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Notes

Convenient Synthesis of Aryl-Substituted (Hetero)arylcarbothioamides from Bromo(hetero)arylcarboxylic Acids

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(Hetero)arylcarbothioamides are interesting molecules due to their diverse pharmacological activities, such as anti-mycobacterial,[1a,b] antifungal,[1c,d] anti-influenza,[1e] and anti-trypanosomal[1f] properties. 5-Phenylfuran-2-carbothioamides also inhibit abscisic acid (ABA) signal transduction[2] and rhodamines containing thiophene-2-carbothioamide core are potent inhibitors of P-glycoprotein.[3] The common cyclic skeletons of (hetero)arylcarbothioamides involve 2-furyl,[2] 2-thienyl,[3] 2-pyridyl,[1a,b] and phenyl[1c-f] groups.

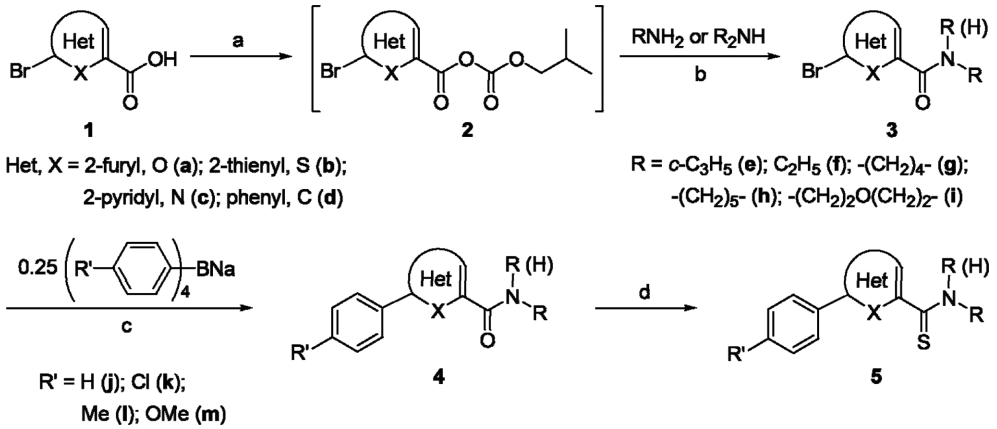
The synthesis of aryl-substituted (hetero)arylcarbothioamides can be accomplished by the conversion of bromo (hetero)arylcarboxylic acids to their carboxamides, cross-coupling with tetraarylborates, and subsequent thionation of the resulting aryl-substituted (hetero)arylcarboxamides. (Hetero)arylcarboxamides have generally been prepared by the acyl substitution of carboxylic anhydride intermediates, which were obtained by treating (hetero)arylcarboxylic acids with alkyl chloroformates[4] or trimethylacetyl chloride,[5] with amines. They were also prepared by one-pot method of (hetero)arylcarboxylic acids and amines using sulfonyl chlorides,[6] trichloroisocyanuric acid/triphenylphosphine,[7] and dialkylcarbodiimide/1-hydroxybenzotriazole as coupling reagents.[8]

The cross-coupling reaction of halo(hetero)arylcarboxylic acids with a variety of arylboronic acids using palladium catalyst provided aryl-substituted (hetero)arylcarboxylic acids.[9] Bromo(hetero)arylcarboxylic acids or their carboxamides were also coupled with sodium tetraphenylborate[10] or phenylboronic acids[8] in the presence of palladium catalyst to give phenyl-substituted (hetero)arylcarboxylic acids or their carboxamides. Conversion of the carbonyl group to thiocarbonyl has generally been accomplished using Lawesson's reagent as effective thionating reagent and thus (hetero)arylcarboxamides were easily thionated by this reagent to give (hetero)arylcarbothioamides at room temperature.[11]

However, reports on the synthesis of aryl-substituted (hetero)arylcarbothioamides are rare. In the previous paper we reported that 5-(chlorophenyl)-2-furancarbothioamides were synthesized from 2-furoic acid *via* diazotization with chloroanilines, conversion to their carboxamides, and thionation.[12] As the extension of our research, we now describe convenient synthesis of aryl-substituted (hetero)arylcarbothioamides containing some cyclic groups from bromo (hetero)arylcarboxylic acids under mild conditions in high yields.

