Efficient Method for the Synthesis of Functionalized Basic Maleimides

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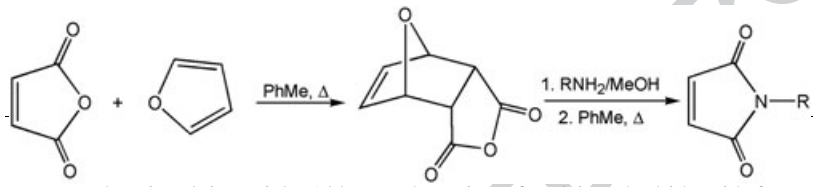
Received January 13, 2012
DOI 10.1002/jhet.1651
Published online 00 Month 2012 in Wiley Online Library (wileyonlinelibrary.com).



A three-step procedure involving Diels–Alder condensation of maleic anhydride with furane, formation of *N*-substituted imide upon reaction with appropriate diamine, and a final retro Diels–Alder regeneration of the maleic carbon–carbon double bond is proposed for an unequivocal synthesis of *N*-substituted basic maleimides. The novel method is characterized by mild reaction conditions, easy work-up, high yields, and no need for additional catalysis.

J. Heterocyclic Chem, **00,** 00 (2012).

INTRODUCTION

Maleimides are widely used as substrates in chemical synthesis, and some of them demonstrate biological activity. They can be applied in organic synthesis in the Michael addition-type reactions, as dienophiles in Diels–Alder reactions, and also in some other condensations [1]. Biological applications of these compounds result from their high reactivity towards thiol groups, including the cysteine residues of proteins [2]. Consequently, maleimides are used as chemical probes of protein structure, and bifunctional maleimides may be useful as conjugating reagents for intramolecular and intermolecular cross-linking of proteins [3]. In the recent years, several functionalized maleimides have been used as reagents for site-directed modifications of peptides or proteins [4], and for the synthesis of novel derivatives of biologically active compounds [5]. Derivatives of daunorubicin of improved biological activity were obtained by the reaction with maleimides under mild conditions [6], and tebaine adducts were synthesized by cycloaddition of maleimides [1c]. There is a need for efficient methods of synthesis of *N*-substituted maleimides bearing different functionalities that could be used for derivatisation of biologically active compounds under mild conditions.

Several methods of maleimide synthesis were reported in literature (Scheme 1). The classical approach involves condensation of an appropriately substituted amine and maleic anhydride, followed by dehydration of the intermediate maleamic acid, usually promoted by acids [7]. This method is limited to amines as starting materials, and final yields are often low. *N*-alkylated maleimides may be obtained by direct alkylation of maleimides with a proper alcohol under conditions of Mitsunobu reaction [8]. However, this method may be only applied to simple alkyl systems and requires additional activating reagents, which results in generation of side products that must be removed at the final step [9].

The previously specified methods are efficient for preparation of *N*-alkyl and *N*-aryl maleimides.

RESULTS AND DISCUSSION

Preparation of maleimide derivatives containing amine functional group(s) in the *N*-alkyl substituents is a particular challenge. Such functional maleimides may be used for modification of biologically active fragile compounds under mild conditions, to raise their basicity and solubility. Synthesis of these compounds by the aforementioned classical methods affords the desired products with low yields, and there are problems with efficient product isolation [1c,7,8]. In the present work, an alternative simple synthetic approach is proposed to obtain basic maleimides with high yields, with no need to use any additional activating reagents.

In our approach, schematically drawn in Table 1, the double bond of maleic anhydride **1** is protected through a Diels–Alder reaction using furan **2** as a diene, before the subsequent reaction with an amine reagent. Introduction of a protective group on the carbon–carbon double bond of maleic anhydride prevents the possibility of a nucleophilic attack by the amine reactants or nucleophile-initiated polymerization. In the second step, the protected derivative **3** reacts with diamine containing primary and tertiary amine functionalities separated by alkyl chains. The tertiary amine does not require any protection, which minimizes a number of synthetic steps. Finally, the retro Diels–Alder reaction affords the desired final product as an *N*-substituted maleimide.

