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2-AMINOPYRROLE-2,5-DIONES
2.* VINYL NUCLEOPHILIC SUBSTITUTION OF THE ALKYLAMINO GROUP IN 1-ALKYL-3-ALKYLAMINOPYRROLE-2,5-DIONES BY ARYLAMINES

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In vinyl nucleophilic substitution ($S_N$vin) with the hydrochlorides or 4-toluenesulfonates of primary arylamines 1-alkyl-3-alkylaminopyrrole-2,5-diones form the corresponding 1-alkyl-3-arylamino-pyrrole-2,5-diones, which are also produced in situ from the corresponding arylaminofumarates and primary alkylamines.

Keywords: arylaminofumarates, pyrrole-2,5-dione, vinyl nucleophilic substitution.

Derivatives of 3-aminopyrrole-2,5-dione are used as kinase inhibitors [2-4], antiallergic and immunotherapeutic agents [5], and local anesthetics [3].

The reaction of 1-methyl-3-methylaminopyrrole-2,5-dione with arylamine hydrochlorides and of 1-(2-hydroxyethyl)-3-(2-hydroxyethylamino)pyrrole-2,5-dione with 4-methoxyaniline hydrochloride leads to $S_N$vin substitution of the alkylamino group by an arylamino group with the formation of the corresponding 1-alkyl-3-arylaminopyrrole-2,5-diones [1]. In a continuation of our investigations it seemed of interest to study this reaction for other 1-alkyl-3-alkylaminopyrrole-2,5-diones. It was established that the corresponding 1-alkyl-3-arylaminopyrrole-2,5-diones **3a-j** (Tables 1 and 2) are formed during the reaction of 1-alkyl-3-alkyl-aminopyrrole-2,5-diones **1a-e** with the hydrochlorides or 4-toluenesulfonates of arylamines **2a-j**.

1-Alkyl-3-arylaminopyrrole-2,5-diones can also be obtained by the reaction of the individual arylaminofumarates with primary aliphatic amines [1]. Since it is difficult in a number of cases to isolate the arylaminofumarates in the individual state we developed a modification of this method, involving the production of the arylaminofumarates **5a**,**b**,**d** *in situ* from dimethyl acetylenedicarboxylate **4** and arylamines.

The motivating force of the $S_N$vin substitution of the alkylamino group in the reaction of 1-alkyl-3-alkylaminopyrrole-2,5-diones with the arylamine hydrochlorides or 4-toluenesulfonates is probably the formation of a weaker conjugate acid (the alkylammonium cation) and a weaker base (the corresponding 1-alkyl-3-arylaminopyrrole-2,5-dione). In actual fact the experimental values of pK_a for all the investigated

* For Communication 1 see [1].

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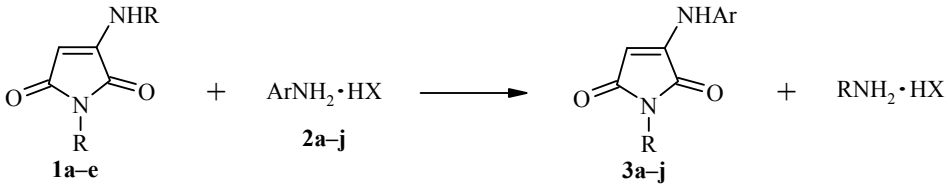
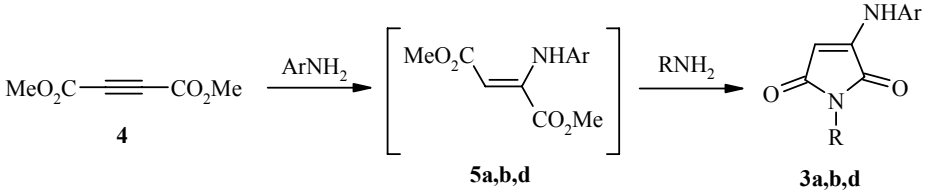


