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A Convenient Synthesis of 3,4-Diaryl(hetaryl)-Substituted Maleimides and Maleic Anhydrides

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Abstract—A convenient procedure has been developed for the synthesis of 3,4-diaryl(or hetaryl)maleimides by cross coupling of N-substituted 3,4-dibromomaleimides with aryl(hetaryl)boronic acids in the presence of $Pd(Ph_3P)_4$ and CsF. The reaction ensures high yields of the products and requires relatively small amount of the catalyst; it can be performed on an enlarged scale. The resulting maleimides are readily converted into the corresponding maleic anhydrides.

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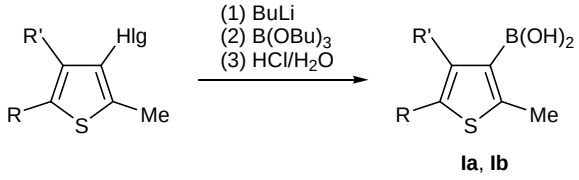
Maleimide and maleic anhydride derivatives having aromatic or heterocyclic substituents in positions *3* and *4* are used as photochromic compounds [1–3] possessing unique properties; in particular, their photoinduced transformations are characterized by thermal irreversibility and high cycling number. Such photochromes are exceptionally promising as materials for optical data recording and storage [4, 5]. In addition, maleimides containing indole rings and related compounds exhibit a very broad spectrum of biological activity [6–10].

Cross coupling of aryl or vinyl halides with organoboron compounds, catalyzed by transition metal salts (mostly by palladium compounds; Suzuki–Miyaura reaction) is a general method for building up new carbon–carbon bonds, which has found wide application in organic synthesis [11–13]. We believed that an obvious and convenient synthetic approach to diaryl(hetaryl)maleimides could be cross coupling of *N*-alkyl-3,4-dibromomaleimides with various aryl- and hetarylboronic acids. However, we have found no published data on reactions of *N*-alkyl-3,4-dibromomaleimides with boronic acids, leading to symmetrically substituted products.

The present article reports the results of our studies aimed at developing a convenient procedure for the synthesis of 3,4-diaryl(hetaryl)maleimides from accessible derivatives of 3,4-dibromomaleimide and aryl- and hetarylboronic acids.

2-Methyl-1-benzothiophen-3-yl- and 2,5-dimethylthiophen-3-ylboronic acids **Ia** and **Ib** were synthesized from 3-bromo-2-methyl-1-benzothiophene [14] and 3-iodo-2,5-dimethylthiophene [15], respectively, as shown in Scheme 1. 3-Chlorophenyl-, 4-methoxyphenyl-, and 3-methoxyphenylboronic acids **Ic**–**Ie** are commercially available. 3,4-Dibromo-*N*-butylmaleimide (**IIa**) was obtained by bromination of *N*-butylmaleimide in glacial acetic acid in the presence of sodium acetate. The synthesis of *N*-benzyl-3,4-dibromomaleimide (**IIb**) was described in [16].

Scheme 1.

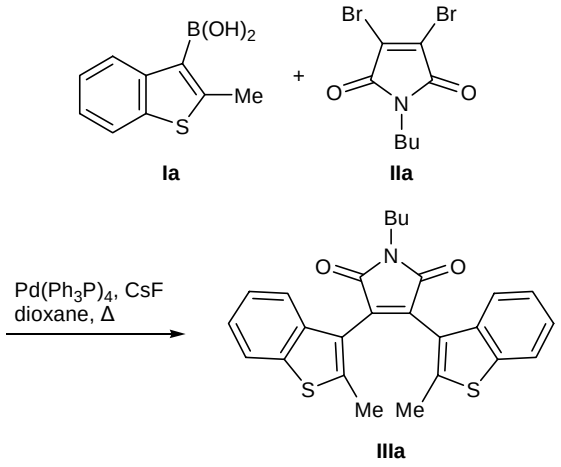


Ia, **Ib**

Hlg = Br, RR' = benzo (**a**, yield 80%); Hlg = I, R = Me, R' = H, (**b**, 76%).

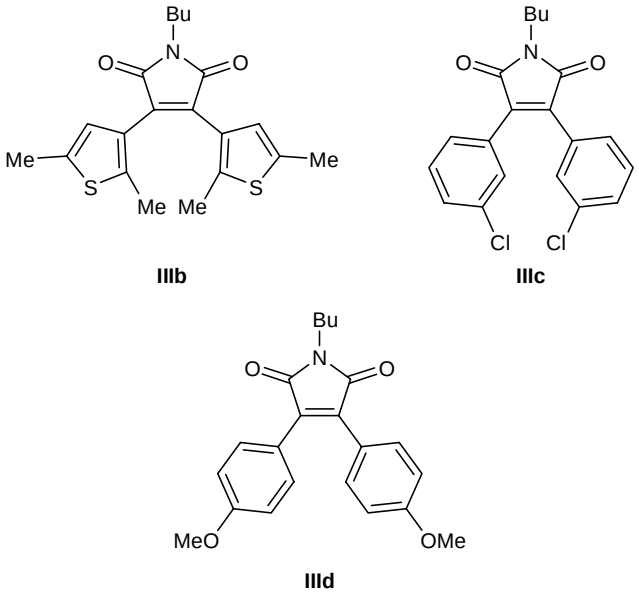
We have found that 2-methyl-1-benzothiophen-3-ylboronic acid (**Ia**) readily reacts with 3,4-dibromo-*N*-butylmaleimide (**IIa**) in dioxane in the presence of $Pd(Ph_3P)_4$ and CsF to give maleimide **IIIa** (see table,

Scheme 2.



