2-Aminothiophene derivatives in a novel synthesis of phthalimidines

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New aminophthalides were synthesized from *o*-formylbenzoic acid and substituted 2-aminothiophenes. Two of these compounds underwent recyclization in boiling Ac_2O to give the previously unknown 3-acetoxy-2-(3-cyano-4,5-dimethylthiophen-2-yl)-1,3-dihydroisoindol-1-one and 3-acetoxy-2-(3-cyano-4,5-tetramethylenethiophen-2-yl)-1,3-dihydroisoindol-1-one. The possible reaction mechanism and factors preventing the recyclization, in particular, the formation of intramolecular hydrogen bonds in the starting phthalides, were discussed. Some reactions of the resulting compounds with C-nucleophiles in trifluoroacetic acid were investigated. Two derivatives containing 4-hydroxy-3,5-di-*tert*-butylphenyl substituents were studied by X-ray diffraction.

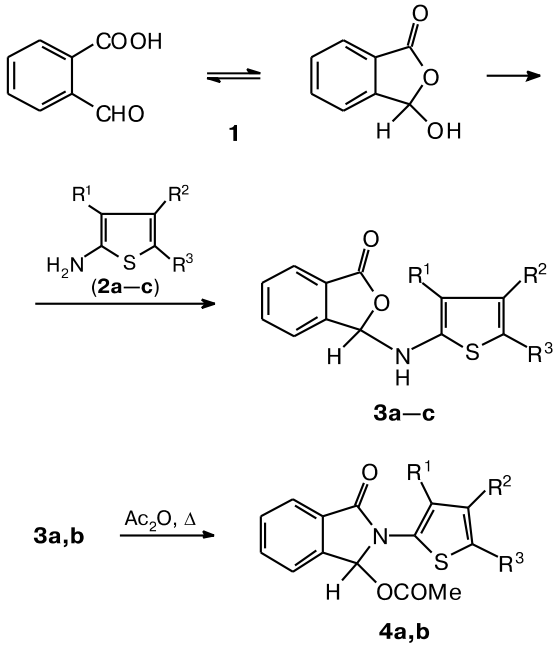
Key words: *o*-formylbenzoic acid, 2-aminothiophenes, 3-hetarylaminophthalides, azomethines of *o*-formylbenzoic acid, acetic anhydride, 2-hetaryl-3-acyloxyphthalimidines, 2,6-di-*tert*-butylphenol, indole, X-ray diffraction study.

Recently, we have reported on the new synthesis of phthalimidines by the recyclization of arylaminophthalides or acyl hydrazones of *o*-formylbenzoic acid (**1**) in acetic anhydride.[1] The resulting phthalimidines were used in the synthesis of potentially biologically active phthalimidines attached *via* an amide bridged to quinoline derivatives.[2]

The aim of the present study was to extend the recyclization of arylaminophthalides of *o*-formylbenzoic acid to the synthesis of phthalimidines containing thiophene substituents at position 2. It was found that tautomeric *o*-formylbenzoic acid (**1**), which reacts with primary aromatic amines to give 3-arylaminophthalides,[1,3] reacts in a similar way with 2-aminothiophene derivatives **2** (Scheme 1).

However, the resulting hetarylaminophthalides **3a—c** sharply differ in the chemical properties. Compounds containing the cyano group **3a,b** easily undergo recyclization in refluxing acetic anhydride to give the corresponding phthalimidines **4a,b** (see Scheme 1), as has been described for arylaminophthalides,[1] whereas compound **3c** containing the ethoxycarbonyl group in the *ortho* position with respect to the amino group is not involved in this reaction. This behavior can be attributed to both the steric and electronic factors. However, the experimental data obtained

Scheme 1



R^1 = CN, R^2 = R^3 = Me (**a**); R^1 = CN, R^2 + R^3 = $(CH_2)_4$ (**b**); R^1 = COOEt, R^2 = H, R^3 = Et (**c**)

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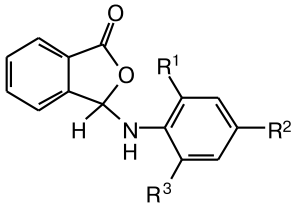
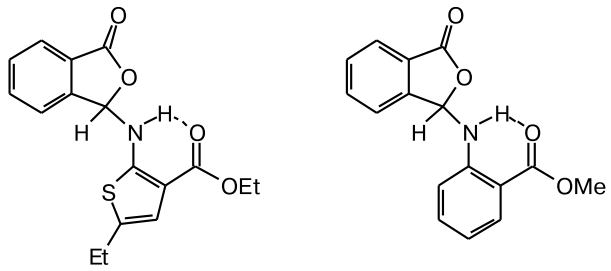
in our studies do not allow unambiguous conclusions to be drawn based only on these facts. For example, earlier[1] we have synthesized phthalides containing the 2-cyanoaniline, 2-chloroaniline, 2,4-dichloroaniline, and 3-nitroaniline moieties, *i.e.*, predominantly electron-withdrawing substituents, and all these compounds were easily transformed into phthalimidines in the reactions with Ac_2O. Hence, it is unlikely that the electron-withdrawing properties of the ethoxycarbonyl group hinder the reaction of **3c** with acetic anhydride. We confirmed this fact by comparing the behavior of 3-(2-methoxycarbonylphenylamino)phthalide (**3d**) and 3-(4-ethoxycarbonylphenyl)aminophthalide (**3e**) in the reactions with Ac_2O.



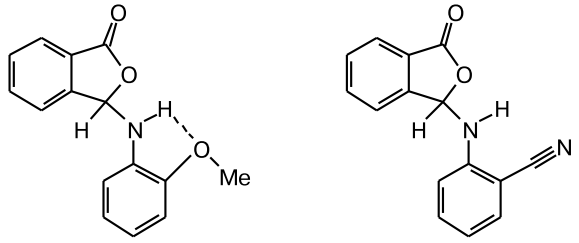
3d—h

Compound	R^1	R^2	R^3
3d	COOMe	H	H
3e	H	COOEt	H
3f	OMe	H	H
3g	Me	Me	Me
3h	CN	H	H

Phthalide **3d**, which was synthesized from *o*-formylbenzoic acid and methyl anthranilate, does not undergo recyclization in refluxing Ac_2O; instead, the recrystallization of **3d** was observed. Phthalide **3e**, which was prepared by the reaction of *o*-formylbenzoic acid with *p*-aminoethyl benzoate, readily undergoes recyclization in refluxing Ac_2O to the corresponding phthalimidine **4c** (Scheme 2). Finally, phthalide **3f** containing the *o*-anisidine moiety (the electron-donating substituent in the *ortho* position) that is formed in quantitative yield also does not undergo recyclization in refluxing Ac_2O. We failed to prepare phthalide and phthalimidine by the reactions with 2,6-dichloroaniline. Taking into account that both reactions occur with 2,4-dichloroaniline, the failure is most likely attributed to the steric factor. By contrast, *o*-formylbenzoic acid (**1**) easily reacts with mesidine **5** to form phthalide **3g**, which is transformed into phthalimidine **4d** in high yield in refluxing Ac_2O, *i.e.*, two methyl groups in the *ortho* position do not hinder the recyclization (see Scheme 2).

