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# 2,5-Diamide-Substituted Five-Membered Heterocycles: Challenging Molecular Synthons

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We describe synthetic routes for preparing previously unknown 2,5-diamide-substituted five-membered heterocycles based on the thiophene, pyrrole, and furan ring systems by exploiting Curtius-like rearrangement reactions. Conformation analysis of the 2,5-diamidothiophene derivatives identified a "closed" conformation, in which the two carbonyl O atoms are in close contact with the thiophene S atom.

## Introduction

Five-membered heterocycles are key molecular components in polymeric or supramolecular assemblies for applications in material science[1–9] and they are also ubiquitous molecular scaffolds in medicinal chemistry.[10–13] Gaining synthetic access to a large variety of differently substituted heterocycles can afford a wider set of molecular modules, thus further expanding their use as core scaffolds for natural products or pharmaceutical compounds.[14,15] Among the different substituted cores, 2,5-diamido-substituted five-membered heterocycles represent a synthetically challenging class of compounds because, to the best of our knowledge, they have not been reported yet (see general structure depicted in Figure 1). Their interest lies in the fact that they can be used as alternative molecular modules for engineering multiple H-bonding recognition motifs, the strengths and patterns of which can be tuned through the nature of the central heteroatom. Some examples of the use of five-membered heterocycles for multiple H-bonding recognition have recently been reported.[16–19] However, their 2,5-diamino-substituted precursors are difficult to obtain due to their inherent instability, resulting from the high electron density, either as free amino or as salt derivatives. Although "bare" monoamino derivatives have occasionally been reported,[20,21] they are often equipped with *electron-density mesomeric relief valves*, in the form of electron-withdrawing substituents on the heterocyclic core or on the amino group.[22–24] To the best of our knowledge, the only 2,5-bisamino derivatives reported so far are 2,5-bis(bisarylamino)thiophenes,[25] 2,5-bis(tosylamino)pyrroles and 2,5-bis(tosylamino)furans,[26] whereas non-stabilized 2,5-diaminothiophenes are still unknown.[27]

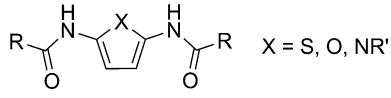


Figure 1. General structure of 2,5-diamido-substituted five-membered heterocycles targeted by this synthetic study.

Thus, in this paper we describe our synthetic efforts involving the daunting task of preparing 2,5-disubstituted five-membered heterocycles with amide functionalities. Different possible routes are amidation cross-coupling reactions,[28–32] Beckmann rearrangement of ketoximes,[33–36] formation of azido intermediates convertible into amide derivatives,[37] or formation of isocyanate intermediates through Curtius rearrangement of acyl azides.[38]

## Results and Discussion

### Thiophene Derivatives

Our exploration begun with thiophene aromatic ring systems (Figure 2). As a first approach, we focused our attention on C–N cross-coupling between aryl halides and amines or amides,[28–32] developed as an expansion and combination of the initial synthetic scopes of Buchwald–

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Hartwig Pd-catalyzed amination on one hand,[39,40] and of Goldberg's Cu-catalyzed amidation on the other.[41] Considering the possible limitations caused by a likely poisoning effect of the thiophene sulfur atom on Pd metal centres, we decided to commence our investigations with Cu-based catalysts under the conditions reported by Buchwald and co-workers, who described a modified version of Goldberg's Cu-catalyzed amidation of aryl halides, including of 2-halothiophene derivatives.[42] In our hands, however, when acetamide was treated with 2,5-dibromothiophene in the presence of a catalytic mixture consisting of CuI and *N*,*N*′-dimethylethylenediamine, together with $K_2CO_3$ in 1,4-dioxane or DMF, no reaction took place and only starting material was recovered.

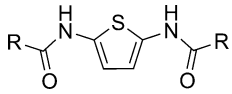


Figure 2. Target thiophene derivative.

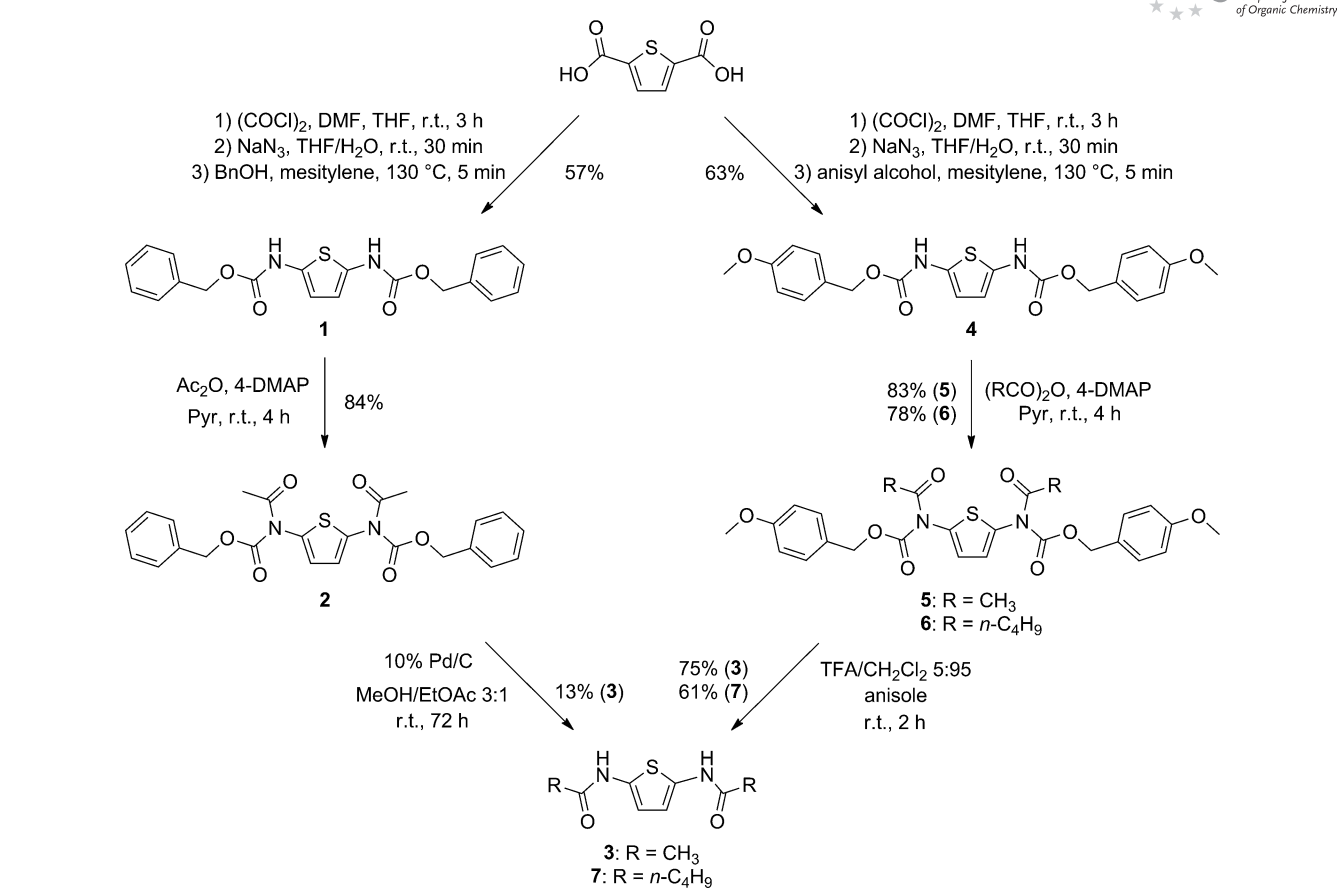
In a second approach we turned our gaze to those synthetic routes involving azido precursors, because these can easily be converted into their amide derivatives by treatment with thioacids.[37] This approach is particularly attractive to us because, as demonstrated by Williams and co-workers,[43] amine intermediates are not formed during the reaction, which instead proceeds through the formation of thiatriazoline species. The synthesis of aryl azides is based on a more limited selection of transformations than that of aliphatic ones.[44,45] They are commonly prepared from the corresponding amines, either via diazonium salt intermediates[46–49] or directly by treatment with triflyl azide.[50] However, alternative methods have been investigated, such as nucleophilic aromatic substitutions on activated aryl halides[51] and $Cu^I$-catalyzed Ullmann-type cross-coupling reactions with $NaN_3$.[52,53] The latter reaction was reported also to work for inactivated aryl halides at temperatures low enough to allow the survival of the azide, in the presence of proline[54] or a bisamine[55] as ligands. Inspired by these findings, we tried the literature conditions with 2-bromothiophene, but no reaction took place and only starting material was recovered. Thus, we turned to the protocol of Zanirato and co-workers, who reported, to the best of our knowledge, the only example of isolation of 2-azidothiophene.[56,57] In this two-step procedure, 2-bromothiophene is lithiated and then treated with $TsN_3$ to generate the corresponding triazene salt, which is then treated with $Na_4P_2O_7{\cdot}10H_2O$ to afford 2-azidothiophene. Li/halogen exchange was thus performed on 2,5-dibromothiophene with *n*BuLi, and the obtained dilithium thiolyl derivative was added to a solution of $TsN_3$. However, subsequent treatment with $Na_4P_2O_7$ resulted in decomposition, likely because, as noted by Zanirato and Spagnolo,[56] the triazene intermediate is unstable under the workup conditions, thus making this synthetic route rather inefficient for our purposes.

Finally we turned to Curtius-type reactions involving the nucleophilic rearrangement of acyl nitrenes, formally generated by the thermal deazotation of acyl azides, into isocyanate derivatives.[38,58] Although a few scattered reports on double Curtius rearrangements onto α-positions of five-membered heterocycles exist in the literature,[59–62] use of this strategy to prepare 2,5-disubstituted bisamides has not yet been reported. Starting from the commercially available 2,5-disubstituted thiophenedicarboxylic acid, by treatment with $(COCl)_2$ in the presence of a catalytic amount of DMF, followed by addition of $NaN_3$, the 2,5-diacylazido-substituted thiophene derivative was obtained. Because of its instability, this intermediate was only characterized by mass spectrometry and stored as a solution in $CH_2Cl_2$ (1 M) at –20 °C. The corresponding 2,5-diisocyanate was then prepared by thermal treatment and, in the presence of the desired alcohol, it yielded the corresponding carbamate derivative.

