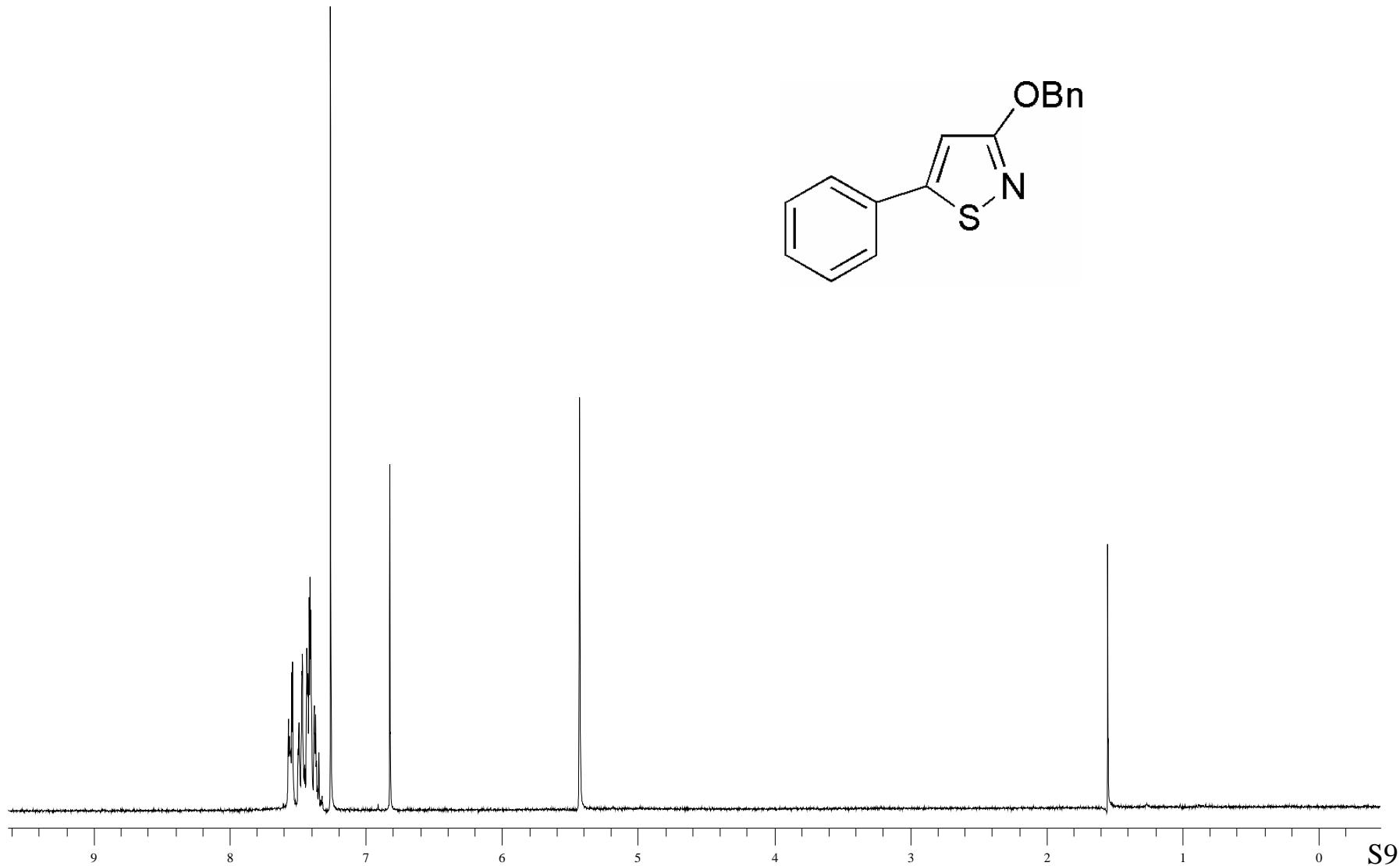
5-(5,5-Dimethyl-[1,3,2]-2-dioxaborianyl)-3-benzyloxyisothiazole **3**



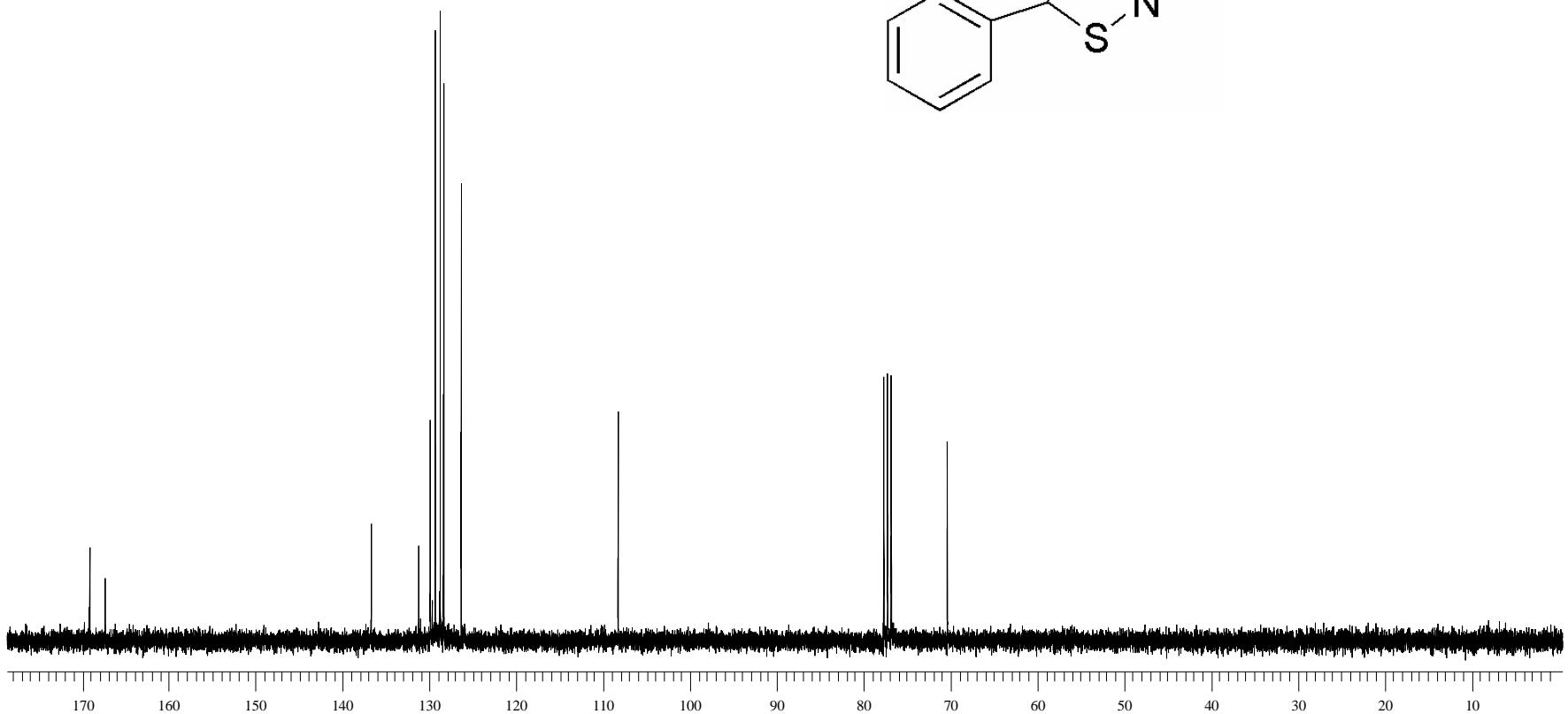
5-(5,5-Dimethyl-[1,3,2]-2-dioxaborianyl)-3-benzyloxyisothiazole **3**