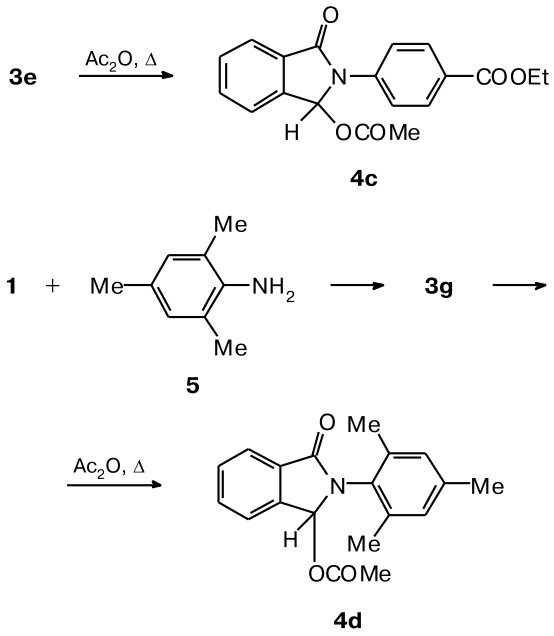


3c **3d**



3f **3h**

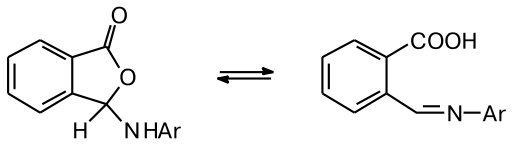
Scheme 2



4c **5** **4d**

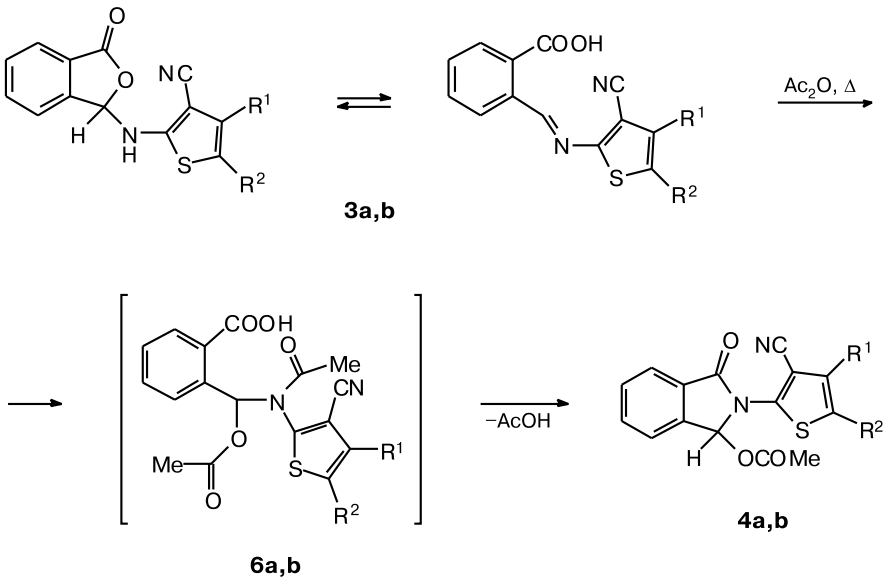
All these facts can be explained by assuming that azomethine rather than aminophthalide, which is in equilibrium with the former compound, reacts with acetic anhydride. The possibility of this "electrophilic tautomerism" was discussed in the review[4] and in the study[5] (Scheme 3).

Scheme 3



If, for one or other reason, aminophthalide cannot be transformed into the tautomeric azomethine form, it does

Scheme 4



$R^1 = R^2 = Me$ (**a**); $R^1 + R^2 = (CH_2)_4$ (**b**)

not undergo recyclization to phthalimidine. In all the above-mentioned cases, the tautomeric transformation into azomethine can be hindered by the formation of an intramolecular hydrogen bond between the proton at the nitrogen atom and the oxygen atom of the *ortho* group resulting in the formation of six- and five-membered rings. In the case of the *o*-cyano group, the formation of this intramolecular hydrogen bond is impossible because of the geometric factors, and aminophthalide **3h** (see Ref. 1) easily undergoes recyclization in Ac_2O.

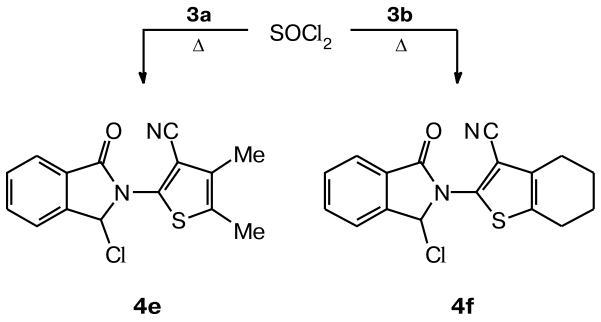
The proposed mechanism of the recyclization involves the acylation of the C=N bond of the tautomeric azomethine form and the phthalimidine ring closure accompanied by elimination of acetic acid (Scheme 4).

Other acylating agents, for example, acid chlorides, can be used for the recyclization of aminophthalides to phthalimidines. 3-Chloro-2-(3-cyano-4,5-dimethylthiophen-2-yl)-1,3-dihydroisoindol-1-one (**4e**) and 3-chloro-2-(3-cyano-4,5-tetramethylenethiophen-2-yl)-1,3-dihydroisoindol-1-one (**4f**) were synthesized by heating phthalides **3a,b**, respectively, with $SOCl_2$ (Scheme 5).

In trifluoroacetic acid, compounds **4a,b** react with C-nucleophiles like their analogs containing aryl substituents.[1] As in the study,[1] 2,6-di-*tert*-butylphenol (**7**) giving compound **8** and indole (**9**) producing compounds **10** (Scheme 6) were used as C-nucleophiles.

