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Full Papers

Arylethenylbenzofuroxan Derivatives as Drugs for Chagas Disease: Multigram Batch Synthesis using a Wittig–Boden Process‡

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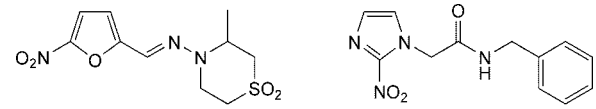
Abstract:

In the present work, we developed robust processes for the preparation of new antitrypanosomal benzofuroxans, *E* and *Z* isomers of 5-arylethenylbenzo[1,2-*c*]1,2,5-oxadiazole *N*[1]-oxide 1–6, in multigram batch through Wittig–Boden conditions as the key synthetic step. In these conditions, the generation of the benzofurazans, as secondary byproduct, was minimized.

Introduction

Chagas' disease (CD) or American trypanosomiasis is extensively distributed in Central and South America with 20 million persons infected and 100 million people at risk, which results in 50,000 deaths annually.[1] CD is the third largest disease burden in Latin America after malaria and schistosomiasis (all grouped in so-called neglected diseases). This disease is caused by *Trypanosoma cruzi*, a protozoan parasite transmitted to humans by the triatominea insect or directly by transfusion of infected blood.[2] The only drugs used in the chemotherapy of CD are Nifurtimox ((4-([5-nitrofurfurylidene]-amino)-3-methylthiomorpholine-1,1-dioxide; Nfx, Lampit, Figure 1), now discontinued, and Benznidazole (*N*-benzyl-2-nitro-1-imidazolacetamide; Bnz, Rochagan, Figure 1), both introduced over 3 decades ago.[3] These drugs are effectives for the acute phase infection of the disease, but the efficacy is very low in the chronic phase. Moreover, the strain resistance and toxicity are other disadvantages of these drugs.[4,5] For these reasons the search for new drugs against this parasitic disease is primordial and urgent.[6] With this objective, our research group has investigated and developed new agents derived from the benzofuroxan (benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide) heterocycle.[7] The developed compounds have been excellent in vitro anti-*T. cruzi* agents against different strains of the epimastigote form of the parasite.[8–12] Moreover, the new benzofuroxan derivatives were less or as cytotoxic as the reference drugs (Nfx, Bnz, ketoconazole, and terbinafine).[13,14] From the first developed structural series,[15,16] new lead compounds, 5-(2-phenylethenyl)benzofuroxan (isomers *E* and *Z*, **1** and **2**, respectively, Figure 2) were identified that showed excellent in vitro and in vivo efficacies and low toxicity in an acute toxicity trial. Furthermore, derivatives **1** and **2** were attractive lead compounds as a result of their chemical-modulating structure that allows further synthetic variations. To this end, we have developed a second generation of 5-(2-phenylethenyl)benzofuroxan derivatives with excellent in vitro activities against the epimastigote form of three strains



Nfx Bnz

Figure 1. **Structure of the drugs currently used in the chemotherapy of Chagas disease.**

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‡ Part of this research is presented in the Uruguayan patent of invention: Cerecetto, H.; Di Maio, R.; González, M.; Porcal, W.; Denicola, A. UR Patent No. 28.019, 2003; Derivados de 5-etenilbenzofuroxano, procedimiento de preparación y utilización.

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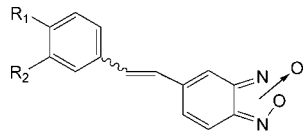

1, *E*, -R_1= -R_2= -H
2, *Z*, -R_1= -R_2= -H
3, *E*, -R_1= -Cl, -R_2= -H
4, *Z*, -R_1= -Cl, -R_2= -H
5, *E*, -R_1,-R_2= -OCH_2O-
6, *Z*, -R_1,-R_2= -OCH_2O-

Figure 2. **Structure of the 5-(2-phenylethenyl)benzofuroxan derivatives with anti-*T. cruzi* activity.**

of *T. cruzi*, Tulahuen 2, CL Brener, and Y, and lower effect against human macrophages THP-1.[14] On the basis of these promising results, six antitrypanosomal benzofuroxans, 5-[2-phenylethenyl]benzofuroxan *E* and *Z* isomers (**1** and **2**), 5-[2-4-chlorophenylethenyl]benzofuroxan *E* and *Z* isomers (**3** and **4**), and 5-[2-(3,4-methylendioxyphenyl)ethenyl]benzofuroxan *E* and *Z* isomers (**5** and **6**), Figure 2, have been object of the following preclinical studies: in vivo efficacy, in vitro toxicity, safety, and pharmaceutical feasibility. These studies were performed as part of a research project supported by DNDi (Drugs for Neglected Disease initiative) organization,[17] which has as a primary objective the development of new and more effective drugs for people suffering from neglected diseases in developing countries. For these reasons, the large-scale production of the benzofuroxan derivatives **1–6** was necessary.