Scheme 2). The maximal yield of compound **IIIa** was obtained with the use of 2.2 mol of boronic acid **Ia**, 4 mol % of $Pd(Ph_3P)_4$, and 5 mol of CsF per mole of dibromide **IIa**, the amount of the solvent (dioxane) being 100 ml per gram of **Ia**. The nature of the base is important: in the presence of CsF (see table, run no. 1), the yield of imide **IIIa** was 76% in 4 h, while in the presence of other bases, the yield was considerably lower even after prolonged heating at the boiling point; moreover, in the latter case, the main reaction direction was the transformation of acid **Ia** into 2-methyl-1-benzothiophene.

The proposed modified procedure is general, and it was successfully extended to other heterocyclic and aromatic boronic acids. Under the above conditions, we obtained symmetrically substituted maleimides **IIIb**–**IIId** in 86–98% yield. Neither chromatographic



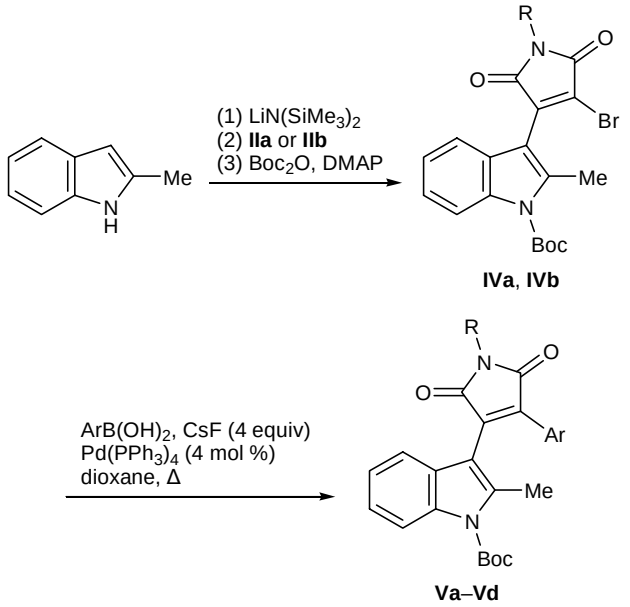
Cross coupling of 2-methyl-1-benzothiophen-3-ylboronic acid (**Ia**) with *N*-butyl-3,4-dibromomaleimide (**IIa**)

Run no.	Base	Reaction time, h	Yield of **IIIa**, %
1	CsF	4	76
2	K_3PO_4	30	30
3	Na_2CO_3	30	22
4	K_2CO_3	30	13
5	$NaHCO_3$	30	6
6	Cs_2CO_3	30	5

treatment nor recrystallization was necessary to isolate compounds **IIIa** and **IIIc** with a sufficient purity.

The developed procedure turned out to be efficient for the synthesis of unsymmetrically substituted maleimides as well. By reactions of quite accessible *N*-butyl- and *N*-benzyl-3-bromo-4-[(1-*tert*-butoxycarbonyl)-2-methylindol-3-yl]maleimides **IVa** and **IVb** with 2-methyl-1-benzothiophen-3-yl, 2,5-dimethylthiophen-3-yl-, 3-chlorophenyl-, and 4-methoxyphenylboronic acids (reaction time 1–5 h) we obtained the corresponding disubstituted products **Va**–**Vd** in 71–90% yield (Scheme 3).

Scheme 3.



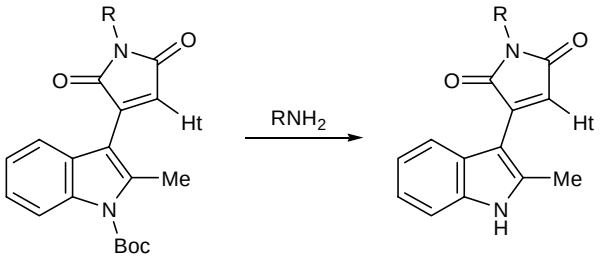
IV, R = Bu (**a**), $PhCH_2$ (**b**); **V**, R = Bu, Ar = 4-ClC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**), 2-methyl-1-benzothiophen-3-yl (**c**), 2,5-dimethylthophen-3-yl (**d**).

There are only two published examples of cross coupling of *N*-alkyl-3-bromo-4-(indolyl)maleimides with boronic acids. Routier et al. [17] described the

cross coupling of 3-methoxynaphthalen-2-ylboronic acid with 3-bromo-*N*-methyl-4-(1-phenylsulfonyl-1*H*-indol-3-yl)maleimide in the presence of 10% of $Pd(OAc)_2$ as catalyst using 1.5 equiv of the boronic acid (yield 80%). Here, protection of the indole nitrogen atom with *tert*-butoxycarbonyl group was ineffective, so that the authors used phenylsulfonyl protection. Wang et al. [18] reported on the synthesis of a benzothienyl analog of anticarcinogenic drug rebeccamycin, which included cross coupling of 5,6-difluoro-1-benzothiophen-3-ylboronic acid with 3-bromo-*N*-(4-*tert*-butylbenzyl)-4-(5,6-difluoro-1*H*-indol-3-yl)maleimide; the yield in this step was 82%, but the amount of $Pd(Ph_3P)_2Cl_2$ (catalyst) was 20%.

Removal of the protecting group from the indole nitrogen atom in compounds **Vc** and **Vd** was not difficult. By heating maleimides **Vc** and **Vd** with butylamine and benzylamine, respectively, we obtained in high yields compounds **VIa** and **VIb** having no substituent on the indole nitrogen atom (Scheme 4).

Scheme 4.