In the IR spectra of compounds **8a,b**, the stretching vibrations of the sterically hindered hydroxy group are observed as strongly broadened absorption bands shifted to lower frequencies (~3400 cm^{-1}). Earlier, we have described an analogous situation associated with the formation of

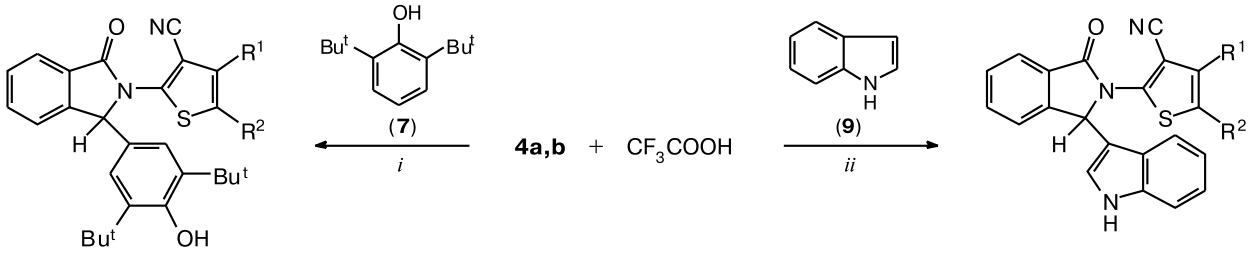
Scheme 5



intermolecular hydrogen bonds for 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,2,3,5-tetrahydrophenazine.[6] The X-ray diffraction study of compounds **8a,b** showed that the anomalies in their IR spectra are also associated with the formation of intermolecular hydrogen bonds. It should be noted that the formation of such bonds has not been observed in 2-arylphthalimidines containing the 4-hydroxy-3,5-di-*tert*-butylphenyl substituent at position 3, which have been synthesized earlier.[1]

There is one molecule per asymmetric unit cell of compound **8a**, whereas the asymmetric unit cell of compound **8b** contains two independent molecules labeled with A and B. Molecules **8a** and **8b** differ by the substituent at the carbon atoms of the thiophene ring: two methyl groups in **8a** and the cyclic moiety in **8b** (Fig. 1). The structural difference between molecules **8a**, **8b**(A), and **8b**(B) is related primarily to the mutual orientation of the cyclic moieties and the different conformation of the cyclohexene

Scheme 6



i. 72 °C, 1 min; *ii*. 20 °C, 3 h.
$R^1 = R^2 = Me$ (**a**); $R^1 + R^2 (CH_2)_4$ (**b**)

moiety in **8b**(A) and **8b**(B), where it adopts a half-chair and envelop conformation, respectively. All aromatic moieties in all molecules are planar. The isoindolone and 3,5-di-*tert*-butyl-4-hydroxyphenyl rings are almost perpendicular to each other, like those in tetrahydrophenazine studied earlier.[6] The dihedral angle α and the C(1)—N(1)—C(23)—S(1) torsion angle determining the orientation of the thiophene moiety are given below.

Compound	α	Angle/deg C(1)—N(1)—C(23)—S(1)
8a	83.38(6)	−24.3(3)
8b(A)	85.13(7)	−33.5(4)
8b(B)	77.40(7)	−44.3(3)

In spite of the presence of the *tert*-butyl substituents, the hydroxy groups in both structures are involved in the hydrogen bonding with the O(1) atom (Table 1) to form chains, like those in tetrahydrophenazine, where the nitrogen atom of the pyrazine ring serves as the proton acceptor. In the structures of **8a** and **8b**, the chains run along the crystallographic axis *a* and the molecules are related by the translation along this axis, the hydrogen bonds in **8b** being formed between the molecules of one type (A...A and B...B) (Fig. 2).

The stoichiometry of compounds **10a** and **10b** was confirmed by mass spectrometry and elemental analysis. However, the ^{1}H NMR spectra of these compounds are more similar to the spectra of mixtures of isomers (Table 2). In compound **10a**, the methyl groups give two multiplets, and the CH_2 groups of the cyclohexane moiety of compound **10b** appear as two broadened singlets. The region of aromatic protons is particularly complicated, the signals

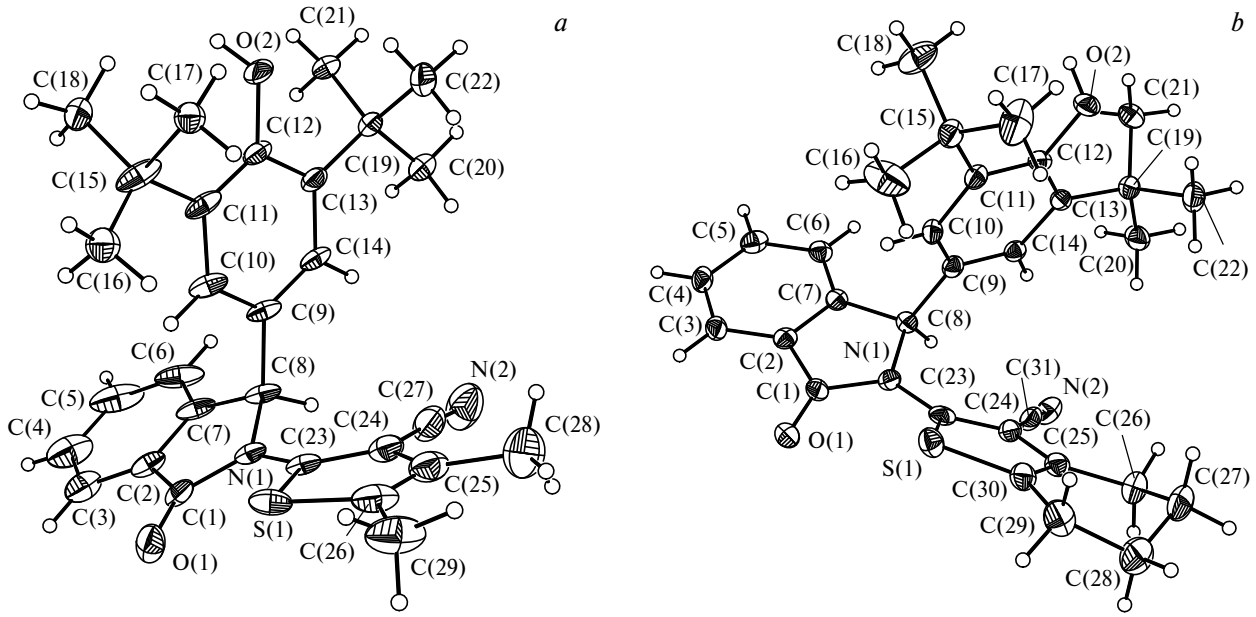


Fig. 1. Molecular structures of **8a** (*a*) (the second position of the disordered *tert*-butyl group is not shown) and **8b**(A) (*b*) with displacement ellipsoids drawn at the 50% probability level.