The chemical properties of the benzofuroxan system have been reviewed in detail in the past years.[7] The traditional methods used in the synthesis of benzofuroxans have included oxidation of *o*-nitroanilines, thermo or photochemical intramolecular cyclization of *o*-nitroarylazides, and oxidation of *o*-benzoquinone dioxime (Figure 3). This heterocyclic system reacts very easily with a large number of electron-rich species, i.e., amines, thiols, enolates, strong bases, and hydrides (Figure 3), yielding ring-opening products (*o*-benzoquinone dioxime, *o*-nitrosoaniline, and *o*-nitroaniline), heterocycle derivatives (quinoxaline 1,4-dioxide, benzimidazole 1,3-dioxide), and deoxygenated analogues (benzofurazan).[18–22] For example, Wittig-type reactions between substituted benzofuroxans and phosphorus ylide have yielded benzofurazan derivatives, the deoxygenated benzofuroxan analogues (Figure 3).[23]

The initial medicinal chemistry (medchem) route used in the preparation of the ethenylbenzofuroxans **1** and **2** is shown in Scheme 1. Basically, we performed a Wittig reaction under Boden′s mild condition[24] followed by the synthesis of the heterocyclic system (**11a** to **1** and **2**, Scheme 1) using commercially available 4-methyl-2-nitroaniline, **7**, and benzaldehyde as starting materials. In this procedure the ylide was formed in situ by deprotonation of the phosphonium salt **10** employing potassium carbonate as base and catalytic amount of 18-crown-6.[14,16,24] However, using the medchem route we were unable to produce the desired products **3–6** adequately (Figure S1, Supporting Information). On the one hand, the Wittig−Boden reactions between salt **10** and *p*-chlorobenzaldehyde or piperonal yielded the desired alkenes, **11b,c** (Figure S1), marginally. The low reactivity of *p*-chlorobenzaldehyde and piperonal in these conditions promoted the decomposition of the phosphonium salt, yielding compounds **7** and **8** (Figure S1) as main products. On the other hand, the formation of the heterocyclic system by oxidative cyclization with NaOCl promoted a complete decomposition of the *o*-nitroacetanilides (Figure S1).[14]

In this manuscript, we present the results of the scale-up procedure for the syntheses of multigram quantitites of compounds **1–6** following the reaction sequence shown in Scheme 2.

Results and Discussion

The medchem procedure shown in Scheme 1 was used to obtain initial small quantities of benzofuroxans **1** and **2** on 100 mg scale. The synthetic strategy involved acetylation of the commercially available *o*-nitroaniline **7** producing the corresponding acetanilide, **8**, which was converted into derivative **9** by bromination of the benzylic position using NBS in CCl_4 and in the presence of PDBO. The nucleophilic substitution with PPh_3 yielded the phosphonium salt **10**, which reacted with benzaldehyde in Wittig−Boden conditions, yielding the olefin **11a** as chromatographically separable *Z* and *E* isomers. Finally, the desired compounds **1** and **2** were obtained in a one-pot process via deprotection and oxidative cyclization of the substituted *o*-nitroacetanilide **11a**.

The medchem route was evaluated critically and deemed inapplicable for scale-up. First, the benzylic bromination step involves the use of several toxic and potentially hazardous reagents.[25–27] Second, reactions with ethanol and sodium hypochlorite, NaClO, have been recently discussed as dangerous for multigram-batch procedures[28] as result of the production of both volatile and explosive ethylhypochlorite.[29] Third, this synthetic route has a low overall yield for the formation of the desired compounds **1** and **2**, and it is inapplicable for the preparation of derivatives **3–6**.

To this end, we have studied a second process for the preparation of the desired ethenylbenzofuroxan derivatives in a multigram batch through Wittig−Boden conditions between phosphonium salts (**16–18**) and 5-formylbenzofuroxan **19** (Scheme 2) to develop a more efficient synthetic strategy