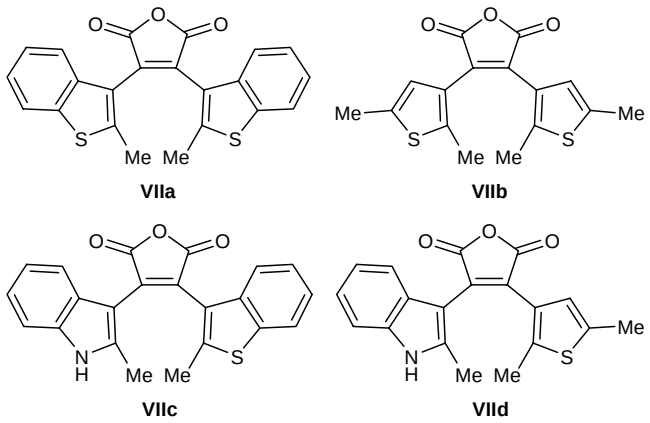
Vc, **Vd** **VIa**, **VIb**

Vc, **VIa**, R = Bu, Ht = 2-methyl-1-benzothiophen-3-yl;
Vd, **VIb**, R = $PhCH_2$, Ht = 2,5-dimethylthiophen-3-yl.

Accessibility of maleimide derivatives prompted us to use them as starting compounds in the synthesis of the corresponding disubstituted maleic anhydrides. Like photochromes based on maleimides, analogous maleic anhydride derivatives are promising as optical memory elements [4, 5]. Compounds **IIIa**, **IIIb**, **VIa**, and **VIb** were converted into the corresponding maleic anhydrides by heating in aqueous 1,4-dioxane containing potassium hydroxide and subsequent acidification. As a result, maleic anhydrides **VIIa**–**VIId** were obtained in 64–94% yield.

The structure of the newly synthesized compounds was confirmed by the ^{1}H NMR and mass spectra and elemental analyses.

The developed procedure is the first example of cross coupling of *N*-substituted 3,4-dibromomaleimides with boronic acids, leading to symmetric 3,4-diaryl(hetaryl)maleimides. Also, the procedure makes it possible to synthesize in high yield unsymmetrically substituted maleimides having an indole fragment. The reaction requires relatively small amount of catalyst (4%), and the resulting maleimides can be converted into the corresponding maleic anhydrides.



EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-250 (250 MHz) and Bruker AM-300 (300 MHz) spectrometers using DMSO-d_6 and $CDCl_3$ as solvents. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT instrument. The melting points were determined on a Boetius melting point apparatus coupled with a microscope; uncorrected values are given. The progress of reactions and the purity of products were monitored by TLC on Merck 60 F_{254} plates. Tetrahydrofuran, 1,4-dioxane, and diethyl ether were distilled over sodium diphenylketyl prior to use. Hexane and ethyl acetate were distilled over calcium hydride. Silica gel Merck 60 (0.040–0.063 mm) was used for flash chromatography. All reactions were carried out in preliminarily calcined glassware. 1,4-Dioxane was subjected to triple evacuation–pressurization under argon just before use in cross-coupling reactions.

2-Methyl-1-benzothiophen-3-ylboronic acid (Ia). A solution of 8.6 g (38 mmol) of 3-bromo-2-methylbenzothiophene [14] in 100 ml of THF was cooled to –78°C, and 27 ml of a 1.6 M solution of butyllithium in hexane was added under argon. The mixture was stirred for 15 min at that temperature, 15.3 ml (13.07 g, 56 mmol) of tributyl borate was added in one portion, the mixture was stirred for 1 h at –78°C, the cooling bath was removed, and the mixture was left overnight.

Methanol, 5 ml, was added, the mixture was evaporated on a rotary evaporator at a bath temperature not exceeding 50°C, 100 ml of diethyl ether was added to the residue, the mixture was cooled with ice, and a mixture of 5 ml of concentrated hydrochloric acid and 35 ml of water was added. The mixture was stirred for 1 h, the organic phase was separated, and the aqueous phase was extracted with diethyl ether (3 × 20 ml). The extracts were combined with the organic phase and washed with water and a 5% solution of sodium hydroxide (4 × 20 ml). The alkaline solution was washed with diethyl ether (2 × 20 ml), cooled to –5°C, and acidified with 10 ml of concentrated hydrochloric acid under stirring. The precipitate was filtered off, washed with a small amount of water, and dried in a desiccator. Yield 5.29 g (80%). Compound **Ia** had no distinct melting point; according to the ^{1}H NMR and mass spectra, it was a trimeric cyclic anhydride, tris(2-methyl-1-benzothiophen-3-yl)boroxine. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 3.05 s (3H, CH_3), 7.23–7.43 m (3H, H_{arom}), 8.55 d (1H, H_{arom}, J = 7.8 Hz). Mass spectrum, m/z (I_{rel}, %): 523 (7) $[M + 1]^+$, 522 (85) $[M]^+$, 173 (39), 148 (82), 147 (100). Found, %: C 62.42; H 4.43; S 18.50. $C_{27}H_{21}B_3O_3S_3$. Calculated, %: C 62.12; H 4.05; S 18.42. M 522.07.

2,5-Dimethylthiophen-3-ylboronic acid (Ib) was synthesized in a similar way from 3-iodo-2,5-dimethylthiophene [15]. Yield 76%, mp 180–183°C. According to the ^{1}H NMR and mass spectra, the product was a trimeric cyclic anhydride. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 2.45 s (3H, CH_3), 2.82 s (3H, CH_3), 7.09 s (1H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 414 (65) $[M + 1]^+$, 413 (48) $[M]^+$, 137 (100), 111 (95). Found, %: C 52.32; H 5.23; S 23.50. $C_{18}H_{21}B_3O_3S_3$. Calculated, %: C 52.22; H 5.11; S 23.24. M 413.97.