Scheme 1. The classical methods for preparation of maleimides [7,8].

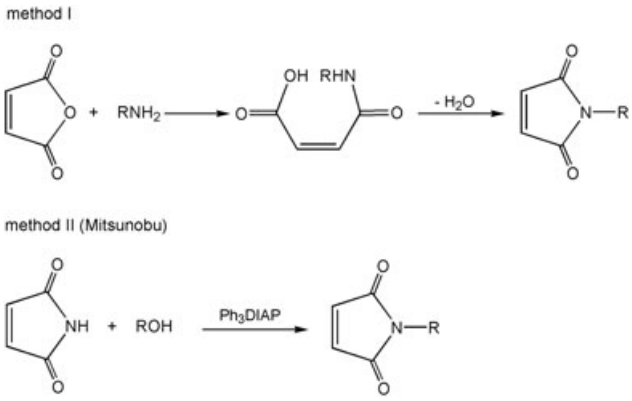


Table 1

Products.

Entry	R	Yield of **5** (%)	Yield lit. (%)
a	$-CH_2CH_2N(CH_3)_2$	91	58 [1c]
b	$-CH_2CH_2CH_2N(CH_3)_2$	80	~15 (picrate) [10]
c		82	[12]
d		88	31 [11]
e		68	–
f	$-CH_2C(CH_3)_2CH_2N(CH_3)_2$	81	–
g		72	38 [13]
h		76	–
i		70	57 [14c]
j	$-CH_2CH_2OH$	54	40 [15]
k		–	–

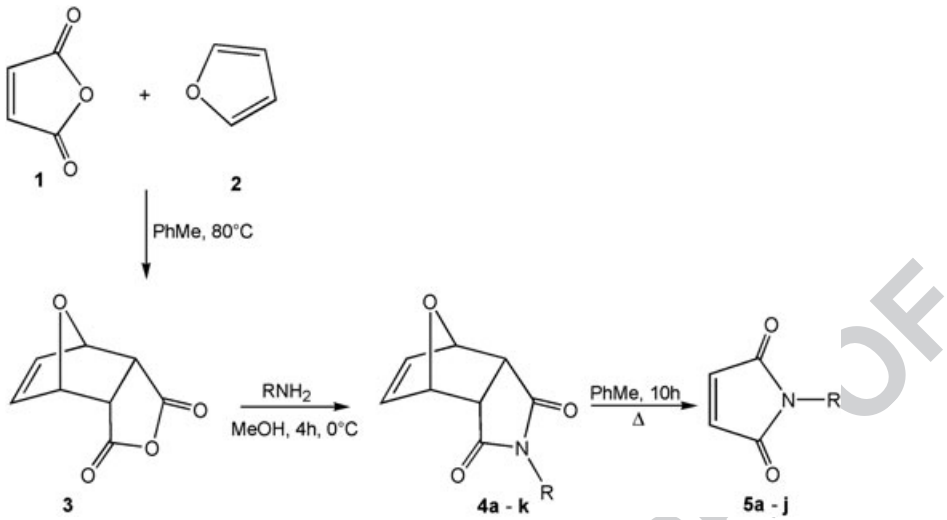
Cycloaddition of furane **2** to maleic anhydride **1** was performed in toluene as a solvent at 80°C for 20 h. After cooling the mixture, the semi-product **3** (7-oxabicyclo[2.2.1] hept-2-ene-5,6-dicarboxylic acid anhydride) crystallized as a mixture of two isomers, *exo* and *endo*. The isomers were not separated because both are equally reactive, and at the last step, the protective group was removed to regenerate the double bond. The imides were synthesized by condensation of equimolar amounts of **3** with an appropriate diamine. The reaction was carried out in anhydrous methanol for 3 h. No acid-promoted dehydration was required at this step. The yields of the obtained condensation products **4a–k** were high (>90%), and their purity was excellent. Most of the products were crystallized from anhydrous ethanol, which obviously facilitated purification. At the final step, the protective group was removed by the retro Diels–Adler reaction. Heating the imide products for 10 h in toluene lead to the final maleimide basic derivatives with 80–90% yield (**5a–h**). Shorter reaction periods resulted in incomplete deprotection. The final products obtained in high yields were crystalline. Because of the high purity, there was no need for further chromatographic purification. Using this novel procedure, we obtained eight basic maleimides **5a–h**, where compounds **5e**, **5f**, and **5h** are novel compounds, **5b** was previously obtained as a picrate in low yield [10] and the previously described methods of synthesis of **5a** [1c], and **5d** [11] and **5g** [13] were poorly efficient. The method was also used for the synthesis of well-known *N*-substituted non-basic maleimides **5i–j**, to demonstrate its universality. In the case of compound **4k**, the protective group could not be removed, so that the *N*-[3-(imidazol-1-yl)propyl] maleimide was not obtained (Scheme 2).

