Reaction between Furan- or Thiophene-2-carbonyl Chloride, Isocyanides, and Dialkyl Acetylenedicarboxylates: Multicomponent Synthesis of 2,2′-Bifurans and 2-(Thiophen-2-yl)furans

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An efficient multi-component synthesis of highly functionalized 2,2′-bifurans and 2-(thiophen-2-yl)furans is described. A mixture of furan- or thiophene-2-carbonyl chloride, an isocyanide, and a dialkyl acetylenedicarboxylate undergoes a smooth addition reaction in dry CH_2Cl_2 at ambient temperature to produce 2-amino-5-(4-chlorofuran-2-yl)furan-3,4-dicarboxylates and 2-amino-5-(4-chlorothiophen-2-yl)furan-3,4-dicarboxylates. A single-crystal X-ray-analysis of a derivative conclusively confirms the structure of these 2,2′-bifurans and 2-(thiophen-2-yl)furans. A novel electrophilic aromatic substitution reaction can justify the formation of the Cl-substituted furan or thiophene rings.

Introduction. – Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple, since all the organic reagents employed are consumed and are incorporated into the target compound [1]. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area [1j][1k].

Furans and their reduced forms are common structural motifs in naturally occurring compounds such as pheromones, polyether antibiotics, and furano-terpenes [2–7]. Moreover, they are useful building blocks in the total synthesis of natural products and pharmaceuticals [8–11]. Some furan derivatives have been shown to possess antitumor and cytotoxic [12], antimicrobial [13], antispasmodic [14], and anti-inflammatory properties [15], inhibition of cholesterol acyltransferase, and several other useful biological activities [3][4]. Furthermore, furan heterocycles are found in synthetic materials, such as agrochemical bioregulators, essential oils, cosmetics, dyes, photo-sensitizers, flavoring and fragrance compounds, textiles and fibers, surface active agents and detergents, fire retardants, and polymer materials, and in fossil fuel industry

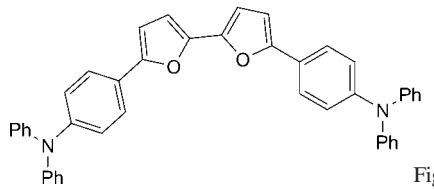


Fig. 1. *A 2,2′-bifuryl with blue photoluminescence emission*

[4][16]. 5,5′-Bis[4-(*N*,*N*-diphenylamino)phenyl]-2,2′-bifuryl (*Fig. 1*) has been used as a blue photoluminescence emitting compound [17].

Because of their broad range of applications, chemists have paid considerable attention to the development of furan ring synthesis. By far, the most common synthetic routes reported for the preparation of furan derivatives involve: *i*) cyclizations, classified on the basis of the number of ring atoms in each of the components being cyclized: *ia*) single bond-formation (C–O or C–C bond), *ib*) formation of two bonds, from [4 + 1] or [3 + 2] atom fragments, *ic*) formation of three bonds, from [2 + 2 + 1] atom fragments, and *ii*) by transformation of an existing heterocyclic ring including expansion of smaller rings, contraction of larger rings, and transformation of other five-membered rings [18]. Due to the unique properties of furans, the development of synthetic methods which enable facile access to these useful entities is desirable.

Results and Discussion. – In 2008, it was reported that the 1:1 zwitterionic intermediate generated by the addition of isocyanides to dialkyl acetylenedicarboxylates was trapped by benzoyl chlorides to yield functionalized 2,5-dihydro-1*H*-pyrroles and/or 2-amino-5-arylfuran-3,4-dicarboxylates [19]. In 2011, *Azizian* and co-workers reported that the *in situ* prepared α-ketophosphonates from triethyl phosphite and acyl chlorides reacted with isocyanides and dialkyl acetylenedicarboxylates to produce 5-(alkylimino)-2-(diethoxyphosphoryl)-2,5-dihydrofuran-3,4-dicarboxylates [20]. We were prompted to use furan- or thiophene-2-carbonyl chloride as the acyl chloride component in this MCR. This could allow variation of the skeleton of the products, thus increasing the versatility of the reaction and potentially leading to useful new building blocks for the construction of chemical libraries.

As part of our current studies on the development of new efficient strategies for the preparation of interesting bioactive molecules and drug cores [21], herein, we report an efficient synthesis of 2,2′-bifurans and 2-(thiophen-2-yl)furans.