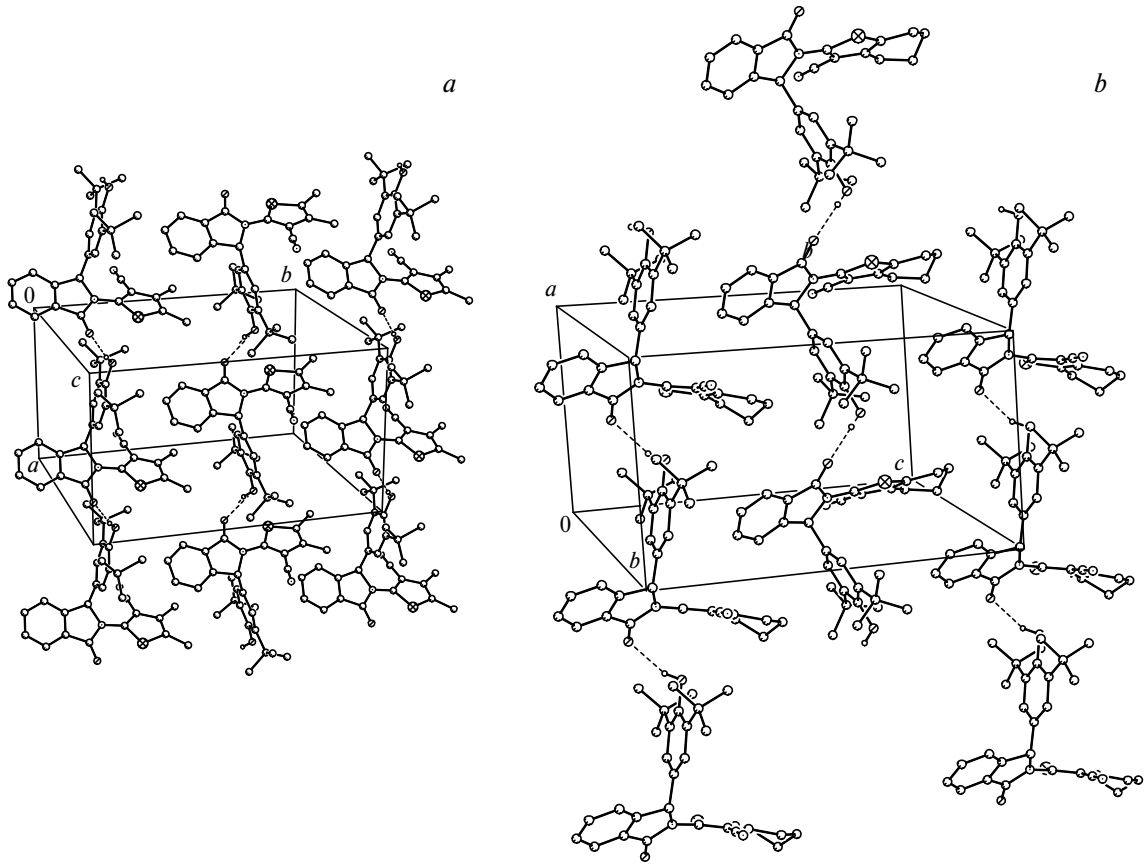


Fig. 2. Fragments of the crystal structures of **8a** (*a*) and **8b** (*b*); hydrogen-bonded ribbons running along the crystallographic direction *a* are shown. The central chain in the structure of **8b** consists of molecules A; two terminal chains consist of molecules B.

in this region being doubled and broadened. The absence of signals at δ 6.0—6.3 in the spectra of both compounds suggests that indole is attached at position 3, although other directions of the amidomethylation of indoles in strongly acidic media were also described in the literature.[7] Apparently, this character of the ^{1}H NMR spectra of compounds **10a,b** is associated with the formation of rotational isomers. This phenomenon has recently been described in detail in the study[8] on the new catalytic method for the synthesis of phthalimidines containing the indole substituents at position 3 from the corresponding hydroxy derivatives.

Table 1. Geometric parameters of hydrogen bonds in the structures of **8a** and **8b**

Compound	D—H...A	D—H	H...A	D...A	D—H...A /deg
		Å			
8a	O(2)—H(2)...O(1)^{i}	0.85	1.99	2.799	158
8b(A)	O(2)—H(2)...O(1)^{ii}	0.85	1.99	2.820	166
8b(B)	O(2′)—H(2′)...O(1′)^{ii}	0.85	2.20	2.929	144

Symmetry codes: (*i*) −1 + *x*, *y*, *z*; (*ii*) 1 + *x*, *y*, *z*.

Experimental

The IR spectra were recorded on a Varian Excalibur 3100 FI-IR instrument using the attenuated total internal reflection (ATR) technique. The ^{1}H NMR spectra were measured on a Varian UNITY-300 spectrometer. The mass spectra were obtained on a Finnigan MAT INCOS 50 GC-mass spectrometer using a direct inlet probe (EI, ionization energy was 70 eV).

2-Amino-3-cyano-4,5-dimethylthiophene (**2a**), 2-amino-3-cyano-4,5-tetramethylenethiophene (**2b**), and 2-amino-3-ethoxycarbonyl-5-ethylthiophene (**2c**) were synthesized according to the Gewald method[9] by the condensation of carbonyl compounds with malonodinitrile (**2a,b**) or ethyl cyanoacetate (**2c**) and sulfur in the presence of bases.

The ^{1}H NMR spectra of the compounds synthesized are given in Table 2.