3,4-Dibromo-*N*-butylmaleimide (IIa). *N*-Butylmaleimide, 12.73 g (83 mmol), was dissolved in 100 ml of glacial acetic acid, 14 g (0.16 mol) of sodium acetate was added, the mixture was cooled to 0°C, and a solution of 39.8 g (0.25 mol) of bromine in 20 ml of glacial acetic acid was added dropwise. The mixture was heated for 3 h under reflux, poured into 500 ml of water, and extracted with ethyl acetate (3 × 100 ml). The organic phase was washed with a 10% solution of Na_2SO_3 (2 × 50 ml), water (3 × 50 ml), and a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated on a rotary evaporator. The residue was treated with 50 ml of methanol, the mixture was heated to the boiling point and filtered, and the filtrate was cooled in a refrigerator. The precipitate was filtered off and additionally recrystallized from methanol. Yield 7.5 g (29%), mp 75–77°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 0.92 t (3H, C**H**$_3$CH$_2$, J = 7.5 Hz), 1.23–1.40 m (2H, CH$_3$C**H**$_2$), 1.52–1.66 m (2H, CH$_3$CH$_2$C**H**$_2$), 3.61 t (2H, CH$_2$N, J = 7.4 Hz). Mass spectrum, m/z (I_{rel}, %): 312 (100) $[M + 1]^+$, 311 (63) $[M]^+$, 269 (95), 254 (24), 189 (11), 133 (71), 56 (32). Found, %: C 30.79; H 2.81; N 4.43. $C_8H_9Br_2NO_2$. Calculated, %: C 30.90; H 2.92; N 4.50. M 310.97.

Cross coupling of aryl(hetaryl)boronic acids with 3,4-dibromo-*N*-butylmaleimide (*general procedure***).** A mixture of 3,4-dibromo-*N*-butylmaleimide (**IIa**), the corresponding boronic acid [2.2 equiv, calculated on $ArB(OH)_2$], 4 mol % of $Pd(Ph_3P)_4$, and CsF (5 equiv with respect to **IIa**) in 1,4-dioxane (100 ml per gram of the boronic acid) was heated at the boiling point under argon with vigorous stirring using a magnetic stirrer. The mixture was then poured into water and extracted with chloroform, the organic phase was washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator, and the residue was purified by flash chromatography on silica gel.

***N*-Butyl-3,4-bis(2-methyl-1-benzothiophen-3-yl)-maleimide (IIIa)** was synthesized from 2.2 g (11.4 mmol) of boronic acid **Ia**, 1.62 g (5.2 mmol) of 3,4-dibromo-*N*-butylmaleimide (**IIa**), 3.95 g (26 mmol) of CsF, and 0.24 g of $Pd(Ph_3P)_4$ in 220 ml of dioxane; reaction time 4 h. The residue obtained after evaporation of the chloroform extract was ground with diethyl ether, and the orange crystals were filtered off, washed with cold diethyl ether, and dried in a desiccator. Yield 1.77 g (76%), mp 172–173°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 1.02 t (3H, C**H**$_3$CH$_2$, J = 8.5 Hz), 1.40–1.56 m (2H, CH$_3$C**H**$_2$), 1.70–1.83 m (2H, CH$_3$CH$_2$C**H**$_2$), 2.08 s (3H, CH$_3$), 2.28 s (3H, CH$_3$), 3.74 t (2H, CH$_2$N, J = 8.2 Hz), 7.06 t (1H, H_{arom}, J = 9.1 Hz), 7.15–7.35 m (4H, H_{arom}), 7.45 d (1H, H_{arom}, J = 7.4 Hz), 7.64–7.72 m (2H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 446 (11) $[M + 1]^+$, 445 (100) $[M]^+$, 384 (48.5), 318 (15), 56 (30), 43 (28). Found, %: C 70.30; H 5.27; N 3.35. $C_{26}H_{23}NO_2S_2$. Calculated, %: C 70.08; H 5.20; N 3.14. M 445.59.

***N*-Butyl-3,4-bis(2,5-dimethylthiophen-3-yl)maleimide (IIIb)** was synthesized from 2.5 g (16 mmol) of boronic acid **Ib**, 2.26 g (7.3 mmol) of maleimide **IIa**, 5.51 g (36 mmol) of CsF, and 0.33 g of $Pd(Ph_3P)_4$ in 250 ml of dioxane; reaction time 4 h. The product was isolated by flash chromatography on silica gel using

hexane–diethyl ether (12:1) as eluent. Yield 2.33 g (86%), mp 117–120°C; published data [3]: mp 116–118°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 0.95 t (3H, C**H**$_3$CH$_2$, J = 7.4 Hz), 1.30–1.47 m (2H, CH$_3$C**H**$_2$), 1.57–1.70 m (2H, CH$_3$CH$_2$C**H**$_2$), 1.88 s (6H, CH$_3$), 2.42 s (6H, CH$_3$), 3.64 t (2H, CH$_2$N, J = 7.4 Hz), 6.71 s (2H, H$_{arom}$). Mass spectrum, m/z (I_{rel}, %): 375 (14) $[M + 2]^+$, 374 (1) $[M + 1]^+$, 373 (100) $[M]^+$, 358 (86), 312 (28), 259 (38), 246 (41), 231 (86), 69 (36). Found, %: C 64.40; H 6.47; N 3.59. $C_{20}H_{23}NO_2S_2$. Calculated, %: C 64.31; H 6.21; N 3.75. M 375.53.