In a pilot experiment, a solution of furan-2-carbonyl chloride (**1**), cyclohexyl isocyanide (**2a**), and dimethyl acetylenedicarboxylate (DMAD, **3a**) was stirred in dry CH_2Cl_2 at ambient temperature. The reaction went to completion within 24 h to afford dimethyl 4′-chloro-5-(cyclohexylamino)-2,2′-bifuran-3,4-dicarboxylate (**4a**, 1:1:1 adduct) and dimethyl 4′-chloro-5-{cyclohexyl[(1*E*,2*E*)-*N*-cyclohexyl-4-methoxy-2-(methoxycarbonyl)-4-oxobut-2-enimidoyl]amino}-2,2′-bifuran-3,4-dicarboxylate (**5**, 1:2:2 adduct) in 33 and 62% yields, respectively (relative to furan-2-carbonyl chloride). TLC and ^{1}H-NMR analysis of the reaction mixture clearly indicated formation of the corresponding 2,2′-bifurans **4a** and **5**. This reaction was first carried out using the three components **1**, **2a**, and **3a** in a 1:1:1 ratio. TLC and ^{1}H-NMR analysis of the reaction mixture confirmed the formation of **4a** and **5** in 15 and 42% yields,

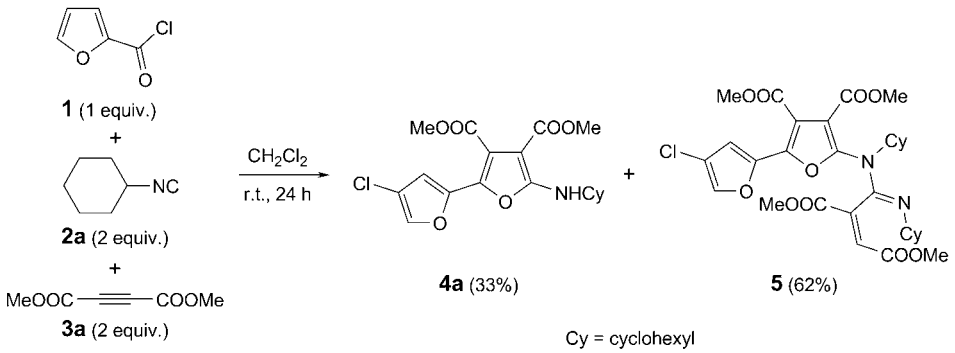
respectively. The reaction was repeated, and the best results were obtained when **1**, **2a**, and **3a** reacted in a 1:2:2 ratio (see *Scheme 1* and *Exper. Part*).

To show the generality and scope of this reaction, we used different isocyanides **2** and dialkyl acetylenedicarboxylates **3**. But, interestingly, we could only detect and isolate the corresponding 2,2′-bifurans **4b**–**4f** (1:1:1 adduct), and the corresponding 1:2:2 adducts were not found. The best results were obtained, when **1**, **2**, and **3** were reacted in 1:1:1 ratios. Carrying out the reaction in 1:2:2 ratios, we obtained the isocyanide-dialkyl acetylenedicarboxylate adducts in addition to **4**. The results are shown in *Scheme 2*.

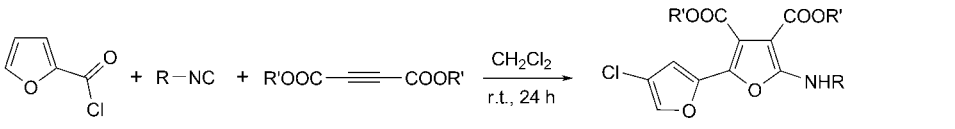
The reaction was also carried out by using thiophene-2-carbonyl chloride (**6**), an isocyanide **2**, and a dialkyl acetylenedicarboxylate **3** (in 1:1:1 ratios) under the same conditions and afforded the corresponding dialkyl 2-(alkylamino)-5-(4-chlorothiophen-2-yl)furan-3,4-dicarboxylate **7a**–**7d** in 82–91% yields. The results are shown in *Scheme 3*.

The structures of the isolated products **4**, **5**, and **7** were deduced on the basis of IR, ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry, and elemental analysis. The IR spectrum of **4e** showed absorptions at 3345, 1738, and 1675 cm^{-1}, indicating the presence of NH and C=O functionalities. The mass spectrum of **4e** displayed the molecular-ion (M^+) peaks at *m*/*z* 413 and 411, which were consistent with the 1:1:1 adduct of **1**, **2c**, and **3a**. The ^{1}H-NMR spectrum of **4e** exhibited five sharp *singlet*s at