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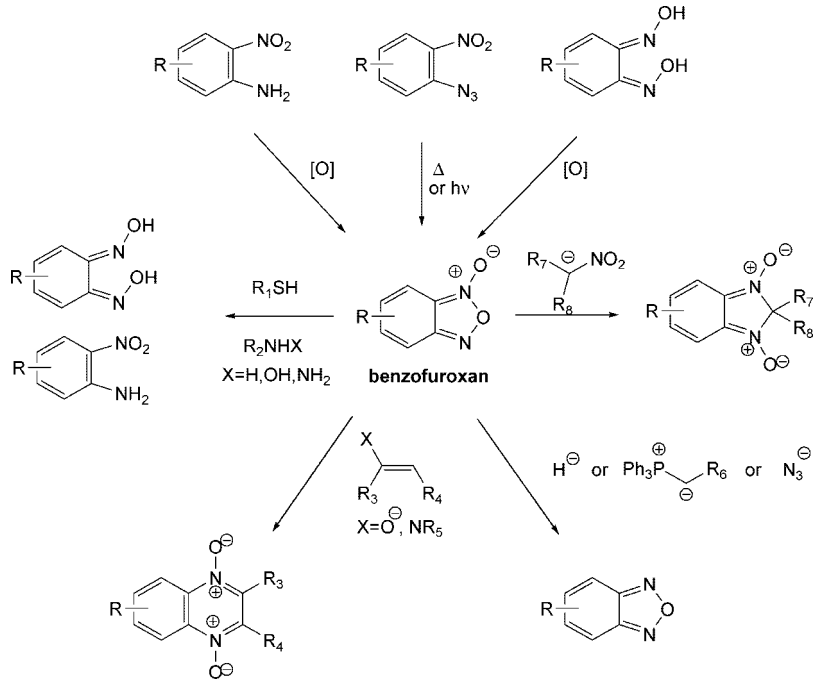
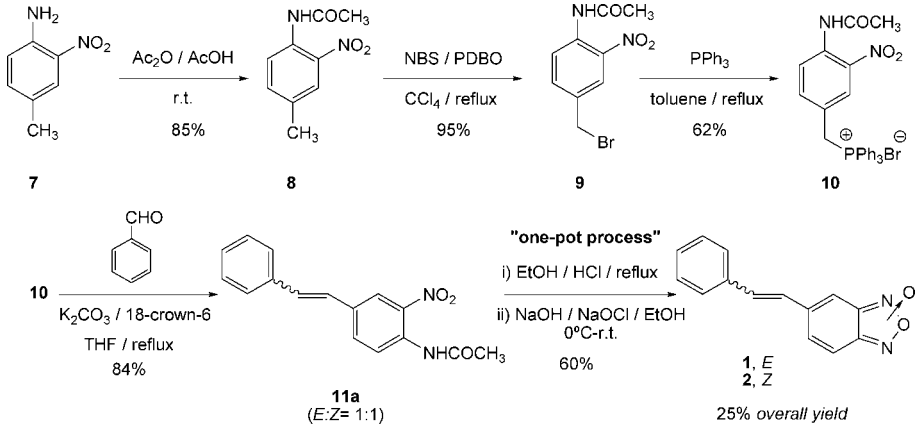


Figure 3. **Syntheses and reactivity of benzofuroxans.**

Scheme 1. **Medicinal chemistry synthesis of the anti-*T. cruzi* benzofuroxans 1 and 2**



minimizing the formation of byproduct (deoxygenated analogues). The first step was the preparation of the phosphonium salts **16–18** using a conventional synthesis that involved the reaction between PPh_3 and the corresponding benzylchloride. The benzylchlorides **13** and **14** are commercially available, and derivative **15** was obtained from commercially available piperonylic alcohol, **12**, as Scheme 2 shows. To increase the yields of the phosphonium salts in the multigram-batch preparations, different solvents, times, and temperatures have been studied. According to the results (Table 1) the yield depends on the solvent polarity and the reaction temperature. Higher solvent polarity, expressed as E^N_T[30] in Table 1, produces higher yield (compare results from entries **1**, **3**, and **6**). On the other hand, higher solvent boiling point produces higher yield (compare results from entries **1** and **4** or **2** and **5**, Table 1).

The second step was the preparation of 5-formylbenzofuroxan **19** in a multigram batch. This heterocyclic aldehyde was obtained in a one-pot process from 4-chloro-3-nitrobenzaldehyde, **20**, (Scheme 3) via S_NAr with azide and subsequent cyclization in DMSO as result of the pyrolysis of the *o*-nitrophenylazide intermediate, **21**. Both reactions run at different temperatures and yielded the desired product in good yield (65%, after purification). The azide anion is a good *N*-oxide reducing agent (Figure 3);[31] however, in these reaction conditions (0.95 equiv of NaN_3) no benzofurazan was observed after purification. The medchem route for this compound involved two steps, nucleophilic displacement of the halogen group by azide to give the azide **21** and cyclization by heating under reflux in toluene or acetic acid.[32] In these conditions 59% of overall yield was obtained, so we developed a more efficient synthetic strategy to prepare the 5-formylbenzofuroxan **19** in a multigram batch (65% overall yield).