At this point the intriguing possibility of forming the desired amide bond by treatment with organometallic reagents was considered. However, repeated attempts using MeMgBr always led to decomposition. Therefore, an alternative three-step strategy, consisting of the formation of a carbamate intermediate, acylation of the carbamic nitrogen and subsequent cleavage of the carbamate, was envisaged (Scheme 1). We began with the preparation of 2,5-dicarbamate derivative **1**. The reaction was performed by adding a solution of diacylazidothiophene to a mesitylene solution of BnOH at 130 °C, affording derivative **1** (57% yield) as a white, crystalline solid. Acetylation of compound **1** in pyridine with $Ac_2O$ in the presence of 4-dimethylaminopyridine (4-DMAP) yielded conjugated **2** (84%). A small transparent crystal of **2**, suitable for X-ray diffraction, was obtained by slow evaporation from a $CHCl_3$ solution. The ORTEP representation of the crystal structure (belonging to the monoclinic space group *Pc*), shown in Figure 3, reveals the quasi-orthogonal arrangement of the two carbamate groups with respect to the plane of the thiophene ring. The next step was the cleavage of the two benzylcarbamate (Cbz) *N*-protecting groups. However, our attempts using TMSI were unsuccessful, resulting either in recovery of the starting material or in decomposition. Therefore, we turned to Pd-catalyzed hydrogenolysis, which allowed us to obtain the desired product **3** in low yield (13%).

In the light of these results, the Cbz protecting group was replaced with *p*-methoxybenzyl carbamate (Moz), cleavable under milder acidic conditions (Scheme 1, right-hand side).[63] Curtius rearrangement of the diacylazide in the presence of anisyl alcohol afforded carbamate derivative **4** in 63% yield after chromatographic purification. The rearrangement reaction was followed by the acylation step, conducted with either acetic or valeric anhydride, in the presence of 4-DMAP, to yield protected amido derivatives **5** and **6**, respectively. Simultaneous removal of both Moz groups was eventually achieved by acidic solvolysis in a 5% $TFA/CH_2Cl_2$ mixture, in the presence of an excess of anisole as carbocation scavenger, to afford compounds **3** and **7** in high yields (75% and 61%, respectively).




Scheme 1. Synthetic approaches for preparing 2,5-diamido-substituted thiophene heterocycles.

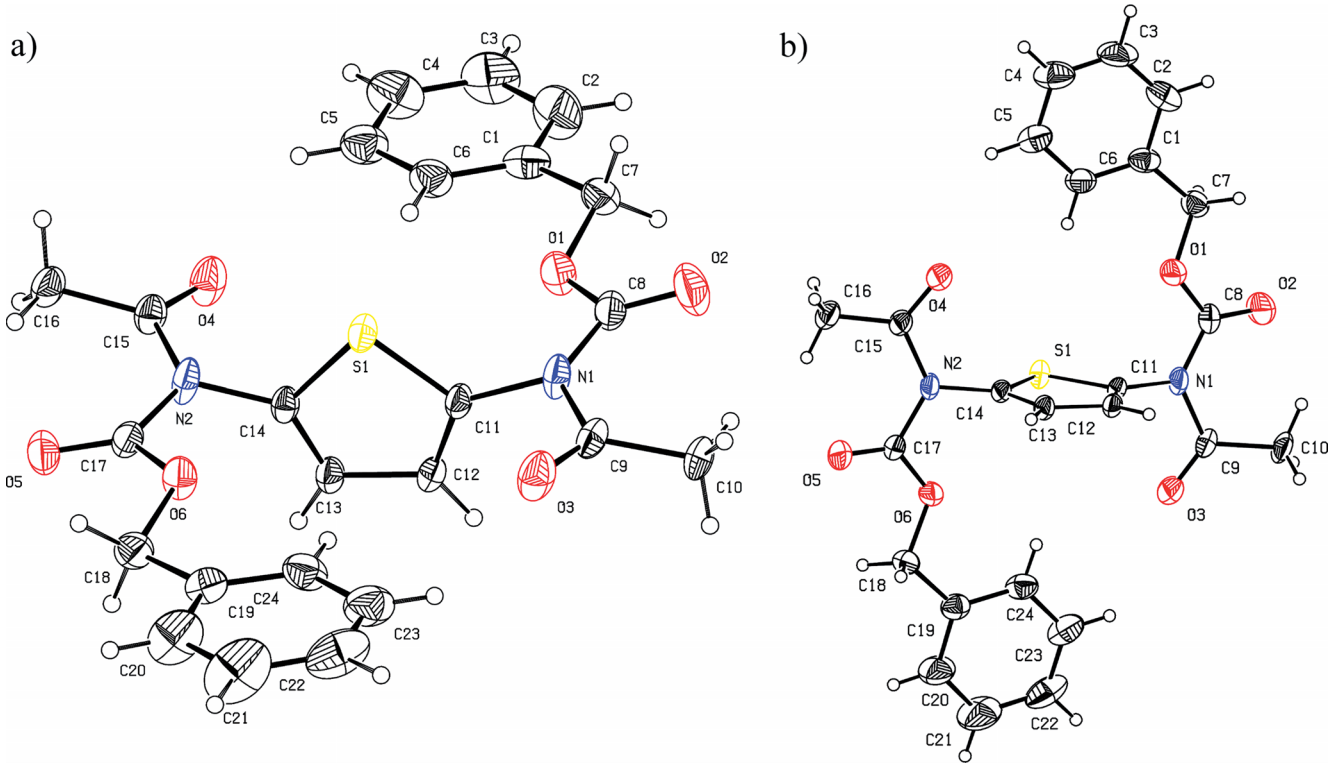
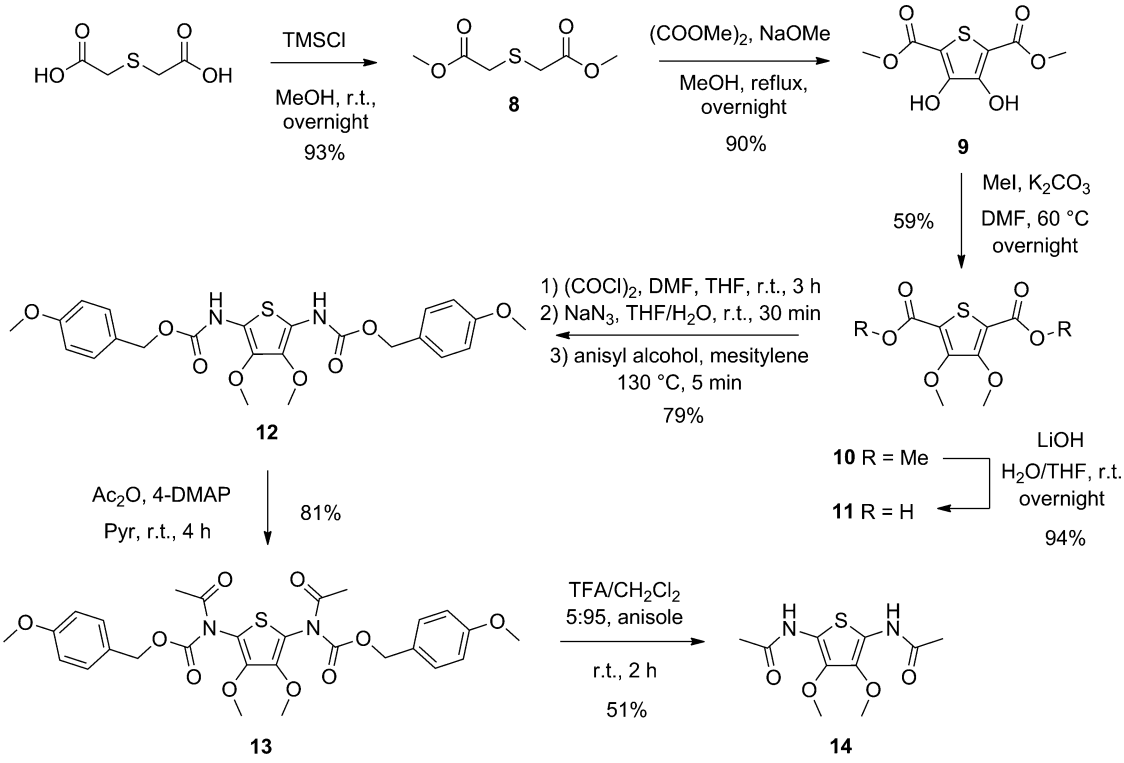



Figure 3. ORTEP representations of compound **2** as determined by X-ray diffraction analysis (displacement ellipsoids are drawn at the 30% probability level). (a) Front and (b) side views are shown.




Scheme 2. Synthetic approach for preparing electron-rich 2,5-diamido-substituted thiophene heterocycles.

With the aim of establishing how far we could push the system in terms of electron density, we decided to synthesize thiophene **14**, which is an exceptionally electron-rich derivative of **3**. The core unit, bearing two methoxy groups at the two β-positions, was obtained by a four-step procedure (Scheme 2). Commercially available thiodiacetic acid was methylated with TMSCl in MeOH, after which the resulting diester **8** underwent Hinsberg condensation with dimethyl oxalate in the presence of NaOMe to yield intermediate **9**.[64] The hydroxy groups in the two β-positions were then methylated with MeI, and the methyl carboxylate groups in the two α-positions were finally cleaved to yield the 2,5-dicarboxylic acid derivative **11**.[64] Like in the previous case, we proceeded with the transformation of the carboxylic groups into carbamates, preparing the diacylazido derivative with the chlorination/azidation one-pot procedure, followed by Curtius rearrangement in the presence of anisyl alcohol. The whole procedure afforded, after silica gel chromatographic purification, 2,5-dicarbamate derivative **12** in an overall yield of 79%. Subsequently, acetylation afforded derivative **13** in 81% yield and the final deprotection led to compound **14** in 51% yield.

## Pyrrole Derivatives

The strategy for the preparation of targeted 2,5-diamido-substituted pyrroles (Figure 4) follows the same synthetic route as successfully developed for the thiophene analogues, with the Curtius rearrangement of acylazide intermediates (Scheme 3).