1 a R = $PhCH_2$, **b** R = $MeOCH_2CH_2$, **c** R = $PhCH_2CH_2$, **d** R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$, **e** R = 2-furfuryl; **2, 3, 5 a** Ar = Ph, X = Cl, R = $PhCH_2$, **b** Ar = 3-$HOCH_2CH_2OC_6H_4$, X = Cl, R = $PhCH_2$, **c** Ar = 3-$O_2NC_6H_4$, X = TsO, R = $MeOCH_2CH_2$, Ar = 2-$MeOC_6H_4$, X = Cl, R = $MeOCH_2CH_2$, **e** Ar = 4-$Me_2NC_6H_4$, X = Cl, R = $PhCH_2CH_2$, **f** Ar = 4-$HO_2CC_6H_4$, X = TsO, R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$, **g** Ar = 4-$MeO_2CC_6H_4$, X = TsO, R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$, **h** Ar = 2-$HO_2CC_6H_4$, X = TsO, R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$, **i** Ar = 3-$MeOC_6H_4$, X = Cl, R = 2-furfuryl, **j** Ar =1-naphthyl, X = Cl, R = 2-furfuryl



nucleophiles are significantly lower than for the corresponding nucleofuges (Table 3). The pK_a values of aryl- and alkylamines calculated by means of the ACD/pK_a DB program [6] agree well with the experimental data (Table 3). On this basis we calculated the pK_a values of all the possible protonated forms **6a-d** for one of the initial compounds 1-benzyl-3-benzylaminopyrrole-2,5-dione **1a** [**6a** (-3.16 ± 0.40) < **6b** (2.83 ± 0.20) < **6c** (3.49 ± 0.20) < **6d** (3.63 ± 0.20)] and for the corresponding reaction product 1-benzyl-3-phenylaminopyrrole-2,5-dione **3a** [**6a** (−3.50 ± 0.40) < **6b** (−2.73 ± 0.20) < **6c** (1.39 ± 0.20) < **6d** (3.31 ± 0.40)]; the smallest pK_a values for each of the tautomers are given. According to the Kabachnik rule [7] the protonated forms **6c**,**d**, as having the lowest acidity, should predominate in the equilibrium mixture. From comparison of the calculated

TABLE 1. The Characteristics of Compounds **3a-j**

Com-pound	Empirical formula	Found N, % / Calculated N, %	mp, °C	Yield, %
3a	$C_{17}H_{14}N_2O_2$	9.93 / 10.07	164-166 165-166 [1]	73
3b	$C_{19}H_{18}N_2O_4$	8.45 / 8.28	147.5-149.5	51
3c	$C_{13}H_{13}N_3O_5$	14.30 / 14.43	194-195	69
3d	$C_{14}H_{16}N_2O_4$	10.02 / 10.14	121-122	73
3e	$C_{20}H_{21}N_3O_2$	12.37 / 12.53	199-200.5	41
3f	$C_{21}H_{20}N_2O_6$	7.12 / 7.07	223-226	74
3g	$C_{22}H_{22}N_2O_6$	6.95 / 6.83	206-209	93
3h	$C_{21}H_{20}N_2O_6$	7.16 / 7.07	220-222	78
3i	$C_{16}H_{14}N_2O_4$	9.20 / 9.39	144-145	55.5
3j	$C_{19}H_{14}N_2O_3$	8.92 / 8.80	135-136	40.5

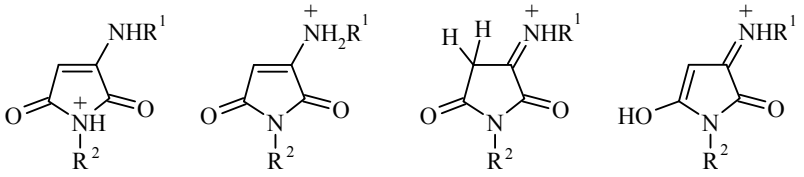
TABLE 2. Spectral Characteristics of Compounds **3a-j**

