

A facile synthesis and fungicidal activities of 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones

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Preliminary Communication

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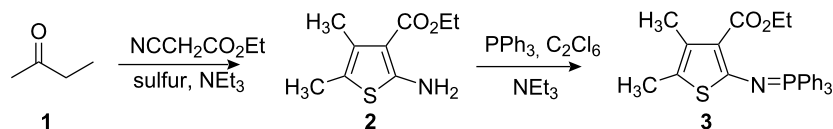
Abstract

The aza-Wittig reactions of iminophosphorane **3** with aromatic isocyanates generated carbodiimides **4**, which were reacted with alkylamines under mild conditions to give a series of 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6** and **8** in satisfactory yield. Their structures were confirmed by ¹H NMR, EI-MS, IR and elementary analysis, and compound **8c** was further analyzed by single-crystal X-ray diffraction. The preliminary bioassays indicated that these compounds showed excellent fungicidal activities against six kinds of fungi.

Introduction

Over the past ten years, aza-Wittig reactions of functionalized iminophosphoranes with isocyanates have been applied to produce carbodiimides, functional groups consisting of the formula N=C=N, able to undergo a plethora of heterocyclization reactions [1-6]. At the same time, many heterocycles containing thienopyrimidine system are of great importance for use as potential drugs because of their remarkable biological activity. For example, some 2-alkylthio- or 2-alkyl-substituted thienopyrimidinones show significant antifungal and antibacterial activities [7,8], whereas others exhibit good anticon-

vulsant and angiotensin or H₁ receptor antagonistic activities [9]. The chemistry of thienopyrimidinones has also received attention because their starting materials, 2-amino-3-carboxythiophenes, can be conveniently synthesized by Gewald reaction [10]. Synthetically useful approaches to thienopyrimidinones starting from easily accessible 2-amino-3-carboxythiophenes are therefore of great importance. Recently we have been interested in the synthesis of a series of new heterocyclic compounds *via* aza-Wittig reaction of α - or β -(ethoxycarbonyl)-substituted iminophosphoranes with



Scheme 1: Preparation of iminophosphorane 3.

aromatic isocyanates and subsequent reaction with various nucleophiles under mild conditions [11-14]. Herein we wish to report an efficient synthesis of 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones via iminophosphorane 3. Bioassays indicated that these compounds showed good to excellent fungicidal activities against six kinds of fungi.

Results and Discussion

Synthesis

The ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (2), easily obtained by cyclization of 2-butanone (1) with ethyl 2-cyanoacetate and sulfur under basic conditions [10], was converted to iminophosphorane 3 via reaction with triphenylphosphine, hexachloroethane and triethylamine (Scheme 1).

Iminophosphorane 3 reacted with aromatic isocyanates to give carbodiimides 4, which were allowed to react with secondary amines to provide guanidine intermediates 5. Even in refluxing toluene, compounds 5 did not cyclize. However, in the presence of a catalytic amount of sodium ethoxide, compounds 5 were converted easily to 2-(dialkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones 6 in satisfactory yields at room temperature (Scheme 2). The results are listed in Table 1.

The reaction of carbodiimides 4 with primary amine RNH₂ in the presence of EtONa provided only 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones 8 (Scheme 3), one of the possible regioisomers. We obtained only 8 from the reaction mixture after recrystallization; the other isomer 9 was not found by ¹H NMR analysis of the reaction mixture.

The structure of 8 was deduced from its ¹H NMR data. For example, the ¹H NMR spectrum in 8b (R = *n*-C₄H₉) shows the signals of NH at 4.01 ppm as a broad absorption and NCH₂ at 3.38–3.31 ppm as a multiple absorption, which strongly suggests the existence of a NHCH₂CH₂CH₂CH₃ group in 8b. Furthermore a single crystal of 8c was obtained from a methylene dichloride solution of 8c and X-ray structure analysis verified again the proposed structure [15]. The solitary formation of 8 can be rationalized in terms of a base catalyzed cyclization of the guanidine intermediate 7 to give 8 across the arylamino group rather than the alkylamino one. This may prob-

ably be due to the preferential generation of –N[–]Ar from more acidic –NHAr. The results are also listed in Table 1.