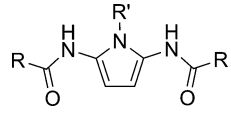
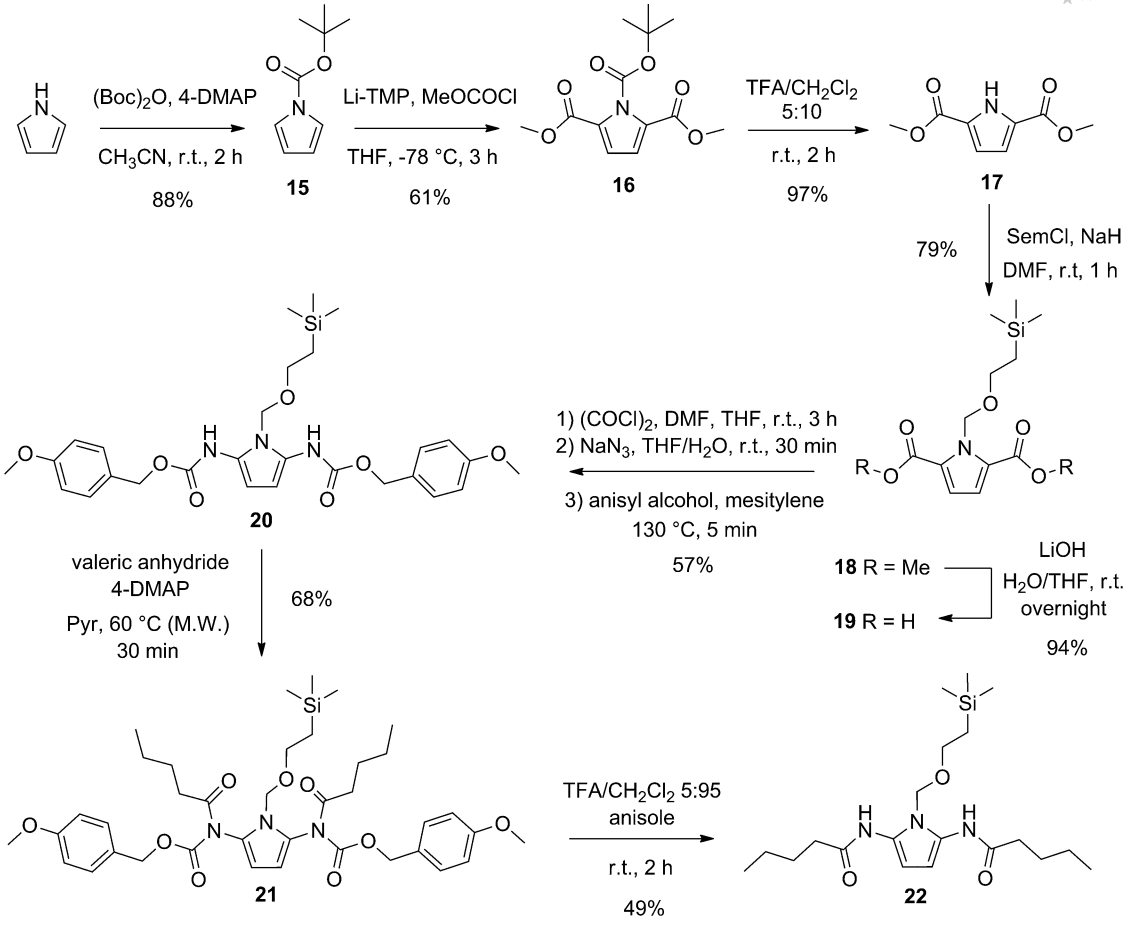


Figure 4. Target pyrrole derivative.

The first step involved *tert*-butyl carbamate (Boc) protection of the pyrrole nitrogen,[65] followed by deprotonation at the α-positions and treatment with methyl chloroformate to afford 2,5-diester derivative **16**.[66] In view of the high lability of the Boc protecting group under acidic conditions,[63] this function was removed by treatment with TFA in order to subsequently to introduce a more resistant protecting group. Fully protected 2,5-diaminopyrrole **20** was thus synthesized, with a *N*-[2-(trimethylsilyl)ethoxy]methyl (Sem) group on the pyrrole nitrogen and with two Moz groups masking the α-amine nitrogen atoms. The diacyl azide intermediate was prepared by the developed protocol under the conditions described above and underwent Curtius rearrangement in the presence of anisyl alcohol to provide 2,5-dicarbamate derivative **20** in 57% yield. Afterwards, acylation was performed with valeric anhydride, affording highly soluble derivative **21**. Subsequent removal of the Moz groups by acidic solvolysis in a TFA/$CH_2Cl_2$ mixture (with an excess of anisole) afforded 2,5-diamido-substituted pyrrole derivative **22** in 49% yield after precipitation from pentane.




Scheme 3. Synthetic approach for preparing 2,5-diamido-substituted pyrrole heterocycles.

## Furan Derivatives

In the case of furan, the developed route was tested for two classes of derivatives: bis-β-substituted and β-unsubstituted furan rings (Figure 5).

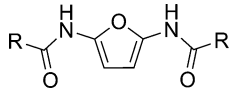
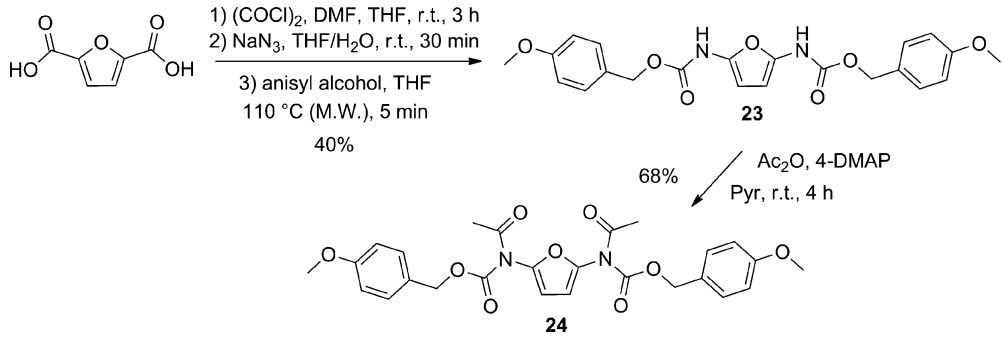


Figure 5. Target furan derivative.

For the β-unsubstituted furan ring system we started from furan-2,5-dicarboxylic acid, which was converted into the diacylazide derivative in two steps by chlorination with $(COCl)_2$ in THF and subsequent treatment with $NaN_3$ (Scheme 4). The 2,5-diacylazide underwent Curtius rearrangement in THF, in the presence of anisyl alcohol, under microwave irradiation conditions at 110 °C, and the desired product **23** was isolated in 40% yield. Moreover, it needs to be underlined that the purification procedure strongly influences the reaction outcome, in terms of amount of isolated product. Furan derivative **23** proved to be extremely susceptible to acidic environments, and even the residual acidity of $CH_2Cl_2$ or $CHCl_3$ could suffice for its degradation. Therefore, after performing the Curtius rearrangement, great care should be taken in rapidly purifying the crude reaction product. Afterwards, the acylation of intermediate **23** was performed by use of an excess of $Ac_2O$ and 4-DMAP, and the desired diacylated compound **24** was recovered in 68% yield after chromatographic purification.

The deprotection of **24** was firstly attempted by treatment with TFA, with use of an excess of anisole as cationic scavenger. On performing the reaction in $CH_2Cl_2$ only decomposition occurred, whereas in $Et_2O$ the reaction proceeded at slower rate, allowing the isolation of the monodeprotected product, identified by mass analysis and by $^1H$ and $^{13}C$ NMR spectroscopy. However, even after increasing the reaction time and dilution it was not possible to isolate the fully deprotected derivative and we observed only decomposition. The use of hydracids also proved fruitless. Most probably, the acid sensitivity of a furan ring bearing two amide moieties in its α-positions is incompatible with the acid cleavage of any protecting groups. This result suggests that if one wants to access the fully deprotected furan derivative, a protecting group cleavable under basic condition should be used for further developments or applications.

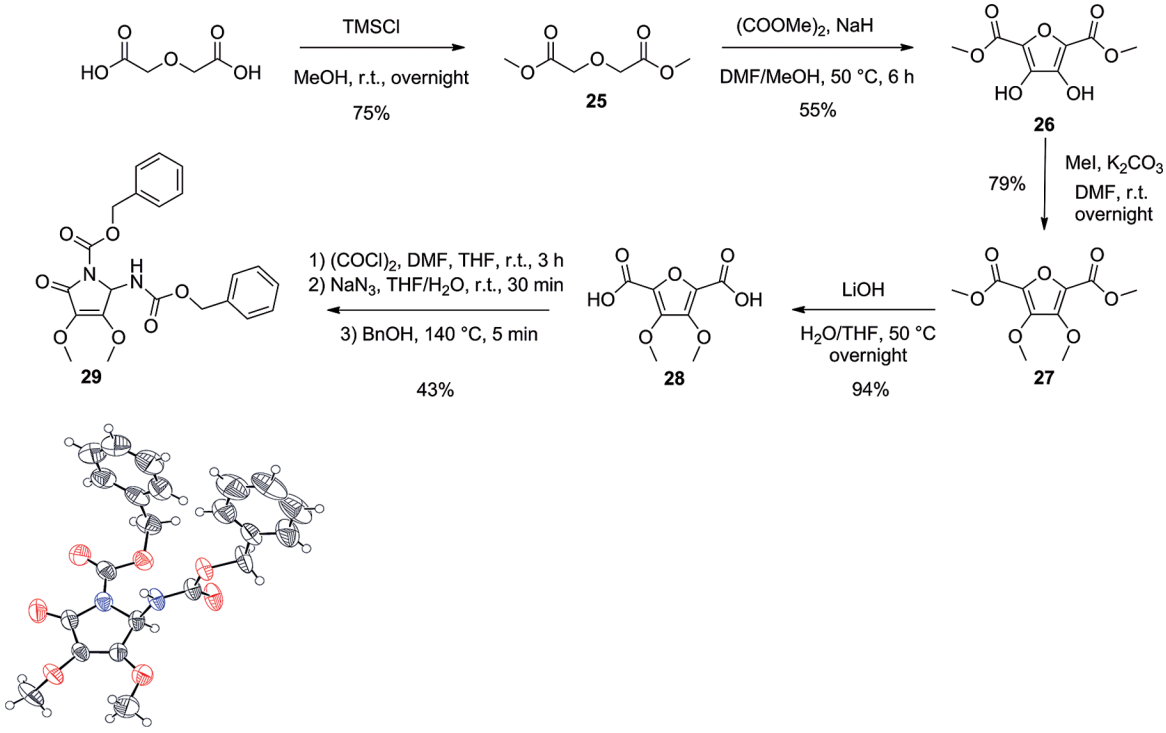
  




Scheme 4. Synthetic approach for preparing 2,5-diamido-substituted furan heterocycles.

