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Zinc(II) Triflate-Catalyzed Divergent Synthesis of Polyfunctionalized Pyrroles

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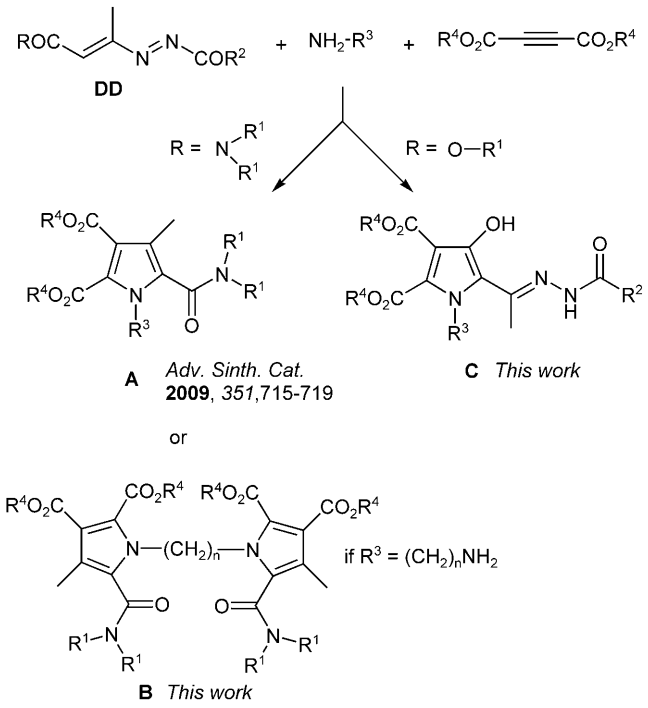
Abstract: The zinc(II) triflate-catalyzed synthesis of highly functionalized pyrroles is described. The sequence involves the preliminary preparation of α-aminohydrazones by Michael addition of primary amines to 1,2-diaza-1,3-dienes. The treatment of these intermediates with dialkyl acetylenedicarboxylates produces α-(*N*-enamino)-hydrazones that are converted into the corresponding pyrroles. The substituents on the carbon in position four of 1,2-diaza-1,3-dienes drive the regioselectivity of the ring closure process. Starting from 4-aminocarbonyl-1,2-diaza-1,3-dienes only dialkyl 1-substituted 5-aminocarbonyl-1*H*-pyrrole-2,3-dicarboxylates are achieved by Lewis acid-catalyzed ring closure. A screening of several Lewis/Brønsted acid catalysts is performed. Zinc(II) triflate is the most efficient catalyst. Under similar reaction conditions, employing 4-alkoxycarbonyl-1,2-diaza-1,3-dienes, only 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates are synthesized. These latter reactions can be accomplished regioselectively also in one pot. Using 4-aminocarbonyl-1,2-diaza-1,3-dienes, diamines and dialkyl acetylenedicarboxylates the sequence provides the corresponding α,ω-di(*N*-pyrrolyl)alkanes.

Keywords: alkynes; 1,2-diaza-1,3-dienes; Lewis acids; Michael addition; pyrroles

Introduction

Pyrroles continue to draw a lot of attention from the scientific community due to their prevalence in natural products and wide range of biological and materials science applications.[1,2] Pyrroles can be found in immunosuppressants,[3a] antitumor agents,[3b] and anti-inflammatory agents.[3c] Within these large classes of relevant products, tetrasubstituted pyrroles are extremely important, displaying antibacterial, antiviral, anticonvulsant and antioxidant activities as well as inhibiting cytokine-mediated diseases.[4] 3-Hydroxypyrroles are employed as synthetic ligands in the shape-selective recognition of base pairs in the DNA sequence.[5] Similarly, polypyrroles are of growing relevance in material science, non-linear optics, and supramolecular chemistry as molecular sensors and devices.[6–9] As a consequence, much attention has been paid to their preparation by classical methods such as the Knorr,[10] Hantzsch,[11] and Paal–Knorr[12] syntheses. However, these approaches usually present significant limitations in terms of substituents that can be introduced, the substitution pattern, or regioselectivity. Several recent variations in the formation of pyrrole rings are based on metal-catalyzed reactions[13] and catalytic multicomponent coupling methodologies[14] which can improve usefully the classical synthetic approaches.