Scheme 1. *One-Pot Synthesis of 2,2′-Bifurans* **4a** *and* **5**

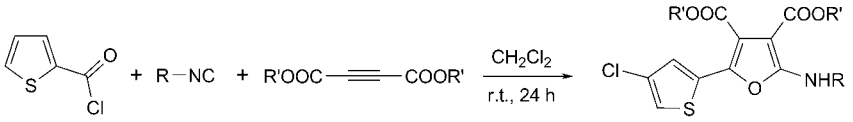


Scheme 2. *One-Pot Synthesis of 2,2′-Bifurans* **4b**–**4f**



	R	R'	Yield [%]
4b	Cyclohexyl	Et	90
4c	^{t}Bu	Me	92
4d	^{t}Bu	Et	86
4e	1,1,3,3-Tetramethylbutyl	Me	88
4f	1,1,3,3-Tetramethylbutyl	Et	85

Scheme 3. *One-Pot Synthesis of 2-(thiophen-2-yl)furans* **7a**–**7d**



	R	R'	Yield [%]
7a	Cyclohexyl	Me	91
7b	^{t}Bu	Me	89
7c	1,1,3,3-Tetramethylbutyl	Me	86
7d	1,1,3,3-Tetramethylbutyl	Et	82

δ(H) 1.00 (due to Me_3C), 1.49 (for Me_2C), 1.75 (arising from CH_2), 3.75, and 3.89 ppm (due to MeO). A fairly broad signal was observed at 6.97 ppm for the NH group. Two *doublet*s were seen at 6.20 and 6.54 ppm with a long-range coupling constant ($^4J = 3.6$) confirming the presence of a furan ring with 2,4-substitution pattern. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4e** showed 17 distinct resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the *Exper. Part*.

Single-crystal X-ray-analysis of **5** confirmed conclusively its structure, and by analogy, those of the other isolated products **4** and **7**. An ORTEP diagram of **5** is shown in *Fig. 2*.

A mechanistic rationalization for the reaction involving furan-2-carbonyl chloride (**1**) is provided in *Scheme 4*. On the basis of the chemistry of isocyanides [1j][1k][22], it is reasonable to assume that the reactive 1:1 zwitterionic intermediate **8**, generated *in situ* from the reaction between the isocyanide **2** and the acetylenic ester **3**, may attack at **1** to produce the tetrahedral nitrilium alkoxide intermediate **9**. The nitrilium function

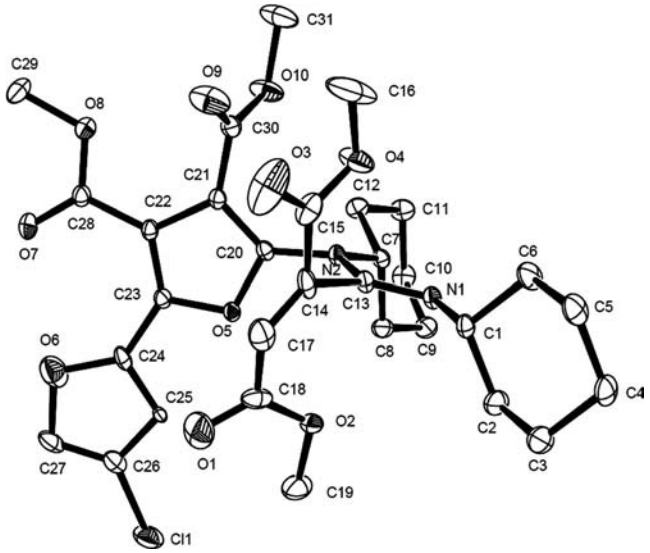
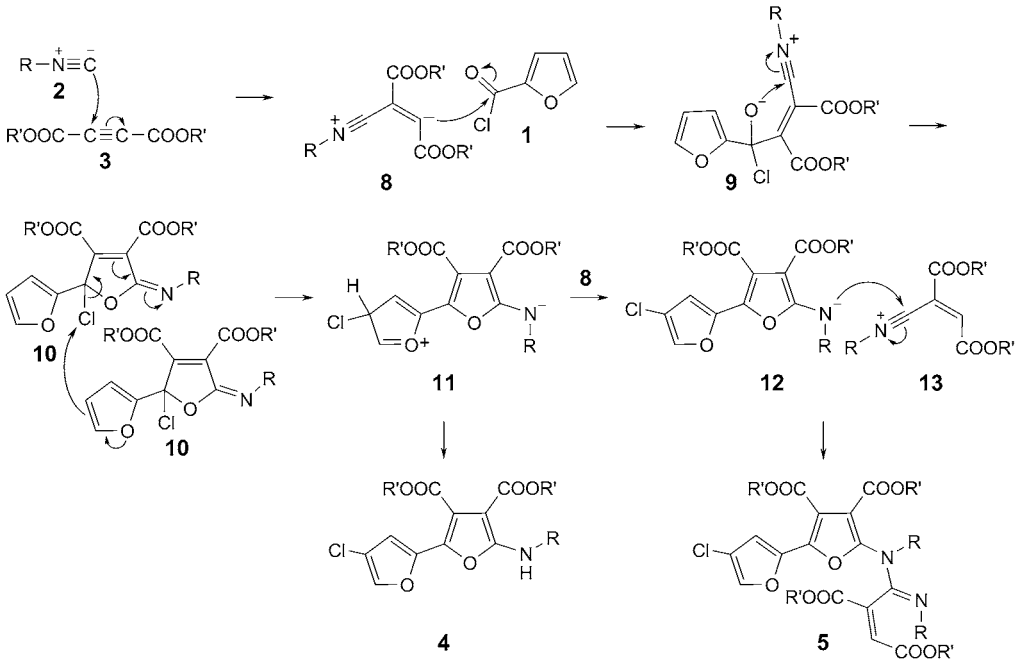