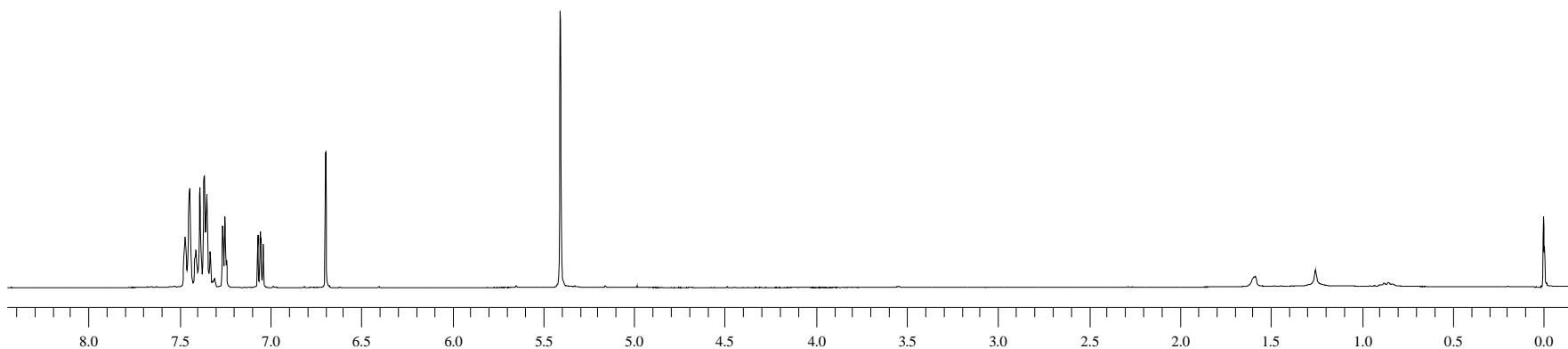
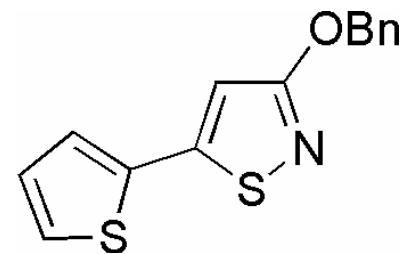
3-Benzylxy-5-phenylisothiazole **4a**



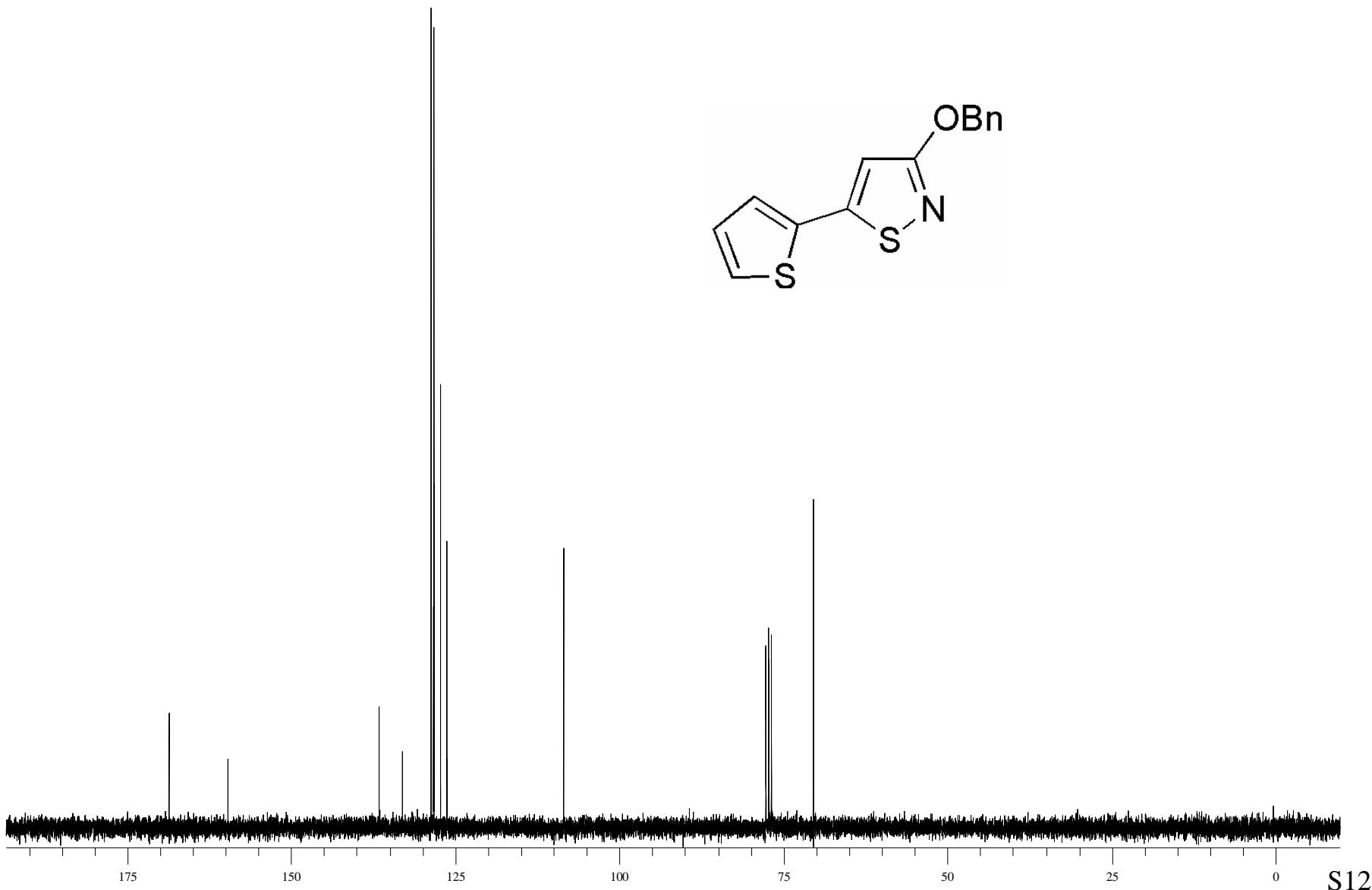