In summary, we have developed a facile and highly efficient method of preparation of functionalized basic maleimides. One of the advantages of this method is the fact that most of the byproducts and final products are crystalline/solids that obviously facilitate their isolation in pure form, without any need of further processing. This was also due to the proper choice of solvents at every step, different from those used in the previous methods. The yields obtained in our syntheses were much higher (80–90%) than those previously reported for other methods (15–58%) [1c,10–17]. To summarize, the novel method is characterized by mild reaction conditions, easy work-up, high yields, and no need for additional catalysis. Moreover, the method may be applied for preparation of *N*-substituted maleimides containing hydroxyl functionality in the nitrogen substituent.

EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded on Varian Unity Plus (Varian Inc., Palo Alto, CA, USA) (500 MHz for ^1H) or Gemini Varian (200 MHz for ^1H) using $CDCl_3$ or CD_3OD as a solvent. Chemical shifts are expressed in ppm with TMS as an internal standard for ^1H. ^{13}C NMR spectra are referenced to $CDCl_3$ (77.0 ppm). The mass spectra (ESI-ms) were measured with micrOTOF-Q II™ ESI-Qq-TOF Bruker mass spectrometer (Bruker BioSpin, Billerica, MA, USA). Elemental analyses were

Scheme 2. Synthesis of basic maleimides.



Q8 performed on the analyzer EA 1108 Carlo Ebra. Melting points are uncorrected. All solvents and reagents were used as obtained from commercial source.

7-Oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic acid anhydride (3). To the suspension of 10 g (0.102 mol) of maleic anhydride (**1**) in toluene (150 mL) warmed for 80°C, 11.3 mL of furane (**2**) was added slowly. The solution was stirred at this temperature for 16 h. Then, the mixture was cooled to room temperature, and small white crystals were filtered off. The filtrate was left for additional 24 h, and after this period, additional amount of crystalline **3** was collected and combined with the primary crystals. The product was obtained as white crystals with all yield 94%, mp 115°C (lit. mp 114–115°C [11], 124–127°C [17d], 118°C [18b,c]); ^{1}H NMR (200 MHz, CD_3OD): δ 6.6 (s, 2H, CH = CH), 5.5 (s, 2H, CHO), 3.2 (s, 2H, CHCO). ^{13}C NMR (50.3 MHz, CD_3OD): δ 172.7, 138.3, 83.8, 50.5.

General procedure for the synthesis of imides (4). The suspension 3 g (0.018 mol) of **3** in 100 mL methanol was cooled to 0°C. Next, a solution 0.018 mol of diamine in 20 mL methanol was added slowly to this cooled mixture. After 10 min with stirring at 0°C, the solution was warmed to room temperature, left for additional 1 h, and then refluxed for 3 h. Finally, the mixture was cooled to room temperature, and solvent was removed under reduce pressure. The residue was crystallized from an appropriate solvent.