We have demonstrated that the reactions between 1,2-diaza-1,3-dienes (DDs) and carbonyl compounds[15] or enol silyl derivatives[16] represent useful and convenient entries to 1-aminopyrroles. More recently, we have introduced a new and flexible Knorr-related strategy for the construction of amply functionalized pyrroles **A** (Scheme 1).[17] The typical Knorr approach utilizes α-amino ketones and carbonyl derivatives containing an activated methylene group as starting materials.[10] A variation of this synthesis implicates the use of alkynes as reagents rather than carbonyl compounds.[18] In our methodology, the α-amino ketones are replaced with α-aminohydrazones. The advantages of this technique are, first of



Scheme 1. Different pyrroles obtained from DDs, amines and dialkyl acetylenedicarboxylates.

all, the easiness of the preparation of a wide range of different α-aminohydrazones. Moreover, the latter substrates are solids that are appreciably more stable to storage and handling than α-amino ketones. In fact, no self-condensation of α-aminohydrazones has been observed. Furthermore, since with this methodology the "construction" of the heterocyclic structure requires the assembly of three building blocks, it is possible to widely plan *ab initio* the substituents of the pyrroles by changing one or more starting materials.

Herein, we report full details of these studies. With regard to our preliminary communication, the scope considerably extends the applicability of this protocol, involving both diamines and different substituted DDs. In this way it was possible to obtain new bispyrroles **B** through a double process, or different and interesting hydroxypyrroles **C** by means of distinct and complete chemoselectivity in the heterocyclization process (Scheme 1).

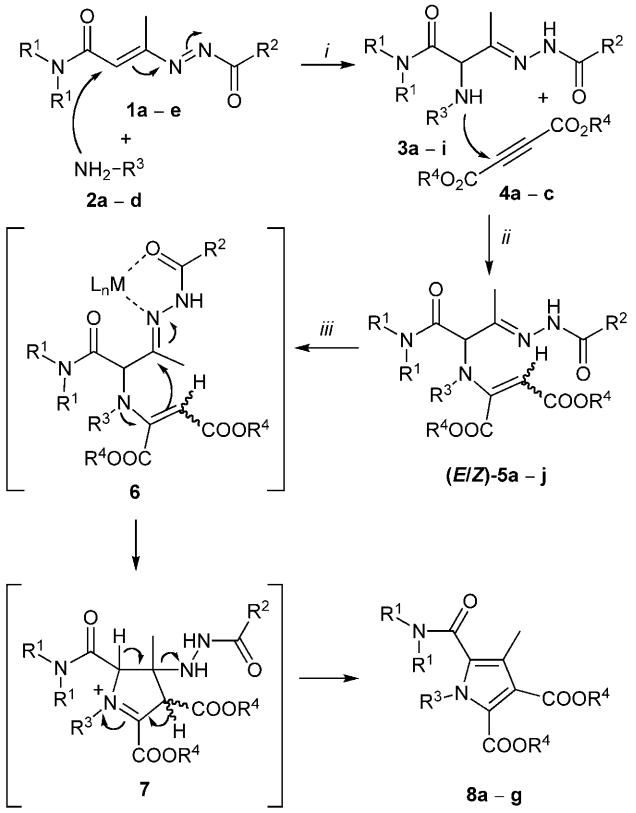
As regards to the synthesis of the hydroxypyrroles **C**, a novel tandem reaction sequence was also developed whereby sequential transformations can be performed without isolation or purification of intermediates in a single-pot with minimal work-up.

Results and Discussion

4-Aminocarbonyl DDs **1a–e** readily react with primary amines **2a–d** in tetrahydrofuran at room temperature in the case of **1a–c**, **e**, or under reflux for **1d** producing the desired α-aminocarbonyl α-aminohydrazones **3a–i** in high yields. The reaction takes place by means of the nitrogen-nucleophilic attack of **2a–d** to the terminal carbon atom of the azo-ene system of the DDs **1a–e** (Scheme 2, Table 1).[15b,19]

By reacting the α-aminocarbonyl α-aminohydrazones **3a–g** with dialkyl acetylenedicarboxylates **4a–c** in ethanol under reflux, the same nitrogen gives a further nucleophilic attack onto the *sp*-carbon of **4**, producing α-aminocarbonyl α-(*N*-enamino)-hydrazones **5a–j** as *E*/*Z* mixtures in 2–4 h in good yields (Scheme 2, Table 1). The α-aminocarbonyl α-aminohydrazones **3h**, **i** derived from *p*-toluidine **2c**, and *p*-anisidine **2d** do not furnish the corresponding α-aminocarbonyl α-(*N*-enamino)-hydrazones **5**.