Compound	IR spectrum, ν, cm^{-1}				^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
	NH	$(CO)_{as}$	$(CO)_s$	C=C	
3a	3315	1760	1715	1660	4.65 (2H, s, CH_2); 5.54 (1H, s, CH); 7.03-7.45 (10H, m, $2C_6H_5$); 9.62 (1H, br. s, NH)
3b	3315	1755	1695	1640	3.72 (2H, dt, *J* = 4.6, *J* = 5.1, CH_2OH); 3.99 (2H, t, *J* = 4.6, CH_2O); 4.63 (2H, s, CH_2N); 4.88 (1H, br. t, *J* = 5.1, OH); 5.68 (1H, s, CH); 6.66-6.73 (1H, m, H_{Ar}-2); 6.94-7.03 (2H, m, H_{Ar}-4,6); 7.22-7.39 (6H, m, H_{Ar}-5 + C_6H_5); 9.72 (1H, br. s, NH)
3c	3370	1755	1705	1645	3.24 (3H, s, OCH_3); 3.48 (2H, t, *J* = 5.6, CH_2O); 3.61 (2H, t, *J* = 5.6, NCH_2); 5.85 (1H, s, CH); 7.60-7.70 (1H, m, H_{Ar}-5); 7.77-7.87 (1H, m, H_{Ar}-6); 7.87-7.97 (1H, m, H_{Ar}-4); 8.21-8.29 (1H, m, H_{Ar}-2); 10.06 (1H, br. s, NH)
3d	3365	1750	1710	1650	3.36 (3H, s, CH_3OCH_2); 3.58 (2H, t, *J* = 5.6, CH_2O); 3.75 (2H, t, *J* = 5.6, NCH_2); 3.93 (3H, s, OCH_3); 5.53 (1H, s, CH); 6.94 (1H, d, *J* = 8.4, H_{Ar}-3); 6.97-7.05 (1H, m, H_{Ar}-5); 7.05-7.15 (1H, m, H_{Ar}-4); 7.19 (1H, d, *J* = 7.6, H_{Ar}-6); 7.86 (1H, br. s, NH)*
3e	3360	1750	1710	1655	2.85 (2H, t, *J* = 7.2, CH_2); 2.88 (6H, s, 2 CH_3); 3.65 (2H, t, *J* = 7.2, CH_2N); 5.34 (1H, s, CH); 6.72 (2H, d, *J* = 8.8, H_{Ar}-2,6); 7.16-7.31 (7H, m, H_{Ar}-3,5 + C_6H_5); 9.47 (1H, br. s, NH)
3f	3340	1750	1705	1645	2.79 (2H, t, *J* = 7.0, CH_2); 3.66 (2H, t, *J* = 7.0, CH_2N); 3.69 (3H, s, OCH_3); 3.71 (3H, s, OCH_3); 5.86 (1H, s, CH); 6.67 (1H, dd, ^3J = 8.0, ^4J = 1.6, H_{Ar}-5'); 6.77 (1H, d, ^4J = 1.6, H_{Ar}-3'); 6.83 (1H, d, *J* = 8.0, H_{Ar}-6'); 7.49 (2H, d, *J* = 8.8, H_{Ar}-3,5); 7.91 (2H, d, *J* = 8.8, H_{Ar}-2,6); 9.89 (1H, br. s, NH); 12.78 (0.8H, br. s, CO_2H)
3g	3360	1765	1720	1640	2.79 (2H, t, *J* = 7.2, CH_2); 3.67 (2H, t, *J* = 7.2, CH_2N); 3.69 (3H, s, OCH_3); 3.71 (3H, s, OCH_3); 3.83 (3H, s, CO_2CH_3); 5.89 (1H, s, CH); 6.67 (1H, dd, ^3J = 8.0, ^4J = 1.6, H_{Ar}-5'); 6.77 (1H, d, ^4J = 1.6, H_{Ar}-3'); 6.83 (1H, d, *J* = .0, H_{Ar}-6´); 7.52 (2H, d, *J* = 8.8, H_{Ar}-3,5); 7.93 (2H, d, *J* = 8.8, H_{Ar}-2,6); 9.93 (1H, br. s, NH)
3h	3350	1760	1715	1650	2.80 (2H, t, *J* = 7.2, CH_2); 3.66 (2H, t, *J* = 7.2, CH_2N); 3.70 (3H, s, OCH_3); 3.72 (3H, s, OCH_3); 6.01 (1H, s, CH); 6.69 (1H, dd, ^3J = 8.0, ^4J = 1.6, H_{Ar}-5'); 6.78 (1H, d, ^4J = 1.6, H_{Ar}-3'); 6.84 (1H, d, *J* = 8.0, H_{Ar}-6'); 7.18 (1H, t, *J* = 7.8, H_{Ar}-5); 7.54 (1H, d, *J* = 8.3, H_{Ar}-3); 7.61–7.69 (1H, m, H_{Ar}-4); 8.06 (1H, dd, ^3J = 7.8, ^4J = 1.5, H_{Ar}-6); 11.23 (1H, br. s, NH); 13.83 (0.8H, br. s, CO_2H)
3i	3345	1755	1715	1635	3.76 (3H, s, OCH_3); 4.61 (2H, s, CH_2); 5.67 (1H, s, CH); 6.29-6.33 (1H, m, H_{Fur}-3); 6.38–6.42 (1H, m, H_{Fur}-4); 6.66-6.73 (1H, m, H_{Ar}-2); 6.94-7.01 (2H, m, H_{Ar}-4,6); 7.23-7.32 (1H, m, H_{Ar}-5); 7.54-7.59 (1H, m, H_{Fur}-5); 9.67 (1H, br. s, NH)
3j	3400	1760	1710	1650	4.63 (2H, s, CH_2); 4.96 (1H, s, CH); 6.35 (1H, d, *J* = 3.1, H_{Fur}-3); 6.42 (1H, dd, *J* = 3.1, *J* = 1.7, H_{Fur}-4); 7.49-7.64 (5H, m, H_{Ar}-2,4,6,7 + H_{Fur}-5); 7.87 (1H, d, *J* = 7.6, H_{Ar}-5); 7.94-8.03 (2H, m, H_{Ar}-3,8); 9.87 (1H, br. s, NH)