***N*-Butyl-3,4-bis(3-chlorophenyl)maleimide (IIIc)** was synthesized from 0.55 g (3.5 mmol) of boronic acid **Ic**, 0.5 g (1.6 mmol) of maleimide **IIa**), 1.22 g (8.0 mmol) of CsF, and 0.075 g of Pd(Ph$_3$P)$_4$ in 40 ml of dioxane; reaction time 30 min. The residue obtained after evaporation of the chloroform extract was ground with diethyl ether, and the lemon yellow crystals were filtered off, washed with cold ether, and dried in a desiccator. Yield 0.58 g (96%), mp 92–95°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.96 t (3H, C**H**$_3$CH$_2$, J = 8.5 Hz), 1.34–1.48 m (2H, CH$_3$C**H**$_2$), 1.62–1.73 m (2H, CH$_3$CH$_2$C**H**$_2$), 3.66 t (2H, CH$_2$N, J = 8.3 Hz), 7.29–7.35 m (4H, H$_{arom}$), 7.35–7.42 m (2H, H$_{arom}$), 7.52 s (2H, H$_{arom}$). Mass spectrum, m/z (I_{rel}, %): 374 (30) $[M + 1]^+$, 373 (100) $M]^+$, 246 (32), 176 (51), 56 (46). Found, %: C 64.28; H 4.27; N 3.65. $C_{20}H_{17}Sl_2NO_2$. Calculated, %: C 64.18; H 4.58; N 3.74. M 374.27.

***N*-Butyl-3,4-bis(4-methoxyphenyl)maleimide (IIId)** was synthesized from 0.53 g (3.4 mmol) of boronic acid **Id**, 0.5 g (1.6 mmol) of maleimide **IIa**, 1.22 g (8.0 mmol) of CsF, and 0.075 g of Pd(Ph$_3$P)$_4$ in 40 ml of dioxane; reaction time 1.5 h. The product was isolated by flash chromatography on silica gel using hexane–diethyl ether (6:1) as eluent. Yield 0.57 g (98%), light yellow crystals, mp 110–112°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.97 t (3H, C**H**$_3$CH$_2$, J = 8.5 Hz), 1.34–1.46 m (2H, CH$_3$C**H**$_2$), 1.62–1.73 m (2H, CH$_3$CH$_2$C**H**$_2$), 3.64 t (2H, CH$_2$N, J = 8.3 Hz), 3.84 s (6H, OCH$_3$), 6.87 d (4H, H$_{arom}$, J = 10.0 Hz), 7.49 d (4H, H$_{arom}$, J = 10.1 Hz). Mass spectrum, m/z (I_{rel}, %): 366 (33) $[M + 1]^+$, 365 (100) $[M]^+$, 238 (16), 223 (25), 152 (18), 133 (23), 43 (18). Found, %: C 72.28; H 6.27; N 3.65. $C_{22}H_{23}NO_4$. Calculated, %: C 72.31; H 6.34; N 3.83. M 365.43.

3-Bromo-4-[1-(*tert*-butoxycarbonyl)-2-methyl-1*H*-indol-3-yl]-*N*-butylmaleimide (IVa). A solution of 1.01 g (7.7 mmol) of 2-methylindole in 24 ml of THF was cooled to –20°C, and 16 ml of a 20% solution of LiN(SiMe$_3$)$_2$ in THF was added dropwise under argon. The mixture was stirred for 15 min at that temperature, and a solution of 2.4 g (7.7 mmol) of maleimide **IIa** in 24 ml of THF was added. The mixture was allowed to warm up to room temperature, poured into 90 ml of 0.2 N hydrochloric acid, and extracted with ethyl acetate (3×30 ml). The organic phase was washed with 30 ml of a 5% solution of NaHCO$_3$, water (3×20 ml), and a saturated solution of sodium chloride and dried over MgSO$_4$. The solvent was removed to leave 2.55 g (92%) of 4-bromo-*N*-butyl-3-(2-methylindol-3-yl)maleimide as a chromatographically pure (TLC, hexane–ethylacetate, 4:1) dark red oily substance. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.96 t (3H, C**H**$_3$CH$_2$, J = 7.6 Hz), 1.32–1.48 m (2H, CH$_3$C**H**$_2$), 1.62–1.77 m (2H, CH$_3$CH$_2$C**H**$_2$), 2.49 s (3H, CH$_3$), 3.67 t (2H, CH$_2$N, J = 7.5 Hz), 7.15–7.25 m (2H, H$_{arom}$), 7.31 t (1H, H$_{arom}$, J = 10.0 Hz), 7.49 d (1H, H$_{arom}$, J = 7.7 Hz), 8.44 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 363 (13) $[M + 2]^+$, 362 (64) $[M + 1]^+$, 361 (24) $[M]^+$, 262 (87), 182 (100), 154 (28), 108 (39), 57 (61). Found, %: C 56.42; H 4.53; N 7.59. $C_{17}H_{17}BrN_2O_2$. Calculated, %: C 56.52; H 4.74; N 7.75. M 361.24.

4-Bromo-*N*-butyl-3-(2-methyl-1*H*-indol-3-yl)maleimide, 2.5 g (7 mmol), was dissolved in 100 ml of THF, 50 mg of 4-dimethylaminopyridine was added, and a solution of 2.0 g (9.1 mmol) of Boc$_2$O in 20 ml of THF was added dropwise over a period of 10 min. The mixture was stirred for 1 h at room temperature (until the initial compound disappeared according to the TLC data; hexane–ethyl acetate, 4:1) and evaporated on a rotary evaporator, the residue was treated with 10 ml of methanol, and the mixture was ground with a glass rod to initiate crystallization. An additional portion of methanol, 10 ml, was added, and the mixture was vigorously stirred for 5 h using a magnetic stirrer. The yellow precipitate was filtered off, washed with a small amount of cold methanol, and dried in a desiccator to isolate 3.03 g (95%) of compound **IVa** as a bright yellow powder with mp 92–94°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 0.96 t (3H, C**H**$_3$CH$_2$, J = 8.6 Hz), 1.30–1.47 m (2H, CH$_3$C**H**$_2$), 1.59–1.69 m (2H, CH$_3$CH$_2$C**H**$_2$), 1.70 s (9H, *t*-Bu), 2.58 s (3H, CH$_3$), 3.67 t (2H, CH$_2$N, J = 7.7 Hz), 7.20–7.35 m (3H, H$_{arom}$), 8.12 d (1H, H$_{arom}$, J = 7.9 Hz). Mass spectrum, m/z (I_{rel}, %): 461 (1) $[M]^+$, 406 (18), 361 (7), 281 (8), 182 (36), 154 (19), 57 (100). Found, %: C 57.40; H 5.57; N 6.29. $C_{22}H_{25}BrN_2O_4$. Calculated, %: C 57.28; H 5.46; N 6.07. M 461.36.