Fungicidal activity

The fungicidal activities of compounds 6 and 8 were screened against six kinds of fungi, *Fusarium oxysporum*, *Rhizoctonia solani*, *Botrytis cinerea*, *Gibberella zaeae*, *Dothiorella gregaria*, *Colletotrichum gossypii* at a concentration of 50 mg/L according to the reported method [16]. Bioassays indicated that these compounds showed good to excellent fungicidal activities against six kinds of fungi. For example, 6b, 6d, 8a, 8c, 8d showed 100% inhibition of *Botrytis cinerea*. See Table 2.

In conclusion, we have developed an efficient synthesis of 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones via base-catalyzed reaction of functionalized carbodiimides with various amines. Due to the mild reaction conditions, good yields, easily accessible starting material and straightforward product isolation, we think that the versatile synthetic approach discussed here in many cases compares favorably with other existing methods. The preliminary bioassay of the compounds indicated that the 2-amino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones can be used as lead structure for developing novel fungicides. Further bioassay, optimization and structure-activity relationships of the title compounds are underway.

Experimental

Melting points were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. IR were recorded on a

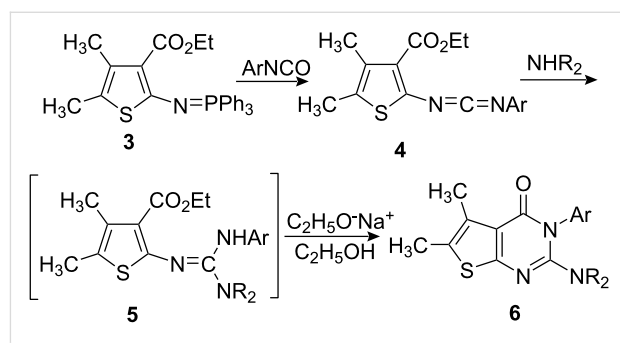
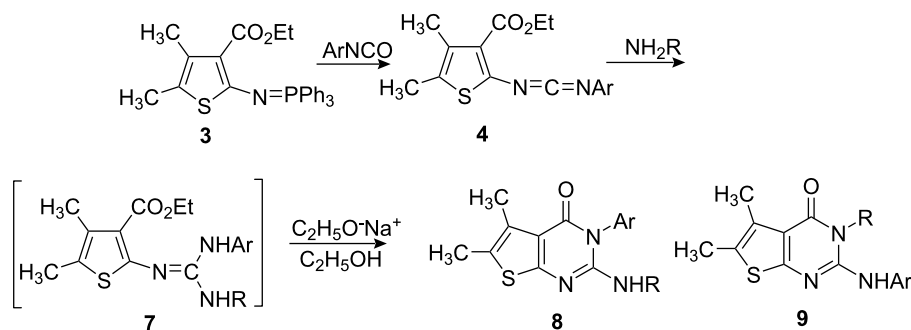
Scheme 2: Preparation of 2-(dialkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones 6.

Table 1: Preparation of 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones.

Entry	Product	Ar	-NR ₂ (or -NHR)	Conditions	Yield (%) ^a
1	6a	Ph		r.t./4 h	76
2	6b	Ph		r.t./4 h	73
3	6c	Ph	-N(<i>n</i> -C ₄ H ₉) ₂	r.t./6 h	70
4	6d	Ph	-N(<i>n</i> -C ₆ H ₁₃) ₂	r.t./6 h	61
5	6e	Ph	-N(Me)Ph	r.t./4 h	74
6	6f	4-Me-C ₆ H ₄		r.t./4 h	78
7	6g	4-Cl-C ₆ H ₄		r.t./5 h	86
8	8a	Ph	-NH(<i>t</i> -C ₄ H ₉)	r.t./6 h	71
9	8b	3-Me-Ph	-NH(<i>n</i> -C ₄ H ₉)	r.t./5 h	77
10	8c	Ph		r.t./5 h	75
11	8d	Ph	-NH(<i>n</i> -C ₃ H ₇)	r.t./4 h	73
12	8e	4-Cl-C ₆ H ₄		r.t./6 h	71

^aYields of isolated products based on iminophosphorane **3**.**Scheme 3:** Preparation of 2-alkylamino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **8**.

PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1} . ^1H NMR spectra were recorded in CDCl_3 on a Varian Mercury 400 spectrometer and resonances are given in ppm (δ) relative to TMS. Elementary analyses were taken on a Perkin-Elmer CHN 2400 elementary analysis instrument.