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Scheme 2

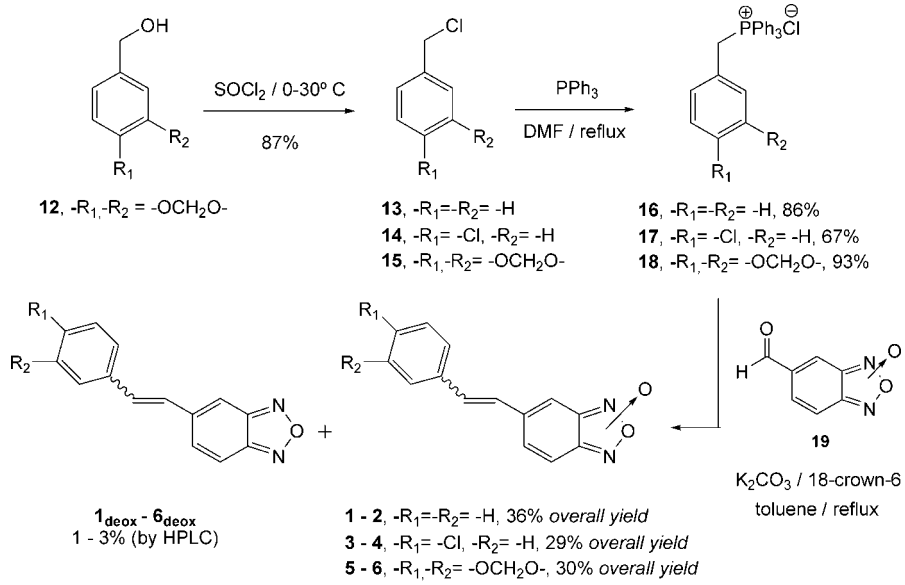
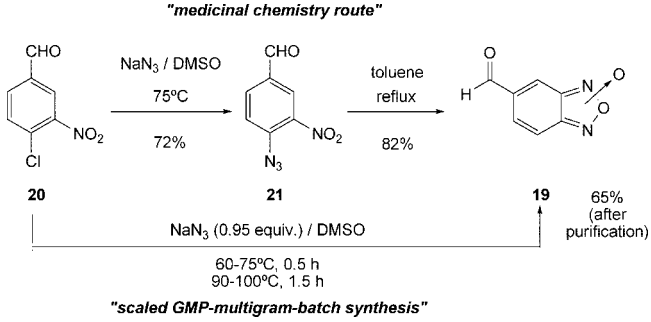


Table 1. **Effect of solvent, time, and temperature on the preparation of phosphonium salt 16**

entry	solvent	bp (°C)[a]	E^N_T[b]	time (h)[c]	temperature	yield (%)[d]
1	THF	66.0	37.5	8	reflux	7
2				16	reflux	13
3	toluene	110.6	33.9	8	66.0[e]	4
4				8	reflux	32
5				16	reflux	50
6	DMF	153.0	43.8	8	66.0[e]	34
7				2	reflux	60
8				4	reflux	86

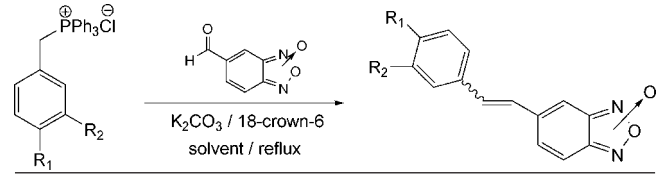
[a] bp: boiling point at 760 mmHg. [b] E^N_T: empirical parameter of solvent polarity. [c] Reaction conditions: benzyl chloride (14.5 mmol, 1 equiv), PPh_3 (16.0 mmol, 1.1 equiv), and solvent (15 mL/g of benzyl chloride). All reactions were heated under nitrogen atmosphere and monitored by TLC and HPLC. [d] Determination of yields of the isolated products: the collected crystalline solid was first washed one time with the reaction solvent and then with petroleum ether until absence of PPh_3 (checked by TLC). Finally the product was dried in vacuum until constant weight. [e] Temperature in °C.

Scheme 3



Finally, the desired phenylethenylbenzofuroxans were obtained, as was already mentioned, through a Wittig−Boden process. The ylides were formed in situ by deprotonation of the phosphonium salts **16–18** using potassium carbonate as bases in presence of 18-crown-6 as catalyst and toluene as solvent. Under these conditions, the reactions produced mixtures of the *E* and *Z* geometric isomers that were separated by chromatography or by differential solubility. From the reaction crude the *E*/*Z* ratio was determined using ^{1}H NMR spectroscopy

Table 2. **Multigram olefination processes: geometric isomers ratios and yields in different solvents**



-R_1	-R_2	solvent	*E*:*Z* ratio[a]	yield (%)[a,b]
-H	-H	THF	3.8:1.0	63
		toluene	2.1:1.0	65
-OCH_2O-		THF	1.8:1.0	65
		toluene	1.2:1.0	56

[a] Calculated from purified product (see Experimental Section). [b] Overall yield considering both geometric isomers.

and HPLC analysis (Figure S2, Supporting Information). The stereochemistry around the olefinic carbon−carbon bond was established using the corresponding ^{1}H NMR coupling constant. The solvent effect on the stereochemical outcome of the olefination reaction depends on the nature of the ylide.[33–36] In our case, in the milligram-scale syntheses (medchem route), using semistabilized ylide (compound **10**, Scheme 1), the use of different solvents did not affect the stereoselectivity of the olefination reaction (data not shown); in the different solvents studied the *E*:*Z* ratio for compounds **11a** and **11c** (Scheme 1 and Figure S1, Supporting Information) was near to 1. In the multigram-scale syntheses, using our semistabilized ylides **16–18** (Scheme 2), the *E*:*Z* ratio was studied in two different solvents, namely, THF and toluene, for the preparation of derivatives **1**, **2**, **5**, and **6** (Table 2). In both solvents the *E*-alkenes, derivatives **1** and **5**, were the main products.