Fig. 2. *ORTEP Diagram of the molecular structure of* **5**

Scheme 4. *Proposed Mechanism for the Reaction*



may undergo intramolecular nucleophilic addition of the alkoxide moiety to form the iminolactone intermediate **10** [19]. Intermolecular electrophilic substitution reaction on the furan ring of **10** by the *in situ* generated electrophilic chlorine cation from another iminolactone **10** probably give the *Wheland* intermediate **11**. This intermediate may undergo proton shift to yield 2-(alkylamino)-5-(4-chlorofuran-2-yl)furan-3,4-dicarboxylate **4**. The *Wheland* intermediate **11** can also protonate the zwitterionic intermediate **8**. The nitrilium butenedioate intermediate **13** may undergo nucleophilic addition by the amide anion **12** to afford **5**.

Conclusions. – We have developed an efficient synthesis of 2,2′-bifurans and 2-(thiophen-2-yl)furans which are of potential chemical, synthetic, and pharmacological interest. A similar 2-aminofuran skeleton has been reported for the reaction between isocyanides, dialkyl acetylenedicarboxylates, and benzoyl chloride. However, the presence of electron-withdrawing groups such as NO_2 and Cl at the *para*-position of benzoyl chloride would change the reaction pathway and leads to the formation of the 2,5-dihydro-1*H*-pyrrole scaffold [19]. Considering the availability of the starting materials, the simple one-pot procedure and high yields of the products in this chemical process provide a straightforward route to construct highly functionalized 2,2′-bifurans and 2-(thiophen-2-yl)furans. The reactions have been performed under neutral conditions, and the starting materials have been mixed without any activation or modification.

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Experimental Part

General. All the chemicals were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. Column chromatography (CC): silica gel 230–240 (*Merck*). M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-500 AVANCE* (at 500.1 and 125.8 MHz, resp.) and *Bruker DRX-400* (at 400.1 and 100.6 MHz, resp.) instruments; in $CDCl_3$ soln.; δ in ppm rel. to Me_4Si as internal standard, J in Hz. EI-MS (20 eV): *Agilent Technologies* (*HP*) *5973* mass spectrometer; in *m*/*z* (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer. X-Ray crystallography: *Bruker SMART* diffractometer; CCD area detector; graphite monochromatized MoK_α radiation.

Procedure for the Preparation of 2,2′-Bifurans **4a** *and* **5**. To a magnetically stirred soln. of furan-2-carbonyl chloride (**1**; 0.130 g, 1 mmol) and dimethyl acetylenedicarboxylate (**3a**; 0.284 g, 2 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise a soln. of cyclohexyl isocyanide (**2a**; 0.218 g, 2 mmol) in dry CH_2Cl_2 (1 ml) at 25° over 10 min. The mixture was stirred for 24 h. Then, the solvent was removed, and the residue was separated by CC using hexane/AcOEt (3:1) as eluent. The solvent was removed, and the products were obtained.