Although generally weaker than aliphatic ones, aromatic amines are able to give the 1,4-hydroamination of the azo-ene system of DDs.[20] However, the nucleophilicity of the nitrogen atom in the resulting aminohydrazones **3** could be reduced by the presence of electron withdrawing groups on the α-carbon atom. For this reason, the subsequent nucleophilic attack by this nitrogen atom at the triple bond of alkynes failed.



Scheme 2. Synthesis of α-aminocarbonyl-α-aminohydrazones **3a–i**, α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5a–j** and dialkyl 1-substituted-5-aminocarbonyl-1*H*-pyrrole-2,3-dicarboxylates **8a–g**. *Reaction conditions: i*: THF, room temperature for **1a–c**, **e**; THF, reflux for **1d**; *ii*: EtOH, reflux. *iii*: CH_2Cl_2, reflux, $Zn(OTf)_2$.

Table 1. Yields of the α-aminocarbonyl-α-aminohydrazones **3a–i**, bis-α-aminocarbonyl-α-aminohydrazones **3j–n**, α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5a–j**, bis-α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5k–p**, dialkyl 1-substituted-5-aminocarbonyl-1*H*-pyrrole-2,3-dicarboxylates **8a–g** and α,ω-di(*N*-pyrrolyl)alkanes **8h–k**.

1	R^1	R^2	**2**	R^3	**3**	Yield [%][a]	**4**	R^4	**5**	*E*-isomer, yield [%][b,c]	*Z*-isomer, yield [%][b,c]	**8**	Yield [%][d]
1a	Me	NH_2	**2a**	Cy	**3a**[e]	83	**4a**	Et	**5a**[e]	75	/	**8a**[e]	87
1b	Me	NHPh	**2a**	Cy	**3b**[e]	97	**4a**	Et	**5b**[e]	76	/	**8a**[e]	91
1b	Me	NHPh	**2a**	Cy	**3b**[e]	97	**4b**	Me	**5c**[e]	74	/	**8b**[e]	86
1b	Me	NHPh	**2a**	Cy	**3b**[e]	97	**4c**	*t*-Bu	**5d**[e]	66	/	**8c**[e]	88
1c	Me	3F-NHPh	**2a**	Cy	**3c**[e]	74	**4b**	Me	**5e**[e]	56	/	**8b**[e]	91
1d	Et	NH_2	**2a**	Cy	**3d**	83	**4b**	Me	**5f**	68	/	**8d**	86
1a	Me	NH_2	**2b**	Bn	**3e**[e]	91	**4a**	Et	**5g**[e]	55	19	**8e**[e]	88
1b	Me	NHPh	**2b**	Bn	**3f**[e]	81	**4b**	Me	**5h**[e]	68	25	**8f**[e]	93
1b	Me	NHPh	**2b**	Bn	**3f**[e]	81	**4a**	Et	**5i**[e]	80	14	**8e**[e]	89
1d	Et	NH_2	**2b**	Bn	**3g**[e]	69	**4b**	Me	**5j**[e]	57	28	**8g**[e]	92
1e	Me	O-*t*-Bu	**2c**	4-Me-NHPh	**3h**	96							
1e	Me	O-*t*-Bu	**2d**	3-MeO-NHPh	**3i**	92							
1e	Me	O-*t*-Bu	**2e**	$(CH_2)_3NH_2$	**3j**	74	**4b**	Me	**5k**	46	/	**8h**	54
1e	Me	O-*t*-Bu	**2e**	$(CH_2)_3NH_2$	**3j**	74	**4a**	Et	**5l**	54	/	**8i**	69
1f	Me	OMe	**2e**	$(CH_2)_3NH_2$	**3k**	53	**4a**	Et	**5m**	51	/	**8i**	76
1b	Me	NHPh	**2f**	$(CH_2)_6NH_2$	**3l**[f,g]	85	**4b**	Me	**5n**[f,g]	70	/	**8j**	98
1f	Me	OMe	**2f**	$(CH_2)_6NH_2$	**3m**[g,h]	98	**4a**	Et	**5o**[g,h]	75	/	**8k**	52
1e	Me	O-*t*-Bu	**2f**	$(CH_2)_6NH_2$	**3n**[g,i]	99	**4a**	Et	**5p**[g,i]	76	/	**8k**	56