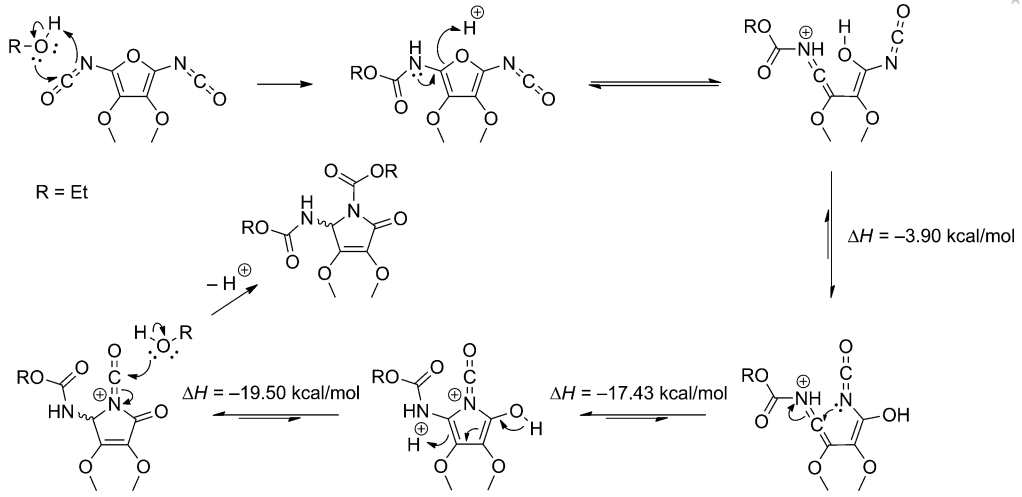
As pursued for the thiophene derivative, the preparation of derivatives bearing methoxy groups in the two β-positions was attempted, and led to unexpected results (Scheme 5). The synthesis started with the esterification of diglycolic acid by treatment with TMSCl in the presence of MeOH, giving the desired diester **25** in 75% yield. Compound **25** was subsequently condensed with $(COOMe)_2$, in the presence of NaH in DMF at 50 °C.[67] Methylation of the hydroxy groups in the β-positions with MeI,[68] followed by saponification with LiOH in THF,[69] yielded compound **28**. Conversion of the obtained carboxylic acids into acylazides was achieved by the general protocol involving a chlorination step followed by addition of $NaN_3$. Afterwards, Curtius rearrangement was performed with use of BnOH as nucleophile to trap the transient isocyanate intermediate resulting from the thermal transformation of the diacylazide. To our great surprise, the outcome of the reaction was not the expected 2,5-dicarbamate derivative, but the chiral (racemic) derivative **29**, as shown by NMR and X-ray analyses. Suspecting that the high temperature employed might have triggered the ring-opening of the furan nucleus, we decided to repeat the reaction at lower temperatures, in toluene, with stoichiometric quantities of BnOH. Despite the tuning of the conditions, compound **29** was again obtained as the only product. The structure of **29** was confirmed by X-ray diffraction. Suitable crystals belonging to the monoclinic space group *Pc* were obtained by vapour diffusion of hexane into a $CH_2Cl_2$ solution containing derivative **29** (ORTEP representation is depicted in Scheme 5).

A hypothetical mechanism accounting for the formation of molecule **29** is presented in Scheme 6. After the formation of a first carbamate group, the protonation of the furan




Scheme 5. Toward 2,5-diamido-substituted furan heterocycles. ORTEP representation of compound **29** as determined by X-ray diffraction analysis (displacement ellipsoids are drawn at the 50% probability level). Only one of the two molecules in the asymmetric unit is shown for sake of clarity.




Scheme 6. Proposed mechanism for the formation of **29** starting from the corresponding diisocyanate precursor. For purposes of calculation the Bn groups were replaced by Et groups. All intermediates were optimized at the B3LYP/6-311G** level of theory, and the calculated enthalpies (Δ*H*) for the hypothesized steps are reported.

O atom could trigger the opening of the electron-rich ring, leading to a ketenimine intermediate, most likely stabilized by the presence of the methoxy groups. After a configurational equilibrium, nucleophilic attack of the isocyanate nitrogen at the keteniminic group leads to ring closure, forming a peculiar pyrrole-like intermediate. Final keto–enol tautomerism results in the dearomatization of the ring and the formation of **29** as a racemic mixture (the calculated Δ*H*° value for the keto derivative is 19.50 kcal mol$^{-1}$ lower than the corresponding enol tautomer).

### Conformation Analysis of 2,5-Diamidothiophene 3

A monocrystal suitable for X-ray diffraction was also obtained for thiophene conjugate **3**, by slow evaporation of a 9:1 $CHCl_3$/MeOH solution. Two different crystals were found, belonging to the monoclinic *Cc* (depicted in Figure 6, a) and *Pcca* space groups. In each crystal, the solved structure clearly shows a "closed" conformation for the two α substituents, with the two carbonyl groups pointing towards the S atom. With the goal of elucidating the structural properties of thiophene **3**, density functional theory (DFT) calculations were performed at the B3LYP/6-311G** level of theory for the "closed" and "open" conformations, which proved both to be actual local minima. Indeed, the "closed" one proved to be the most favoured, with an enthalpy difference of 2.7 kcal mol$^{-1}$ (Figure 6, b). For purposes of comparison, the "closed" and "open" conformations for 2,6-diacetamidopyridine (DAP), a known six-membered heterocyclic analogue used in triple H-bonded motifs, were also investigated at the same level of theory. In agreement with the experimental observations (Figure 6, c),[70,71] the "open" conformation is energetically favoured for DAP, with a considerable difference in energy of 16.3 kcal mol$^{-1}$. The main reason for the opposite behaviour of the two molecules is probably related to noncovalent intramolecular interactions, acting as conformational locks. The distance between the carbonyl O atom and the heterocyclic C–H bond might or might not allow the existence of a H-bonding interaction. This contact is probably the dominating attractive feature governing the stability of the "open" conformation in 2,6-diacetamidopyridine (experimentally determined values for O···H 2.17, 2.16 Å, CSD code: DOPDAN,[70] calculated value for O···H 2.24 Å). On the other hand, thiophene derivative **3** is probably stabilized in the "closed" conformation by two sulfur–oxygen non-bonding interactions. The contact distance obtained from the optimized geometry of molecule **3** (S···O 2.85 Å), perfectly matches that from the X-ray structures (S···O 2.82, 2.86 Å) and is much shorter than the sum of the van der Waals radii of the two atoms (3.25 Å), consistently with an attractive nature of such an interaction. Experimentally determined and calculated distances are summarized in Table 1. This hypothesis prompted us to investigate the electronic properties of molecule **3** by plotting the molecular electrostatic potential on its van der Waals surface, as shown in Figure 6, d. Moreover, Mulliken atomic charges were calculated (Table 2), showing a positive partial charge for thiophene S (0.36 esu), bigger than those calculated for the unsubstituted thiophene (0.25 esu).

Because of the well-known basis-set sensibility of the Mulliken population analysis,[72,73] the Bader charges were calculated too,[74] and confirmed the reliability of the partial charge investigation (Table 2). These findings correlate well with the presence of Coulombic stabilized non-bonding interactions with the two O atoms, as already reported by others for similar systems.[75–79]

Crystals suitable for diffraction were also obtained for thiophene **14**, from a 95:5 $CHCl_3$/MeOH solution (monoclinic space group $P2_1/c$). The ORTEP representation (Figure 7) reveals the quasi-planar arrangement of the molecule in the "closed" conformation, most probably stabilized by non-bonding interactions (S1···O3 and S1···O4), as already observed for molecule **3**.

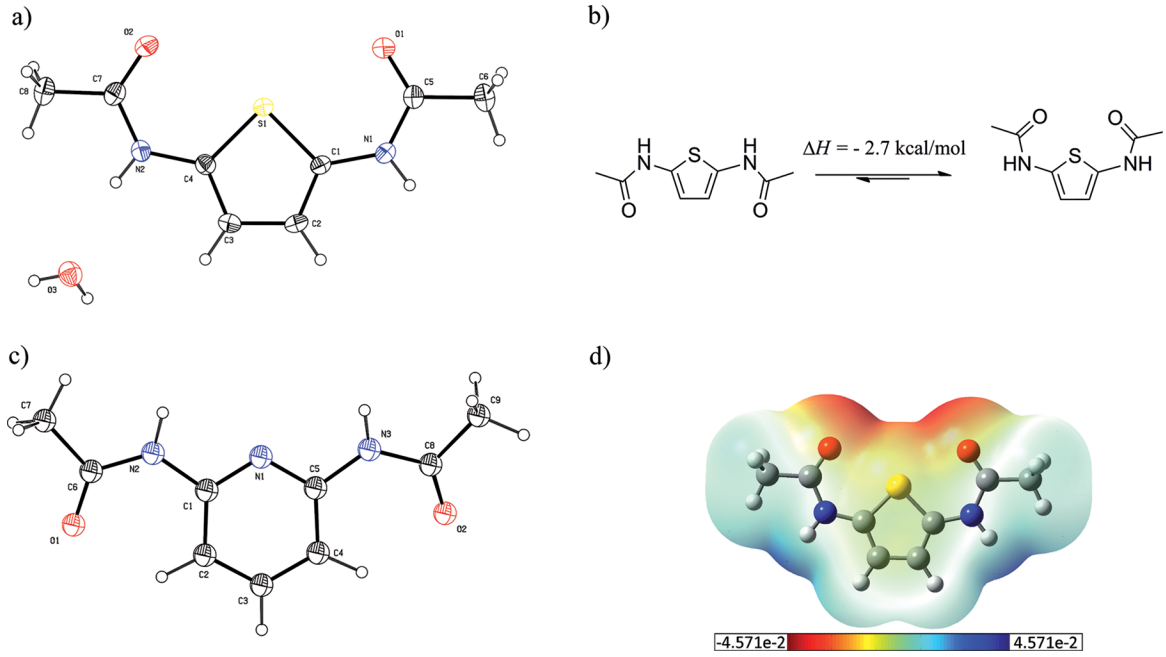



Figure 6. (**a**) ORTEP representation of compound **3** in the "closed" conformation as determined by X-ray diffraction analysis (displacement ellipsoids are drawn at the 30% probability level). (**b**) Calculated enthalpy ($\Delta H$) for the "open"⇌"closed" equilibrium of thiophene **3**. (**c**) ORTEP representation of 2,6-diacetamidopyridine as determined by X-ray diffraction analysis (displacement ellipsoids are drawn at the 30% probability level) [CSD code: DOPDAN].[70] (**d**) Molecular electrostatic potential plotted on the van der Waals surface of compound **3** in the "closed" conformation.