Bromo(hetero)arylcarboxamides (**3**) were prepared through mixed carboxylic carbonic anhydrides as activated intermediates (*Scheme* 1). The addition of isobutyl chloroformate to a mixture solution of bromo(hetero)arylcarboxylic acids (**1**) and triethylamine afforded the corresponding mixed carboxylic carbonic anhydrides (**2**). The nucleophilic acyl substitution of **2** proceeded smoothly by regioselective attack of amines to the carbon atom of carboxylic carbonyl group to give **3** together with the liberation of carbon dioxide and isobutyl alcohol. This one-pot reaction was completed within 1 h between −10 ºC and 0 ºC, regardless of the skeletons of (hetero)aryl groups in **1**. Various **3** were obtained in 79–96% yields after the usual basic workup and chromatographic separation (**3ae**: 90%, **3ah**: 87%, **3bf**: 96%, **3bg**: 84%, **3bi**: 81%, **3cf**: 80%, **3cg**: 87%, **3ch**: 79%, **3df**: 82%, **3dg**: 84%).

The arylation of **3** was carried out by cross-coupling with sodium tetraarylborates in the presence of palladium(II) chloride catalyst. Sodium tetraarylborates were prepared by the addition of 4 equiv of arylmagnesium bromides to a heterogeneous solution of sodium tetrafluoroborate in THF according to the previous similar method.[13] To find out the optimum conditions of cross-coupling, the effect of bases and solvents was examined for the reaction of 5-bromo-2-furoylpiperidine (**3ah**) and 0.25 equiv of sodium tetraphenylborate in the presence of 0.03 equiv of palladium(II) chloride (*Table* 1). The cross-coupling reaction of **3ah** and sodium tetraphenylborate with 3 equiv of bases such as



***Scheme* 1.** Reagents and conditions: (a) $ClCOOCH_2CH(CH_3)_2$, Et_3N, CH_2Cl_2, -10 °C, 0.5 h; (b) -10 °C~0 °C, 0.5 h; (c) 3 equiv Na_2CO_3, 0.03 equiv $PdCl_2$, CH_3OH, rt, 1~2 h; (d) 0.5 equiv (*p*-MeO-C_6H_4)$_2P_2S_4$, CH_2Cl_2, rt, 1~4 h; rt, 36 h for **5aej**.

***Table* 1.** Effect of bases and solvents on the cross-coupling of 5-bromo-2-furoylpiperidine (**3ah**) and 0.25 equiv of Ph_4BNa with 0.03 equiv of $PdCl_2$

Bases (equiv)	Solvents	Reaction time (h)	Isolated yields (%)
Na_2CO_3 (3)	CH_3OH	0.5	83
Na_2CO_3 (1.2)	CH_3OH	12	68
$NaHCO_3$ (3)	CH_3OH	12	67
Et_3N (3)	CH_3OH	12	43
Na_2CO_3 (3)	CH_3CN	1	76
Na_2CO_3 (3)	CH_3COCH_3	24	7
Na_2CO_3 (3)	THF	24	5

Na_2CO_3, $NaHCO_3$, and Et_3N afforded (5-phenylfuran-2-yl)(piperidin-1-yl)methanone (**4ahj**) in 83%, 67%, and 43% yields, respectively, after 0.5 h, 12 h, and 12 h, respectively, in CH_3OH at room temperature. The corresponding reaction using 1.2 equiv of Na_2CO_3 proceeded slowly at room temperature, and **4ahj** was obtained in 68% after 12 h. When CH_3CN, CH_3COCH_3, and THF were employed as solvents in place of CH_3OH in the presence of 3 equiv of Na_2CO_3, **4ahj** was obtained in 76%, 7%, and 5% yields, respectively, after 1 h, 24 h, and 24 h, respectively, at room temperature. Thus, the cross-coupling reaction of **3** with 0.25 equiv of sodium tetraarylborates was carried out using 3 equiv of Na_2CO_3 in the presence of 0.03 equiv of palladium(II) chloride in CH_3OH at room temperature. The reaction was generally completed within 2 h, and aryl-substituted (hetero)arylcarboxamides (**4**) were obtained in 71–90% yields after the usual workup and chromatographic separation.