Dimethyl 4′-Chloro-5-(cyclohexylamino)-2,2′-bifuran-3,4-dicarboxylate (**4a**). Pale-red oil. Yield: 0.126 g (33%). IR (KBr): 3359 (NH), 1737 and 1676 (C=O), 1610, 1470, 1361, 1226, 1148, 1101, 1075, 1014, 940, 915, 779, 732, 651. ^1H-NMR (400.1 MHz, $CDCl_3$): 1.20–2.08 (*m*, 10 H); 3.68–3.74 (*m*, 1 H); 3.80 (*s*, 3 H); 3.92 (*s*, 3 H); 6.24 (*d*, $^4J = 3.6$, 1 H); 6.60 (*d*, $^4J = 3.6$, 1 H); 6.69 (br. *d*, $J = 8.4$, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 24.5; 25.4; 33.5; 51.2; 51.4; 52.4; 86.6; 108.1; 109.7; 113.5; 133.7; 136.6; 143.4; 161.4; 164.2; 164.9. EI-MS: 383 (32, $M^+(^{37}Cl)$), 381 (100, $M^+(^{35}Cl)$), 350 (9), 322 (17), 299 (18), 267 (41), 240 (40), 204 (13), 129 (29), 83 (21), 55 (67), 41 (51). Anal. calc. for $C_{18}H_{20}ClNO_6$ (381.81): C 56.62, H 5.28, N 3.67; found: C 56.53, H 5.40, N 3.52.

*Dimethyl 4′-Chloro-5-{cyclohexyl[(1*E*,2*E*)-*N*-cyclohexyl-4-methoxy-2-(methoxycarbonyl)-4-oxobut-2-enimidoyl]amino}-2,2′-bifuran-3,4-dicarboxylate* (**5**). Pale-orange crystals. Yield: 0.393 g (62%). M.p. 132–133°. IR (KBr): 1734 (C=O), 1645, 1610, 1550, 1437, 1343, 1314, 1241, 1118, 1058, 1022, 942, 891, 783. ^1H-NMR (400.1 MHz, $CDCl_3$): 1.07–2.29 (*m*, 20 H); 2.90–3.00 (*m*, 1 H); 3.77 (*s*, 3 H); 3.80 (*s*, 3 H); 3.81 (*s*, 3 H); 3.84 (*s*, 3 H); 4.39–4.47 (*m*, 1 H); 6.32 (*d*, $^4J = 3.6$, 1 H); 6.73 (*s*, 1 H); 7.27 (*d*, $^4J = 3.6$, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 24.3; 24.4; 25.7; 25.8; 25.9; 26.0; 30.2; 30.5; 34.0; 34.1; 52.0; 52.1; 52.2; 52.9; 56.7; 59.3; 108.8; 111.8; 115.3; 116.8; 130.7; 138.3; 138.8; 142.7; 143.3; 145.9; 148.0; 162.3; 162.4; 163.6; 163.8. EI-MS: 635 (17, $M^+(^{37}Cl)$), 633 (54, $M^+(^{35}Cl)$), 601 (8), 573 (14), 515 (7), 491 (6), 364 (17), 268 (10), 252 (50), 192 (9), 170 (32), 129 (27), 112 (13), 98 (9), 83 (80), 55 (100). Anal. calc. for $C_{31}H_{37}ClN_2O_{10}$ (633.09): C 58.81, H 5.89, N 4.42; found: C 58.80, H 5.84, N 4.34.

Selected X-Ray Crystallographic Data for Compound **5**. $C_{31}H_{37}ClN_2O_{10}$, triclinic, space group = *P*1, $a = 10.9455(6)$ Å, $b = 12.0493(7)$ Å, $c = 12.8634(7)$ Å, $\alpha = 79.903(1)°$, $\beta = 86.726(1)°$, $\gamma = 73.155(1)°$, $V = 1598.52(15)$ Å^3, $T = 295(2)$ K, $Z = 2$, $D_{calc.} = 1.311$ g cm^{-3}, $\mu = 0.178$ mm^{-1}, 3412 observed reflections, final $R_1 = 0.107$, $wR_2 = 0.303$ and for all data $R_1 = 0.154$, $wR_2 = 0.364$. CCDC-852558 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

Procedure for the Preparation of 2,2′-Bifurans **4b**–**4f** *and 2-(Thiophen-2-yl)furans* **7a**–**7d**. To a magnetically stirred soln. of the appropriate carbonyl chloride (**1** or **6**; 1 mmol) and the appropriate dialkyl acetylenedicarboxylate **3** (1 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise a soln. of the appropriate isocyanide **2** (1 mmol) in dry CH_2Cl_2 (1 ml) at 25° over 10 min. The mixture was stirred for 24 h. Then, the solvent was removed, and the residue was separated by CC using hexane/AcOEt (3:1) as eluent.