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Table 3. **Synthetic results of the Wittig−Boden process**

-R	isomer	ref	isolation	crystallization	yield (%)[a]	-R	isomer	ref	yield (%)
-Ph	*E*	**1**	CC[b]	PE[c]:EtOAc (85:15)	44	-Ph	*E*	$\mathbf{1_{deox}}$	2[d]
	Z	**2**		PE	21		*Z*	$\mathbf{2_{deox}}$	2[d]
	E	**3**	filtration	EtOH	54		*E*	$\mathbf{3_{deox}}$	1[e]
-*p*-ClPh	*Z*	**4**	CC	PE:EtOAc (90:10)	13	-*p*-ClPh	*Z*	$\mathbf{4_{deox}}$	2[e]
	E	**5**	filtration	EtOH	31		*E*	$\mathbf{5_{deox}}$	2[d]
f	*Z*	**6**	CC	PE:EtOAc (90:10)	25	*f*	*Z*	$\mathbf{6_{deox}}$	3[d]

[a] Calculated from purified product (see Experimental Section). [b] CC: column chromatography. [c] PE: petroleum ether (fraction 60–70 °C). [d] Isolated by chromatographic column. [e] No isolated. Characterized by NMR and quantified by HPLC analysis. [f] Benzo[*d*][1,3]dioxol-5-yl.

However, in refluxing toluene a better proportion of the desired derivatives **2** and **6**, *Z*-isomers, were obtained. No modification in the *E*:*Z* ratio was observed with longer reaction time (data not shown). In these conditions, toluene at reflux, the corresponding deoxygenated analogues were isolated or removed as secondary products in very low yields (Table 3).

Conclusions

The preparation in multigram scale of both stereoisomers of three 5-arylethenylbenzofuroxans has been achieved with very good yields, in an efficient, safe, and inexpensive manner. These considerations are in agreement with the aims of obtaining drugs for treatment of Chagas' disease.

A scaleable synthetic route to the 5-arylethenylbenzofuroxans was developed on the basis of a modified medchem route. Compounds **1–6** were finally synthesized in 29–36% overall yields under multigram-batch laboratory conditions. The overall yields of the desired compounds were enhanced in comparison to the yield of the medchem route. The major improvements in the multigram-batch scaling processes were made in the following three steps. First, the optimal conditions to obtain the phosphonium salts **16–18** were identified. Second, the Wittig−Boden reaction produced higher yields of the mixture of the desired products, **1–6**, than the corresponding values in the medchem route along with minimal deoxygenated byproduct production (Scheme 2, Tables 2 and 3). Third, the overall yield of the aldehyde **19** synthesis was enhanced to 65% in comparison to the yield of 59% of the medchem route.

Studies for a scale-up route for more than 100 g of compounds **1–6** are currently in progress. In these studies some modifications are being analyzed, for example, avoiding the use of 18-crown-6 or the use of chromatographic procedures. In the first case, the development of Wittig–Horner−Emmons[37–39] methodology is being studied as a safety route for 100-g batch preparation. In reference to the isolation and purification processes of **1–6** we are studying the differential precipitation of *E*-isomers by solvent changes and only recrystallization as purification methods.

Experimental Section

Most chemical and solvents were analytical grade and used without further purification. All reactions were carried out in a nitrogen atmosphere. Melting points were determined with an electrothermal melting point apparatus (Electrothermal 9100) and are uncorrected. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400.13 MHz for proton and were performed using either dimethyl sulfoxide-d_6 or chloroform-*d* as solvent. The coupling constants (*J*) are reported in hertz. Infrared spectra were obtained as KBr pellets on a Perkin-Elmer Spectrum 1000 infrared spectrophotometer. Mass spectra were determined on Hewlett-Packard MSD 5973 and LC/MSD Series 100 spectrometers with electronic ionization mass spectroscopy (EI) and electrospray ionization mass spectroscopy (ESI), respectively. Microanalyses were performed in a Fisons EA 1108 CHNS-O equipment and were within ±0.4% of the calculated compositions. HPLC was carried out with a Perkin-Elmer LC-135C/LC-235C Diode Array Detector, Series 410 LC BIO PUMP. All compounds are measured under the same conditions: wavelength, 300 nm; flow rate, 0.8 mL/min (**1**, **2**, and deoxygenated analogues) or 1.0 mL/min (for **3–6** and deoxygenated analogues); column, Supelco LC-18, 250 mm × 4.6 mm i.d., particle size 5 μM (Supelco Inc., Bellefonte, Pa., USA); temperature, 27 °C; mobile phase, MeOH/CH_3CN/H_2O (45:5:50) (for **1**, **2**, and deoxygenated analogues), CH_3CN/H_2O (40:60) (for **3**, **4**, and deoxygenated analogues), MeOH/CH_3CN/H_2O (5:35:60) (for **5**, **6**, and deoxygenated analogues); injection volume, 50 μL. Column chromatography was carried out using silica flash (Macherey-Nagel) and neutral alumina (Merck).