3-Benzyl-5-phenylisothiazole **4a**



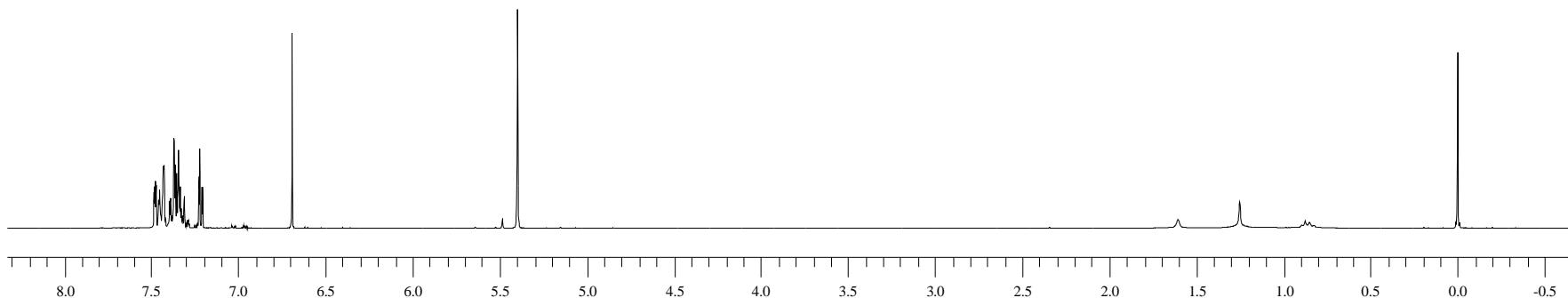
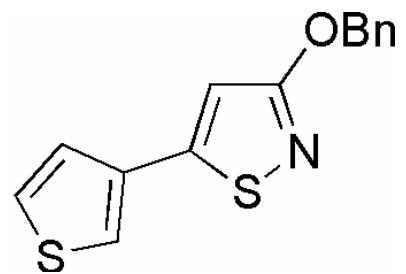
3-Benzyl-5-(2-thienyl)isothiazole **4b**



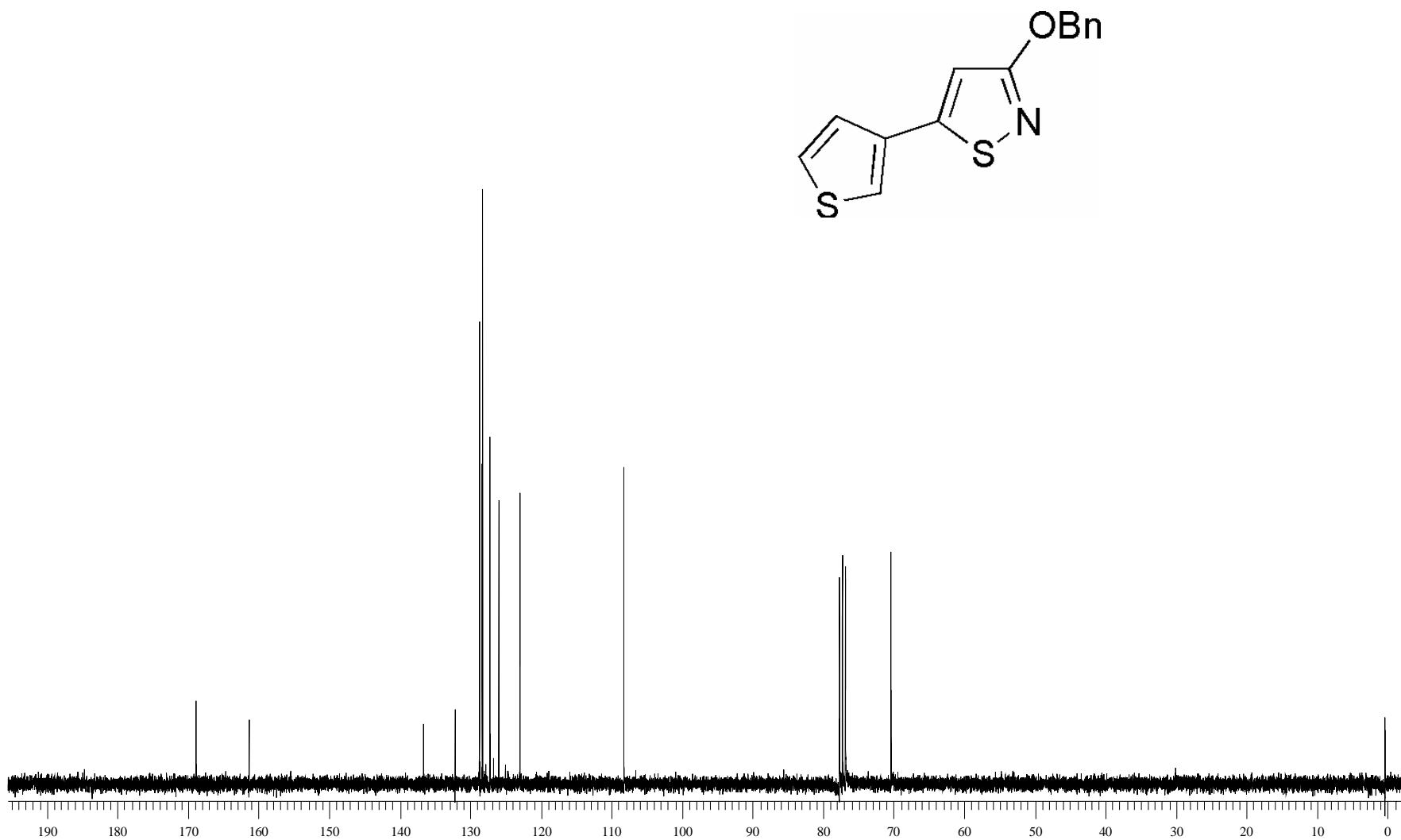