Diethyl 4′-Chloro-5-(cyclohexylamino)-2,2′-bifuran-3,4-dicarboxylate (**4b**). Pale-red oil. Yield: 0.369 g (90%). IR (KBr): 3349 (NH), 1735 and 1673 (C=O), 1610, 1464, 1370, 1346, 1316, 1223, 1148, 1099, 1072, 1015, 940, 779, 732, 637. ^1H-NMR (400.1 MHz, $CDCl_3$): 1.20–2.05 (*t*, $J = 7.2$, 3 H; *t*, $J = 7.2$, 3 H; *m*, 10 H); 3.67–3.77 (*m*, 1 H); 4.23 (*q*, $J = 7.2$, 2 H); 4.37 (*q*, $J = 7.2$, 2 H); 6.22 (*d*, $^4J = 3.2$, 1 H); 6.56

(*d*, ^4J = 3.2, 1 H); 6.68 (br. *d*, *J* = 8.0, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 14.1; 14.4; 24.5; 25.4; 33.5; 51.3; 59.7; 61.5; 86.9; 108.1; 109.2; 114.9; 133.2; 136.4; 143.6; 161.3; 163.9; 164.5. EI-MS: 411 (35, M^+(^{37}Cl)), 409 (100, M^+(^{35}Cl)), 364 (20), 336 (31), 327 (14), 292 (7), 281 (23), 254 (46), 246 (19), 226 (7), 218 (23), 209 (20), 200 (8), 182 (8), 129 (21), 83 (21), 55 (66), 41 (42). Anal. calc. for $C_{20}H_{24}ClNO_6$ (409.87): C 58.61, H 5.90, N 3.42; found: C 58.63, H 5.84, N 3.36.

*Dimethyl 5-(*tert*-Butylamino)-4′-chloro-2,2′-bifuran-3,4-dicarboxylate* (**4c**). Pale-red oil. Yield: 0.327 g (92%). IR (KBr): 3331 (NH), 1738 and 1675 (C=O), 1605, 1467, 1411, 1363, 1305, 1261, 1209, 1154, 1089, 1051, 1014, 940, 915, 778, 700, 624. ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.43 (*s*, 9 H); 3.74 (*s*, 3 H); 3.87 (*s*, 3 H); 6.18 (*d*, ^4J = 3.4, 1 H); 6.54 (*d*, ^4J = 3.4, 1 H); 6.85 (*s*, 1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 29.8; 51.1; 52.4; 53.0; 87.6; 108.1; 109.4; 113.0; 134.1; 136.6; 143.5; 161.7; 164.2; 165.0. EI-MS: 357 (26, M^+(^{37}Cl)), 355 (93, M^+(^{35}Cl)), 324 (8), 299 (30), 267 (19), 240 (19), 204 (6), 129 (23), 73 (16), 57 (100), 41 (74). Anal. calc. for $C_{16}H_{18}ClNO_6$ (355.78): C 54.02, H 5.10, N 3.94; found: C 54.22, H 5.03, N 3.87.

*Diethyl 5-(*tert*-Butylamino)-4′-chloro-2,2′-bifuran-3,4-dicarboxylate* (**4d**). Pale-red oil. Yield: 0.330 g (86%). IR (KBr): 3335 (NH), 1735 and 1673 (C=O), 1605, 1466, 1421, 1370, 1346, 1302, 1260, 1204, 1154, 1087, 1049, 1015, 940, 779, 698, 637. ^{1}H-NMR (400.1 MHz, $CDCl_3$): 1.30 (*t*, *J* = 7.2, 3 H); 1.39 (*t*, *J* = 7.2, 3 H); 1.46 (*s*, 9 H); 4.23 (*q*, *J* = 7.2, 2 H); 4.37 (*q*, *J* = 7.2, 2 H); 6.22 (*d*, ^4J = 3.6, 1 H); 6.54 (*d*, ^4J = 3.6, 1 H); 6.88 (*s*, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 14.1; 14.3; 29.8; 52.9; 59.8; 61.5; 87.8; 108.1; 108.8; 113.1; 133.4; 136.4; 143.7; 161.6; 163.9; 164.6. EI-MS: 385 (27, M^+(^{37}Cl)), 383 (95, M^+(^{35}Cl)), 338 (13), 327 (100), 292 (9), 281 (43), 254 (65), 246 (22), 218 (33), 209 (35), 200 (12), 181 (12), 129 (28), 57 (90), 41 (69). Anal. calc. for $C_{18}H_{22}ClNO_6$ (383.83): C 56.33, H 5.78, N 3.65; found: C 56.19, H 5.68, N 3.50.