[a] Yield of the isolated purified compounds **3a–n** based on the DDs **1a–f**.
[b] Yield of the isolated purified compounds (*E*/*Z*) **5a–p** based on the hydrazones **3a–n**.
[c] The *E* and *Z* geometry was assigned on the basis of the vicinal heteronuclear coupling constant between the esteric carbon and the vinylic ^{1}H nucleus.
[d] Yield of the isolated purified compounds **8a–k** based on **5a–p**.
[e] Compound reported in a preliminary paper.[17]
[f] Mixture of diastereoisomers in ratio 96:4.
[g] The diastereoisomers ratios were determined considering the integral values in the ^{1}H NMR spectra.
[h] Mixture of diastereoisomers in ratio 99:1.
[i] Mixture of diastereoisomers in ratio 98:2.

The C=C bond geometry of compounds **5** is determined by NMR measurements, considering the value of vicinal heteronuclear coupling constant between the esteric carbon and the vinylic proton ($^3J_{C,H}$ of *E* isomers 9.3–12.0 Hz, $^3J_{C,H}$ of *Z* isomers 3.4–3.6 Hz).[17] We have observed that the *N*-cyclohexyl α-(*N*-enamino)-hydrazono compounds **5a–f** are only in the *E* forms, while the *N*-benzyl α-(*N*-enamino)-hydrazones **5g–j** are obtained as a mixture of *E*/*Z* isomers (*E* 55–80%, *Z* 14–28%).[17] The X-ray diffraction study of (*E*)-**5h** (Figure 1) unambiguously supports the assigned structure.[21]

We have then explored the conversion of the α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5a–j** into the corresponding pyrroles **8a–g** by acid-catalyzed intramolecular ring closure. Among the different types of the tested Lewis/Brønsted acids,[17] only the Lewis ones exhibit remarkable catalytic activity, and this occurrence is probably due to the chelation effect of the *N*-carbonylhydrazones towards metal catalysts (Scheme 2).[22] The discovered optimized conditions for this conversion require a catalytic amount (20%) of $Zn(OTf)_2$ in dichloromethane under reflux.[17]

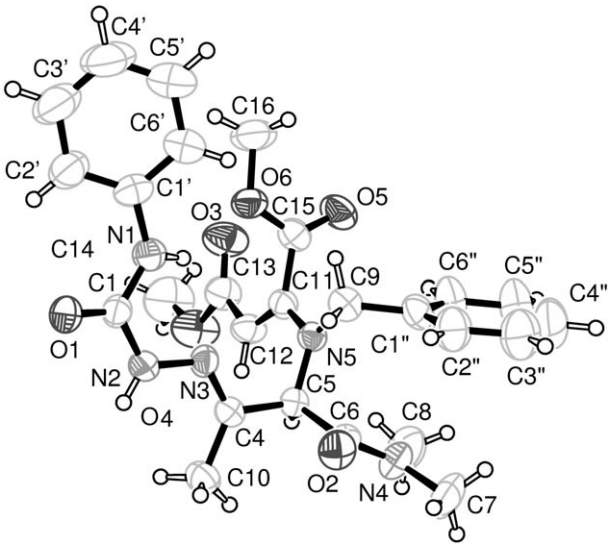
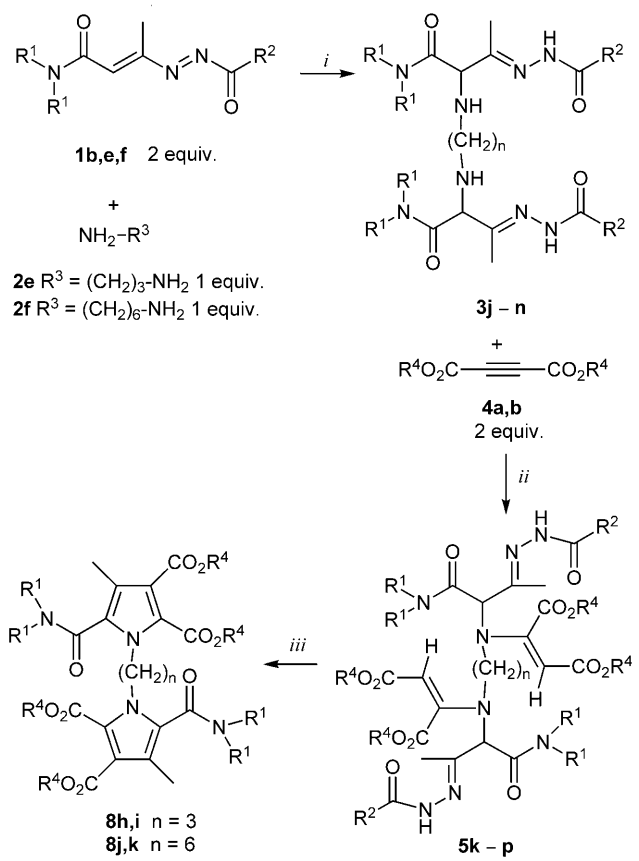


Figure 1. X-ray structure of compound (*E*)-**5h**. Ellipsoids for non-hydrogen atoms enclose 50% probability.