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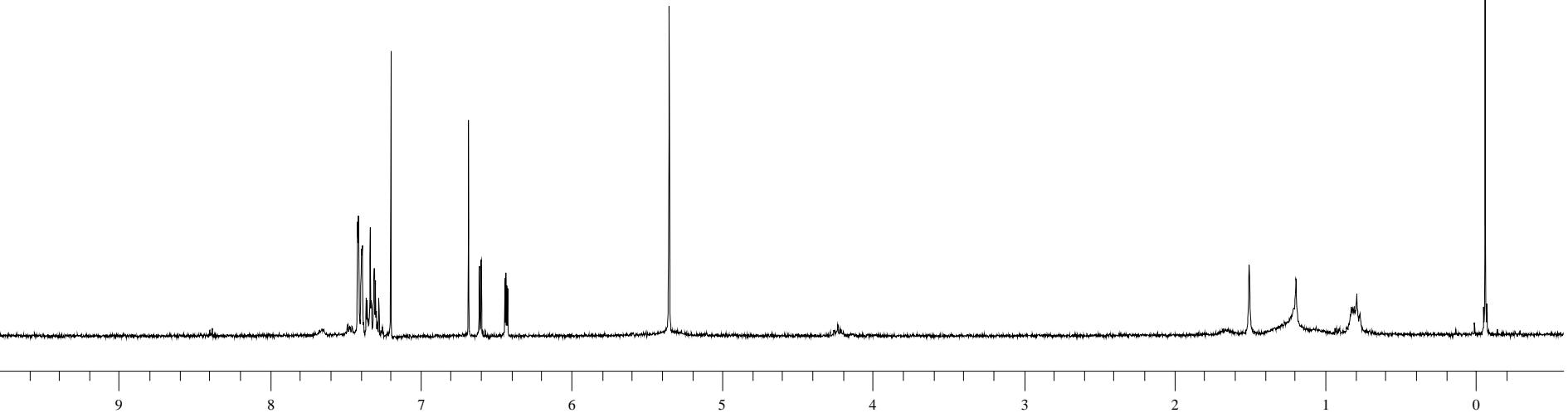
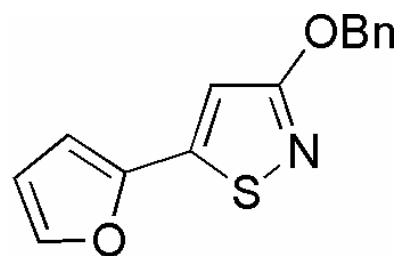
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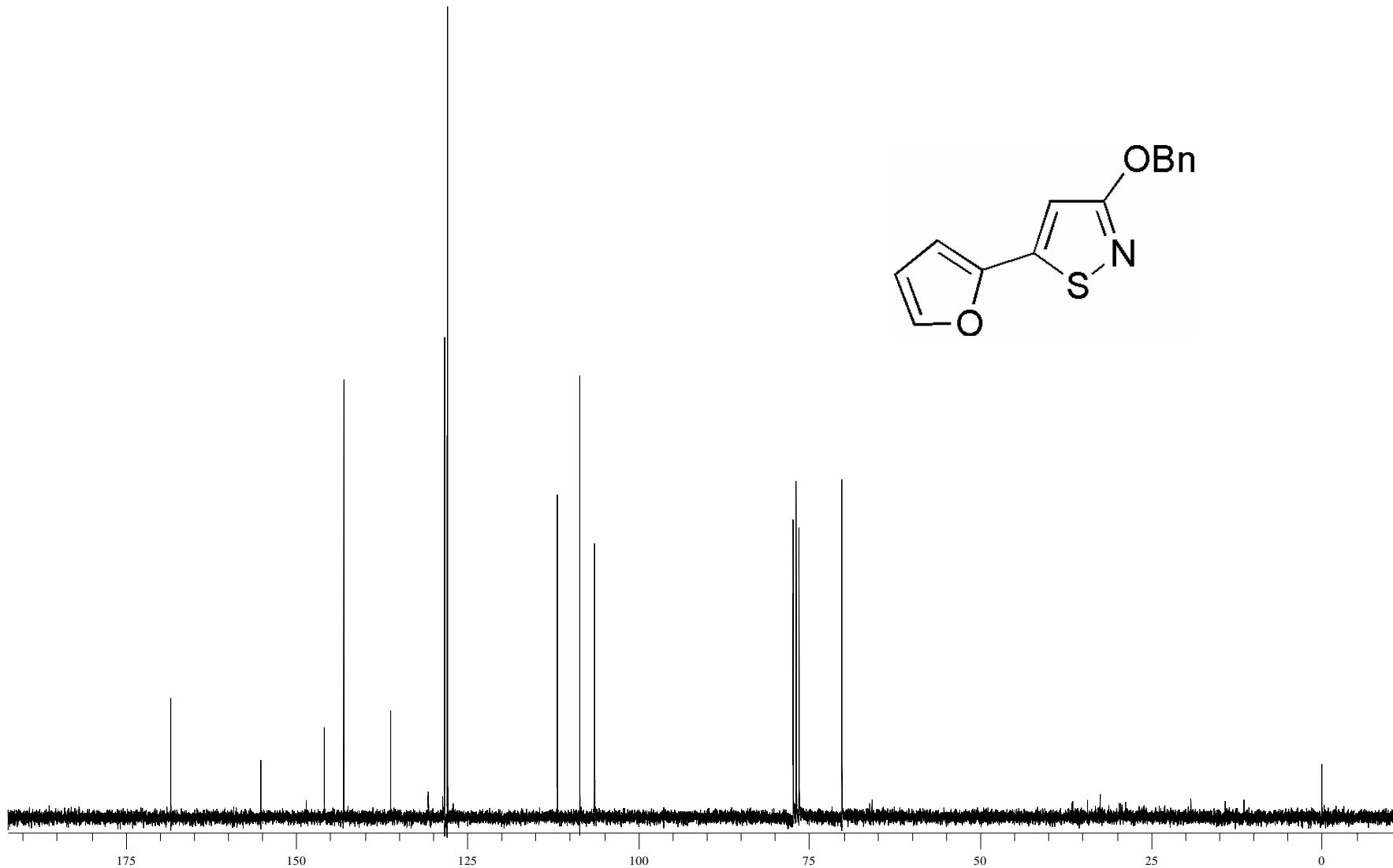