Dimethyl 4′-Chloro-5-[(1,1,3,3-tetramethylbutyl)amino]-2,2′-bifuran-3,4-dicarboxylate (**4e**). Pale-red oil. Yield: 0.362 g (88%). IR (KBr): 3345 (NH), 1738 and 1675 (C=O), 1605, 1469, 1409, 1362, 1213, 1151, 1088, 1051, 1014, 940, 780, 733, 699, 642. ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.00 (*s*, 9 H); 1.49 (*s*, 6 H); 1.75 (*s*, 2 H); 3.75 (*s*, 3 H); 3.89 (*s*, 3 H); 6.20 (*d*, ^4J = 3.6, 1 H); 6.54 (*d*, ^4J = 3.6, 1 H); 6.97 (br. *s*, NH). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 30.1; 31.4; 31.6; 51.1; 52.4; 53.2; 56.6; 87.2; 108.0; 109.0; 112.8; 133.8; 136.5; 143.5; 161.5; 164.3; 165.0. EI-MS: 413 (6, M^+(^{37}Cl)), 411 (15, M^+(^{35}Cl)), 299 (88), 267 (39), 240 (35), 208 (12), 154 (21), 129 (83), 84 (18), 57 (100), 41 (31). Anal. calc. for $C_{20}H_{26}ClNO_6$ (411.88): C 58.32, H 6.36, N 3.40; found: C 58.18, H 6.37, N 3.31.

Diethyl 4′-Chloro-5-[(1,1,3,3-tetramethylbutyl)amino]-2,2′-bifuran-3,4-dicarboxylate (**4f**). Pale-red oil. Yield: 0.374 g (85%). IR (KBr): 3329 (NH), 1735 and 1671 (C=O), 1605, 1468, 1370, 1297, 1212, 1151, 1086, 1049, 940, 865, 780, 733, 689, 641. ^{1}H-NMR (400.1 MHz, $CDCl_3$): 1.02 (*s*, 9 H); 1.30 (*t*, *J* = 7.2, 3 H); 1.40 (*t*, *J* = 7.2, 3 H); 1.50 (*s*, 6 H); 1.77 (*s*, 2 H); 4.22 (*q*, *J* = 7.2, 2 H); 4.38 (*q*, *J* = 7.2, 2 H); 6.22 (*d*, ^4J = 3.6, 1 H); 6.53 (*d*, ^4J = 3.6, 1 H); 6.98 (br. *s*, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 14.1; 14.3; 30.2; 31.4; 31.7; 53.2; 56.6; 59.7; 61.5; 87.6; 108.1; 108.6; 113.4; 133.4; 136.4; 143.8; 161.4; 164.0; 164.6. EI-MS: 441 (6, M^+(^{37}Cl)), 439 (17, M^+(^{35}Cl)), 327 (100), 292 (6), 281 (33), 254 (43), 218 (20), 209 (26), 129 (26), 84 (11), 57 (96), 41 (40). Anal. calc. for $C_{22}H_{30}ClNO_6$ (439.94): C 60.06, H 6.87, N 3.18; found: C 59.83, H 6.97, N 3.04.

Dimethyl 2-(4-Chlorothiophen-2-yl)-5-(cyclohexylamino)furan-3,4-dicarboxylate (**7a**). Pale-red oil. Yield: 0.362 g (91%). IR (KBr): 3346 (NH), 1732 and 1673 (C=O), 1613, 1522, 1471, 1362, 1229, 1148, 1101, 1076, 1017, 891, 780, 754, 639. ^{1}H-NMR (400.1 MHz, $CDCl_3$): 1.25–2.10 (*m*, 10 H); 3.64–3.72 (*m*, 1 H); 3.79 (*s*, 3 H); 3.92 (*s*, 3 H); 6.69 (br. *d*, *J* = 8.0, 1 H); 6.86 (*d*, ^4J = 4.0, 1 H); 7.13 (*d*, ^4J = 4.0, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 24.4; 25.4; 33.4; 51.2; 51.6; 52.3; 86.9; 112.6; 124.1; 126.5; 129.5; 130.3; 138.1; 161.2; 164.5; 165.0. EI-MS: 399 (27, M^+(^{37}Cl)), 397 (43, M^+(^{35}Cl)), 363 (17), 315 (9), 283 (46), 249 (21), 225 (18), 217 (9), 197 (9), 145 (50), 128 (15), 111 (88), 97 (11), 83 (100), 71 (25), 55 (78), 41 (74). Anal. calc. for $C_{18}H_{20}ClNO_5S$ (397.88): C 54.34, H 5.07, N 3.52; found: C 54.30, H 5.12, N 3.46.