3-(3-Cyano-4,5-dimethylthiophen-2-ylamino)phthalide (3a). A hot solution of *o*-formylbenzoic acid **1** (1.5 g, 10 mmol) in Pr^{i}OH (5 mL) was added to a hot solution of 2-amino-3-cyano-4,5-dimethylthiophene (**2a**) (1.52 g, 10 mmol) in Pr^{i}OH (10 mL). The reaction mixture was refluxed for 2 min, cooled, and kept on ice for 1 h. The precipitate that formed was filtered off, washed with cold Pr^{i}OH and petroleum ether, and dried. A colorless compound was obtained in a yield of 1.3 g, m.p. 170—175 °C. Water (5 mL) was added to the filtrate, and the mixture was kept on ice for 2 h. An additional amount (0.82 g) of the colorless

Table 2. ^{1}H NMR spectra ($CDCl_3$) of compounds **3a—g**, **4a—f**, **8a,b**, and **10a,b**

Compound	δ, *J*/Hz
3a	2.09 (d, 3 H, Me, *J* = 0.9); 2.19 (d, 3 H, Me, *J* = 0.6); 5.39 (d, 1 H, NH, *J* = 9.75); 6.56 (d, 1 H, CH, *J* = 9.75); 7.50—7.80 (m, 3 H, CH_{arom}); 7.93 (d, 1 H, C(7)H, *J* = 6.9)
3b	1.80 (m, 4 H, CH_2); 2.55 (m, 4 H, CH_2); 5.44 (d, 1 H, NH, *J* = 9.8); 6.59 (d, 1 H, CH, *J* = 9.8); 7.50—7.85 (m, 3 H, CH_{arom}); 7.95 (d, 1 H, C(7)H, *J* = 6.7)
3c	1.23 (t, 3 H, Me, *J* = 7.5); 1.29 (t, 3 H, Me, *J* = 7.0); 2.65 (q, 2 H, CH_2, *J* = 7.5); 4.20 (q, 2 H, CH_2, *J* = 7.0); 6.62 (d, 1 H, CH, *J* = 10.0); 6.73 (t, 1 H, C(4´)H, *J* = 1.2); 7.50—7.80 (m, 3 H, CH_{arom}); 7.93 (m, 1 H, CH_{arom}); 8.12 (d, 1 H, NH, *J* = 10.0)
3d	3.82 (s, 3 H, Me); 6.83 (d, 1 H, CH, *J* = 9.0); 6.91 (m, 1 H, CH_{arom}); 7.28 (d, 1 H, CH_{arom}, *J* = 8.4); 7.50 (m, 1 H, CH_{arom}); 7.55—7.85 (m, 3 H, CH_{arom}); 7.90—8.10 (m, 2 H, CH_{apom}); 8.65 (d, 1 H, NH, *J* = 9.0)
3e	1.37 (t, 3 H, Me, *J* = 7.0); 4.33 (q, 2 H, CH_2, *J* = 7.0); 5.02 (d, 1 H, NH, *J* = 10.5); 6.83 (d, 1 H, CH, *J* = 10.5); 6.93 (m, 2 H, CH_{arom}); 7.40—7.80 (m, 3 H, CH_{arom}); 7.90—8.20 (m, 3 H, CH_{arom})
3f	3.80 (s, 3 H, Me); 5.23 (d, 1 H, NH, *J* =10.8); 6.70—7.00 (m, 4 H, CH, CH_{arom}); 7.13 (m, 1 H, CH_{arom}); 7.50—7.80 (m, 3 H, CH_{arom}); 7.93 (d, 1 H, C(7)H, *J* = 7.5)
3g	2.25 (s, 3 H, Me); 2.36 (s, 6 H, Me); 3.70 (d, 1 H, NH, *J* =12.0); 6.38 (d, 1 H, CH, *J* =12.0); 6.89 (s, 2 H, C(3´)H, C(5´)H); 7.60 (m, 1 H, CH_{arom}); 7.75 (m, 2 H, CH_{arom}); 7.91 (d, 1 H, C(7)H, *J* = 7.5)
4a	2.18 (s, 3 H, Me); 2.25 (d, 3 H, Me, *J* = 0.5); 2.35 (d, 3 H, Me, *J* = 0.5); 7.56 (s, 1 H, CH); 7.65 (m, 2 H, CH_{arom}); 7.77 (d, 1 H, CH_{arom}, *J* = 7.3); 7.92 (d, 1 H, CH_{arom}, *J* = 6.9)
4b	1.87 (m, 4 H, CH_2); 2.18 (s, 3 H, Me); 2.69 (m, 4 H, CH_2); 7.55 (s, 1 H, CH); 7.57—7.80 (m, 3 H, CH_{arom}); 7.92 (d, 1 H, C(7)H, *J* = 7.0)
4c	1.38 (t, 3 H, Me, *J* = 7.1); 2.06 (s, 3 H, Me); 4.36 (q, 2 H, CH_2, *J* = 7.1); 7.50—7.80 (m, 6 H, CH, CH_{arom}); 7.90 (m, 1 H, CH_{arom}); 8.10 (m, 2 H, CH_{arom})
4d	1.98 (s, 3 H, COMe); 2.14, 2.23, 2.28 (all s, 9 H, Me); 6.94 (d, 2 H, C(3´)H, C(5´)H, *J* = 2.4); 7.21 (s, 1 H, CH); 7.60 (m, 3 H, CH_{arom}); 7.91 (m, 1 H, C(7)H)
4e	2.25, 2.35 (both s, 6 H, Me); 7.27 (s, 1 H, CH); 7.40—7.80 (m, 3 H, CH_{apom}); 7.93 (d, 1 H, C(7)H, *J* = 7.5)
4f	1.87 (m, 4 H, CH_2); 2.69 (m, 4 H, CH_2); 7.26 (s, 1 H, CH); 7.40—7.80 (m, 3 H, CH_{arom}); 7.93 (d, 1 H, C(7)H, *J* = 7.5)
8a	1.34 (s, 18 H, Bu^t); 2.11, 2.25 (both s, 6 H, Me); 5.22 (s, 1 H, OH); 6.44 (s, 1 H, CH); 6.96 (s, 2 H, C(2´)H, C(5´)H); 7.29 (m, 1 H, CH_{arom}); 7.53 (m, 2 H, CH_{arom}); 7.98 (d, 1 H, C(7)H, *J* = 7.2)
8b	1.35 (s, 18 H, Bu^t); 1.78 (m, 4 H, CH_2); 2.30—2.90 (m, 4 H, CH_2); 5.23 (s, 1 H, OH); 6.42 (s, 1 H, CH); 6.96 (s, 2 H, C(2´)H, C(6´)H); 7.29 (m, 1 H, CH_{arom}); 7.53 (m, 2 H, CH_{arom}); 7.98 (d, 1 H, C(7)H, *J* = 7.5)
10a	2.03 (m, 3 H, Me); 2.15 (m, 3 H, Me); 6.30—8.10 (m, 10 H, CH, CH_{arom}); 8.30 (m, 1 H, NH)
10b	1.73 (br.s, 4 H, CH_2); 2.52 (br.s, 4 H, CH_2); 6.35—8.20 (m, 10 H, CH, CH_{arom}); 8.35 (m, 1 H, NH)

compound characterized by the identical IR spectrum was obtained, m.p. 170—173 °C. The total yield of phthalide **3a** was 2.12 g (75%). Found (%): C, 63.43; H, 4.55; S, 11.65. $C_{15}H_{12}N_2O_2S$. Calculated (%): C, 63.36; H, 4.25; S, 11.27. IR, ν/cm^{-1}: 3253 (NH), 2214 (CN), 1774 (CO), 1560 (arom.), 1058, 901 (C—O—C). MS, *m/z*: 284 $[M]^+$.