Table 1. Intramolecular distances observed in the X-ray crystal structures of compound **3** and of DAP [CSD code: DOPDAN][70] and in the "open" and "closed" B3LYP/6-311G** optimized conformations.

| Molecule | Contact distance [Å] | |
|---|---|---|
| "open" conformation | exp. O···H | calcd. O···H |
| Thiophene **3** | – | 2.37 |
| DAP | 2.17/2.16 | 2.24 |
| "closed" conformation | exp. O···X | calcd. O···X |
| Thiophene **3** | 2.82/2.86 | 2.85 |
| DAP | – | 2.92 |

Table 2. Atomic partial charges calculated by Mulliken and Bader methods for the "open" and "closed" conformations of molecule **3**, with bare thiophene as a reference.

| Molecule | Atom | Atomic charges (ESU) | |
|---|---|---|---|
| | | Mulliken | Bader |
| "open" **3** | S | 0.18 | 0.17 |
| | O | –0.35 | –1.39/–1.46 |
| "closed" **3** | S | 0.36 | 0.50 |
| | O | –0.35 | –1.87/–1.85 |
| Thiophene | S | 0.25 | 0.24 |

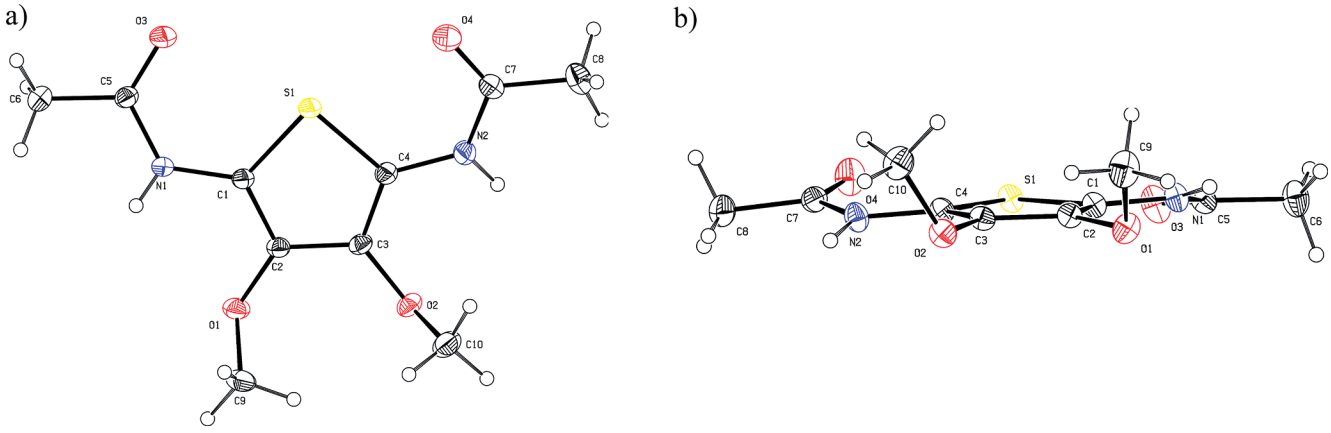



Figure 7. ORTEP representations of compound **14** as determined by X-ray diffraction analysis (displacement ellipsoids are drawn at the 30% probability level). (a) Front and (b) side views are shown.

## Conclusions

In this work we have been able, by exploiting the Curtius rearrangement, to prepare a series of previously unknown 2,5-diamido derivatives of five-membered heterocycles. Other synthetic attempts to obtain the same molecular modules based on amidation cross-coupling and on formation of azido intermediates were unsuccessful in our hands. In the case of the furan derivative bearing two methoxy groups in its β-positions, Curtius rearrangement unexpectedly gave rise to saturated pyrrole derivative **29**. Furthermore, theoretically conformation analysis performed for 2,5-diamidothiophene **3** displayed a higher stability for the "closed" conformation than for the "open" one. Such results suggest that, if one could stabilize the "open" conformation, featuring two NH H-bond donors and the central S atom capable of participating in Coulombic non-bonding interactions, the system might possibly be used as a new supramolecular recognition platform exploiting complementary noncovalent interactions.

## Experimental Section

**General Information**: Chemicals were purchased from Sigma–Aldrich, Acros Organics, Alfa Aesar or ABCR. Pyrrole was filtered through basic alumina before use. The other chemicals were used as received. Solvents were purchased from Sigma–Aldrich, and deuterated solvents from Euriso-Top. When anhydrous reaction conditions were required, reaction flasks were dried with a heating gun (300–500 °C), placed under high vacuum with a Schlenk line and purged with Ar. To keep the atmosphere dry and inert, balloons filled with Ar were used. Anhydrous THF was distilled from Na/benzophenone, and the other anhydrous solvents were purchased from Acros Organics. Microwave reactions were performed with a Biotage AB Initiator microwave instrument producing controlled irradiation at 2.450 GHz. Model: initiator EXP EU 355301, 10634–13U. TLC was carried out on Machery–Nagel pre-coated aluminium plates with silica gel 60 $F_{254}$. Column chromatography (CC) was carried out with Merck silica gel 60 (particle size 40–63 μm), and purifications were performed either with classical column chromatography equipment or with Büchi sepacore, an automatic chromatography system. $^1$H and $^{13}$C NMR spectra were obtained with a 400 MHz instrument (Jeol JNM EX-400) working at 25 °C, if not differently specified. Chemical shifts ($\delta$) are reported in ppm with use of the solvent residual signal as internal reference ($CDCl_3$: $\delta_H$ = 7.26 ppm, $\delta_C$ = 77.16 ppm, $CD_3OD$: $\delta_H$ = 3.31 ppm, $\delta_C$ = 49.00, [D$_6$]DMSO: $\delta_H$ = 2.50 ppm, $\delta_C$ = 39.52 ppm). Coupling constants ($J$) are given in Hz, and the resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), sex (sextuplet), m (multiplet), and/or br (broad signal). Carbon spectra were acquired with complete proton decoupling. Infrared (IR) spectra were recorded with a Perkin–Elmer spectrum RX I FTIR System. Mass analysis was performed either with an Agilent 6200 series TOF mass spectrometer (APCI or ESI), or with a Waters QToF2 mass spectrometer (ESI). Mass values simulation was performed with IsoPro 3.1 software.

Single-crystal X-ray diffraction (SCXRD) was performed with a Gemini Ultra R system (four-circle kappa platform, Ruby CCD detector) and use of MoK\α ($\lambda$ = 0.71073 Å) or CuK\α ($\lambda$ = 1.54178 Å) radiation. Selected crystals were mounted on the tip of a quartz pin with cyanoacrylate (commercial glue). Cell parameters were estimated from a pre-experiment run, and full data sets were collected at room temperature. Structures were solved by direct methods with the SHELXS-97 program and then refined on $F^2$ by use of SHELXL-97 software.[80] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms (not implicated in H-bonds) in the riding mode with isotropic temperature factors fixed at 1.2 times $U$(eq) of the parent atoms (1.5 times for methyl groups). Hydrogen atoms implicated in H-bonds were localized by Fourier difference maps ($\Delta F$). CCDC-950747 (for **29**), -950748 (for **14**), -950749 (for **3**), -950750 (for **3**) and -950751 (for **2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Density functional theory (DFT) calculations were performed with the Gaussian 03 package.[81] Geometry optimizations were conducted with Becke's three-parameter exchange functional,[82] the Lee–Yang–Parr correlation functional[83] (B3LYP) and the 6-311G** basis set. In geometry optimizations every bond length, angle and dihedral angle was allowed to relax, free of constraints. The nature of stationary points ("closed" and "open" isomers) was confirmed by vibrational frequency analysis. Mulliken charges were extracted from a single-point energy calculation performed on the optimized geometries at the B3LYP/6-311G** level of theory. Bader charge analysis was carried out with the program written by Henkelman et al.[74,84]

**Synthetic Procedures:** The following compounds were prepared by previously reported procedures, with only slight modifications when specified: compound **9**[64,85] (the sodium salt of the product was protonated by addition of concentrated aq. HCl, followed by filtration, washing with $H_2O$ and azeotropic distillation with toluene), compound **11**[64] (LiOH was used instead of NaOH), compound **15**,[65] compound **16**,[66] compound **26**,[67,69] compound **27**,[68,69] and compound **28**[69] (LiOH was used instead of NaOH).

In the paragraphs describing general procedures, the values given between brackets indicate the volume of a given solvent or solution used per mmol of starting material.

**General Procedure for Acyl Azide Formation:** DMF (0.2 equiv.) and $(COCl)_2$ (2.2 equiv.) were added with stirring at 0 °C to a solution of the 2,5-dicarboxylic acid derivative of each differently substituted heterocycle in anhydrous THF (4 mL mmol$^{-1}$), and the mixture was stirred at room temp. for 3 h. The solvents were then removed under vacuum, and the residue was redissolved in anhydrous THF (2.5 mL mmol$^{-1}$). The resulting solution was added dropwise to saturated aq. $NaN_3$ (0.4 mL mmol$^{-1}$), stirred for 30 min, diluted with $Et_2O$ (5 mL mmol$^{-1}$), and then washed with saturated aq. $NaHCO_3$ (5 mL mmol$^{-1}$) and $H_2O$ (5 mL mmol$^{-1}$ × 2). The organic phase was dried with $MgSO_4$, and the solvent was partially evaporated under vacuum (final volume: ca. 0.5 mL mmol$^{-1}$). This procedure was applied for compounds **1**, **4**, **12**, **20**, **23** and **29**, followed by the Curtius rearrangement step.