***N*-Benzyl-3-bromo-4-[1-(*tert*-butoxycarbonyl)-2-methyl-1*H*-indol-3-yl]maleimide (IVb).** A solution of 2.62 g (20 mmol) of 2-methyl-1*H*-indole in 70 ml of THF was cooled to –20°C, 42 ml of a 20% solution of $LiN(SiMe_3)_2$ in THF was added dropwise under argon, the mixture was stirred for 30 min at that temperature, and a solution of 7.0 g (20 mmol) of *N*-benzyl-3,4-dibromomaleimide [15] in 70 ml of THF was added dropwise. The mixture was allowed to warm up to room temperature, poured into 200 ml of 0.2 N hydrochloric acid, and extracted with ethyl acetate (3× 50 ml). The organic extracts were washed with 50 ml of a 5% solution of $NaHCO_3$, water (3×30 ml), and a saturated solution of NaCl, dried over $MgSO_4$, and evaporated on a rotary evaporator. The residue was dissolved in 100 ml of THF, 0.1 g of 4-dimethylaminopyridine was added, and a solution of 5.0 g (23 mmol) of Boc_2O in 30 ml of THF was added dropwise over a period of 10 min. The mixture was stirred for 1 h and evaporated on a rotary evaporator, and the residue was subjected to flash chromatography on silica gel using hexane–ethyl acetate (10:1) as eluent. Yield 7.0 g (70%), light yellow crystals, mp 150–151°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 1.71 s (9H, *t*-Bu), 2.58 s (3H, CH_3), 4.82 s (2H, PhC**H**$_2$), 7.20–7.50 m (8H, H_{arom}), 8.12 d (1H, H_{arom}, *J* = 7.9 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 495 (13) $[M]^+$, 395 (22), 91 (58), 57 (100). Found, %: C 60.62; H 4.55; N 5.47. $C_{25}H_{23}BrN_2O_4$. Calculated, %: C 60.62; H 4.68; N 5.65. *M* 495.37.

Cross coupling of aryl(hetaryl)boronic acids with *N*-butyl- and *N*-benzyl-3-bromo-4-[1-(*tert*-butoxycarbonyl)-2-methyl-1*H*-indol-3-yl]maleimides (*general procedure*). A mixture of maleimide **IVa** or **IVb**, the corresponding aryl(hetaryl)boronic acid [1.15 mol per mole of **IVa** or **IVb**; calculated on $ArB(OH)_2$], 4 mol % of $Pd(Ph_3P)_4$, CsF (4 mol per mole of **IVa** or **IVb**), and 1,4-dioxane (100 ml per gram of the boronic acid) was heated at the boiling point in an argon atmosphere under vigorous stirring. The mixture was then poured into water and extracted with chloroform, the extract was washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator, and the residue was purified by flash chromatography on silica gel.

3-[1-(*tert*-Butoxycarbonyl)-2-methyl-1*H*-indol-3-yl]-*N*-butyl-4-(3-chlorophenyl)maleimide (Va) was synthesized from 0.16 g (1.0 mmol) of boronic acid **Ic**, 0.42 g (0.9 mmol) of maleimide **IVa**, 0.55 g (36 mmol) of CsF, and 0.04 g of $Pd(Ph_3P)_4$ in 20 ml of dioxane; reaction time 1 h. The product was isolated by flash chromatography on silica gel using hexane–ethyl acetate (14:1) as eluent. Yield 0.32 g (71%), orange oily substance. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 0.96 t (3H, C**H**$_3$CH$_2$, *J* = 8.0 Hz), 1.39–1.50 m (2H, CH$_3$C**H**$_2$), 1.60–1.79 m (2H, CH$_3$CH$_2$C**H**$_2$), 1.70 s (9H, *t*-Bu), 2.42 s (3H, CH_3), 3.70 t (2H, CH_2N, *J* = 8.0 Hz), 6.92–7.40 m (6H, H_{arom}), 7.70 s (1H, H_{arom}), 8.12 d (1H, H_{arom}, *J* = 8.9 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 493 (1.6) $[M]^+$, 394 (28), 392 (100), 265 (23), 131 (8), 57 (11), 43 (17). Found, %: C 68.41; H 5.70; N 5.54. $C_{28}H_{29}ClN_2O_4$. Calculated, %: C 68.22; H 5.93; N 5.68. *M* 493.00.