* The spectrum was obtained in $CDCl_3$.

pK_a values of the protonated forms **6c**,**d** of the initial 1-alkyl-3-alkylaminopyrrole-2,5-diones **1a-e** and final 3-arylamino derivatives **3a-j** (Tables 3 and 4) it then follows that the weaker bases 1-alkyl-3-arylaminopyrrole-2,5-diones are always formed in the $S_N$vin reaction.

Both the imine and the enamine forms of 3-aminopyrrole-2,5-dione derivatives were examined in [8, 9], but later investigations showed that they exist exclusively in the enamine form [1-5, 10-16]. It's pronation in accodance with the conducted analysis of the tautomers results in predominance of imine forms **6c,d**. Accordingly, protonation on account of increase in the effective electronegativity of the nitrogen atom stabilizes the imine form in the derivatives of 3-aminopyrrole-5-dione compared with the enamine form, and this gives rise to the possibility of nucleophilic addition of the arylamine at the imine carbon atom followed by removal of the alkylamine, securing the realization of the $S_N$vin reaction.



6a **6b** **6c** **6d**

R^1 = Alk or Ar; R^2 = Alk

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on Varian VXR-300 (3006 MHz) (compound **3i** and 2-(3-aminophenoxy)ethanol) and Varian GEMINI-2000 (400 MHz) (compounds **1b** and **3a-h**,**j**) with TMS as internal standard, and the signals were assigned by means of ACD/HNMR DB software [6]. The IR spectra were recorded on a UR-20 spectrometer in tablets with potassium bromide. The 1-alkyl-3-alkylaminopyrrole-2,5-diones (**1a**,**c-e**) were obtained by the method in [16], dimethyl aminofumarate by the method in [18], and 2-(3-nitrophenoxy)ethanol by the method in [19]. The reactions and the individuality of the substances were monitored by chromatography on Silufol UV-254 plates in the 10:1 chloroform–methanol system with development in UV light and/or in iodine vapor.

1-(2-Methoxyethyl)-3-(2-methoxyethylamino)pyrrole-2,5-dione (1b). 2-Methoxyethylamine (4.1 g, (Merck) 4.75 ml, 54 mmol) to a solution was added of dimethyl aminofumarate (4.0 g, 25 mmol) in of 90% aqueous methanol (10 ml). The mixture was heated at 75°C for 9 h and left overnight. The solvent was removed at reduced pressure, and the residue was extracted with benzene (2×25 ml). The extract was filtered, and the filtrate was evaporated under vacuum. The residue was cooled to 0°C, triturated with of methanol (5 ml), and left overnight at 0°C. The precipitate was filtered off, washed with cold methanol, and dried under vacuum at 35°C. Yield of compound **1b** 3.3 g (58%); mp 62-64°C. Found, %: N 12.45. $C_{10}H_{16}N_2O_4$. Calculated, %: N 12.27. ^{1}H NMR spectrum, δ, ppm: 3.21 (3H, s, OCH_3); 3.25 (3H, s, OCH_3); 3.38-3.54 (8H, m, $4CH_2$); 4.90 (1H, s, CH); 7.65 (1H, br. s, NH).