**Compound 1:** The starting material was thiophene-2,5-dicarboxylic acid (2.08 g, 12.1 mmol). The obtained solution was added to a solution of benzyl alcohol (3.75 mL, 36.2 mmol) in mesitylene (6 mL) at 130 °C, stirred for 5 min and then allowed to cool to room temp. and poured into pentane (100 mL). The precipitate was collected by vacuum filtration and purified by silica gel chromatography (cyclohexane/EtOAc 7:3) to afford a white solid (2.65 g, 6.93 mmol, 57% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.31 (m, 10 H, Ph*H*), 6.94 (br. s, 2 H, N*H*), 6.35 (s, 2 H, thiophene-*H*), 5.18 (s, 4 H, O*C*$H_2$Ph) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 153.76, 135.82, 132.97, 128.75, 128.59, 112.46, 67.82 ppm. IR (KBr): $\tilde{\nu}$ = 3285, 2949, 1713, 1698, 1586, 1552, 1503, 1454, 1379,

1290, 1245, 1062, 1049, 972, 910, 845, 799, 784, 736, 653, 590, 577, 515, 485, 410 $cm^{-1}$. HRMS (APCI$^+$): calcd. for $[C_{20}H_{18}N_2O_4S + H]^+$ 383.1065; found 383.1101.

**Compound 4:** The starting material was thiophene-2,5-dicarboxylic acid (1.30 g, 7.60 mmol). The obtained solution was added to a solution of anisyl alcohol (2.83 mL, 22.8 mmol) in mesitylene (5 mL) at 130 °C, stirred for 5 min and then allowed to cool to room temp. and poured into pentane (100 mL). The precipitate was collected by vacuum filtration and purified by silica gel chromatography (cyclohexane/EtOAc 7:3) to afford a white solid (2.10 g, 4.75 mmol, 63% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.30 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 7.01 (br. s, 2 H, N*H*), 6.87 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.32 (s, 2 H, thiophene-*H*), 5.10 (s, 4 H, OC$H_2$Ph), 3.80 (s, 6 H, OC$H_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 159.83, 153.95, 132.92, 130.44, 127.93, 114.06, 112.42, 67.59, 55.40 ppm. IR (KBr): $\tilde{\nu}$ = 3287, 2958, 2838, 1698, 1691, 1615, 1586, 1554, 1516, 1466, 1377, 1338, 1284, 1239, 1174, 1109, 1075, 1032, 953, 817, 790, 772, 762, 645, 522, 512, 489 $cm^{-1}$. HRMS (ESI$^+$): calcd. for $[C_{22}H_{22}N_2O_6S + Na]^+$ 465.1096; found 465.1102.

**Compound 12:** The starting material was compound **11** (1.00 g, 4.31 mmol). The obtained solution was added to a solution of anisyl alcohol (1.61 mL, 12.9 mmol) in mesitylene (4 mL) at 130 °C, stirred for 5 min and then allowed to cool to room temp. and poured into pentane (80 mL). The precipitate was collected by vacuum filtration and purified by silica gel chromatography (cyclohexane/EtOAc 7:3) to afford a white solid (1.71 g, 3.40 mmol, 79% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.33 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.89 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.67 (br. s, 2 H, N*H*), 5.13 (s, 4 H, OC$H_2$Ph), 3.81 (s, 6 H, OC$H_3$), 3.79 (s, 6 H, OC$H_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 159.88, 153.78, 136.51, 130.46, 127.90, 115.41, 114.08, 67.66, 60.61, 55.39 ppm. IR (KBr): $\tilde{\nu}$ = 3351, 3272, 2960, 2991, 2545, 2063, 1727, 1694, 1615, 1586, 1571, 1515, 1483, 1445, 1401, 1365, 1303, 1243, 1218, 1173, 1118, 1110, 1082, 1053, 1036, 1005, 960, 946, 848, 828, 815, 808, 760, 738, 722, 670, 570, 547, 514, 427 $cm^{-1}$. HRMS (ESI$^+$): calcd. for $[C_{24}H_{26}N_2O_8S + K]^+$ 541.1047; found 541.1022. $C_{24}H_{26}N_2O_8S$ (502.54): calcd. C 57.36, H 5.21, N 5.57, S 6.38; found C 57.19, H 5.22, N 5.55, S 6.01.

**Compound 20:** The starting material was compound **19** (1.00 g, 3.50 mmol). The obtained solution was added to a solution of anisyl alcohol (1.30 mL, 10.5 mmol) in mesitylene (3 mL) at 130 °C, stirred for 5 min and then allowed to cool to room temp. The solvent was removed under vacuum, and the crude residue was purified by silica gel chromatography (cyclohexane/EtOAc 8:2) to afford the product (1.10 g, 1.98 mmol, 57% yield). $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 8.94 (br. s, 2 H, N*H*), 7.32 (br. d, 4 H, Ph*H*), 6.93 (d, $J$ = 8.2 Hz, 4 H, Ph*H*), 5.77 (s, 2 H, pyrrole-*H*), 5.00 (s, 4 H, OC$H_2$Ph), 4.96 (s, 2 H, NC$H_2$O), 3.75 (s, 6 H, OC$H_3$), 3.33–3.25 (m, 2 H, OC$H_2$CH$_2$Si), 0.77–0.67 (m, 2 H, OCH$_2$C$H_2$Si), –0.07 [s, 9 H, Si(C$H_3$)$_3$] ppm. $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 159.12, 155.25, 129.94, 128.54, 123.34, 113.78, 102.23, 69.95, 65.79, 64.78, 55.11, 17.30, –1.40 ppm. IR (KBr): $\tilde{\nu}$ = 3606, 3443, 3262, 3000, 2953, 2898, 2836, 1697, 1614, 1588, 1518, 1466, 1419, 1368, 1304, 1293, 1248, 1219, 1135, 1082, 1065, 1038, 961, 862, 834, 772, 759, 557, 522, 444 $cm^{-1}$. HRMS (APCI$^+$): calcd. for $[C_{28}H_{37}N_3O_7Si + H]^+$ 556.2479; found 556.2407; (ESI$^+$): calcd. for $[C_{28}H_{37}N_3O_7Si + Na]^+$ 578.2299; found 578.2311. $C_{28}H_{37}N_3O_7Si$ (555.70): calcd. C 60.33, H 6.68, N 7.64; found C 60.52, H 6.71, N 7.56.

**Compound 23:** The starting material was furan-2,5-dicarboxylic acid (140 mg, 0.900 mmol). The obtained solution was dried, and the crude solid was dissolved in THF (2 mL) and transferred to a microwave vessel. Anisyl alcohol (335 μL, 2.70 mmol) was added, and the vessel was sealed and heated in the microwave oven at 110 °C for 5 min. The solvent was then removed under vacuum, and the crude product was purified by filtration through a short silica gel plug (cyclohexane/EtOAc 7:3). Precipitation from EtOAc solution upon pentane addition afforded **23** as a white solid (154 mg, 0.360 mmol, 40% yield). $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 9.89 (br. s, 2 H, N*H*), 7.37–7.27 (m, 4 H, Ph*H*), 6.96–6.90 (m, 4 H, Ph*H*), 5.94 (s, 2 H, furan-*H*), 5.03 (s, 4 H, OC$H_2$Ph), 3.75 (s, 6 H, OC$H_3$) ppm. $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 159.20, 153.68, 130.30, 130.01, 128.24, 127.47, 113.71, 66.06, 55.13 ppm. IR (KBr): $\tilde{\nu}$ = 3277, 2957, 1764, 1698, 1639, 1612, 1513, 1463, 1377, 1348, 1303, 1243, 1220, 1200, 1173, 1112, 1061, 1028, 926, 851, 818, 770, 712, 666, 637, 565, 517 $cm^{-1}$. HRMS (ESI$^+$): calcd. for $[C_{22}H_{22}N_2O_7 + Na]^+$ 449.1325; found 449.1345.

**Compound 29:** The starting material was compound **28** (400 mg, 1.85 mmol), and the last extraction in the acyl azide formation procedure was performed with $CH_2Cl_2$ instead of $Et_2O$. The solution obtained in the end was added dropwise to benzyl alcohol (3 mL) at 140 °C and stirred for 5 min. The benzyl alcohol was then removed by bulb-to-bulb distillation, and a final precipitation with pentane or cyclohexane afforded **29** (335 mg, 0.790 mmol, 43% yield). $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 8.13 (d, $J$ = 9.1 Hz, 1 H, N*H*), 7.41–7.28 (m, 10 H, Ph*H*), 5.96 (d, $J$ = 9.1 Hz, 1 H, NC*H*NH), 5.20 (d, $J$ = 12.7 Hz, 1 H, OC*H*Ph), 5.15 (d, $J$ = 12.7 Hz, 1 H, OC*H*Ph), 5.04 (d, $J$ = 12.3 Hz, 1 H, OC*H*Ph), 4.99 (d, $J$ = 12.3 Hz, 1 H, OC*H*Ph), 3.99 (s, 3 H, OC$H_3$), 3.72 (s, 3 H, OC$H_3$) ppm. $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 164.04, 155.15, 153.22, 149.15, 136.64, 135.72, 128.39, 128.36, 128.04, 127.94, 127.79, 127.75, 125.42, 66.81, 65.78, 61.89, 60.30, 59.09 ppm. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.28 (m, 10 H, Ph*H*), 5.90 (br. d, 1 H, NC*H*NH), 5.45 (br. s, 1 H, N*H*), 5.24 (d, $J$ = 12.3 Hz, 1 H, OC*H*Ph), 5.18 (d, $J$ = 12.3 Hz, 1 H, OC*H*Ph), 5.06 (m, 2 H, OC$H_2$Ph), 4.04 (s, 3 H, OC$H_3$), 3.81 (s, 3 H, OC$H_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.35, 155.00, 152.31, 149.91, 135.94, 135.24, 128.67, 128.52, 128.48, 128.43, 128.26, 126.14, 68.17, 67.47, 62.31, 60.68, 59.59 ppm. IR (KBr): $\tilde{\nu}$ = 3282, 3061, 2955, 1794, 1702, 1681, 1545, 1456, 1377, 1359, 1331, 1282, 1255, 1221, 1191, 1150, 1093, 1056, 1008, 976, 957, 916, 871, 823, 778, 748, 735, 705, 695, 641, 599, 579, 557, 510, 494 $cm^{-1}$. HRMS (APCI$^+$): calcd. for $[C_{22}H_{22}N_2O_7 + Na]^+$ 449.1325; found 449.1317.