3-[1-(*tert*-Butoxycarbonyl)-2-methyl-1*H*-indol-3-yl]-*N*-butyl-4-(3-methoxyphenyl)maleimide (Vb) was synthesized from 0.16 g (1.0 mmol) of boronic acid **Ie**, 0.42 g (0.9 mmol) of maleimide **IVa**, 0.55 g (36 mmol) of CsF, and 0.04 g of $Pd(Ph_3P)_4$ in 20 ml of dioxane; reaction time 2 h; the product was isolated by flash chromatography on silica gel using hexane–ethyl acetate (10:1) as eluent. Yield 0.4 g (90%), orange oily substance. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 0.96 t (3H, C**H**$_3$CH$_2$, *J* = 8.0 Hz), 1.37–1.49 m (2H, CH$_3$C**H**$_2$), 1.61–1.75 m (2H, CH$_3$CH$_2$C**H**$_2$), 1.69 s (9H, *t*-Bu), 2.41 s (3H, CH_3), 3.51 s (3H, OCH_3), 3.69 t (2H, CH_2N, *J* = 8.0 Hz), 6.85 m (1H, H_{arom}), 6.97–7.29 m (6H, H_{arom}), 8.12 d (1H, H_{arom}, *J* = 9.0 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 489 (1.3) $[M + 1]^+$, 488 (4.5) $[M]^+$, 389 (18), 388 (100), 365 (7), 261 (18), 57 (8), 43 (12). Found, %: C 71.35; H 6.76; N 5.65. $C_{29}H_{32}N_2O_5$. Calculated, %: C 71.29; H 6.60; N 5.73. *M* 488.58.

3-[1-(*tert*-Butoxycarbonyl)-2-methyl-1*H*-indol-3-yl]-*N*-butyl-4-(2-methyl-1-benzothiophen-3-yl)maleimide (Vc) was synthesized from 1.20 g (6.2 mmol) of boronic acid **Ia**, 2.507 g (5.4 mmol) of maleimide **IVa**, 3.80 g (25 mmol) of CsF, and 0.25 g $Pd(Ph_3P)_4$ in 200 ml of dioxane; reaction time 5 h. The product was isolated by flash chromatography on silica gel using hexane–ethyl acetate (14:1) as eluent. Yield 2.40 g (83%), orange oily substance. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 1.02 t (3H, C**H**$_3$CH$_2$, *J* = 8.5 Hz), 1.39–1.51 m (2H, CH$_3$C**H**$_2$), 1.65 s (9H, *t*-Bu), 1.69–1.83 m (2H, CH$_3$CH$_2$C**H**$_2$), 2.12–2.40 3 br.s (6H, CH_3), 3.74 t (2H, CH_2N, *J* = 8.0 Hz), 7.10–7.45 m (6H, H_{arom}), 7.69 d (1H, H_{arom}, *J* = 8.9 Hz), 8.02 d (1H, H_{arom}, *J* = 9.0 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 528 (1.4) $[M]^+$, 472 (13), 429 (100), 315 (18), 287 (19), 101 (21). Found, %: C 70.30; H 6.27; N 5.35. $C_{31}H_{32}N_2O_4S$. Calculated, %: C 70.43; H 6.10; N 5.30. *M* 528.67.

***N*-Benzyl-3-[1-(*tert*-butoxycarbonyl)-2-methyl-1*H*-indol-3-yl]-4-(2,5-dimethylthiophen-3-yl)maleimide (Vd)** was synthesized from 0.95 g (6.1 mmol) of boronic acid **Ib**, 2.57 g (5.2 mmol) of maleimide **Vb**, 3.2 g (21 mmol) of CsF, and 0.24 g of $Pd(Ph_3P)_4$ in 150 ml of dioxane; reaction time 2 h. The product was isolated by flash chromatography on silica gel using hexane–diethyl ether (10:1) as eluent. Yield 2.32 g (85%), light yellow crystals, mp 132–135°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 1.69 s (9H, *t*-Bu), 1.79 s (3H, CH_3), 2.36 s (3H, CH_3), 2.39 s (3H, CH_3), 4.82 s (2H, PhC**H**$_2$), 6.80 s (1H, H_{arom}), 7.0–7.11 m (2H, H_{arom}), 7.19–7.40 m (4H, H_{arom}), 7.48 d (2H, H_{arom}, J = 6.5 Hz), 8.09 d (1H, H_{arom}, J = 7.2 Hz). Mass spectrum, m/z (I_{rel}, %): 527 (1) $[M + 1]^+$, 526 (3) $[M]^+$, 427 (77), 91 (100). Found, %: C 70.56; H 5.76; N 5.55. $C_{31}H_{30}N_2O_4S$. Calculated, %: C 70.70; H 5.74; N 5.32. M 526.65.

***N*-Butyl-3-(2-methyl-1-benzothiophen-3-yl)-4-(2-methyl-1*H*-indol-3-yl)maleimide (VIa).** A mixture of 2.4 g (4.5 mmol) of compound **Vc** and 30 ml of butylamine was heated for 4 h under reflux. The mixture was cooled, poured into a mixture of 300 ml of water and 40 ml of concentrated hydrochloric acid, and extracted with ethyl acetate (3×100 ml). The extract was washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator, and the residue was purified by flash chromatography on silica gel using hexane–ethyl acetate (4.5:1) as eluent. Yield 1.55 g (80%), dark red crystals, decomposition point 280°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 1.01 t (3H, C**H**$_3$CH$_2$, J = 8.5 Hz), 1.38–1.55 m (2H, CH_3C**H**$_2$), 1.68–1.72 m (2H, CH_3CH_2C**H**$_2$), 1.97 s (3H, CH_3), 2.21 s (3H, CH_3), 3.73 t (2H, CH_2N, J = 7.2 Hz), 6.94 t (1H, H_{arom}, J = 8.0 Hz), 7.02–7.39 m (6H, H_{arom}), 7.68 d (1H, H_{arom}, J = 8.9 Hz), 8.17 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 429 (19) $[M + 1]^+$, 428 (100) $[M]^+$, 413 (79), 367 (73), 314 (82), 301 (45), 300 (44), 286 (60). Found, %: C 72.87; H 5.49; N 6.42. $C_{26}H_{24}N_2O_2S$. Calculated, %: C 72.87; H 5.64; N 6.54. M 428.55.