Scheme 3. Synthesis of bis-α-aminocarbonyl-α-aminohydrazones **3j–n**, bis-α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5k–p** and α,ω-di(*N*-pyrrolyl)alkanes **8h–k**. *Reaction conditions: i*: THF, room temperature; *ii*: EtOH, reflux; *iii*: CH_2Cl_2, reflux, $Zn(OTf)_2$.

The reaction proceeds by means of the intramolecular nucleophilic attack of the ene-amino carbon to the hydrazono moiety of the intermediate **6**, activated by coordination with the Lewis acid. This process produces the pyrrolium intermediates **7** that provide the final aromatic dialkyl 1-substituted 5-aminocarbonyl-1*H*-pyrrole-2,3-dicarboxylates **8**, by elimination of the hydrazino moiety (Scheme 2, Table 1).

It is noteworthy that the Knorr equivalent starting α-amino α-amido ketones are not commercially available products and also difficult to prepare by other methods.

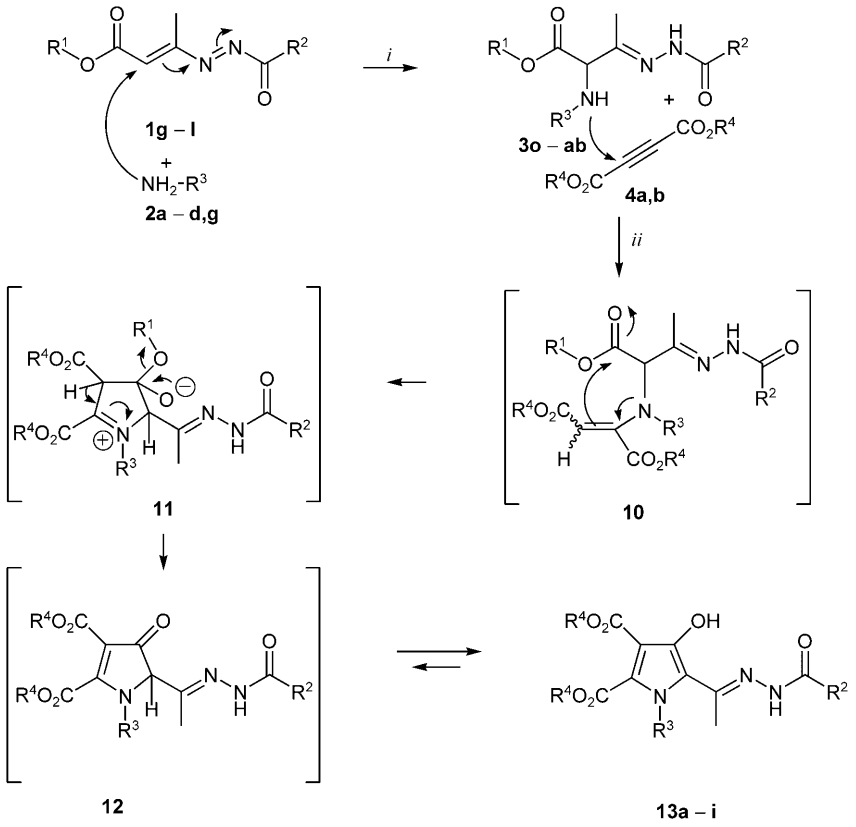
To improve the usefulness of our synthetic protocol and with the aim to prepare new molecules containing two differently spaced pyrrole rings, we have next applied our procedure to diamines **2e**, **f**. The double nucleophilic attack of the 1,4-diaminopropane **2e**, or 1,6-diaminohexane **2f**, to two equivalents of 4-aminocarbonyl DDs **1b**, **e**, **f** furnishes the bis-α-aminocarbonyl-α-aminohydrazones **3j–n**, that in turn, are converted in to the corresponding bis-α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5k–p** by reaction with two equivalents of dialkyl acetylenedicarboxylates **4a**, **b**. The values of the vicinal heteronuclear coupling constant between the esteric carbon and the vinylic proton (9.1–10.8 Hz) indicate that compounds **5k–p** are achieved exclusively as *E* isomer. Their final acid-catalyzed ring closure process produces new and amply functionalized α,ω-di(*N*-pyrrolyl)alkanes **8h–k** (Scheme 3, Table 1). Such compounds can find application in the recognition of the minor groove of DNA,[23] in the construction of conducting polymers,[24] or as chelate ligands in organoplatinum complexes.[25]