2-(3-Aminophenoxy)ethanol. ***Preparation of Catalyst.*** Sodium hydroxide (6×2 g, 0.3 mol) was added to a suspension of a reduction alloy of nickel with aluminum (10.0 g) in water (70 ml). The mixture was allowed to stand for 15 min and kept at 75°C for 35 min. The liquid above the catalyst was decanted, and the catalyst was washed successively with water (2×25 ml) and with methanol (2×20 ml). ***Reduction.*** The catalyst was added with stirring to a solution of 2-(3-nitrophenoxy)ethanol (50.0 g, 0.273 mol) and 80% aqueous $N_2H_4 \cdot H_2O$ (d_4^{20} 1.034) (43.4 g, 42 ml, 0.685 mol) in methanol (400 ml) over 1 h at 50°C. The mixture was kept at 65°C for 25 min and boiled for 1 h. The reaction mixture was cooled, the catalyst was filtered off, and the

TABLE 3. The pK_a Values at 25°C and Ionic Strength $I = 0$

Compound	Conjugate acid	pK_a	
		Experiment [6]	Calculation
Benzylamine	RNH_3^+	9.35	9.40±0.10
2-Methoxyethylamine		9.43	8.80±0.10
2-Phenylethylamine		9.92±0.04 (0.1)	9.90±0.10
2-(3,4-Dimethoxyphenyl)ethylamine		9.88±0.01 (0.1)	9.74±0.10
2-Furfurylamine		8.89 (1.0/30)	9.12±0.29
Aniline	$ArNH_3^+$	4.60	4.61±0.10
2-(3-Aminophenoxy)ethanol		—	4.09±0.10
3-Nitroaniline		2.46	2.46±0.10
2-Methoxyaniline		4.53	4.54±0.10
4-Aminobenzoic acid (4-ABA)		2.41±0.04	2.51±0.10
Methyl ester of 4-ABA		2.47	2.47±0.10
2-Aminobenzoic acid		2.11	2.10±0.10
3-Methoxyaniline		4.20	4.17±0.10
1-Naphthylamine		3.94±0.02	3.94±0.10
N,N-Dimethyl-1,4-diaminobenzene	$Me_2\overset{+}{N}HC_6H_4NH_2$	6.59	6.64±0.12
	$Me_2\overset{+}{N}HC_6H_4\overset{+}{N}H_3$	—	2.68±0.10

TABLE 4. The Calculated pK_a Values

Compound	pK_a	
	6c*	**6d*[2]**
1a	3.49±0.20	3.63±0.20
1b	2.45±0.20	3.37±0.20
1c	3.28±0.20	3.57±0.20
1d	3.02±0.20	3.51±0.20
1e	2.02±0.20	3.34±0.20
3a	1.39±0.20	3.31±0.40
3b	0.80±0.20	2.72±0.40
3c	-1.17±0.20	0.94±0.40
3d	-0.10±0.20	2.01±0.40
3e	2.51±0.20	3.34±0.20
3f	-0.39±0.20	1.68±0.40
3g	-0.46±0.20	1.62±0.40
3h	0.07±0.20	2.15±0.40
3i	0.47±0.20	2.56±0.40
3j	0.95±0.20	3.04±0.40

* pK_a^{NH+}.

*[2] The smallest of the two possible pK_a values is given (pK_a^{OH} for compounds **1a-e** and **3e**; pK_a^{NH+} for compounds **3a-d**, **f-j**); most of the enaminones have pK_a values in the range of 2.8-3.1 [17].

filtrate was boiled for 3 min with 1.5 g of active carbon. The carbon was then filtered off, and the filtrate was evaporated under vacuum. The residue was triturated with ether and cooled to 5°C, and the precipitate was filtered off, washed with cold ether, and dried. The product (37.5 g) was distilled under vacuum. Yield of **2-(3-aminophenoxy)ethanol** 32.6 g, (80%); bp 155.5-157°C (1 mm Hg), mp 52-53°C (mp 52°C [19])

(hydrochloride **2b**, mp 134.5-139.5°C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm): 2.88 (1H, br. s, OH); 3.72 (2H, br. s, NH_2); 3.84-3.93 (2H, m, $C\underline{H_2}OH$); 3.93-4.02 (2H, m, OCH_2); 6.20-6.24 (1H, m, H_{Ar}-2); 6.26-6.34 (2H, m, H_{Ar}-4,6); 6.97-7.10 (1H, m, H_{Ar}-5).

1-Benzyl-3-phenylaminopyrrole-2,5-dione (3a). A solution of the hydrochloride **2a** (0.45 g, 3.5 mmol) in methanol (5 ml) was added to a solution of compound **1a** (1.0 g, 3.4 mmol) in methanol (25 ml). The mixture was boiled for 1 h and left overnight at 5°C. The precipitate was filtered off, washed with methanol, and recrystallized from 2-propanol. We obtained compound **3a** (0.69 g).