3-(3-Cyano-4,5-tetramethylenethiophen-2-ylamino)phthalide (3b) was synthesized analogously to **3a** from a solution of **1** (0.75 g, 5 mmol) in Pr^iOH (10 mL) and a solution of 2-amino-3-cyano-4,5-tetramethylenethiophene (**2b**) (0.9 g) in Pr^iOH (15 mL). After cooling, an emulsion was precipitated with water, and the mixture was kept for 1 day. The precipitate that formed was filtered off, washed with H_2O, and dried. The yield was 1.2 g (77%). Analytically pure compound **3b** was obtained by recrystallization from Pr^iOH. A colorless compound, m.p. 155—157 °C (from Pr^iOH). Found (%): C, 65.53; H, 4.62; S, 10.60. $C_{17}H_{14}N_2O_2S$. Calculated (%): C, 65.79; H, 4.55; S, 10.33. IR, ν/cm^{-1}: 3267 (NH), 2210 (CN), 1756 (CO), 1559 (arom.), 1067, 877 (C—O—C). MS, *m/z*: 310 $[M]^+$.

3-(3-Ethoxycarbonyl-5-ethylthiophen-2-ylamino)phthalide (3c) was synthesized analogously to **3a** from a solution of **1** (3 g, 20 mmol) in EtOH (5 mL) and a solution of 2-amino-3-carbethoxy-5-ethylthiophene (**2c**) (3.5 g, 17 mmol) in EtOH (5 mL). The reaction mixture was cooled with ice and triturated. Then EtOH (10 mL) was added to the solidified mixture. The crystals that formed were filtered off, washed with EtOH, and dried. A colorless compound was obtained in a yield of 3.75 g, m.p. 115 °C. After 1 day, an addition amount (0.93 g) of the product, which was characterized by the identical IR spectrum, was isolated from the filtrate, m.p. 110—113 °C. The total yield was 4.68 g (80%). Found (%): C, 61.57; H, 5.32; S, 9.90. $C_{17}H_{17}NO_4S$. Calculated (%): C, 61.62; H, 5.17; S, 9.68. IR, ν/cm^{-1}: 3263 (NH), 1770, 1665 (CO), 1567, 1551 (arom.), 1052, 893 (C—O—C). MS, *m/z*: 331 $[M]^+$.

3-(2-Methoxycarbonylphenylamino)phthalide (3d). ***A.*** A mixture of compound **1** (0.5 g, 3.3 mmol) and methyl anthranilate (0.6 mL) was heated over a stove. The solidification of the mixture accompanied by elimination of water was observed. Then Pr^iOH (3 mL) was added, the mixture was refluxed, the precipitate was triturated, and the mixture was cooled. The precipitate that formed was filtered off, washed with Pr^iOH, and dried. A colorless compound. The yield was 0.87 g (92%). Found (%): C, 67.92; H, 4.83; N, 4.76. $C_{16}H_{13}NO_4$. Calculated (%): C, 67.84; H, 4.63; N, 4.94. IR, ν/cm^{-1}: 3322 (NH); 1764,

1682 (CO); 1587, 1518 (arom.); 1063, 886 (C—O—C). MS, *m/z*: 283 $[M]^+$.

B. Methyl anthranilate (0.6 mL) was added to a boiling solution of *o*-formylbenzoic acid (0.5 g, 3.3. mol) in Pr^iOH (5 mL). After a short period of time, almost immediate crystallization occurred. The reaction mixture was cooled. The precipitate that formed was filtered off, washed with cold Pr^iOH and petroleum ether, and dried. A colorless compound, m.p. 202—204 °C (from Pr^iOH). The yield was 0.9 g (95%).

3-(4-Ethoxycarbonylphenylamino)phthalide (3e). A hot solution of compound **1** (0.5 g, 3.3 mmol) in Pr^iOH (3 mL) was added to a hot solution of 4-aminoethyl benzoate (0.55 g, 3.3 mmol) in Pr^iOH (5 mL). The reaction mixture was heated to reflux, cooled, and triturated. The precipitate that formed was filtered off, washed with cold Pr^iOH and petroleum ether, and dried. A colorless compound, m.p. 190—192 °C. The yield was 0.86 g (87%). Found (%): C, 68.43; H, 5.32; N, 4.59. $C_{17}H_{15}NO_4$. Calculated (%): C, 68.68; H, 5.09; N, 4.71. IR, ν/cm^{-1}: 3314 (NH); 1732, 1692 (CO); 1604, 1524 (arom.); 1078, 873 (C—O—C). MS, *m/z*: 297 $[M]^+$.

3-(2-Methoxyphenylamino)phthalide (3f) was synthesized analogously to **3e** from a solution of compound **1** (0.5 g, 3.3 mmol) in Pr^iOH (5 mL) and *o*-anisidine (0.5 mL, 4.5 mmol). A colorless compound, m.p. 161—162 °C. The yield was 0.82 g (96%). Found (%): C, 70.39; H, 5.24; N, 5.52. $C_{15}H_{13}NO_3$. Calculated (%): C, 70.58; H, 5.13; N, 5.49. IR, ν/cm^{-1}: 3373 (NH); 1747 (CO); 1600, 1505 (arom.); 1020, 855 (C—O—C). MS, *m/z*: 255 $[M]^+$.

3-(2,4,6-Trimethylphenylamino)phthalide (3g). 2,4,6-Trimethylaniline (**5**) (0.5 mL) was added to a hot solution of compound **1** (0.5 g, 3.3 mmol) in Pr^iOH (3 mL). The reaction mixture was heated to reflux, cooled with ice water, and triturated. An equal volume of petroleum ether was added to the voluminous crystalline precipitate. Then the precipitate was filtered off, washed with petroleum ether, and dried. A colorless compound, m.p. 130 °C. The yield was 0.65 g (quantitative). Found (%): C, 76.19; H, 6.70; N, 5.56. $C_{17}H_{17}NO_2$. Calculated (%): C, 76.38; H, 6.41; N, 5.24. IR, ν/cm^{-1}: 3357 (NH); 1757 (CO); 1615, 1486 (arom.); 1065, 867 (C—O—C). MS, *m/z*: 267 $[M]^+$.

