An Efficient Synthesis of \(N,N\)-Dialkyl-5-(chlorophenyl)-2-furancarbothioamides from 2-Furoic Acid

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Thioamides are an important compound class due to their pharmacological activities, such as anti-influenza virus, antitumor, and anthelmintic properties.\(^1\) Many furan compounds substituted at the 2- and 5-positions occur in nature, and their hydrazide derivatives exhibit diverse activities including fungicidal and herbicidal properties.\(^2\) Among these, \(5-(3,4\text{-dichlorophenyl})\text{furan-2-yl}(\text{piperidin-1-yl})\text{methylene}(\text{DFPM}),\) which contains a 2,5-disubstituted furan skeleton, downregulates abscisic acid (ABA)-dependent gene expression and also inhibits ABA signal transduction.\(^3\) Recently DFPM was found to generate specific growth arrest in the roots of the Arabidopsis plant.\(^4\)

The synthesis of 5-(chlorophenyl)-2-furancarbothioamides consisted of preparation of 5-(chlorophenyl)-2-furoic acids, conversion to the amides, and subsequent thionation of the amides. 5-Phenyl-2-furoic acids have generally been prepared via oxidation of 5-phenyl-2-furaldehydes, which were obtained by Meerwein phenylation of 2-furancarboxaldehyde.\(^5\) 5-Phenyl-2-furoic acids were also prepared by diazotization of 2-furoic acid using benzenediazonium salts\(^6\) or by the cross-coupling reaction of 5-bromo-2-furoic acid with sodium tetraphenylborate in the presence of catalytic Pd/C under microwave irradiation or in open air.\(^7\)

5-Phenyl-2-furancarboxamides have generally been synthesized by the acyl substitution of 5-phenyl-2-furoyl chlorides, derived from 5-phenyl-2-furoic acids, and thionyl chloride, with amines.\(^8\) The one-pot reaction of 5-phenyl-2-furoic acids and arylamines using phenylsulfonyl chloride also afforded \(N\)-aryl-5-phenyl-2-furancarboxamides.\(^9\) Alternatively, the condensation of 5-bromo-2-furoic acid with arylamines using EDCI/HOBt afforded \(N\)-aryl-5-bromo-2-furancarboxamides.\(^10\) These amides were coupled with phenylboronic acid in the presence of \(\text{Pd}(\text{PPh}_3)_4\) to give \(N\)-aryl-5-phenyl-2-furancarboxamides.\(^11\) Conversion of 5-phenyl-2-furancarboxamides to their corresponding thioamides were typically carried out using 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide (Lawesson's reagent), which was widely used in the thionation of carbonyl groups.\(^11\)

However, there have been no reports on the synthesis of 5-(chlorophenyl)-2-furancarbothioamides including DFPM. In this paper we describe an efficient synthesis of \(N,N\)-dialkyl-5-(chlorophenyl)-2-furancarbothioamides from 2-furoic acid under mild conditions as inhibitor candidates of plant growth.

5-(Chlorophenyl)-2-furoic acids (3a–d) were prepared by treating 2-furoic acid with chlorobenzenediazonium salts (2a–d). The addition of sodium nitrite to a solution of chloroanilines (1a–d) in aqueous HCl solution at 0 °C afforded the corresponding 2a–d (Scheme 1). When 2-furoic acid and a catalytic amount of copper(II) chloride were added to 2, highly regioselective electrophilic substitution occurred with phenylation at the 5-position of the furan ring. The reaction was complete in several hours, and 3a–d were obtained in 56–65% yields after the usual work-up and recrystallization (3a: 57%, 3b: 56%, 3c: 62%, 3d: 65%).