The thionation of the carbonyl group in **4** was carried out using Lawesson's reagent. The addition of 0.5 equiv of Lawesson's reagent to a solution of **4** in CH_2Cl_2 afforded thiaoxaphosphetane intermediates by nucleophilic attack of the sulfur atom to the carbon atom of the carbonyl group in **4**. Metathiophosphonate (*p*-$MeOC_6H_4POS$) was eliminated from these intermediates to give aryl-substituted (hetero)-arylcarbothioamides (**5**). The reaction was generally completed within 4 h at room temperature. However, the thionation of *N*-cyclopropyl-5-phenyl-2-furancarboxamide (**4aej**) proceeded sluggishly over 36 h at room temperature, presumably due to the decreased electrophilicity of the carbonyl group, to give *N*-cyclopropyl-5-phenyl-2-furancarbothioamide (**5aej**) in 90% yield. After completion of the reaction, the condensed mixture was directly subjected to silica gel column chromatography. The yellow bands of **5** were easily separated from metathiophosphonate, and **5** were obtained in 87–94% yields.

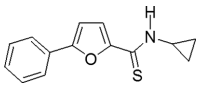
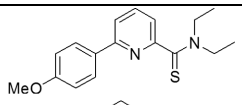
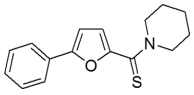
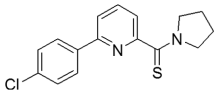
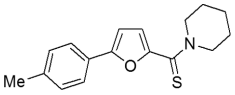
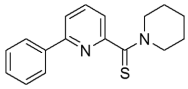
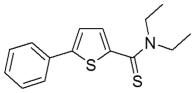
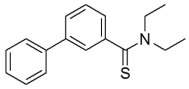
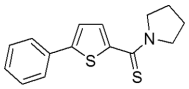
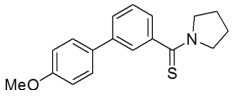
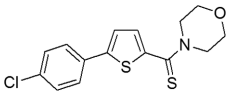
As shown in *Table* 2, various aryl-substituted (hetero)-arylcarbothioamides (**5**) were synthesized from bromo (hetero)arylcarboxylic acids (**1**) in high overall yields (51-68%). The cross-coupling reaction of **3** with sodium tetraarylborates proceeded well at room temperature, regardless of the skeletons of (hetero)aryl groups. The cross-coupling reaction also worked well with both electron-donating substituents (**4ahl**, **4cfm**, **4dgm**) and electron-withdrawing substituents (**4bik**, **4cgk**) in the aryl groups of tetraarylborates. Furthermore, the thionation of the carbonyl group in **4** using Lawesson's reagent proceeded smoothly at room temperature, regardless of the structures of (hetero)aryl groups and tertiary amides under the present conditions.

EXPERIMENTAL

Preparation of 5-bromo-2-furoylpiperidine (3ah)

To a solution of 5-bromo-2-furoic acid (**1a**, 764 mg, 4.0 mmol) in methylene chloride (16 mL) were added triethylamine (558 μL, 4.0 mmol) and isobutyl chloroformate (519 μL,

***Table* 2.** Synthesis of aryl-substituted (hetero)arylcarbo(thio)amides **4** and **5**

Entry	Thioamides	Yields, %[a]		Entry	Thioamides	Yields, %[a]	
		4	**5**			**4**	**5**
aej		72	90 (58)	**cfm**		81	94 (61)
ahj		83	92 (66)	**cgk**		71	90 (56)
ahl		83	93 (67)	**chj**		72	90 (51)
bfj		81	87 (68)	**dfj**		78	92 (59)
bgj		89	89 (67)	**dgm**		73	88 (54)
bik		90	87 (63)				

[a]The numbers in parentheses indicate the overall yields of **5** from **1** in three steps.

4.0 mmol) at −10 °C. After stirring for 0.5 h, piperidine (415 μL, 4.2 mmol) was slowly added to the resulting solution of 5-bromo-2-furyl isobutyl carbonic anhydride at −10 °C. Stirring was continued for 0.5 h between −10 °C and 0 °C. The mixture was poured into a saturated $NaHCO_3$ solution (40 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 40% EtOAc/*n*-hexane to give **3ah** (898 mg, 87%). mp 48–49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, J = 3.5 Hz, 1H), 6.41 (d, J = 3.5 Hz, 1H), 3.58–3.78 (m, 4H), 1.50–1.75 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 150.0, 123.7, 118.0, 113.1, 26.1, 24.6 (overlapped); Ms *m/z* (%) 259 (M^++2, 70), 257 (M^+, 72), 175 (99), 173 (100), 150 (57), 84 (54).