***N*-[2-(*N*,*N*-Dimethylamino)ethyl]-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboximide (4a)**. This compound was crystallized from ethanol to yield 4.08 g (96%) as pale yellow crystals, mp 99–100°C (lit. [19a] mp 100–101°C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.5 (s, 2H, CH = CH), 5.25 (s, 2H, CHO), 3.60 (t, J = 6.8 Hz, 2H, CH_2NCO), 2.88 (s, 2H, COCH), 2.52 (t, 2H, J = 3.3 Hz, CH_2N), 2.29 (s, 6H, NCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 178.8, 137.9, 82.5, 57.2, 50.2, 45.7, 37.3.

***N*-[3-(*N*,*N*-Dimethylamino)propyl]-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboximide (4b)**. This compound was crystallized from ethanol to yield 4 g (89%) as yellow solid, mp 43–44°C (lit. [19a] mp 49–50°C/ligroine); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.5 (s, 2H, CH = CH), 5.25 (s, 2H, CHO), 3.52 (t, J = 7.3 Hz, 2H, CH_2NCO), 2.82 (s, 2H, COCH), 2.27 (t, J = 7.3 Hz, 2H, CH_2N), 2.20 (s, 6H, NCH_3), 1.73 (quin, J = 7.3 Hz, 2H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 178.8, 137.9, 82.6, 57.7, 49, 45.3, 37.8, 26.3.

***N*-(2-Piperidin-1-yl-ethyl)-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4c)**. This compound was crystallized from toluene:hexane to yield 4.8 g (97%) as colorless crystals, mp 86–87°C (lit. [19b] mp 96–98°C/EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.5 (s, 2H, CH = CH), 5.25 (s, 2H, CHO), 3.62 (t, J = 6.8 Hz, 2H, CH_2NCO), 2.85 (s, 2H, COCH), 2,53 (t, 2H, J = 6.8 Hz, CH_2N), 2.49 (m, 4H, CH_2N), 1.56 (t, J = 5.5 Hz, 4H, CH_2), 1.41 (m, 2H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 178.8, 137.9, 82.5, 56.7, 55.6, 49.3, 36.6, 26.6, 25.2.

***N*-(2-Morpholin-1-yl-ethyl)-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4d)**. This compound was crystallized from ethanol to yield 4.7 g (94%) as yellow solid, mp 117–118°C (lit. [19b] mp 119–120°C/EtOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.5 (s, 2H, CH = CH), 5.24 (s, 2H, CHO), 3.74 (m, 4H, CH_2O), 3.65 (t, J 3.3, 2H, CH_2NCO), 2.88 (s, 2H, COCH), 2.65 (m, 6H, CH_2N); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 178.8, 137.9, 82.5, 67.9, 56.5, 54.7, 49, 36.6.

***N*-[2-(4-Methylpiperazin-1-yl)ethyl]-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4e)**. This compound was crystallized from ethanol to yield 3.77 g (72%) as pale yellow solid, mp 64–65°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.48 (s, 2H, CH = CH), 5.23 (s, 2H, CHO), 3.57 (t, J = 6.6 Hz, 2H, CH_2NCO), 2.82 (s, 2H, COCH), 2.73 (m, 2H, NCH_2CH_2N), 2.49 (t, J = 6.6 Hz, 2H, $CH_2N(CH_2)_2$), 2.4 (m, 6H, NCH_2CH_2N), 2.24 (s, 3H, NCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 176.7, 137, 81.4, 55.4, 55.1, 53.0, 47.9, 46.2, 36.7.

***N*-[3-(*N*,*N*-Dimethylamino)-2,2-dimethylpropyl]-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4f)**. This compound was crystallized from ethanol to yield 4.46 g (89%) as white solid, mp 104–105°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.5 (s, 2H, CH = CH), 5.25 (s, 2H, CHO), 3.42 (s, 2H, CH_2NCO), 2.83 (s, 2H, COCH), 2.36 (s, 6H, $N(CH_3)_2$), 2.22 (s, 2H, CH_2N), 0.9 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 176.8, 136.5, 81.0, 69.0, 48.5, 47.4, 47.2, 38.6, 24.3.