***N*-Benzyl-4-(2,5-dimethylthiophen-3-yl)-3-(2-methyl-1*H*-indol-3-yl)maleimide (VIb).** A mixture of 1.67 g (3.2 mmol) of compound **Vd** and 30 ml of benzylamine was heated for 40 min under reflux. The mixture was cooled, poured into a mixture of 300 ml of water and 40 ml of concentrated hydrochloric acid, and extracted with ethyl acetate (3×100 ml). The extract was washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator, and the residue was purified by flash chromatography on silica gel using hexane–ethyl acetate (4.5:1) as eluent. Yield 1.35 g (100%), dark red crystals, mp 235–238°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 1.71 s (3H, CH_3), 2.15 s (3H, CH_3), 2.41 s (3H, CH_3), 4.83 s (2H, PhC**H**$_2$), 6.80 s (1H, H_{arom}), 7.0 t (1H, H_{arom}, J = 7.1 Hz), 7.06–7.42 m (6H, H_{arom}), 7.50 d (2H, H_{arom}, J = 7.3 Hz), 8.28 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 428 (32) $[M + 2]^+$, 427 (40) $[M + 1]^+$, 426 (100) $[M]^+$, 411 (53), 278 (52), 265 (40), 148 (39), 91 (92). Found, %: C 73.14; H 5.40; N 6.30. $C_{26}H_{22}N_2O_2S$. Calculated, %: C 73.21; H 5.20; N 6.57. M 426.53.

Hydrolysis of 3,4-diaryl(hetaryl)maleimides (*general procedure*). A 500-ml round-bottomed flask equipped with a reflux condenser was charged with a solution of the corresponding maleimide in 75 ml of 1,4-dioxane, 230 ml of a 10% solution of potassium hydroxide was added, and the mixture was heated at the boiling point in an argon atmosphere under vigorous stirring (using a magnetic stirrer) for a time indicated below. The mixture was allowed to cool down to room temperature, poured into a mixture of 300 ml of water and 50 ml of concentrated hydrochloric acid, stirred for 1.5 h, and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and evaporated on a rotary evaporator, and the residue was purified by flash chromatography on silica gel.

3,4-Bis(2-methyl-1-benzothiophen-3-yl)maleic anhydride (VIIa) was obtained from 1.95 g (4.4 mmol) of compound **IIIa**; reaction time 60 h; eluent hexane–ethyl acetate (6:1). Yield 1.376 g (80%), orange crystals, mp 241–243°C; published data [19]: mp 238–240°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 2.11 s (3H, CH_3), 2.29 s (3H, CH_3), 7.05–7.49 m (6H, H_{arom}), 7.61 d.d (2H, H_{arom}, J = 9.1 Hz). Mass spectrum, m/z (I_{rel}, %): 391 (19) $[M + 1]^+$, 390 (72) $[M]^+$, 344 (100), 318 (40). Found, %: C 67.72; H 3.47. $C_{22}H_{14}O_3S_2$. Calculated, %: C 67.67; H 3.61. M 390.47.

3,4-Bis(2,5-dimethylthiophen-3-yl)maleic anhydride (VIIb) was obtained from 1.5 g (4 mmol) of maleimide **IIIb**; reaction time 60 h; eluent hexane–THF (6.5:1). Yield 1.20 g (94%), yellow–orange crystals, mp 198–200°C; published data [1]: mp 201–202°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 1.91 s (6H, CH_3), 2.42 s (6H, CH_3), 6.76 s (2H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 319 (10) $[M + 1]^+$, 318 (45) $[M]^+$, 303 (26), 273 (100), 245 (70). Found, %: C 60.62; H 4.45. $C_{16}H_{14}O_3S_2$. Calculated, %: C 60.35; H 4.43. M 318.41.

3-(2-Methyl-1-benzothiophen-3-yl)-4-(2-methyl-1*H*-indol-3-yl)maleic anhydride (VIIc) was obtained from 1.44 g (3.4 mmol) of compound **VIa**; reaction

time 60 h; eluent hexane–THF (4:1). Yield 0.8 g (64%), dark red crystals, mp 217–220°C. ^{1}H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm: 2.05 s (3H, CH_3), 2.17 s (3H, CH_3), 6.80 t (1H, H_{arom}, J = 8.3 Hz), 7.02 t (1H, H_{arom}, J = 8.4 Hz), 7.09 d (1H, H_{arom}, J = 9.0 Hz), 7.14–7.33 m (3H, H_{arom}), 7.55 d (1H, H_{arom}, J = 9.2 Hz), 7.88 d (1H, H_{arom}, J = 9.2 Hz), 11.71 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 375 (14) $[M + 2]^+$, 374 (40) $[M + 1]^+$, 373 (100) $[M]^+$, 328 (80), 302 (40), 301 (73), 300 (76), 148 (42). Found, %: C 70.82; H 4.19; N 3.52. $C_{22}H_{15}NO_3S$. Calculated, %: C 70.76; H 4.05; N 3.75. M 373.43.

3-(2,5-Dimethylthiophen-3-yl)-4-(2-methyl-1*H*-indol-3-yl)maleic anhydride (VIId) was obtained from 1.241 g (2.9 mmol) of maleimide **VIb**; reaction time 3 h; eluent hexane–THF (4:1). Yield 0.715 g (73%), dark red crystals, mp 200–202°C. ^{1}H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 1.77 s (3H, CH_3), 2.27 s (3H, CH_3), 2.42 s (3H, CH_3), 6.81 s (1H, H_{arom}), 7.0–7.40 m (4H, H_{arom}), 8.47 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 339 (22) $[M + 2]^+$, 337 (100) $[M]^+$, 292 (52), 264 (54), 105 (75), 82 (60), 76 (92), 55 (69). Found, %: C 67.80; H 4.43; N 4.38. $C_{19}H_{15}NO_3S$. Calculated, %: C 67.64; H 4.48; N 4.15. M 337.39.

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