Preparation of (5-phenylfuran-2-yl)(piperidin-1-yl)-methanone (4ahj)

To a solution of **3ah** (774 mg, 3.0 mmol) in CH_3OH (15 mL) were added sodium tetraphenylborate (257 mg, 0.75 mmol), Na_2CO_3 (954 mg, 9.0 mmol), and palladium(II) chloride (16 mg, 0.09 mmol) at room temperature. After stirring for 1 h, CH_3OH was evaporated *in vacuo*. The resulting black mixture was transferred into 5% NaCl solution (30 mL) and extracted with methylene chloride (3 × 20 mL). The condensed residue was purified by silica gel column chromatography using 50% EtOAc/*n*-hexane to give **4ahj** (636 mg, 83%). mp 45–46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.71 (m, 2H), 7.36–7.43 (m, 2H), 7.28–7.34 (m, 1H), 7.05 (d, J = 3.5 Hz, 1H), 6.71 (d, J = 3.5 Hz, 1H), 3.64-3.82 (m, 4H), 1.60–1.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 154.7, 147.5, 130.0, 128.8, 128.3, 124.2, 117.9, 106.3, 26.3, 24.8 (overlapped); Ms *m/z* (%) 255 (M^+, 100), 171 (97), 144 (84), 115 (96), 84 (15).

Preparation of (5-phenylfuran-2-yl)(piperidin-1-yl)-methanethione (5ahj)

A solution of **4ahj** (511 mg, 2.0 mmol) and Lawesson's reagent (405 mg, 1.0 mmol) in methylene chloride (8 mL) was stirred for 2 h at room temperature. After evaporation of methylene chloride, the resulting yellow residue was directly subjected to silica gel column chromatography using 30% EtOAc/*n*-hexane to give **5ahj** (499 mg, 92%) as a yellow solid. mp 76–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.71 (m, 2H), 7.22–7.44 (m, 3H), 7.20 (d, J = 3.5 Hz, 1H), 6.72 (d, J = 3.5 Hz, 1H), 4.05–4.36 (m, 2H), 3.76–4.05 (m, 2H), 1.62–1.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 154.1, 151.7, 130.0, 128.9, 128.4, 124.2, 120.4, 107.3, 53.9, 53.5, 52.7, 26.3, 24.4; Ms *m/z* (%) 271 (M^+, 100), 187 (40), 170 (81), 115 (34), 84 (17).

***N*-Cyclopropyl-5-phenyl-2-furancarbothioamide (5aej):** viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (br s, 1H), 7.55–7.64 (m, 2H), 7.37 (d, J = 3.7 Hz, 1H), 7.22–7.34 (m, 3H), 6.63 (d, J = 3.7 Hz, 1H), 3.23–3.32 (m, 1H), 0.89–

0.99 (m, 2H), 0.67–0.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.6, 155.1, 151.2, 129.5, 128.9 (overlapped), 124.6, 120.0, 108.5, 28.1, 7.6; Ms *m/z* (%) 243 (M^+, 63), 228 (100), 187 (91), 115 (78), 77 (21).

[5-(4-Methylphenyl)furan-2-yl](piperidin-1-yl)methanethione (5ahl): mp 100–101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 3.5 Hz, 1H), 6.66 (d, *J* = 3.5 Hz, 1H), 4.15–4.36 (m, 2H), 3.86–4.05 (m, 2H), 2.39 (s, 3H), 1.77–1.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 154.4, 151.3, 138.5, 129.6, 127.3, 124.2, 120.9, 106.7, 53.9, 52.2, 27.0, 26.0, 24.5, 21.4; Ms *m/z* (%) 285 (M^+, 100), 201 (31), 184 (82), 129 (23), 84 (17).