**General Procedure for Acylation:** 4-DMAP (1 equiv.) and acetic or valeric anhydride (5 equiv.) were added to a solution of the biscarbamate derivative in pyridine (3–5 mL mmol$^{-1}$), and the solution was stirred at room temp. for 4 h. The mixture was then diluted with EtOAc (15 mL mmol$^{-1}$) and washed with aq. HCl (1 N, 15 mL mmol$^{-1}$), saturated aq. $NaHCO_3$ (15 mL mmol$^{-1}$) and $H_2O$ (15 mL mmol$^{-1}$). The organic phase was dried with $MgSO_4$, and the solvent was removed under vacuum. Purification by silica gel chromatography (cyclohexane/EtOAc 8:2) afforded the desired product. This procedure was applied for compounds **2**, **5**, **6**, **13**, **21** and **24**, with slight modifications in the case of compound **21**, as specified.

**Compound 2:** The starting materials were compound **1** (357 mg, 0.930 mmol) and acetic anhydride, and the reaction yielded the desired product as a white solid (364 mg, 0.780 mmol, 84% yield). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.36–7.27 (m, 6 H, Ph*H*), 7.23–7.18 (m, 4 H, Ph*H*), 6.72 (s, 2 H, thiophene-*H*), 5.20 (s, 4 H, OC$H_2$Ph), 2.58 (s, 6 H, COC$H_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.10, 153.32, 137.85, 134.89, 128.76, 128.49, 127.52, 125.53, 68.87, 26.26 ppm. IR (KBr): $\tilde{\nu}$ = 3028, 2947, 1744, 1712, 1584,

1562, 1468, 1382, 1286, 1251, 1100, 967, 904, 762, 735, 626, 580, 554, 513, 464, 420 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $[C_{24}H_{22}N_2O_6S + K]^+$ 505.0835; found 505.0841.

**Compound 5:** The starting materials were compound **4** (1.80 g, 4.07 mmol) and acetic anhydride, and the reaction yielded the desired product as a white solid (1.77 g, 3.36 mmol, 83% yield). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.16 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.84 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.67 (s, 2 H, thiophene-*H*), 5.12 (s, 4 H, OC$H_2$Ph), 3.77 (s, 6 H, OC$H_3$), 2.55 (s, 6 H, COC$H_3$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 172.09, 159.82, 153.34, 137.83, 129.60, 126.99, 125.37, 114.06, 68.83, 55.35, 26.19 ppm. IR (KBr): $\tilde{\nu}$ = 2997, 2942, 2843, 1894, 1750, 1717, 1645, 1586, 1615, 1511, 1465, 1417, 1375, 1304, 1245, 1174, 1100, 1038, 1017, 961, 896, 853, 822, 799, 764, 729, 637, 627, 556, 541, 518, 461, 429 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $[C_{26}H_{26}N_2O_8S + Na]^+$ 549.1307; found 549.1330.

**Compound 6:** The starting materials were compound **4** (1.40 g, 3.16 mmol) and valeric anhydride, and the reaction yielded the desired product as a white solid (1.50 g, 2.46 mmol, 78% yield). $^1H$ NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 7.18 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.87 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.82 (s, 2 H, thiophene-*H*), 5.11 (s, 4 H, OC$H_2$Ph), 3.71 (s, 6 H, OC$H_3$), 2.82 (t, $J$ = 7.4 Hz, 4 H, COC$H_2$CH$_2$), 1.51 (quint, $J$ = 7.4 Hz, 4 H, CH$_2$C$H_2$CH$_2$), 1.26 (sex, $J$ = 7.4 Hz, 4 H, CH$_2$C$H_2$CH$_3$), 0.85 (t, $J$ = 7.4 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}C$ NMR (100 MHz, [$D_6$]DMSO): $\delta$ = 174.55, 159.10, 152.71, 137.57, 129.20, 127.11, 125.53, 113.76, 68.03, 55.03, 36.68, 26.50, 21.62, 13.78 ppm. IR (KBr): $\tilde{\nu}$ = 3085, 2958, 2871, 2838, 2358, 1902, 1748, 1724, 1614, 1587, 1564, 1512, 1481, 1466, 1454, 1375, 1375, 1303, 1283, 1269, 1240, 1206, 1181, 1076, 1030, 975, 849, 822, 803, 768, 753, 716, 683, 576, 558, 540.75, 517.31, 409 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $[C_{32}H_{38}N_2O_8S + Na]^+$ 633.2246; found 633.2243. $C_{32}H_{38}N_2O_8S$ (610.72): calcd. C 62.93, H 6.27, N 4.59, S 5.25; found C 62.09, H 6.41, N 4.60, S 5.04.

**Compound 13:** The starting materials were compound **12** (900 mg, 1.79 mmol) and acetic anhydride, and the reaction yielded the desired product as a white solid (850 mg, 1.45 mmol, 81% yield). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.18 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.84 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 5.13 (s, 4 H, OC$H_2$Ph), 3.77 (s, 6 H, OC$H_3$), 3.69 (s, 6 H, OC$H_3$), 2.53 (s, 6 H, COC$H_3$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.92, 159.79, 153.32, 144.00, 129.55, 127.04, 118.73, 114.04, 68.82, 59.85, 55.35, 25.96 ppm. IR (KBr): $\tilde{\nu}$ = 3421, 3091, 2942, 2837, 2408, 2058, 1893, 1747, 1731, 1615, 1531, 1515, 1456, 1418, 1394, 1376, 1304, 1264, 1242, 1191, 1179, 1128, 1092, 1060, 1035, 1024, 955, 912, 865, 828, 815, 768, 744, 713, 643, 579, 543, 515, 481, 458, 437, 413 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $[C_{28}H_{30}N_2O_{10}S + Na]^+$ 609.1519; found 609.1539. $C_{28}H_{30}N_2O_{10}S$ (586.61): calcd. C 57.33, H 5.15, N 4.78, S 5.47; found C 57.30, H 5.21, N 4.81, S 5.35.

**Compound 21:** The starting materials were compound **20** and valeric anhydride (700 mg, 1.26 mmol), and the reaction was performed in the microwave oven at 60 °C for 30 min. After the general purification procedure described above, the desired product was obtained as a colourless oil (619 mg, 0.860 mmol, 68% yield). $^1H$ NMR (400 MHz, [$D_6$]DMSO, 80 °C): $\delta$ = 7.19 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.87 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.02 (s, 2 H, pyrrole-*H*), 5.08 (s, 4 H, OC$H_2$Ph), 4.71 (s, 2 H, NC$H_2$O), 3.74 (s, 6 H, OC$H_3$), 3.29–3.21 (m, 2 H, OC$H_2$CH$_2$Si), 2.66 (br. t, 4 H, COC$H_2$CH$_2$), 1.53 (quint, $J$ = 7.3 Hz, 4 H, CH$_2$C$H_2$CH$_2$), 1.28 (sex, $J$ = 7.3 Hz, 4 H, CH$_2$C$H_2$CH$_3$), 0.85 (t, $J$ = 7.3 Hz, 6 H, CH$_2$C$H_3$), 0.69–0.61 (m, 2 H, OCH$_2$C$H_2$Si), –0.09 [s, 9 H, Si(C$H_3$)$_3$] ppm. The spectrum was recorded at 80 °C due to the presence of rotamers. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.48, 175.09, 159.75, 153.60, 153.47, 129.73, 127.28, 127.18, 124.59, 124.38, 113.99, 106.69, 106.45, 72.14, 68.41, 66.67, 66.59, 55.31, 37.11, 36.90, 31.06, 22.37, 17.77, 14.01, –1.45 ppm. Some peaks are doubled due to the presence of rotamers. IR (neat): $\tilde{\nu}$ = 2958, 2874, 2838, 1784, 1734, 1614, 1586, 1515, 1465, 1405, 1377, 1248, 1176, 1082, 1035, 980, 940, 924, 860, 835, 769, 694, 668, 637, 613, 576, 522, 494 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $[C_{38}H_{53}N_3O_9Si + Na]^+$ 746.3448; found 746.3491; calcd. for $[C_{38}H_{53}N_3O_9Si + K]^+$ 762.3187; found 762.3233.

**Compound 24:** The starting materials were compound **23** and acetic anhydride (400 mg, 0.940 mmol), and the reaction yielded the desired product as a colourless oil (326 mg, 0.640 mmol, 68% yield). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.18 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.83 (d, $J$ = 8.6 Hz, 4 H, Ph*H*), 6.23 (s, 2 H, furan-*H*), 5.08 (s, 4 H, OC$H_2$Ph), 3.77 (s, 6 H, OC$H_3$), 2.40 (s, 6 H, COC$H_3$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.50, 159.83, 152.48, 141.00, 129.80, 126.87, 113.99, 108.60, 68.83, 55.32, 25.46 ppm. IR (neat): $\tilde{\nu}$ = 3010, 2960, 2388, 2349, 2059, 1788, 1753, 1614, 1588, 1567, 1516, 1464, 1424, 1371, 1304, 1248, 1198, 1091, 1035, 1016, 974, 908, 823, 726, 692, 607, 574 $cm^{-1}$. HRMS (ESI+): calcd. for $[C_{26}H_{26}N_2O_9 + Na]^+$ 533.1536; found 533.1575.

**General Procedure for Moz Removal:** Anisole (10 equiv.) and TFA (5%, v/v) were added to a solution of the Moz-protected derivative in $CH_2Cl_2$ (7–10 mL $mmol^{-1}$), with stirring at 0 °C, and the solution was stirred at room temp. for 2 h. The mixture was then diluted with EtOAc (70 mL $mmol^{-1}$) and washed with saturated aq. $NaHCO_3$ (50 mL $mmol^{-1}$) and $H_2O$ (50 mL $mmol^{-1} \times 2$). The organic phase was dried with $MgSO_4$ and the solvent was removed under vacuum. Precipitation of the residual oil with pentane afforded the desired product. This procedure was applied for compounds **3**, **7**, **14** and **22**.

**Compound 3:** The starting material was compound **5** (340 mg, 0.650 mmol), and the reaction yielded the desired product as a white solid (97 mg, 0.49 mmol, 75% yield). $^1H$ NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 10.78 (s, 2 H, N*H*), 6.32 (s, 2 H, thiophene-*H*), 2.00 (s, 6 H, COC$H_3$) ppm. $^{13}C$ NMR (100 MHz, [$D_6$]DMSO): $\delta$ = 165.73, 132.37, 107.00, 22.43 ppm. IR (KBr): $\tilde{\nu}$ = 3248, 3098, 3001, 1748, 1667, 1645, 1588, 1557, 1480, 1495, 1427, 1370, 1323, 1306, 1288, 1032, 1015, 973, 876, 812, 777, 766, 713, 683, 619, 597, 521 $cm^{-1}$. HRMS ($APCI^+$): calcd. for $[C_8H_{10}N_2O_2S + H]^+$ 199.0541; found 199.0549.