3-Benzylxy-5-(3-thienyl)isothiazole **4c**



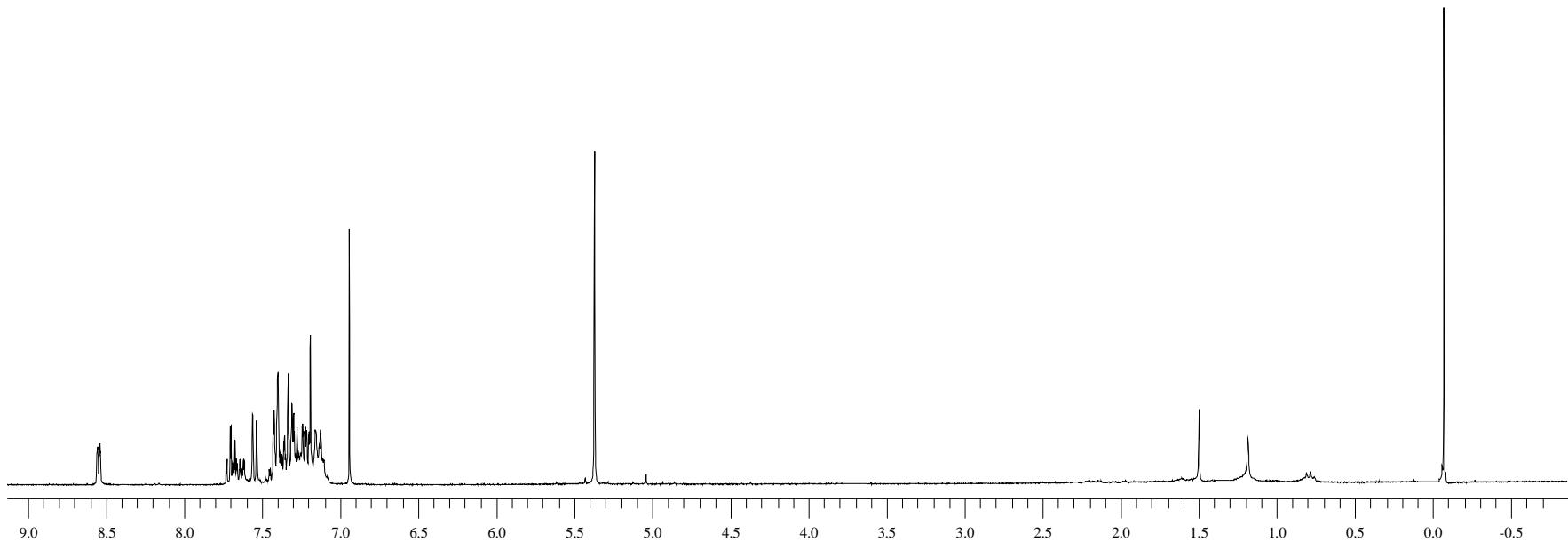
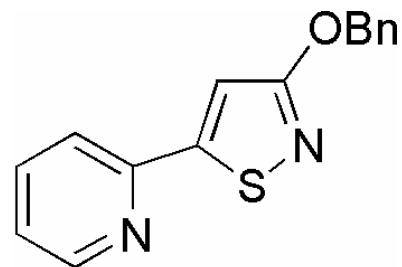
3-Benzylxy-5-(2-furyl)isothiazole **4d**