***N,N*-Diethyl-5-phenyl-2-thiophenecarbothioamide (5bfj):** mp 59–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.65 (m, 2H), 7.30–7.44 (m, 3H), 7.17 (d, *J* = 3.8 Hz, 1H), 7.08 (d, *J* = 3.8 Hz, 1H), 3.52–4.20 (m, 4H), 1.39 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 147.3, 144.2, 133.6, 129.0, 128.2, 126.1, 125.9, 122.5, 47.8 (overlapped), 13.7, 11.5; Ms *m/z* (%) 275 (M^+, 46), 203 (100), 186 (10), 115 (9).

(5-Phenylthiophen-2-yl)(pyrrolidin-1-yl)methanethione (5bgj): mp 161–162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.67 (m, 2H), 7.32–7.44 (m, 3H), 7.28 (d, *J* = 3.9 Hz, 1H), 7.23 (d, *J* = 3.9 Hz, 1H), 3.99–4.08 (m, 2H), 3.91–3.99 (m, 2H), 2.05–2.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 149.7, 145.4, 133.5, 129.0, 128.4, 128.0, 126.0, 123.0, 55.4, 54.4, 27.0, 24.4; Ms *m/z* (%) 273 (M^+, 100), 240 (39), 203 (62), 186 (27), 70 (20).

[5-(4-Chlorophenyl)thiophen-2-yl](morpholino)methanethione (5bik): mp 83–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 3.8 Hz, 1H), 7.06 (d, *J* = 3.8 Hz, 1H), 4.12-4.30 (m, 4H), 3.78–3.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 147.2, 143.7, 134.3, 131.9, 129.3, 127.3, 127.1, 122.9, 66.7, 52.3; Ms *m/z* (%) 325 (M^++2, 35), 323 (M^+, 84), 239 (43), 237 (100), 220 (30), 86 (13).

***N,N*-Diethyl-6-(4-methoxyphenyl)-2-pyridinecarbothioamide (5cfm):** mp 118–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 2H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.53 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 160.6, 159.5, 155.2, 137.4, 131.2, 128.4, 120.6, 118.7, 114.0, 55.4, 48.1, 46.7, 14.0, 11.2; Ms *m/z* (%) 300 (M^+, 32), 229 (100), 185 (16), 72 (10).

[6-(4-Chlorophenyl)pyridin-2-yl](pyrrolidin-1-yl)methanethione (5cgk): mp 99–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 3.92–4.05 (m, 2H), 3.63–3.78 (m, 2H), 1.95–2.13 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 159.8, 139.8, 139.0, 128.9, 128.2, 128.0, 122.9, 122.7, 120.0, 54.0, 53.3, 26.6, 24.2; Ms *m/z* (%) 304 (M^++2, 12), 302 (M^+, 32), 235 (37), 233 (100), 154 (16), 70 (20).

(6-Phenylpyridin-2-yl)(piperidin-1-yl)methanethione (5chj): mp 116–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–8.04 (m, 2H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.42-7.51 (m, 3H), 4.37–4.44 (m, 2H), 3.56–3.63 (m, 2H), 1.69–1.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 159.3, 155.7, 138.7, 137.6, 129.2, 128.7, 127.0, 121.8, 119.7, 53.3, 50.8, 26.9, 25.5, 24.2; Ms *m/z* (%) 282 (M^+, 54), 199 (100), 155 (33), 84 (44).

***N,N*-Diethyl-3-phenylbenzthioamide (5dfj):** mp 80–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.54 (m, 2H), 7.44–7.49 (m, 1H), 7.33–7.40 (m, 4H), 7.25–7.33 (m, 1H), 7.12–7.17 (m, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 144.3, 141.4, 140.4, 128.9, 128.8, 127.6, 127.2, 126.8, 123.9, 123.7, 47.9, 46.1, 14.0, 11.3; Ms *m/z* (%) 269 (M^+, 66), 197 (100), 180 (28), 152 (25).

[3-(4-Methoxyphenyl)phenyl](pyrrolidin-1-yl)methanethione (5dgm): mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.47–7.57 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 3.94–4.05 (m, 2H), 3.87 (s, 3H), 3.46–3.57 (m, 2H), 2.04–2.36 (m, 2H), 1.92–2.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 159.4, 144.4, 140.9, 132.9, 128.8, 128.2, 127.0, 123.9 (overlapped), 114.2, 55.4, 53.9, 53.4, 26.5, 24.7; Ms *m/z* (%) 297 (M^+, 100), 228 (44), 184 (16), 70 (5).

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