3-Acetoxy-2-(3-cyano-4,5-dimethylthiophen-2-yl)-1,3-dihydroisoindol-1-one (4a). A mixture of phthalide **3a** (0.85 g, 3 mmol) and Ac_2O (2.5 mL) was heated until dissolution, refluxed for 2 min, cooled with ice, and triturated. Then Pr^iOH (3 mL) was added, and the mixture was kept on ice for 10 min. The precipitate that formed was filtered off, washed with cold Pr^iOH and petroleum ether, and dried. A yellowish compound, m.p. 155—160 °C. The yield was 0.88 g (90%). Found (%): C, 62.86; H, 4.11; N, 8.69; S, 9.43. $C_{17}H_{14}N_2O_3S$. Calculated (%): C, 62.56; H, 4.32; N, 8.58; S, 9.82. IR, ν/cm^{-1}: 2217 (CN); 1748, 1726 (CO); 1578, 1504. MS, *m/z*: 326 $[M]^+$.

3-Acetoxy-2-(3-cyano-4,5-tetramethylenethiophen-2-yl)-1,3-dihydroisoindol-1-one (4b). A mixture of phthalide **3b** (0.62 g, 2 mmol) and Ac_2O (1.5 mL) was heated until dissolution, refluxed for 1 min, and cooled. Then Pr^iOH (20 mL) was added, and the mixture was cooled with ice. The precipitate that formed was filtered off, washed with cold Pr^iOH and petroleum ether, and dried. A yellowish compound, m.p. 155—160 °C. The yield was 0.55 g (78%). Found (%): C, 64.90; H, 4.12; N, 8.13; S, 8.75. $C_{19}H_{16}N_2O_3S$. Calculated (%): C, 64.76; H, 4.58; N, 7.95; S, 9.10. IR, ν/cm^{-1}: 2214 (CN); 1753, 1723 (CO); 1583, 1508 (arom.). MS, *m/z*: 352 $[M]^+$.

3-Acetoxy-2-(4-ethoxycarbonylphenyl)-1,3-dihydroisoindol-1-one (4c). A mixture of phthalide **3e** (0.6 g, 2 mmol) and Ac_2O (1.5 mL) was heated until dissolution, refluxed for 2 min, and cooled. Then Bu^iOH (5 mL) was added, and the reaction mixture was cooled. The precipitate that formed was filtered off, washed with cold Bu^iOH and petroleum ether, and dried. The yield was 0.5 g (74%). To prepare the chemically pure product, the compound was recrystallized from isooctane. Colorless crystals, m.p. 122—123 °C. Found (%): C, 67.03; H, 5.27; N, 4.25. $C_{19}H_{17}NO_5$. Calculated (%): C, 67.25; H, 5.05; N, 4.13. IR, ν/cm^{-1}: 1731, 1703 (CO); 1606, 1514 (arom.). MS, *m/z*: 339 $[M]^+$.

3-Acetoxy-1,3-dihydro-2-(2,4,6-trimethylphenyl)isoindol-1-one (4d). A mixture of phthalide **3g** (0.53 g, 2 mmol) and Ac_2O (1 mL) was refluxed for 1 min and cooled. Then MeOH (5 mL) and water (25 mL) were added. The oil that formed was triturated with ice cooling until the mixture completely solidified (~3 h). The precipitate was filtered off, washed with water, and dried. A colorless compound, m.p. 100—101 °C. The yield was 0.54 g (87%). After recrystallization from isooctane (20 mL), compound **4d** was obtained in a yield of 0.4 g (64%). Found (%): C, 73.44; H, 6.27; N, 4.82. $C_{19}H_{19}NO_3$. Calculated (%): C, 73.77; H, 6.19; N, 4.53. IR, ν/cm^{-1}: 1746, 1712 (CO); 1611, 1486, 1466 (arom.). MS, *m/z*: 309 $[M]^+$.

Synthesis of compounds 4e,f (general procedure). Thionyl chloride (0.25 mL) was added to phthalide **3a** or **3b** (1 mmol). After the cessation of gas evolution and the formation of a homogeneous mixture, an excess of $SOCl_2$ was removed *in vacuo*. The residue was recrystallized from isooctane (60—80 mL).

3-Chloro-2-(3-cyano-4,5-dimethylthiophen-2-yl)-1,3-dihydroisoindol-1-one (4e). A pale-yellow crystalline compound, m.p. 143—144 °C (from isooctane). The yield was 0.41 g (68%). Found (%): C, 59.90; H, 3.93; Cl, 11.40; S, 10.23. $C_{15}H_{11}ClN_2OS$. Calculated (%): C, 59.50; H, 3.66; Cl, 11.71; S, 10.59. IR, ν/cm^{-1}: 2213 (CN); 1727 (CO); 1615, 1573, 1504 (arom.). MS, *m/z*: 302 $[M]^+$.

3-Chloro-2-(3-cyano-4,5-tetramethylenethiophen-2-yl)-1,3-dihydroisoindol-1-one (4f). A pale-yellow crystalline compound, m.p. 161—163 °C (from isooctane). The yield was 0.2 g (61%). Found (%): C, 61.73; H, 4.11; Cl, 10.41; S, 9.30. $C_{17}H_{13}ClN_2OS$. Calculated (%): C, 62.10; H, 3.99; Cl, 10.78; S, 9.75. IR, ν/cm^{-1}: 2210 (CN); 1726 (CO); 1613, 1574, 1505 (arom.). MS, *m/z*: 328 $[M]^+$.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-(3-cyano-4,5-dimethylthiophen-2-yl)-1,3-dihydroisoindol-1-one (8a). A mixture of phthalimidine **5a** (0.33 g, 1 mmol), 2,6-di-*tert*-butylphenol (**7**) (0.3 g, 1.4 mmol), and CF_3COOH (0.2 mL) was refluxed for 1 min and cooled. Then Pr^iOH (5 mL) was added, and the mixture was heated until homogenezation, after which colorless crystals formed. The reaction mixture was cooled with ice. The precipitate that formed was filtered off, washed with cold EtOH and petroleum ether, and dried. A colorless compound, m.p. 200—203 °C. The yield was 0.39 g (82%). Found (%): C, 74.03; H, 7.01; N, 6.18; S, 6.95. $C_{29}H_{32}N_2O_2S$. Calculated (%): C, 73.70; H, 6.82; N, 5.93; S, 6.78. IR, ν/cm^{-1}: 3475 br. (OH); 2205 (CN); 1695 (CO); 1600, 1595, 1567 (arom.). MS, *m/z*: 472 $[M]^+$.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-(3-cyano-4,5-tetramethylenethiophen-2-yl)-1,3-dihydroisoindol-1-one (8b). A mixture of phthalimidine **5b** (0.35 g, 1 mmol), 2,6-di-*tert*-butylphenol (**7**) (0.3 g, 1.4 mmol), and CF_3COOH (0.2 mL) was refluxed for 1 min and cooled. Then Pr^iOH (5 mL) was added