The synthesis of \(N,N\)-dialkyl-5-(chlorophenyl)-2-furancarboxamides (5) was carried out by the acyl substitution of 2-pyridyl 5-(chlorophenyl)-2-furoate intermediates 4 with amines. The addition of di-2-pyridyl carbonate (2-DPC)\(^12\) to a solution of 3 in methylene chloride afforded the corresponding mixed carboxylic anhydrides, which was further converted to 4 with a catalytic amount of 4-(dimethylamino)pyridine (4-DMAP)\(^13\) together with evolution of carbon dioxide. For instance, the reaction of 5-(3,4-dichlorophenyl)-2-furoic acid (3d) and 2-DPC in the presence of 0.1 equiv of 4-DMAP afforded 2-pyridyl 5-(3,4-dichlorophenyl)-2-furoate (4d) in 95% yield. The characteristic \(^1\)H NMR values of pyridine ring were observed at \(\delta\ 8.46\ (dd, J = 4.9, 1.6\ Hz, 1H), 7.82–7.89\ (m, 1H), 7.24–7.31\ (m, 2H)
and the FT-IR carbonyl stretching peak was observed at 1739 cm\(^{-1}\) for 4d. Typically, the synthesis of 5 was carried out in a one-pot process without isolation of 4. Thus, amines were directly added to a solution of 4 in methylene chloride at 0°C, and the reaction was complete in 0.5 h. After the usual basic work-up and chromatographic separation, 5 were obtained in 81–96% yields.

Conversion of 5 to \(N,N\)-dialkyl-5-(chlorophenyl)-2-furancarbothioamides (6) was carried out using Lawesson’s reagent as an effective thionating agent of the carbonyl group. When Lawesson’s reagent was added to a solution of 5 in methylene chloride, the sulfur atom of dithiophosphine ylide attacked the carbon atom of the carbonyl group in 5 to produce thiaoxaphosphetanes. These intermediates were cycloeliminated to give 6 together with metathiophosphinate (\(\text{p-MeOC}_6\text{H}_4\text{POS})\). The thionation of 5 using Lawesson’s reagent was complete in 0.5–3.5 h at room temperature, and 6 were obtained in 87–96% yields after chromatographic separation. In the case of \(N\)-cyclopropyl-5-(4-chlorophenyl)-2-furancarboxamide (5be), thionation proceeded sluggishly in methylene chloride over 48 h at room temperature to give \(N\)-cyclopropyl-5-(4-chlorophenyl)-2-furancarbothioamide (6be) in 73% yield. However, the corresponding reaction of 5be was complete in THF after 1.5 h at 65°C to give 6be in 90% yield.

As shown in Table 1, various \(N,N\)-dialkyl-5-(chlorophenyl)-2-furancarbothioamides were synthesized from 2-furoic acid in high overall yields (42–57%). Although thionation of secondary amide such as 5be proceeded sluggishly, the conversion of other tertiary amides to the corresponding thioamides proceeded smoothly at room temperature. The condensation reaction of 3 with amines and thionation of 5 worked well under the present reaction conditions, regardless of the position of the chloro group in the 5-phenyl ring.

**EXPERIMENTAL**

**Preparation of 5-(2,4-dichlorophenyl)-2-furoic acid (3c).**

To a suspension of 2,4-dichloroaniline (1c, 3.37 g, 20.8 mmol) in \(\text{H}_2\text{O}\) (10 mL), 18% HCl solution (8 mL) was added at 0°C. After stirring for 20 min, a solution of sodium nitrite (1.44 g, 20.9 mmol) in \(\text{H}_2\text{O}\) (10 mL) was added, and the mixture was stirred further for 20 min. To the resulting solution of 2,4-dichlorobenzenediazonium chloride was added a solution of 2-furoic acid (1.46 g, 13.0 mmol) in acetone (7 mL), followed by the addition of copper(II) chloride (523 mg, 3.9 mmol) in \(\text{H}_2\text{O}\) (5 mL). The mixture was stirred for 6 h between 0°C and room temperature. After evaporation of acetone, the mixture was poured into brine (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over anhydrous MgSO\(_4\), filtered, and concentrated in vacuo. The residue was washed with \(n\)-hexane and then recrystallized in 50% EtOAc/\(n\)-hexane to give 3c (2.08 g, 62%) as a yellow solid. mp 223–225°C; \(^1\)H NMR (300 MHz, \(\text{CD}_3\text{COCD}_3\)) \(\delta\) 13.58 (s, 1H), 7.97 (d, \(J = 8.6\) Hz, 1H), 7.69 (d, \(J = 1.6\) Hz, 1H), 7.58 (dd, \(J = 8.6, 1.6\) Hz, 1H), 7.33 (d, \(J = 3.6\) Hz, 1H), 7.30 (d, \(J = 3.6\) Hz, 1H); \(^{13}\)C NMR (75 MHz, \(\text{CD}_3\text{COCD}_3\)) \(\delta\) 159.3, 151.7, 145.3, 134.3, 131.3, 130.5, 129.9, 128.0, 127.0, 118.9, 113.1; Ms m/z (%).
Preparation of [5-(2,4-dichlorophenyl)furan-2-yl] (piperidin-1-yl)methanone (5ch). To a suspension of 3c (771 mg, 3.0 mmol) in methylene chloride (18 mL), di-2-pyridyl carbonate (649 mg, 3.0 mmol) and 4-DMAP (37 mg, 0.3 mmol) was added at room temperature. After stirring for 3 h, the mixture was cooled to 0 °C, and piperidine (326 μL, 3.3 mmol) was slowly added to the resulting 2-pyridyl 5-(2,4-dichlorophenyl)-2-furoate over 2 min. Stirring was continued for 0.5 h, and then the mixture was poured into saturated NaHCO₃ solution (40 mL) and extracted with methylene chloride (3 × 25 mL). The concentrated residue was purified by short pathway silica gel column chromatography using 50% EtOAc/n-hexane to give 5ch (856 mg, 88%). mp 87–89 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 8.5, 2.0 Hz, 1H), 7.14 (d, J = 3.6 Hz, 1H), 7.02 (d, J = 3.6 Hz, 1H), 3.68–3.86 (m, 4H), 1.61–1.79 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.0, 150.0, 147.6, 134.1, 131.3, 130.6, 129.0, 127.4, 127.1, 117.2, 112.2, 26.2, 24.7 (overlapped); Ms m/z (%) 327 (M⁺+4, 10), 325 (M⁺+2, 64), 323 (M⁺, 100), 241 (69), 239 (95), 185 (56), 183 (92).