5-(Chloromethyl)benzo[*d*]1,3-dioxole (15).[40] Piperonylic alcohol, **12**, (20.0 g, 132 mmol) was dissolved in $SOCl_2$ (50 mL, 685 mmol) at 0 °C and stirred for 30 min. The mixture was maintained at 30 °C for 2 h. The excess of $SOCl_2$ was removed in vacuo, and the residue was purified by chromatographic column (Al_2O_3, petroleum ether/EtOAc (30:10)). Pale yellow oil (19.5 g, 87%). TLC: $R_f = 0.80$ (SiO_2, developing solvent, petroleum ether/AcOEt (90:10), detection $\lambda = 254$ nm). ^{1}H NMR ($CDCl_3$) δ (ppm): 4.54 (s, 2H), 5.99 (s, 2H), 6.80 (d, 1H), 6.85–6.90 (m, 2H). MS (ESI) *m*/*z*: 171.2 ($M^{+\bullet} + H$).

General Procedure for the Synthesis of Phosphonium Salts (16–18). A mixture of triphenylphosphine (1.1 equiv) and benzyl chloride derivative (1.0 equiv) in dry DMF (15.0 mL/g of benzyl chloride) was heated at reflux during 4 h. Then the mixture was allowed to cool to room temperature, and the white

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crystalline solid was collected, washed one time with DMF, and then with petroleum ether until absence of PPh_3 in the organic solvent (checked by TLC). The solid was dried in vacuum for 24 h.

Benzyltriphenylphosphonium Chloride (16). Reagents: benzyl chloride (19.0 g, 150 mmol), PPh_3 (40.0 g, 153 mmol). Solvent: DMF (300.0 mL). TLC: $R_f = 0.05$ (SiO_2, developing solvent, CH_2Cl_2/MeOH (90:10); detection $\lambda = 254$ nm). Yield 50.2 g (86%). Mp > 300.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 5.20 (d, 2H, $J = 15.7$ Hz), 6.99 (m, 2H), 7.25 (t, 2H), 7.32 (m, 1H), 7.65–7.77 (m, 12H), 7.91 (m, 3H). MS (ESI) *m*/*z*: 353 ($M^{+\bullet} - 35$). Anal. ($C_{25}H_{22}ClP$) C, H, N.

(4-Chlorobenzyl)triphenylphosphonium Chloride (17). Reagents: 4-chlorobenzyl chloride (35.4 g, 221 mmol), PPh_3 (64.0 g, 244 mmol). Solvent: DMF (430.0 mL). TLC: $R_f = 0.05$ (SiO_2, developing solvent, CH_2Cl_2/MeOH (90:10); detection $\lambda = 254$ nm). Yield 61.5 g (67%). Mp > 300.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 5.26 (d, 2H, $J = 15.8$ Hz), 6.99 (m, 2H), 7.33 (d, 2H), 7.68–7.76 (m, 12H), 7.92 (m, 3H). MS (ESI) *m*/*z*: 387 ($M^{+\bullet} - 35$). Anal. ($C_{25}H_{21}Cl_2P$) C, H, N.

(3,4-Methylendioxobenzyl)triphenylphosphonium Chloride (18). Reagents: 5-(chloromethyl)benzo[*d*]1,3-dioxole, **15**, (22.0 g, 129 mmol), PPh_3 (37.0 g, 142 mmol). Solvent: DMF (200.0 mL). TLC: $R_f = 0.05$ (SiO_2, developing solvent, CH_2Cl_2/MeOH (90:10), detection $\lambda = 254$ nm). Yield 52.0 g (93%). Mp > 300.0 °C. ^{1}H NMR (DMSO-d_6) δ (ppm): 5.09 (d, 2H, $J = 15.1$ Hz), 5.97 (s, 2H), 6.48 (m, 2H), 6.80 (d, 1H), 7.65–7.76 (m, 12H), 7.91 (m, 3H). MS (ESI) *m*/*z*: 397 ($M^{+\bullet} - 35$). Anal. ($C_{26}H_{22}ClO_2P$) C, H, N.

5-Formylbenzo[1,2-*c*]1,2,5-oxadiazole *N*^{1}-Oxide (19). A mixture of 4-chloro-3-nitrobenzaldehyde (19.0 g, 102 mmol) and NaN_3 (6.3 g, 97 mmol) in DMSO (90.0 mL) was heated at 60–75 °C during 0.5 h and subsequently at 90–100 °C during 1.5 h. The residue was treated with H_2O (250.0 mL) and brine (250.0 mL) and extracted with EtOAc (4 × 100.0 mL). After the workup the organic layer was dried with Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatographic column (Al_2O_3, petroleum ether/EtOAc (90:10 to 80:20)). The product was crystallized from petroleum ether/EtOAc (85:15) to give **19** as a yellow solid (10.4 g, 65%). Mp 68.0–69.0 °C. TLC: $R_f = 0.60$ (SiO_2, developing solvent, petroleum ether/EtOAc (90:10), detection $\lambda = 254$ nm). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.71 (br s, 1H), 7.83 (br s, 1H), 7.99 (br s, 1H), 10.03 (s, 1H). MS (EI) *m*/*z* (%): 164 ($M^{+\bullet}$, 100), 148 (7), 103 (37). IR ν (cm^{-1}): 1699, 1605, 1537, 1485. Anal. ($C_7H_4N_2O_2$) C, H, N.