Compounds 3e,**i**,**j** were obtained similarly. Compounds **3i**,**j** were crystallized from methanol.

1-Benzyl-3-[3-(2-hydroxyethoxy)phenylamino]pyrrole-2,5-dione (3b). Methanol (34 ml) was added to a mixture of compound **1a** (1.50 g, 5 mmol) and hydrochloride **2b** (1.07 g, 5.6 mmol) The mixture was boiled for 1 h and left overnight. The solution was evaporated under vacuum, and the residue was triturated with cold water. The precipitate was filtered off, washed with cold water, and dried. The product (1.72 g) was recrystallized twice from 2-propanol and compound **3b** (0.88 g) was obtained.

1-(2-Methoxyethyl)-3-(3-nitrophenylamino)pyrrole-2,5-dione (3c). A solution of 3-nitroaniline (0.64 g, 4.6 mmol) and of 4-toluenesulfonic acid monohydrate (0.84 g, 4.4 mmol) in methanol (10 ml) was added to a solution of compound **1b** (1.01 g, 4.4 mmol) in methanol (5 ml). The mixture was boiled for 1 h and left overnight at 5°C. The precipitate was filtered off, washed with methanol, and recrystallized from 2-propanol. Compound **3c** (0.89 g) was obtained.

Compounds 3f-h were obtained similarly. Compound **3f** was crystallized from methanol. Compounds **3g**,**h** were purified by boiling in methanol.

1-(2-Methoxyethyl)-3-(2-methoxyphenylamino)pyrrole-2,5-dione 3d. Absolute ethanol (10 ml) was added to a mixture of compound **1b** (1.0 g, 4.4 mmol) and the hydrochloride **2d** (0.74 g, 4.6 mmol). The mixture was boiled for 1 h and left overnight at 5°C. The precipitate was filtered off, washed with cold absolute ethanol, and recrystallized from absolute ethanol. Compound **3d** (0.89 g) was obtained.

Dimethyl Phenylaminofumarate (5a). A solution of aniline (2.51 g, 2.45 ml, 27 mmol) in absolute benzene (10 ml) was added dropwise with stirring at 20°C over 10 min to a solution of compound **4** (3.81 g, 3.30 ml, 27 mmol) in absolute benzene (40 ml). The mixture was left overnight, boiled for 4 h, and cooled, and the solvent was removed under vacuum. Compound **5a** (6.32 g, 100%) was obtained.

Compound 5d was obtained similarly.

Dimethyl 3-(2-Hydroxyethoxy)phenylaminofumarate (5b). A solution of compound **4** (1.85 g, 1.60 ml, 13 mmol) in absolute methanol was added dropwise with stirring at 20°C (10 ml) to a solution of 2-(3-aminophenoxy)ethanol (2.0 g, 13 mmol) in absolute methanol (11 ml) over 15 min. The mixture was boiled for 30 min and left overnight, and the solvent was evaporated under vacuum. of compound **5b** (3.85 g, 100%) was obtained.

The obtained arylaminofumarates **5a**,**b**,**d** were used in the following syntheses without additional purification.

1-Benzyl-3-phenylaminopyrrole-2,5-dione (3a). Benzylamine (4.34 g, 4.42 ml, 40.5 mmol) was added to a solution of the phenylaminofumarate **5a** (6.32 g, 27 mmol) in methanol (15 ml). The mixture was kept at 20°C for 10 days. The precipitate was filtered off, washed with methanol, and recrystallized from 2-propanol. Compound **3a** (3.08 g, 41%) was obtained.

Compound 3b was obtained similarly with a yield of 1.09 g (25%).

1-(2-Methoxyphenylamino)pyrrole-2,5-dione (3d). 2-Methoxyethylamine (Merck) (3.0 g, 3.5 ml, 40 mmol) was added to a solution of compound **5d** (7.06 g, 27 mmol) in methanol (10 ml). The mixture was kept at 20°C for 28 days. The solvent was evaporated under vacuum, and the residue was cooled to 5°C, triturated with 5 ml of cold methanol, and left overnight at 5°C. The precipitate was filtered off, washed with cold methanol, and crystallized from methanol. Compound **3d** (2.7 g, 37%) was obtained.

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