Thus, we have extended our investigations to the employ of different DDs **1g–l** in which the amido moiety in position four of the azo-ene system is replaced with an ester group. Also in this case, the 4-alkoxycarbonyl DDs **1g–l** easily react with primary amines **2a–d**, **g** in THF, at room temperature affording the corresponding α-alkoxycarbonyl-α-aminohydrazones **3o–ab** in high yields (Scheme 4, Table 2). By reacting these latter alkoxycarbonyl 1,4-adducts **3o–ab** with the same dialkyl acetylenedicarboxylates **4a**, **b** under the same conditions previously employed for their analogous aminocarbonyl ones **3a–n** (EtOH under reflux) only a complicated reaction mixture is obtained. The hydrazone **3z** and the dimethyl acetylenedicarboxylate **4b** are then chosen to test different solvent and temperature conditions for this reaction. Surprisingly, we have observed that using dichloromethane or chloroform, directly new dimethyl 5-[*N*-(anilinocarbonyl)ethanehydrazonoyl]-1-butyl-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylate **13g** is achieved (Scheme 4).

The structure of **13g** was confirmed by X-ray crystal structure analysis (Figure 2).[26]

The presence of a catalytic amount of Lewis acids does not improve the progress of the reaction, and the best results in terms of yields and reaction times are obtained in chloroform under reflux (see Supporting Information). Having found the optimal conditions, we next examined their extension to other substrates by using the α-alkoxycarbonyl α-aminohydrazones **3o–ab** with diethyl or dimethyl acetylenedicarboxylates **4a**, **b** to test the efficiency of the protocol. In general, the α-alkoxycarbonyl α-aminohydrazones **3q–v**, **y–ab** derived from benzyl **2b**, or *n*-butylamine **2g** give the corresponding dialkyl 5-*N*-(ethanehydrazonoyl)-1-substituted-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i** in 4–14 h without the isolation of the corresponding α-alkoxycarbonyl-α-(*N*-enamino)-hydrazone intermediates **10**. Instead, compounds **3o**, **p**, **w**, **x** derived from relatively hindered primary amines such as the cyclohexylamine **2a**, or from aromatic amines such as *p*-toluidine **2c**, or *p*-anisidine **2d**, do not furnish the pertinent heterocycles (Table 2).

On the basis of these findings, a plausible mechanism for the formation of 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13** involves a double nucleophilic



Scheme 4. Regioselective synthesis of α-alkoxycarbonyl-α-aminohydrazones **3o–ab**, and 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i**. *Multistep procedure: i*: THF, room temperature; *ii*: $CHCl_3$, reflux. *One pot procedure: i*: $CHCl_3$, room temperature; *ii*: $CHCl_3$, reflux.

attack of the amino-nitrogen, initially to the terminal carbon atom of the azo-ene system producing the hydrazones **3o–ab** and then to the *sp* carbon of the dialkyl acetylenedicarboxylate **4** furnishing the non isolable intermediates α-alkoxycarbonyl-α-(*N*-enamino)-hydrazones **10**. The subsequent spontaneous cyclization process occurs by means of intramolecular nucleophilic attack of the ene-amino carbon to the ester function affording the intermediate 3,4-dihydro-2*H*-pyrrolium-3-olates **11**. The loss of an alcohol molecule produces the pyrrol-3-ones **12** that tautomerize to the final 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i**. It is noteworthy that the replacement of an amide with a better electrophile such as an ester group in position four of the starting DD determines a different regioselectivity during the ring closure process. In fact, the nucleophilic attack of the ene-amino carbon happens exclusively onto the hydrazonic functions in the case of α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5a–p** producing 5-aminocarbonyl-1*H*-pyrrole-2,3-dicarboxylates **8a–k** (Scheme 3, Scheme 4), or onto the ester function in the case of the α-alkoxycarbonyl-α-(*N*-enamino)-hydrazono intermediates **10** achieving the 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i** (Scheme 4).