Preparation of [(3-ethoxycarbonyl-4,5-dimethylthiophen-2-yl)imino]triphenylphosphorane (**3**)

To a mixture of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (**2**) (2.0 g, 10 mmol), PPh_3 (5.24 g, 20 mmol) and C_2Cl_6 (4.74 g, 20 mmol) in dry CH_3CN (50 mL), was added

dropwise NEt_3 (4.2 mL, 30 mmol) at room temperature. After stirring for 4–5 h, the solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give iminophosphorane **3** as pale yellow crystals (82% yield), mp 131–133 °C; IR (KBr) cm^{-1} 1693 (C=O), 1484, 1196, 1149, 686; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.86–7.46 (m, 15H, Ph-H), 4.28 (q, $J = 7.2$ Hz, 2H, OCH_2), 2.39 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 1.11 (t, $J = 7.2$ Hz, 3H, CH_3); MS (70 eV) m/z (%): 459 (M^+ , 30), 444 (23), 277 (86), 183 (100), 77 (59). Calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_2\text{PS}$: C, 70.57; H, 5.70; N, 3.05; found: C, 70.45; H, 5.55; N, 3.19.

Table 2: The fungicidal activities of compounds **6** and **8** (50 mg/L).

Compounds	Relative inhibition (%)					
	<i>Fusarium oxysporum</i>	<i>Rhizoctonia solani</i>	<i>Botrytis cinerea</i>	<i>Gibberella zeae</i>	<i>Dothiorella gregaria</i>	<i>Colletotrichum gossypii</i>
6a	56	92	97	61	78	84
6b	74	99	100	86	93	88
6c	63	94	97	67	85	80
6d	74	96	100	69	81	80
6e	56	98	95	72	85	85
6f	70	93	98	64	81	84
6g	67	93	99	64	78	86
8a	70	87	100	82	78	80
8b	74	96	97	65	85	76
8c	52	98	100	68	81	81
8d	66	93	100	82	93	72
8e	71	81	74	44	67	68

Preparation of 2-(dialkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**

To a solution of iminophosphorane **3** (0.92 g, 2 mmol) in dry DCM (15 mL) was added the aromatic isocyanate (2 mmol) under nitrogen at room temperature. After the reaction mixture was stirred for 6–12 h at 0–5 °C, the solvent was removed under reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. After filtration, the solvent was removed to give carbodiimide **4**, which was used directly without further purification.

To a solution of **4** (prepared above) in DCM (15 ml) was added the secondary amine (2 mmol). After the reaction mixture was stirred for 2–4 h, the solvent was removed and anhydrous ethanol (10 ml) with several drops of EtONa in EtOH were added. The mixture was stirred for 6–12 h at room temperature. The solution was condensed and the residue was recrystallized from ethanol to give 2-(dialkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**.

2-Morpholino-3-phenyl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (6a). White crystals (76% yield), mp: 193–194 °C; IR (KBr) cm^{-1} 1694 (C=O), 1535, 1315, 748; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.52–7.33 (m, 5H, Ph-H), 3.40 (t, J = 4.8 Hz, 4H, 2 \times OCH₂), 3.08 (t, J = 4.8 Hz, 4H, 2 \times NCH₂), 2.39 (s, 3H, CH₃), 2.35 (s, 3H, CH₃); MS (70 eV) m/z (%): 340/341 (M^+ , 81), 309 (7), 284 (31), 254 (55), 152 (100), 90 (36), 76 (86); Anal. calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$: C, 63.32; H, 5.61; N, 12.31; found: C, 63.25; H, 5.69; N, 12.45.

2-Piperidino-3-phenyl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (6b). White crystals (73% yield), mp: 140–141 °C; IR (KBr) cm^{-1} 1690 (C=O), 1529, 1319, 745; ^1H NMR

(CDCl_3 , 400 MHz) δ : 7.49–7.31 (m, 5H, Ph-H), 3.05 (t, J = 5.6 Hz, 4H, 2 \times NCH₂), 2.39 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 1.39–1.18 (m, 6H, 3 \times CH₂); MS (70 eV) m/z (%): 339 (M^+ , 100), 310 (21), 254 (49), 194 (37), 152 (97), 76 (71); Anal. calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{OS}$: C, 67.23; H, 6.24; N, 12.38; found: C, 67.16; H, 6.26; N, 12.42.