Preparation of [5-(2,4-dichlorophenyl)furan-2-yl] (piperidin-1-yl)methanethione (6ch). To a solution of 5ch (778 mg, 88%)}
mg, 2.4 mmol) in methylene chloride (12 mL), Lawesson's reagent (486 mg, 1.2 mmol) was added at room temperature, and the mixture was stirred for 5 h. After evaporation of methylene chloride, the residue was subjected to silica gel column chromatography using 30% EtOAc/n-hexane as eluant to give 6ch (767 mg, 94%). The concentrated residue was further recrystallized in 10% EtOAc/n-hexane to give 6ch as a yellow solid. mp 106–107 °C; 1H NMR (300 MHz, CDCl3) δ 7.73 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.30 (dd, J = 8.6, 2.1 Hz, 1H), 7.13 (d, J = 3.7 Hz, 1H), 7.11 (d, J = 3.7 Hz, 1H), 4.22–4.38 (m, 2H), 3.82–3.92 (m, 2H), 1.71–1.86 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 184.4, 151.8, 151.3, 134.1, 129.1, 128.5, 125.4, 120.0, 107.6, 53.7, 52.0, 27.2, 25.9, 24.4; Ms m/z (%) 307 (M+2, 38), 305 (M+, 100), 223 (15), 221 (39), 149 (32).

N,N-Diethyl-5-(2-chlorophenyl)-2-furancarbothioamide (6af): mp 87–88 °C; 1H NMR (300 MHz, CDCl3) δ 7.78 (dd, J = 7.8, 1.6 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.30–7.37 (m, 1H), 7.24–7.30 (m, 2H), 7.15 (d, J = 3.6 Hz, 1H), 3.93–4.19 (m, 2H), 3.82–3.93 (m, 2H), 1.30–1.50 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 184.2, 152.0, 150.5, 131.0, 130.9, 128.9, 128.1, 124.7, 120.2, 113.0, 48.1 (overlapped), 14.3, 11.2; Ms m/z (%) 295 (M+2, 15), 293 (M+, 38), 223 (40), 221 (100), 207 (44), 149 (30).

[5-(2-Chlorophenyl)furan-2-yl](piperidin-1-yl)methanethione (6ah): mp 78–79 °C; 1H NMR (300 MHz, CDCl3) δ 7.78 (dd, J = 7.8, 1.7 Hz, 1H), 7.45 (dd, J = 7.9, 1.3 Hz, 1H), 7.29–7.34 (m, 1H), 7.21–7.27 (m, 1H), 7.15 (d, J = 3.6 Hz, 1H), 7.12 (d, J = 3.6 Hz, 1H), 4.18–4.34 (m, 2H), 3.90–4.05 (m, 2H), 1.73–1.84 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 184.5, 151.7, 150.4, 130.9, 129.0, 128.6, 128.1, 127.0, 119.4 (overlapped), 112.8, 53.9, 52.0, 27.0, 26.1, 24.4; Ms m/z (%) 307 (M+2, 39), 305 (M+, 100), 223 (14), 221 (39), 204 (69), 149 (40).