The absence of catalytic activity by the Lewis acids observed in the synthesis of **13a–i** can be accounted for by considering that the chelation effect of the *N*-carbonylhydrazones towards metal catalysts does not involve the ester group responsible as electrophilic site of the ring closure. The aromaticy and the presence of strong hydrogen bonds, as evidenced from the X-ray analysis of compound **13g** (Figure 2), justifies the exclusively presence of the hydroxy-tautomeric form of the pyrrole derivatives **13a–i**.

The synthesis of **13a–i** is also performed in one pot without the isolation of the hydrazono intermediates **3**. In this case, the reaction between 4-alkoxycarbonyl DDs **1g–l** and primary amines **2b**, **g** is carried out in chloroform, at room temperature until the disappearance of DDs **1g–l**, as evidenced by the vanishing of the typical red colour and by TLC analysis. To the mixture 1.2 equivalents of dialkyl acetylenedicarboxylates **4a**, **b** are then added and the crude is refluxed for 4–11 h obtaining directly the desired the 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i** (Scheme 4, Table 2).

Some differences in the construction of the pyrrole skeleton can be observed with respect to our previous syntheses.

Table 2. Yields of α-alkoxycarbonyl-α-aminohydrazones **3o–ab** and dialkyl 5-*N*-(ethanehydrazonoyl)-1-substituted-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i**.

1	R^1	R^2	**2**	R^3	**3**	Yield [%][a]	**4**	R^4	**13**	Yield [%][b]	Yield [%][c]
1g	Et	NH_2	**2a**	Cy	**3o**	98	**4a**	Et			
1g	Et	NH_2	**2a**	Cy	**3o**	98	**4b**	Me			
1h	Et	O-*t*-Bu	**2a**	Cy	**3p**	89	**4b**	Me			
1i	Me	NH_2	**2b**	Bn	**3q**	97	**4a**	Et	**13a**	61	34
1i	Me	NH_2	**2b**	Bn	**3q**	97	**4b**	Me	**13b**	48	37
1g	Et	NH_2	**2b**	Bn	**3r**	97	**4a**	Et	**13a**	52	31
1g	Et	NH_2	**2b**	Bn	**3r**	97	**4b**	Me	**13b**	47	37
1j	Me	NHPh	**2b**	Bn	**3s**	86	**4b**	Me	**13c**	52	38
1k	Et	NHPh	**2b**	Bn	**3t**	85	**4b**	Me	**13c**	53	33
1l	Me	O-*t*-Bu	**2b**	Bn	**3u**	78	**4a**	Et	**13d**	50	34
1l	Me	O-*t*-Bu	**2b**	Bn	**3u**	78	**4b**	Me	**13e**	46	32
1h	Et	O-*t*-Bu	**2b**	Bn	**3v**	98	**4a**	Et	**13d**	50	36
1h	Et	O-*t*-Bu	**2b**	Bn	**3v**	98	**4b**	Me	**13e**	50	32
1g	Et	NH_2	**2c**	4-Me-NHPh	**3w**	96					
1g	Et	NH_2	**2d**	3-MeO-NHPh	**3x**	93					
1j	Me	NHPh	**2g**	*n*-Bu	**3y**	73	**4a**	Et	**13f**	54	31
1j	Me	NHPh	**2g**	*n*-Bu	**3y**	73	**4b**	Me	**13g**	48	34
1k	Et	NHPh	**2g**	*n*-Bu	**3z**	98	**4a**	Et	**13f**	55	38
1k	Et	NHPh	**2g**	*n*-Bu	**3z**	98	**4b**	Me	**13g**	51	36
1l	Me	O-*t*-Bu	**2g**	*n*-Bu	**3aa**	84	**4a**	Et	**13h**	51	33
1l	Me	O-*t*-Bu	**2g**	*n*-Bu	**3aa**	84	**4b**	Me	**13i**	47	35
1h	Et	O-*t*-Bu	**2g**	*n*-Bu	**3ab**	96	**4a**	Et	**13h**	61	39
1h	Et	O-*t*-Bu	**2g**	*n*-Bu	**3ab**	96	**4b**	Me	**13i**	63	42

[a] Yield of the isolated purified compounds **3o–ab** based on the DDs **1g–l**.
[b] Yield of the isolated purified compounds **13a–i** based on the hydrazones **3o–ab**.
[c] Yield of the isolated purified compounds **13a–i** obtained in a one-pot procedure based on the DDs **1g–l**.