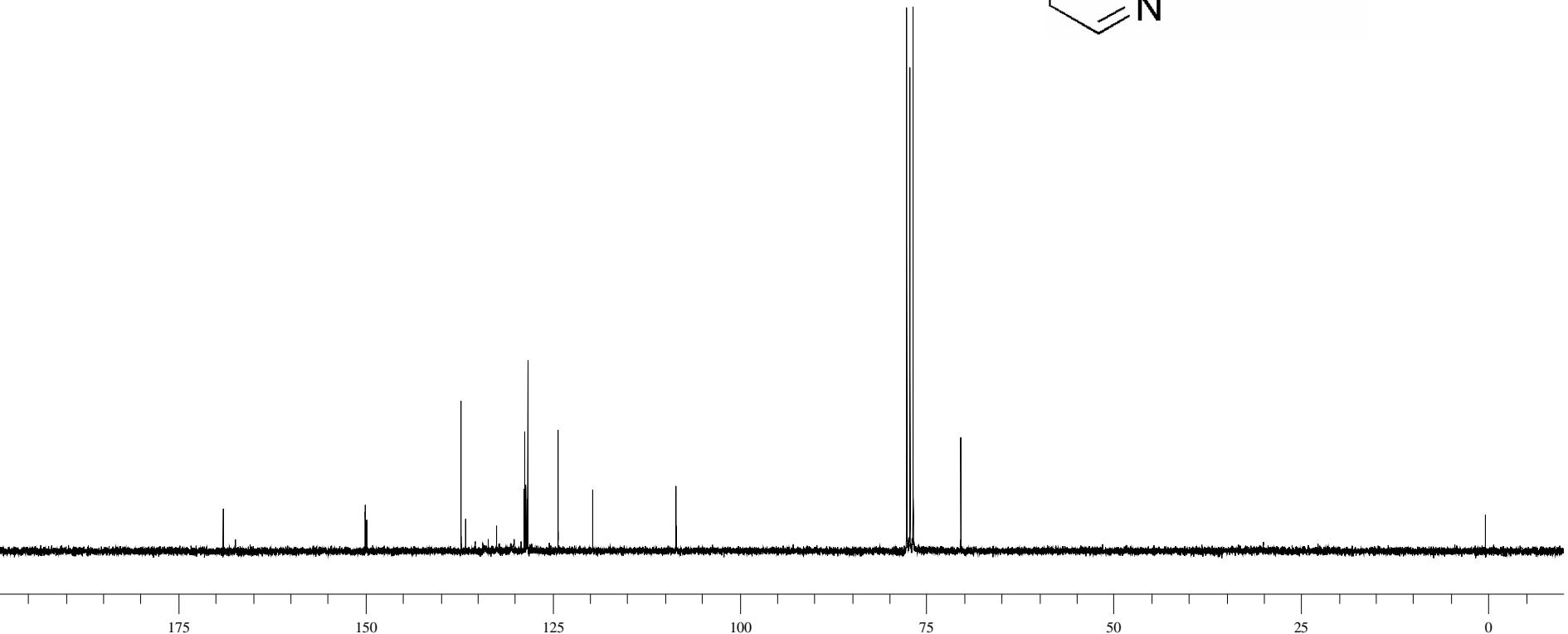
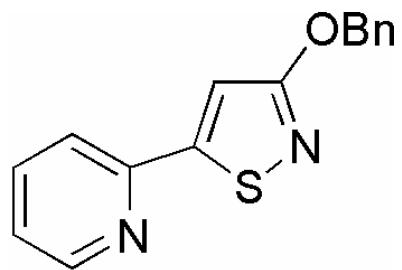
3-Benzylxy-5-(2-furyl)isothiazole **4d**



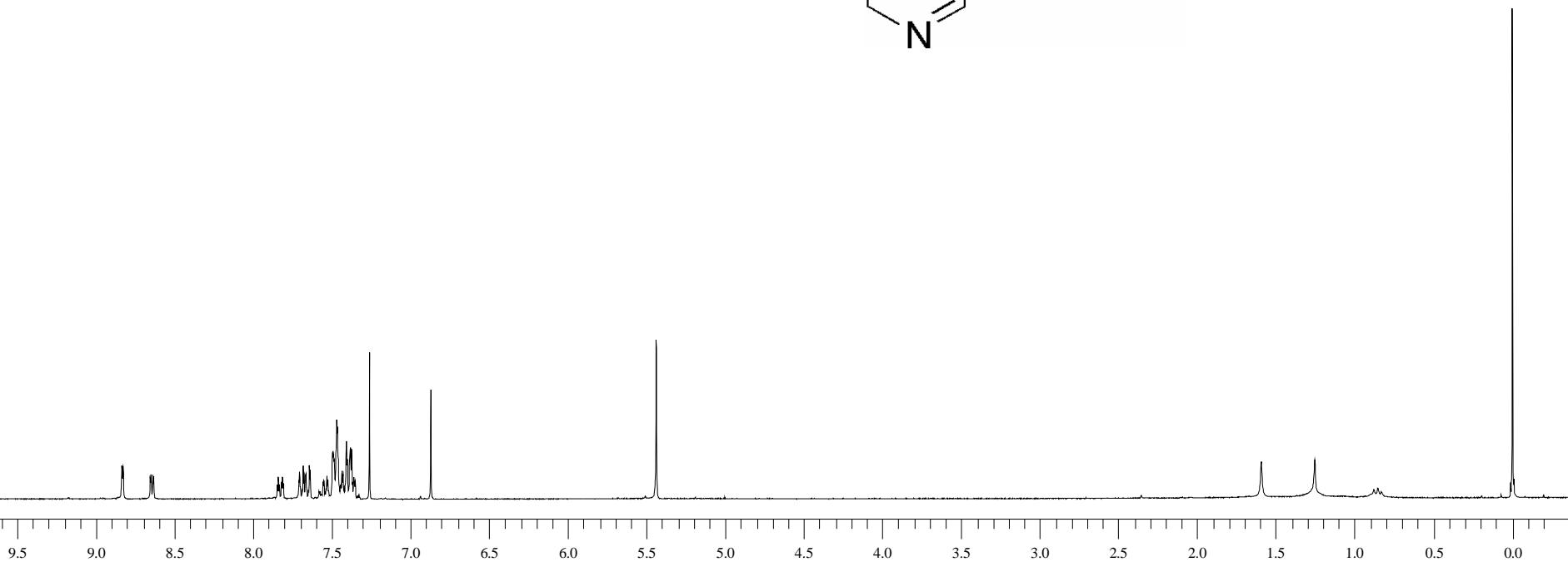
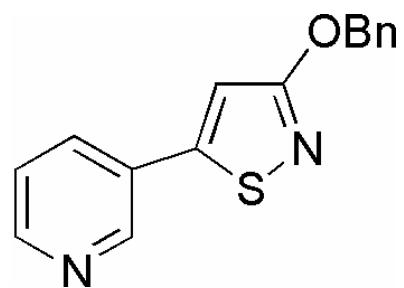