**Compound 7:** The starting material was compound **6** (500 mg, 0.820 mmol), and the reaction yielded the desired product as a white solid (141 mg, 0.500 mmol, 61% yield). $^1H$ NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 10.71 (s, 2 H, N*H*), 6.33 (s, 2 H, thiophene-*H*), 2.27 (t, $J$ = 7.4 Hz, 4 H, COC$H_2$CH$_2$), 1.55 (quint, $J$ = 7.4 Hz, 4 H, CH$_2$C$H_2$CH$_2$), 1.29 (sex, $J$ = 7.4 Hz, 4 H, CH$_2$C$H_2$CH$_3$), 0.88 (t, $J$ = 7.4 Hz, 6 H, CH$_2$C$H_3$) ppm. $^{13}C$ NMR (100 MHz, [$D_6$]-DMSO): $\delta$ = 168.71, 132.30, 107.07, 34.78, 27.29, 21.81, 13.72 ppm. IR (KBr): $\tilde{\nu}$ = 3306, 3272, 2955, 2860, 1652, 1579, 1543, 1498, 1453, 1411, 1381, 1351, 1328, 1286, 1253, 1215, 1183, 1104, 1023, 963, 923, 809, 748, 730, 694, 541, 573, 513 $cm^{-1}$. HRMS ($ESI^+$): calcd. for $[C_{14}H_{22}N_2O_2S + H]^+$ 283.1480; found 283.1478; calcd. for $[C_{14}H_{22}N_2O_2S + Na]^+$ 305.1300; found 305.1299; calcd. for $[C_{14}H_{22}N_2O_2S + K]^+$ 321.1039; found 321.1039. $C_{14}H_{22}N_2O_2S$ (282.40): calcd. C 59.54, H 7.85, N 9.92, S 11.35; found C 59.40, H 7.96, N 10.06, S 10.83.

**Compound 14:** The starting material was compound **13** (400 mg, 0.680 mmol), and the reaction yielded the desired product as a white solid (90 mg, 0.35 mmol, 51% yield). $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ = 3.83 (s, 6 H, OC$H_3$), 2.12 (s, 6 H, COC$H_3$) ppm, N*H* protons are not visible, due to exchange with solvent. $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ = 170.60, 137.21, 117.04, 61.03, 22.23 ppm.

HRMS (APCI$^+$): calcd. for $[C_{10}H_{14}N_2O_4S + H]^+$ 259.0752; found 259.0735.

**Compound 22:** The starting material was compound **21** (500 mg, 0.690 mmol), and the reaction yielded the desired product as a white solid (135 mg, 0.340 mmol, 49% yield). $^1$H NMR (400 MHz, [D$_6$]DMSO, 80 °C): $\delta$ = 9.04 (br. s, 2 H, N*H*), 5.80 (s, 2 H, pyrrole-*H*), 4.98 (s, 2 H, NC$H_2$O), 3.39 (t, $J$ = 8.0 Hz, 2 H, OC$H_2$CH$_2$Si), 2.25 (br. s, 4 H, COC$H_2$CH$_2$), 1.64–1.49 (m, 4 H, CH$_2$C$H_2$CH$_2$), 1.41–1.28 (m, 4 H, CH$_2$C$H_2$CH$_3$), 0.90 (t, $J$ = 6.8 Hz, 6 H, CH$_2$C$H_3$), 0.81 (t, $J$ = 8.0 Hz, 2 H, OCH$_2$C$H_2$Si), –0.02 [s, 9 H, Si(C$H_3$)$_3$] ppm. $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 172.85, 123.96, 102.09, 70.65, 65.49, 35.52, 27.66, 22.49, 18.07, 14.39, –1.09 ppm. IR (KBr): $\tilde{\nu}$ = 3251, 2957, 2931, 2874, 1657, 1584, 1559, 1526, 1467, 1416, 1370, 1291, 1264, 1250, 1189, 1061, 862, 836, 757, 700, 664, 612, 599, 570, 564, 511, 490 cm$^{-1}$. HRMS (ESI$^+$): calcd. for $[C_{20}H_{37}N_3O_3Si + Na]^+$ 418.2502; found 418.2520; calcd. for $[C_{20}H_{37}N_3O_3Si + K]^+$ 434.2241; found 434.2252.

**Compound 8:** Trimethylsilyl chloride (TMSCl) (20.5 mL, 161 mmol) was added dropwise at 0 °C to a solution of 2,2′-thiodiacetic acid (11.0 g, 73.3 mmol) in anhydrous MeOH (50 mL). The solution was then allowed to reach room temp. and was then stirred overnight. The reaction mixture was then diluted with Et$_2$O (40 mL) and washed with saturated aq. NaHCO$_3$ (30 mL × 2) and H$_2$O (30 mL). The organic phase was dried with MgSO$_4$, and the solvent was removed under vacuum to afford the product as a colourless liquid (12.2 g, 68.5 mmol, 93%). Characterization was in agreement with literature data.[64]

**Compound 10:** K$_2$CO$_3$ (5.06 g, 36.6 mmol) and MeI (1.37 mL, 22.0 mmol) were added to a solution of compound **9** (1.70 g, 7.32 mmol) in anhydrous DMF (25 mL), and the mixture was stirred at 30 °C overnight. It was then diluted with CH$_2$Cl$_2$ (100 mL) and washed with aq. HCl (1 N, 100 mL × 2) and H$_2$O (100 mL × 2). The organic phase was dried with MgSO$_4$, and the solvent was removed under vacuum. Purification by silica gel chromatography (cyclohexane/EtOAc 8:2) afforded the product as a white solid (1.12 g, 4.32 mmol, 59% yield). Characterization was in agreement with literature data.[64]

**Compound 17:** TFA (5 mL) was added at 0 °C with stirring to a solution of compound **16** (1.40 g, 4.94 mmol) in CH$_2$Cl$_2$ (10 mL), and the solution was further stirred at room temp. for 2 h. The mixture was then diluted with EtOAc (50 mL) and washed with saturated aq. Na$_2$CO$_3$ (50 mL) and H$_2$O (50 mL × 2). The organic phase was dried with MgSO$_4$, and the solvent was removed under vacuum to afford the product as a white solid (878 mg, 4.79 mmol, 97% yield). Characterization was in agreement with literature data.[86]

**Compound 18:** Compound **17** (2.44 g, 13.3 mmol) was added portionwise to a suspension of NaH (384 mg, 16.0 mmol) in anhydrous DMF (30 mL), and the mixture was stirred at room temp. for 30 min. Sem-Cl (2.59 mL, 14.6 mmol) was then added, and the reaction mixture was stirred for 1 h. Afterwards, the solution was diluted with EtOAc (60 mL) and washed with aq. HCl (1 N, 60 mL), saturated aq. NaHCO$_3$ (60 mL) and H$_2$O (60 mL × 2). The organic phase was dried with MgSO$_4$, and the solvent was removed under vacuum. Purification by silica gel chromatography (cyclohexane/EtOAc 8:2) afforded the product as a colourless oil (3.30 g, 10.5 mmol, 79% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 6.93 (s, 2 H, pyrrole-*H*), 6.24 (s, 2 H, NC$H_2$O), 3.86 (s, 6 H, COOC$H_3$), 3.56–3.49 (m, 2 H, OC$H_2$CH$_2$Si), 0.90–0.83 (m, 2 H, OCH$_2$C$H_2$Si), –0.07 [s, 9 H, Si(C$H_3$)$_3$] ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 161.18, 128.10, 117.62, 73.56, 65.89, 51.87, 17.94, –1.40 ppm. IR (neat): $\tilde{\nu}$ = 2953, 2865, 1734, 1712, 1529, 1436, 1375, 1295, 1233, 1195, 1170, 1097, 1076, 990, 950, 859, 836, 809, 757, 650, 492, 467, 418 cm$^{-1}$. HRMS (ESI$^+$): calcd. for $[C_{14}H_{23}NO_5Si + Na]^+$ 336.1243; found 336.1251.

**Compound 19:** An aq. LiOH solution (2 N, 20 mL) was added to a solution of compound **18** (1.40 g, 4.47 mmol) in THF (10 mL), and the mixture was stirred at room temp. overnight. It was then cooled down to 0 °C, and conc. aq. HCl was slowly added until the formation of a white precipitate, which was collected by vacuum filtration to afford the desired product (1.20 g, 4.21 mmol, 94% yield). $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 12.96 (s, 2 H, COO*H*), 6.87 (s, 2 H, pyrrole-*H*), 6.16 (s, 2 H, NC$H_2$O), 3.42 (t, $J$ = 7.8 Hz, 2 H, OC$H_2$CH$_2$Si), 0.75 (t, $J$ = 7.8 Hz, 2 H, OCH$_2$C$H_2$Si), –0.10 [s, 9 H, Si(C$H_3$)$_3$] ppm. $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 161.63, 128.58, 116.98, 72.60, 64.75, 17.20, –1.42 ppm. IR (KBr): $\tilde{\nu}$ = 2992, 2954, 2895, 2615, 2559, 1860, 1708, 1668, 1519, 1455, 1418, 1375, 1289, 1245, 1195, 1140, 1105, 1089, 1035, 940, 915, 862, 838, 819, 781, 758, 703, 695, 610, 537, 505, 413 cm$^{-1}$. HRMS (ESI-): calcd. for $[C_{12}H_{19}NO_5Si - H]^-$ 284.0954; found 284.0905. $C_{12}H_{19}NO_5Si$ (285.37): calcd. C 50.51, H 6.71, N 4.91; found C 50.44, H 6.81, N 4.86.

**Compound 25:** TMSCl (8.54 mL, 67.3 mmol) was added dropwise at 0 °C to a solution of 2,2′-oxydiacetic acid (4.10 g, 30.6 mmol) in anhydrous MeOH (50 mL). The solution was then allowed to reach room temp. and stirred overnight. The reaction mixture was then diluted with Et$_2$O (40 mL) and washed with saturated aq. NaHCO$_3$ (2 × 30 mL) and H$_2$O (30 mL). The organic phase was dried with MgSO$_4$, and the solvent was removed under vacuum to afford the product as a white solid (3.72 g, 22.9 mmol, 75% yield). Characterization was in agreement with literature data.[87]

**Supporting Information** (see footnote on the first page of this article): copies of $^1$H and $^{13}$C NMR spectra of all the compounds and elemental analysis certificate.

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