and the mixture was kept on ice for 1 h. The precipitate that formed was filtered off, washed with cold EtOH and petroleum ether, and dried. A colorless compound, m.p. 210—213 °C. The yield was 0.3 g (60%). Found (%): C, 74.33; H, 7.01; N, 5.83; S, 6.51. $C_{31}H_{34}N_2O_2S$. Calculated (%): C, 74.66; H, 6.87; N, 5.62; S, 6.43. IR, ν/cm^{-1}: 3420 br. (OH); 2205 (CN); 1695 (CO); 1615, 1600, 1567 (arom.). MS, *m/z*: 498 $[M]^+$.

2-(3-Cyano-4,5-dimethylthiophen-2-yl)-1,3-dihydro-3-(3-indolyl)isoindol-1-one (10a). A mixture of phthalimidine **5a** (0.33 g, 1 mmol), indole (**9**) (0.12 g, 1 mmol), and CF_3COOH (1 mL) was kept at room temperature for 3 h, EtOH (5 mL) was added, and the reaction mixture was cooled with ice. The precipitate that formed was filtered off, washed with cold EtOH and petroleum ether, and dried. Analytically pure pale-yellow compound **10a** was obtained in a yield of 0.06 g, m.p. 200—201 °C (from Pr^iOH). Water (20 mL) was added to the filtrate, and an additional amount (0.25 g) of compound **10a** was isolated. The total yield was 0.31 g (81%). Found (%): C, 71.90; H, 4.40; N, 10.73; S, 8.81. $C_{23}H_{17}N_3OS$. Calculated (%): C, 72.04; H, 4.47; N, 10.96; S, 8.36. IR, ν/cm^{-1}: 3300 br. (NH); 2215 (CN); 1705 (CO); 1614, 1568, 1503 (arom.). MS, *m/z*: 383 $[M]^+$.

2-[2-(3-Cyano-4,5-tetramethylenethiophen-2-yl)]-1,3-dihydro-3-(3-indolyl)isoindol-1-one (10b). A mixture of compound **5b** (0.35 g, 1 mmol), indole (**9**) (0.12 g, 1 mmol), and CF_3COOH (1 mL) was kept at room temperature for 3 h, EtOH (7 mL) was added, and the reaction mixture was cooled with ice. The crystalline precipitate that formed was filtered off, washed with cold EtOH and petroleum ether, and dried. A yellow compound was obtained in a yield of 0.14 g, m.p. 210—211 °C (from Pr^iOH). An additional amount (0.14 g) of compound **10b** was precipitated from the filtrate. The total yield was 0.28 g (68%). Found (%): C, 73.40; H, 4.59; N, 10.34; S, 7.65. $C_{25}H_{19}N_3OS$. Calculated (%): C, 73.33; H, 4.68; N, 10.26; S, 7.83. IR, ν/cm^{-1}: 3328 br. (NH); 2217 (CN); 1709 (CO); 1613, 1568, 1502 (arom.). MS, *m/z*: 409 $[M]^+$.

X-ray diffraction study. Single crystals of compounds **8a** and **8b** were grown by slow evaporation of their solutions in Pr^iOH. The experimental intensities were measured on a SMART APEX2 CCD diffractometer (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, ω-scanning technique). The measured intensities were processed using the SAINT Plus,[10] SADABS,[11] and APEX2 programs.[12] The structures of the complexes were solved

Table 3. Crystallographic data and the X-ray data collection and structure refinement statistics for compounds **8a** and **8b**

Parameter	**8a**	**8b**
Molecular formula	$C_{29}H_{32}N_2O_2S$	$C_{31}H_{34}N_2O_2S$
Molecular weight	472.63	498.66
Crystal color	Colorless	Colorless
Crystal shape	Prism	Plate
Crystal dimensions/mm	0.21×0.18×0.12	0.32×0.26×0.16
T/K	100(2)	100(2)
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
a/Å	9.9095(16)	9.944(2)
b/Å	17.281(3)	15.097(4)
c/Å	15.463(3)	18.067(4)
α/deg	90	96.141(5)
β/deg	90.572(3)	92.267(5)
γ/deg	90	93.588(5)
V/Å^3	2647.8(7)	2688.6(11)
Z	4	4
d_{calc}/g cm^{-3}	1.186	1.232
μ/mm^{-1}	0.150	0.151
F(000)	1008	1064
θ-Scan range/deg	1.77—28.00	1.13—28.00
Number of measured reflections	28662	29921
Number of independent reflections	6380	12911
R_{int}	0.0508	0.0863
Number of refined parameters	315	661
Number of reflections with $I \geq 2\sigma(I)$	5370	6966
Completeness of the data set (%)	99.7	99.6
GOOF	1.120	0.983
$R_1(F)^a$ ($I \geq 2\sigma(I)$)	0.0689	0.0647
$wR_2(F^2)^b$ (based on all reflections)	0.1649	0.1479
Residual electron density (min/max)/$e \cdot$ Å^{-3}	0.578/−0.462	0.473/−0.455

[a] $R_1 = \Sigma||F_0| - |F_c||/\Sigma(F_0)$.
[b] $wR_2 = (\Sigma[w(F_0^2 - F_c^2)^2]/\Sigma[w(F_0^2)^2]^{1/2}$.

by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all nonhydrogen atoms based on F^2_{hkl}. In compound **8a**, the C(16) and C(17) atoms of the *tert*-butyl group are disordered over two sites with equal occupancies and were refined isotropically. The hydrogen atoms, except for the hydrogen atoms at the oxygens, were positioned geometrically. The hydrogen atoms at the oxygens were located in difference electron density maps and then normalized to the distance of 0.85 Å. The positions of all hydrogen atoms were refined using a riding model ($U_{iso}(H) = nU_{eq}$(C,O), where $n = 1.5$ for the carbon atoms of the methyl groups and the oxygen atoms, $n = 1.2$ for the other C atoms). The structure solution and refinement was performed with the use of the SHELXTL program package.[13] Crystallographic data and the X-ray data collection and structure refinement statistics are given in Table 3.

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