3-Benzyl-5-(2-pyridyl)isothiazole **4e**



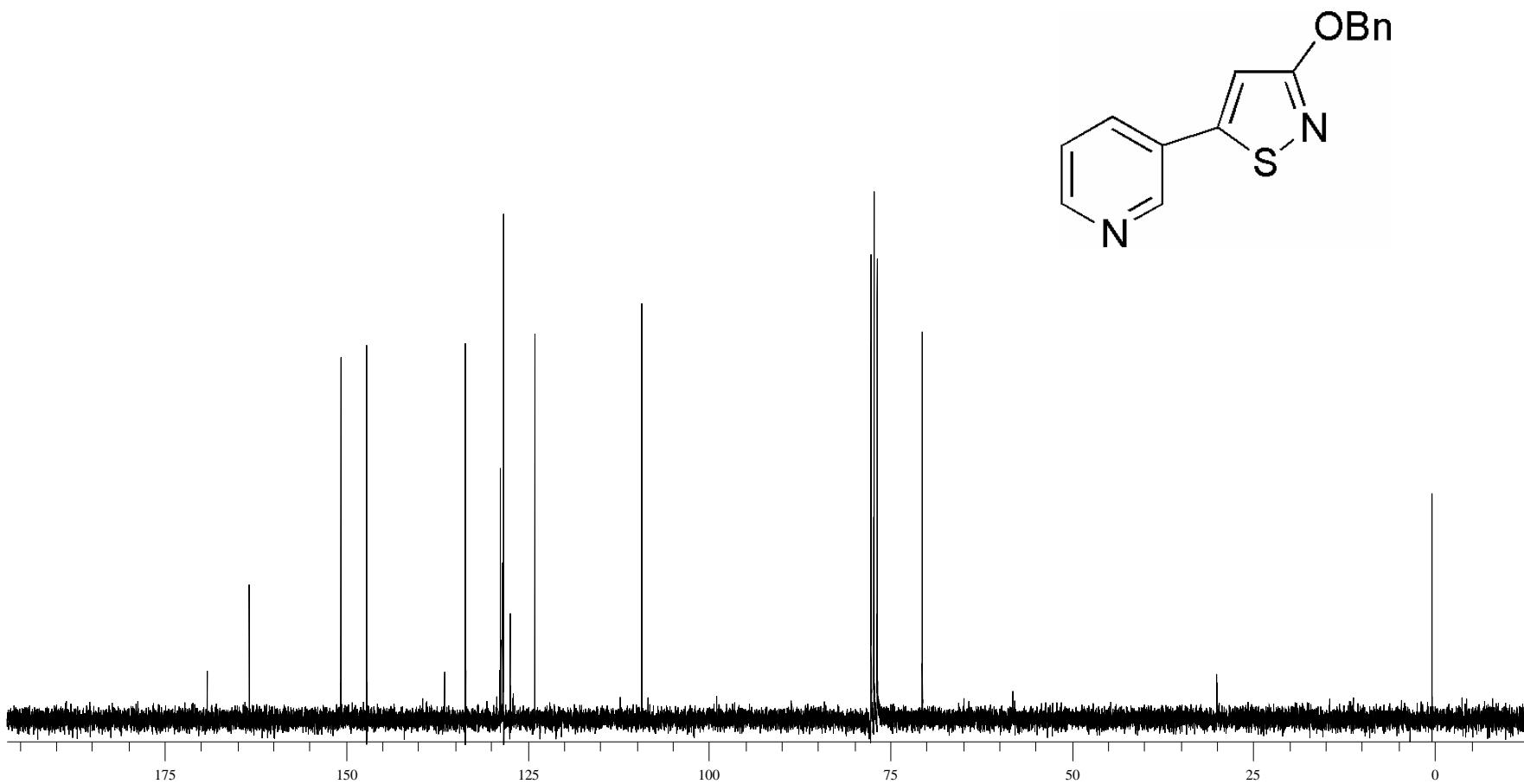
3-Benzylxy-5-(2-pyridyl)isothiazole **4e**



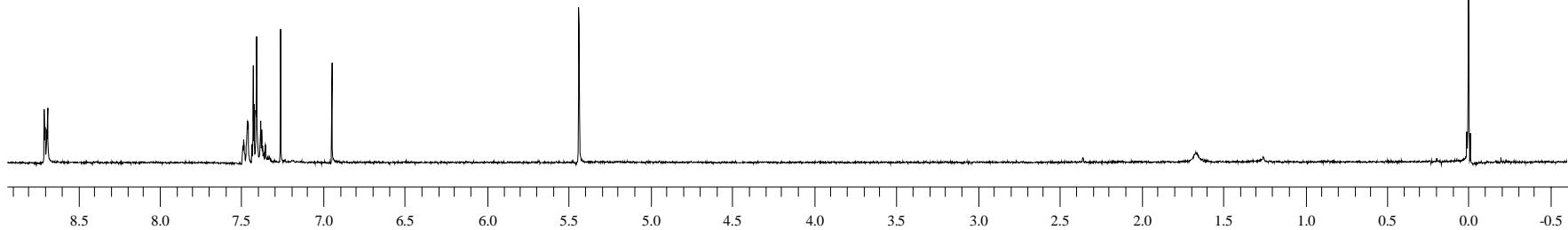
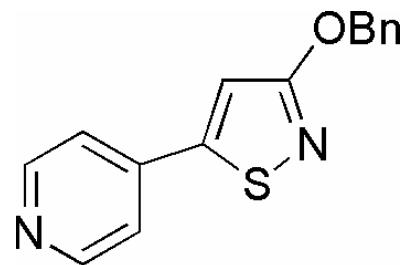
3-Benzyl-5-(3-pyridyl)isothiazole **4f**



3-Benzylxy-5-(3-pyridyl)isothiazole **4f**



3-Benzyl-5-(4-pyridyl)isothiazole **4g**



3-Benzylxy-5-(4-pyridyl)isothiazole **4g**