*Dimethyl 2-(*tert*-Butylamino)-5-(4-chlorothiophen-2-yl)furan-3,4-dicarboxylate* (**7b**). Pale-red oil. Yield: 0.331 g (89%). IR (KBr): 3371 (NH), 1727 and 1673 (C=O), 1613, 1471, 1362, 1229, 1148, 1076, 755, 697, 642. ^{1}H-NMR (400.1 MHz, $CDCl_3$): 1.48 (*s*, 9 H); 3.79 (*s*, 3 H); 3.92 (*s*, 3 H); 6.86 (*d*, ^4J = 4.0, 1 H); 6.90 (br. *s*, 1 H); 7.14 (*d*, ^4J = 4.0, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 29.8; 51.2; 52.4; 53.5; 87.8; 112.2; 123.9; 126.6; 129.6; 130.2; 138.4; 161.4; 164.6; 165.1. EI-MS: 373 (20, M^+(^{37}Cl)), 371 (63, M^+(^{35}Cl)), 354 (18), 343 (100), 281 (16), 254 (48), 144 (31), 57 (86), 41 (67). Anal. calc. for $C_{16}H_{18}ClNO_5S$ (371.84): C 51.68, H 4.88, N 3.77; found: C 51.54, H 4.93, N 3.53.

Dimethyl 2-(4-Chlorothiophen-2-yl)-5-[(1,1,3,3-tetramethylbutyl)amino]furan-3,4-dicarboxylate (**7c**). Pale-red oil. Yield: 0.368 g (86%). IR (KBr): 3324 (NH), 1725 and 1672 (C=O), 1607, 1526, 1470, 1409, 1362, 1250, 1212, 1151, 1087, 1059, 998, 782, 737, 659, 633. ^{1}H-NMR (400.1 MHz, $CDCl_3$): 1.04 (*s*, 9 H); 1.52 (*s*, 6 H); 1.79 (*s*, 2 H); 3.78 (*s*, 3 H); 3.92 (*s*, 3 H); 6.86 (*d*, ^4J = 4.0, 1 H); 7.01 (br. *s*, 1 H); 7.13 (*d*, ^4J = 4.0, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 30.2; 31.5; 31.7; 51.2; 52.4; 53.2; 56.6; 87.6; 112.2; 123.7; 126.7; 129.7; 130.1; 138.2; 161.3; 164.6; 165.1. EI-MS: 429 (20, M^+(^{37}Cl)), 427 (63, M^+(^{35}Cl)), 325 (50), 315 (72), 283 (48), 249 (13), 213 (31), 145 (28), 111 (28), 97 (27), 83 (24), 69 (29), 57 (100). Anal. calc. for $C_{20}H_{26}ClNO_5S$ (427.95): C 56.13, H 6.12, N 3.27; found: C 56.09, H 6.20, N 3.13.

Diethyl 2-(4-Chlorothiophen-2-yl)-5-[(1,1,3,3-tetramethylbutyl)amino]furan-3,4-dicarboxylate (**7d**). Pale-red oil. Yield: 0.374 g (82%). IR (KBr): 3333 (NH), 1722 and 1669 (C=O), 1607, 1470, 1370, 1245, 1213, 1152, 1086, 861, 782, 745. ^{1}H-NMR (400.1 MHz, $CDCl_3$): 1.04 (*s*, 9 H); 1.32 (*t*, *J* = 7.2, 3 H); 1.40 (*t*, *J* = 7.2, 3 H); 1.52 (*s*, 6 H); 1.79 (*s*, 2 H); 4.24 (*q*, *J* = 7.2, 2 H); 4.39 (*q*, *J* = 7.2, 2 H); 6.86 (*d*, ^4J = 4.0, 1 H); 7.02 (br. *s*, 1 H); 7.11 (*d*, ^4J = 4.0, 1 H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 14.2; 14.4; 30.2; 31.5; 31.7; 53.2; 56.5; 59.7; 61.6; 87.8; 112.7; 123.3; 126.7; 129.8; 129.9; 137.7; 161.2; 164.5; 164.7. EI-MS: 457 (25, M^+(^{37}Cl)), 455 (78, M^+(^{35}Cl)), 343 (61), 297 (21), 269 (19), 145 (18), 128 (9), 111 (41), 97 (9), 83 (9), 69 (13), 57 (100). Anal. calc. for $C_{22}H_{30}ClNO_5S$ (456.00): C 57.95, H 6.63, N 3.07; found: C 58.11, H 6.53, N 2.91.

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