***N*-[(Pyridin-4-yl)methyl]-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4g)**. This compound was crystallized from ethanol to yield 3.6 g (78%) as white solid, mp 152–153°C; ^{1}H

NMR (200 MHz, $CDCl_3$): δ 8.53 (d, J = 4.5 Hz, 2H, aromatic CH=CHN), 7.17 (d, J = 6 Hz, 2H, aromatic CH=CHN), 6.53 (s, 2H, CH=CH), 5.31 (s, 2H, CHO), 4.64 (s, 2H, CH_2NCO), 2.92 (s, 2H, COCH); ^{13}C NMR (50.2 MHz, $CDCl_3$): δ 175.6, 150.1, 144, 136.6, 122.4, 81, 47.6, 41.3.

N-[2-(Pyrrolidin-1-yl)ethyl]-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4h). This compound was crystallized from ethanol to yield 3.8 g (81%) as pale orange solid, mp 81–82°C; ^1H NMR (200 MHz, $CDCl_3$): δ 6.5 (s, 2H, CH=CH), 5.24 (s, 2H, CHO), 3.62 (t, J = 7 Hz, 2H, CH_2NCO), 2.85 (s, 2H, COCH), 2,63 (t, 2H, J = 7 Hz, CH_2N), 2.55 (m, 4H, CH_2N), 1.74 (m, 4H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 176.2, 136.5, 80.8, 54.0, 53.9, 52.9, 47.5, 37.9, 23.5.

***N*-(2,4,6-Trimethylphenyl)-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4i)**. This compound was crystallized from ethanol to yield 4.2 g (85%) as pale brown crystals, mp 163–164°C; ^1H NMR (200 MHz, $CDCl_3$): δ 6.95 (s, 2H, aromatic CH), 6.6 (s, 2H, CH=CH), 5.4 (s, 2H, CHO), 23.05 (s, 2H, COCH), 2.29 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.06 (s, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 175.9, 139.9, 137.1, 136.4, 135.6, 129.9, 129.6, 127.9, 81.7, 48.1, 21.6, 18.3, 18.0.

***N*-(2-Hydroxyethyl)-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4j)**. This compound was crystallized from ethanol to yield 2.18 g (58%) as white solid, mp 135–136°C (lit. [20] mp 135–7°C); ^1H NMR (500 MHz, $CDCl_3$): δ 6.5 (s, 2H, CH=CH), 5.27 (s, 2H, CHO), 3.75 (t, J = 8.4 Hz, 2H, CH_2OH), 3.68 (t, J = 8.3 Hz, 2H, CH_2NCO), 2.88 (s, 2H, COCH), 2.47 (s, 1H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 176.5, 137, 81.5, 60.8, 47.9, 42.3.

***N*-[3-(Imidazol-1-yl)propyl]-7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboimide (4k)**. This compound was crystallized from ethanol to yield 4.33 g (88%) as yellow crystals, mp 81–82°C; ^1H NMR (200 MHz, $CDCl_3$): δ 7.47 (s, 1H, aromatic CH), 7.02 (s, 1H, aromatic CH), 6.92 (s, 1H, aromatic CH), 6.5 (s, 2H, CH=CH), 5.25 (s, 2H, CHO), 3.90 (t, J = 6.9 Hz, 2H, CH_2NCO), 3.53 (t, J = 6.5 Hz, 2H, CH_2N), 2.82 (s, 2H, COCH), 2.07 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 176.2, 137.2, 136.5, 129.6, 118.7, 81, 47.4, 44.3, 36.2, 28.8.

General method of synthesis of maleimides (5). The obtained imide **4** (0.016 mol) was suspended in 100-mL toluene, and then the suspension was refluxed for minimum 10 h. After that, the mixture was cooled down, and the solution was transferred to another round-bottom flask. The solvent was removed under reduce pressure, and the residue was crystallized from an appropriate solvent.