N-Cyclopropyl-5-(4-chlorophenyl)-2-furancarbothioamide (6be): mp 109–110 °C; 1H NMR (300 MHz, CDCl3) δ 7.87 (br s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 3.7 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 3.7 Hz, 1H), 3.31–3.40 (m, 1H), 1.01–1.08 (m, 2H), 0.79–0.85 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 183.6, 159.3, 151.9, 134.7, 129.2, 128.0, 125.7, 119.8, 108.9, 28.1, 7.6; Ms m/z (%) 279 (M+2, 12), 277 (M+, 33), 264 (38), 262 (100), 223 (11), 221 (32), 149 (34).

[5-(4-Chlorophenyl)furan-2-yl](pyrrolidin-1-yl) methanethione (6bh): mp 111–112 °C; 1H NMR (300 MHz, CDCl3) δ 7.59 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 3.6 Hz, 1H), 6.69 (d, J = 3.6 Hz, 1H), 4.10–4.38 (m, 2H), 3.82–4.10 (m, 2H), 1.75–1.90 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 184.3, 152.9, 151.9, 134.1, 129.1, 128.5, 125.4, 120.0, 107.6, 53.7, 52.0, 27.2, 25.9, 24.4; Ms m/z (%) 307 (M+2, 38), 305 (M+, 100), 223 (15), 221 (39), 149 (32).

[5-(4-Chlorophenyl)furan-2-yl](piperidin-1-yl) methanethione (6ch): mp 172–174 °C; 1H NMR (300 MHz, CDCl3) δ 7.73 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 3.7 Hz, 1H), 7.33 (dd, J = 8.5, 2.0 Hz, 1H), 7.15 (d, J = 3.7 Hz, 1H), 4.02–4.12 (m, 4H), 2.02–2.16 (m, 4H); 13C NMR (75 MHz, CDCl3) δ 179.9, 152.1, 150.5, 134.3, 131.6, 130.8, 128.8, 127.5, 127.1, 121.0, 113.3, 55.1, 53.7, 27.0, 23.8; Ms m/z (%) 329 (M+4, 11), 327 (M+2, 69), 325 (M+, 100), 292 (43), 258 (41), 256 (59), 183 (30).

[5-(2,4-Dichlorophenyl)furan-2-yl](pyrrolidin-1-yl) methanethione (6ci): mp 163–165 °C; 1H NMR (300 MHz, CDCl3) δ 7.69 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 8.6, 2.1 Hz, 1H), 7.19 (d, J = 3.7 Hz, 1H), 7.11 (d, J = 3.7 Hz, 1H), 4.05–4.35 (m, 4H), 3.80–3.93 (m, 4H); 13C NMR (75 MHz, CDCl3) δ 185.1, 151.3, 149.9, 134.4, 131.5, 130.7, 128.9, 127.6, 126.9, 120.3, 113.1, 66.7, 52.1; Ms m/z (%) 345 (M+4, 10), 343 (M+2, 61), 341 (M+, 90), 259 (11), 257 (71), 255 (100), 183 (59).
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[5-(3,4-Dichlorophenyl)furan-2-yl](morpholino)methanethione (6di): mp 143–145 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.71 (d, \ J = 1.1 \text{ Hz}, 1\text{H}), 7.45–7.49 (m, 2\text{H}), 7.18 (d, \ J = 3.6 \text{ Hz}, 1\text{H}), 6.73 (d, \ J = 3.6 \text{ Hz}, 1\text{H}), 4.13–4.27 (m, 4\text{H}), 108.6, 66.7, 51.3; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 185.0, 152.0, 151.7, 133.4, 132.4, 131.0, 129.6, 125.9, 123.3, 120.7, 108.6, 66.7, 51.3;Ms \(m/z \) (\%) 345 (M\(^+\) + 4, 10), 343 (M\(^+\) + 2, 63), 341 (M\(^+\) , 92), 308 (51), 259 (12), 257 (72), 255 (100), 183 (42).

REFERENCES