General Procedure for the Synthesis of Arylethenylbenzofuroxan Derivatives (1–6). A mixture of 5-formylbenzofuroxan **19** (1.0 equiv), phosphonium salt (**16**, **17**, or **18**, 1.0 equiv), K_2CO_3 (1.0 equiv), 18-crown-6 (0.01 equiv), and dry toluene (5.0 mL/mmol of **19**) as solvent was stirred at reflux until the aldehyde **19** was not present (TLC, SiO_2, petroleum ether/EtOAc (80:20)). The reaction mixture was allowed to reach room temperature, and the crude was purified as indicated in each case.

5-[2(*E*- and *Z*)-Phenylethenyl]benzo[1,2-*c*]1,2,5-oxadiazole *N*^{1}-Oxide (1 and 2). Reagents: 5-formylbenzofuroxan (11.7 g, 71 mmol), phosphonium salt **16** (27.6 g, 71 mmol), K_2CO_3 (9.8 g, 71 mmol), and 18-crown-6 (0.2 g, 0.7 mmol). Solvent: toluene (355.0 mL). Reaction time: 2.5 h. Isolation: the brown solid was collected and washed with toluene (~100.0 mL), and the organic layer was evaporated in vacuo. The residue was a mixture of *E* and *Z* isomers, ratio **1**:**2** = 2.2. Prepurification: the residue was prepurified by column chromatography (SiO_2 flash, petroleum ether/EtOAc (90:10 to 80:20). **1** (*E*-isomer): fractions corresponding to the product (10.0 g, 59%) were crystallized from petroleum ether/EtOAc (85:15) to give 7.4 g (44%) as orange needles. Mp 143.8–145.5 °C. TLC: $R_f = 0.75$ (SiO_2, developing solvent, petroleum ether/EtOAc (85:15), detection $\lambda = 254$ nm). HPLC: $t_R = 13.86$ min ($t_o = 2.29$ min). ^{1}H NMR ($CDCl_3$) δ: 7.09 (d, $J = 16.3$ Hz, 1H), 7.21 (d, $J = 16.3$ Hz, 1H), 7.34 (t, $J = 7.2$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.54 (d, $J = 7.3$ Hz, 2H), 7.60 (br s, 3H). MS (EI) *m*/*z* (%): 238 ($M^{+\bullet}$, 90), 222 (16), 192 (16), 178 (100), 149 (3). IR ν (cm^{-1}): 1614, 1572, 1525, 1485, 962, 758, 735. Anal. ($C_{14}H_{10}N_2O_2$) C, H, N. **2** (*Z*-isomer): the fractions corresponding to the product (4.5 g, 27%) were crystallized from petroleum ether to give 3.5 g (21%) as a pale yellow solid. Mp 61.5–62.9 °C. TLC: $R_f = 0.85$ (SiO_2, developing solvent, petroleum ether/EtOAc (85:15), detection $\lambda = 254$ nm). HPLC: $t_R = 12.30$ min ($t_o = 2.29$ min). ^{1}H NMR ($CDCl_3$) δ: 6.74 (d, $J = 12.2$ Hz, 1H), 6.94 (d, $J = 12.2$ Hz, 1H), 7.18 (br s, 1H), 7.33 (br s, 5H), 7.42 (br s, 2H). MS (EI) *m*/*z* (%): 238 ($M^{+\bullet}$, 3), 222 (30), 192 (25), 178 (26), 149 (40). IR ν (cm^{-1}): 1610, 1570, 1520, 1480. Anal. ($C_{14}H_{10}N_2O_2$) C, H, N.

5-[2(*E* and *Z*)-(4-Chlorophenyl)ethenyl]benzo[1,2-*c*]1,2,5-oxadiazole *N*^{1}-Oxide (3 and 4). Reagents: 5-formylbenzofuroxan (8.2 g, 50 mmol), phosphonium salt **17** (21.2 g, 50 mmol), K_2CO_3 (6.9 g, 50 mmol), and 18-crown-6 (0.1 g, 0.5 mmol). Solvent: toluene (250.0 mL). Reaction time: 2.0 h. Isolation: the brown solid (*E*- isomer, checked by TLC) was collected and washed with toluene (~100.0 mL), acetone (~200.0 mL), and EtOH (~300.0 mL). The mixture of the organic layer together with the reaction solvent was evaporated in vacuo. The residue was a mixture of *E* and *Z* isomers. Prepurification: the residue was prepurified by column chromatography (Al_2O_3, petroleum ether/EtOAc (90:10 to 80:20). Ratio **3**:**4** = 3.6. **3** (*E*-isomer): the brown solid, together with the fractions from the chromatographic column corresponding to the product (8.9 g, 65%) were crystallized from EtOH to give 6.3 g (54%) as an orange solid. Mp 173.0–174.0 °C. TLC $R_f = 0.70$ (SiO_2, developing solvent, petroleum ether/EtOAc (85:15), detection $\lambda = 254$ nm). HPLC: $t_R = 14.52$ min ($t_o = 1.71$ min). ^{1}H NMR ($CDCl_3$) δ: 7.45 (d, $J = 16.2$ Hz, 1H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 16.0$ Hz, 1H), 7.55–7.61 (br s, 1H), 7.72 (d, $J = 8.5$ Hz, 2H), 7.88–7.90 (br s, 2H). MS (EI) *m*/*z* (%): 272 ($M^{+\cdot}$, 100), 256 (24), 226 (8), 212 (64), 177 (46), 149 (9). IR ν (cm^{-1}): 1611, 1522, 957, 843, 689. Anal. ($C_{14}H_9N_2O_2Cl$) C, H, N. **4** (*Z*-isomer): the fractions from chromatographic column corresponding to the product (2.5 g, 18%) were crystallized from petroleum ether:EtOAc (90:10) to give 1.8 g (13%) as yellow solid. mp 116.0–117.0 °C. TLC *Rf* = 0.75 (SiO_2, developing solvent: petroleum ether: EtOAc (85:15), detection: $\lambda = 254$ nm). HPLC: $t_R = 12.00$ min ($t_o = 1.71$ min). ^{1}H NMR ($CDCl_3$) δ: 6.62 (d, $J = 12.2$ Hz, 1H), 6.81 (d, $J = 12.2$ Hz, 1H), 7.00–7.05 (br s, 1H), 7.18