1-[2(N,N-Dimethylamino)ethyl]pyrrole-2,5-dione (5a). This compound was crystallized from toluene:hexane to yield 2.44g (91%) as white solid, mp 155–156°C (lit. [1c] mp 175–8°C/EtOH); ^1H NMR (200 MHz, $CDCl_3$): δ 6.67 (s, 2H, CH=CH), 3.61 (t, J = 6.3 Hz, 2H, CH_2NCO), 2.47 (t, J = 6.4 Hz, 2H, CH_2N), 2.23 (s, 6H, CH_3N); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171, 134, 57, 45.9, 45.8, 36. *Anal*. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.29; H, 7.19; N, 16.90; ESI-ms: *m/z* $[M+H]^+$ calcd for $C_8H_{12}N_2O_2$: 169.0978; found: 169.0960.

1-[3-(N,N-Dimethylamino)propyl]pyrrole-2,5-dione 5b (hydrochloride). This compound was crystallized from methanol to yield 2.32 g (80%) as white solid, mp 171–172°C (lit. [10] mp 144–145°C as a picrate); ^1H NMR (200 MHz, $CDCl_3$): δ 6.65 (s, 2H, CH=CH), 3.54 (t, J = 7.3 Hz, 2H, CH_2NCO), 2.24 (t, J = 7.3 Hz, 2H, CH_2N), 2.16 (s, 6H, CH_3N), 1.7 (qv, J = 7.3 Hz, 2H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171, 134, 57, 45.8, 45.6, 36.6, 27. *Anal*. Calcd for $C_9H_{15}N_2O_2Cl$: C, 49.43; H, 6.91; N, 12.81. Found: C, 49.66; H, 7.11; N, 12.67; ESI-ms: *m/z* $[M+H]^+$ calcd for $C_9H_{14}N_2O_2$: 183.1134; found: 183.1180

1-(2-Piperidin-1-yl-ethyl)pyrrole-2,5-dione (5c). This compound was crystallized from toluene to yield 2,7g (82%) as yellow crystals, mp 49–50°C; ^1H NMR (200 MHz, $CDCl_3$): δ 6.67 (s, 2H, CH=CH), 3.55 (t, J = 6.8 Hz, 2H, CH_2NCO), 2.49 (t, J = 6.8 Hz, 2H, CH_2N), 2.42 (m, 4H, CH_2N), 1.57–1.39 (m, 6H, $CH_2CH_2CH_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171, 134, 56.7, 54.9, 35.7, 26.4, 24.74; *Anal*. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.34, H; 7.73; N, 13.42; ESI-ms: *m/z* $[M+H]^+$ calcd for $C_{11}H_{16}N_2O_2$: 209.1291; found: 209.1260.

1-(2-Morpholin-1-yl-ethyl)pyrrole-2,5-dione (5d). This compound was crystallized from toluene to yield 2.9g (88%) as yellow crystals, mp 45–46°C (lit. [11] oil); ^1H NMR (200 MHz, $CDCl_3$): δ 6.65 (s, 2H, CH=CH), 3.6–3.55 (m, 6H, CH_2O), 2.47–2.39 (m, 6H, CH_2N); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171, 134, 67.4, 56.4, 53.8, 35.2; *Anal*. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 56.98; H, 6.69; N, 13.28; ESI-ms: *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}N_2O_3$: 211.1083; found: 211.1060.

1-[2-(4-Methylpiperazin-1-yl)ethyl]pyrrole-2,5-dione (5e). This compound was crystallized from toluene to yield 2.43 g (68%) as orange solid, mp 46–47°C; ^1H NMR (200 MHz, $CDCl_3$): δ 6.67 (s, 2H, CH=CH), 3.63 (t, J = 6.5 Hz, 2H, CH_2NCO), 2.52 (t, J = 6.5 Hz, 2H, CH_2N), 2.49 (m, 4H, CH_2N), 2.39 (m, 4H, CH_3N), 2.25 (s, 3H, CH_3N); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.2, 134.5, 55.9, 55.5, 53.3, 46.3, 35.6. *Anal*. Calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 58.98; H, 7.69; N, 18.84. ESI-ms: *m/z* $[M]^+$ calcd for $C_{11}H_{17}N_3O_2$: 223.1221; found: 223.1130.