2-(Dibutylamino)-3-phenyl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (6c): White crystals (70% yield), mp: 87–89 °C; IR (KBr) cm^{-1} 1688 (C=O), 1530, 1320, 742; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.70–7.26 (m, 5H, Ph-H), 2.97–2.93 (t, J = 7.2, 4H, 2 \times NCH₂), 2.38 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 1.22–1.09 (m, 8H, 2 \times CH₂CH₂CH₂), 0.82 (t, J = 7.2, 6H, 2 \times CH₃); MS (70 eV) m/z (%): 383 (M^+ , 100), 354 (6), 340 (15), 326 (28), 281/282 (29), 254/255 (34), 90 (11), 76 (32); Anal. calcd for $\text{C}_{22}\text{H}_{29}\text{N}_3\text{OS}$: C, 68.89; H, 7.62; N, 10.96; found: C, 68.76; H, 7.68; N, 10.82.

2-(Dihexylamino)-3-phenyl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (6d): White crystals (61% yield), mp: 70–71 °C; IR (KBr) cm^{-1} 1689 (C=O), 1530, 1323, 745; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.48–7.26 (m, 5H, Ph-H), 2.97–2.93 (t, J = 7.2, 4H, 2 \times NCH₂), 2.38 (s, 3H, CH₃), 2.34 (s, 3H, CH₃), 1.27–1.08 (m, 16H, 2 \times CH₂CH₂CH₂CH₂), 0.86 (t, J = 7.2, 6H, 2 \times CH₃); MS (70 eV) m/z (%): 439 (M^+ , 100), 368 (6), 354 (10), 281/282 (10), 77/76 (6); Anal. calcd for $\text{C}_{26}\text{H}_{37}\text{N}_3\text{OS}$: C, 71.03; H, 8.48; N, 9.56; found: C, 70.94; H, 8.50; N, 9.60.

2-(*N*-Methyl-*N*-phenylamino)-3-phenyl-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (6e): White crystals (74% yield), mp: 194–196 °C; IR (KBr) cm^{-1} 1684 (C=O), 1530, 1315, 746; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.10–6.57 (m,

10H, Ph-H), 3.25 (s, 3H, NCH₃), 2.40 (s, 3H, CH₃), 2.38 (s, 3H, CH₃); MS (70 eV) *m/z* (%): 361/360 (M⁺, 84), 254 (8), 103 (17), 90 (8), 76 (100), 58 (19); Anal. calcd for C₂₁H₁₉N₃OS: C, 69.78; H, 5.30; N, 11.62; found: C, 69.70; H, 5.18; N, 11.53.

2-Morpholino-3-(4-methylphenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (6f): White crystals (78% yield), mp: 164–166 °C; IR (KBr) cm⁻¹ 1685 (C=O), 1524, 1116, 743; ¹H NMR (CDCl₃, 400 MHz) δ: 7.30–7.20 (m, 4H, Ph-H), 3.42 (t, *J* = 4.8 Hz, 4H, 2×OCH₂), 3.09 (t, *J* = 4.8 Hz, 4H, 2×NCH₂), 2.41 (s, 3H, Ph-CH₃), 2.39 (s, 3H, CH₃), 2.35 (s, 3H, CH₃); MS (70 eV) *m/z* (%): 355 (M⁺, 100), 324 (8), 310 (20), 269 (23), 153 (28), 91 (22); Anal. calcd for C₁₉H₂₁N₃O₂S: C, 64.20; H, 5.95; N, 11.82; found: C, 64.06; H, 5.61; N, 11.75.

2-Morpholino-3-(4-chlorophenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (6g): White crystals (86% yield), mp: 173–175 °C; IR (KBr) cm⁻¹ 1689 (C=O), 1528, 1320, 741; ¹H NMR (CDCl₃, 400 MHz) δ: 7.48–7.28 (m, 4H, Ph-H), 3.44 (t, *J* = 4.8 Hz, 4H, 2×OCH₂), 3.08 (t, *J* = 4.8 Hz, 4H, 2×NCH₂), 2.38 (s, 3H, CH₃), 2.35 (s, 3H, CH₃); MS (70 eV) *m/z* (%): 375 (M⁺, 100), 340 (54), 289/290 (19), 162 (24), 110 (78), 90 (29), 77/76 (23); Anal. calcd for C₁₈H₁₈ClN₃O₂S: C, 57.52; H, 4.83; N, 11.18; found: C, 57.45; H, 4.76; N, 11.20.

Preparation of 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones 8

To the solution of 4 (2 mmol) prepared above in DCM (10 ml) was added the primary amine (2 mmol). After the reaction mixture was stirred for 5–6 h, the solvent was removed and anhydrous ethanol (10 ml) with several drops of EtONa in EtOH were added. The mixture was stirred for 6–12 h at room temperature. The solution was condensed and the residue was recrystallized from ethanol to give 2-(alkylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones 8.