(d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 7.28–7.30 (br s, 2H). MS (EI) *m/z* (%): 272 ($M^{+\bullet}$, 100), 256 (21), 226 (9), 212 (77), 177 (63), 149 (24). IR ν (cm^{-1}): 1611, 1522, 957, 843, 689. Anal. ($C_{14}H_9N_2O_2Cl$) C, H, N.

5-[2(*E* and *Z*)-(3,4-Methylendioxyphenyl)ethenyl]benzo[1,2-*c*]1,2,5-oxadiazole N^1-Oxide (5 and 6). Reagents: 5-formylbenzofuroxan (13.8 g, 84 mmol), phosphonium salt **18** (33.4 g, 84 mmol), K_2CO_3 (11.6 g, 84 mmol), and 18-crown-6 (0.2 g, 0.8 mmol). Solvent: toluene (420.0 mL). Reaction time: 3.5 h. Isolation: the brown solid (*E*- isomer, checked by TLC) was collected and washed with toluene (~100.0 mL), EtOAc (~200.0 mL), and acetone (~200.0 mL). The mixture of the organic layer together with the reaction solvent was evaporated in vacuo. The residue was a mixture of *E* and *Z* isomers. Prepurification: the residue was prepurified by column chromatography (SiO_2 flash, petroleum ether/EtOAc (90:10 to 80:20). Ratio **5**:**6** = 1.7. **5** (*E*-isomer): the brown solid, together with the fractions corresponding to the product (11.8 g, 50%) were crystallized from EtOH to give 7.2 g (31%) as an orange-brown solid. Mp 183.7–184.5 °C. TLC $R_f = 0.55$ (Al_2O_3, developing solvent, petroleum ether/EtOAc (90:10), detection $\lambda = 254$ nm). HPLC: $t_R = 10.53$ min ($t_o = 2.73$ min). ^{1}H NMR ($CDCl_3$) δ: 5.98 (s, 2H), 6.91 (d, $J = 8.0$ Hz, 1H), 7.16 (dd, $J = 1.6$ Hz, $J = 7.9$ Hz, 1H), 7.27 (d, $J = 1.6$ Hz, 1H), 7.29 (d, $J = 16.3$ Hz, 1H), 7.48 (d, $J = 16.3$ Hz, 1H), 7.50 (br s, 1H), 7.61 (br s, 1H), 7.86 (br s, 1H). MS (EI) *m/z* (%): 282 ($M^{+\cdot}$, 65), 266 (11), 247 (9), 222 (100), 163 (70). IR ν (cm^{-1}): 1625, 1379, 1273, 1039. Anal. ($C_{15}H_{10}N_2O_4$) C, H, N. **6** (*Z*-isomer): the fractions from chromatographic column corresponding to the product (7.0 g, 30%) were crystallized from petroleum ether/EtOAc (90:10) to give 5.8 g (25%) as a yellow solid. Mp 98.5–100.3 °C. TLC $R_f = 0.65$ (Al_2O_3, developing solvent, petroleum ether/EtOAc (90:10), detection $\lambda = 254$ nm). HPLC: $t_R = 8.84$ min ($t_o = 2.73$ min). ^{1}H NMR ($CDCl_3$) δ: 5.98 (s, 2H), 6.50 (d, $J = 12.0$ Hz, 1H), 6.70 (s, 1H), 6.75 (s, 2H), 6.77 (d, $J = 12.0$ Hz, 1H), 7.12 (br s, 1H), 7.28 (br s, 2H). MS (EI) *m/z* (%): 282 ($M^{+\bullet}$, 70), 266 (5), 247 (11), 222 (100), 163 (70). IR ν (cm^{-1}): 1620, 1514, 873. Anal. ($C_{15}H_{10}N_2O_4$) C, H, N.

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Supporting Information Available

Supplementary figures. This information is available free of charge via the Internet at http: //pubs.acs.org.

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