1-[3-(N,N-Dimethylamino)-2,2-dimethylpropyl]-pyrrole-2,5-dione (5f). This compound was crystallized from toluene to yield 2.72 g (81%) as yellow solid, mp 79–80°C; ^1H NMR (200 MHz, $CDCl_3$ $CDCl_3$): δ 6.72 (s, 2H, CH=CH), 3.41 (s, 2H, CH_2NCO), 2.33 (s, 6H, CH_3N), 2.18 (s, 2H, CH_2N), 0.89 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.9, 134.5, 69.6, 49.2, 47.3, 38.9, 24.8. *Anal*. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.98; H, 8.69; N, 13.19. ESI-ms: *m/z* $[M+H]^+$ calcd for $C_{11}H_{18}N_2O_2$: 211.1447; found: 211,1420

1-[(Pyridin-4-yl)methyl]pyrrole-2,5-dione (5g). This compound was crystallized from toluene to yield 2.17 g (72%) as orange solid, mp 120–1°C (lit. [13] mp 128–30°C); ^1H NMR (200 MHz, $CDCl_3$): δ 8.57 (d, J = 5.9 Hz, 2H, aromatic H), 7.2 (d, J = 5.8 Hz, 2H, aromatic H), 6.77 (s, 2H, CH=CH), 4.67 (s, 2H, CH_2NCO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.3, 150.5, 144.8, 134.6, 122.9, 40.5. *Anal*. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.98; H, 4.29; N, 15.08. ESI-ms: *m/z* $[M+H]^+$ calcd for $C_{10}H_8N_2O_2$: 189.0664; found: 189.0647.

1-[2-(Pyrrolidin-1-yl)ethyl]pyrrole-2,5-dione (5h). This compound was crystallized from toluene to yield 2.36 g (76%) as pale brown solid, mp 157–9°C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.68 (s, 2H, CH=CH), 3.66 (t, J = 6.8 Hz, 2H, CH_2NCO), 2.65 (t, J = 6.8 Hz, 2H, CH_2N), 2.54 (m, 4H, CH_2N), 1.74 (m, 4H, CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.2, 134.6, 54.5, 54.3, 37.4, 23.9. *Anal*. Calcd for $C_{10}H_{14}N_2O_2$: C 61.84; H, 7.27; N, 14.42. Found: C, 61.91; H, 7.31; N, 14.28. ESI-ms: *m/z* $[M+H]^+$ calcd for $C_{10}H_{14}N_2O_2$: 195.1034; found: 195.1092.

1-(2,4,6-Trimethylphenyl)pyrrole-2,5-dione (5i). This compound was crystallized from ethanol to yield 2.4 g (70%) as pale brown crystals, mp 98°C (lit. mp 99–100°C/MeOH [14a,b]; 102.5°C [14c]); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (s, 2H, aromatic H) 6.87 (s, 2H, CH = CH), 2.31 (s, 3H, CH_3), 2.07 (s, 6H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 169.8, 134.5, 131.6, 129.4, 124.4, 121.5, 16.1, 12.9. *Anal*. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.31; H, 6.11; N, 6.45.

1-(2-Hydroxyethyl)pyrrole-2,5-dione (5j). This compound was crystallized from toluene to yield 1.22 g (54%) as white solid, mp 71°C (lit. [15] mp 70–2°C/MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.73 (s, 2H, CH = CH), 3.77 (t, J = 5.4 Hz, 2H, CH_2O), 3.72 (t, J = 5.3 Hz, 2H, CH_2NCO), 2.23 (s, 1H, OH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171,4, 134.5, 61.0, 40.9. *Anal*. Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93. Found: C, 50.98; H, 4.98; N, 10.08.

Acknowledgment. This work was supported by the Polish Ministry for Science and Higher Education.

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