2-(*tert*-Butylamino)-5,6-dimethyl-3-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (8a). White crystals (71% yield), mp: 184–186 °C; IR (KBr) cm⁻¹ 1692 (C=O), 1526, 1120, 748; ¹H NMR (CDCl₃, 400 MHz) δ: 7.56–7.16 (m, 5H, Ph-H), 3.82 (s, 1H, NH), 2.35 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 1.34 (s, 9H, 3×CH₃); MS (70 eV) *m/z* (%): 327 (M⁺, 93), 271 (91), 255 (31), 153 (100), 119 (19), 77 (23); Anal. calcd for C₁₈H₂₁N₃OS: C, 66.02; H, 6.46; N, 12.83; found: C, 66.22; H, 6.57; N, 12.97.

2-(Butylamino)-5,6-dimethyl-3-(3-methylphenyl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (8b). White crystals (77% yield), mp: 202–204 °C; IR (KBr) cm⁻¹ 1697 (C=O), 1543, 1120, 748; ¹H NMR (CDCl₃, 400 MHz) δ: 7.48–7.06 (m, 4H, Ph-H), 4.01 (s, 1H, NH), 3.38–3.31 (m, 2H, NCH₂), 2.42 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 1.49–1.22 (m, 4H, 2×CH₂), 0.88

(t, *J* = 7.2, 3H, CH₃); MS (70 eV) *m/z* (%): 341.2 (M⁺, 95), 285 (60), 153 (100), 133 (18), 105 (26), 91 (39); Anal. calcd for C₁₉H₂₃N₃OS: C, 66.83; H, 6.79; N, 12.31; found: C, 66.79; H, 6.88; N, 12.42.

2-(Cyclohexylamino)-5,6-dimethyl-3-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (8c). White crystals (75% yield), mp: 198–200 °C; IR (KBr) cm⁻¹ 1698 (C=O), 1540, 1128, 740; ¹H NMR (CDCl₃, 400 MHz) δ: 7.48–7.25 (m, 5H, Ph-H), 4.02 (s, 1H, NH), 2.37 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 2.00–1.96 (m, 1H, CH), 1.62–1.60 (m, 4H, 2×CH₂), 1.44–1.02 (m, 6H, 3×CH₂); MS (70 eV) *m/z* (%): 353 (M⁺, 44), 270 (34), 153 (100), 133 (24), 98 (19), 91 (52); Anal. calcd for C₂₀H₂₃N₃OS: C, 67.96; H, 6.56; N, 11.89; found: C, 68.08; H, 6.71; N, 11.78.

2-(Propylamino)-5,6-dimethyl-3-phenylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (8d). White crystals (73% yield), mp: 212–214 °C; IR (KBr) cm⁻¹ 1689 (C=O), 1530, 1130, 740; ¹H NMR (CDCl₃, 400 MHz) δ: 7.61–7.28 (m, 5H, Ph-H), 4.00 (s, 1H, NH), 3.34–3.29 (m, 2H, NCH₂), 2.36 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 1.52–1.46 (m, 2H, CH₂), 0.83 (t, *J* = 7.2, 3H, CH₃); MS (70 eV) *m/z* (%): 313 (M⁺, 77), 270 (79), 255 (22), 153 (100), 119 (31), 77 (34); Anal. calcd for C₁₇H₁₉N₃OS: C, 65.15; H, 6.11; N, 13.41; found: C, 65.28; H, 6.32; N, 13.60.

2-(Benzylamino)-3-(4-chlorophenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (8e). White crystals (71% yield), mp: 248–250 °C; IR (KBr) cm⁻¹ 1698 (C=O), 1538, 1130, 747; ¹H NMR (CDCl₃, 400 MHz) δ: 7.52–7.20 (m, 9H, Ph-H), 4.57 (s, 2H, CH₂), 4.32 (s, 1H, NH), 2.36 (s, 3H, CH₃), 2.31 (s, 3H, CH₃); MS (70 eV) *m/z* (%): 395 (M⁺, 100), 330 (48), 270 (12), 201 (74), 153 (24), 91 (31); Anal. calcd for C₂₁H₁₈ClN₃OS: C, 63.71; H, 4.58; N, 10.61; found: C, 63.80; H, 4.72; N, 10.44.

Acknowledgments

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