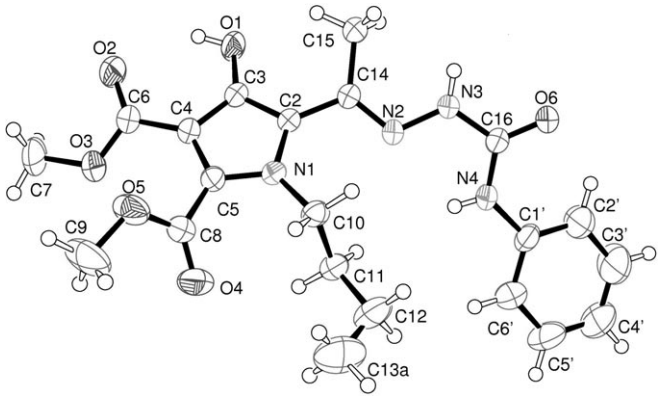


Figure 2. X-ray structure of compound **13g**.

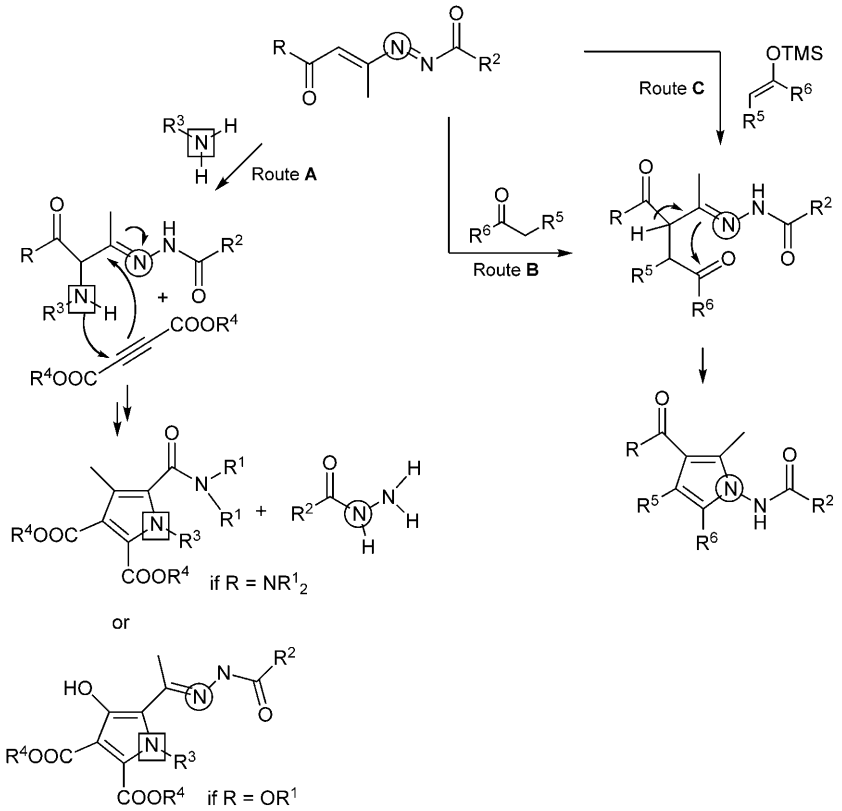
In fact, starting from DDs and carbonyl compounds[15] (Route **B**, Scheme 5) or enol silyl derivatives[16] (Route **C**, Scheme 5), we obtained *N*-substituted-aminopyrroles in which the pyrrole nitrogen is originally situated in the position two of the azo-ene system, while using DDs, primary amines and dialkyl acetylenedicarboxylates, the pyrrole nitrogen derives from the substituted amino reagents **2** (Route **A**, Scheme 5). This fact permits an additional diversification site that can be easily introduced using a variety of amines.

Conclusions

In conclusion, this paper describes a smooth procedure for the preparation of α-aminocarbonyl-α-(*N*-enamino)-hydrazones and amply functionalized pyrroles by reaction between DDs, primary amines and dialkyl acetylenedicarboxylates.

The present investigation has evidenced that the substituents on the carbon in position four of the starting DD drive the regioselectivity of the ring closure process: by using 4-aminocarbonyl DDs, only dialkyl 1-substituted 5-aminocarbonyl-1*H*-pyrrole-2,3-dicarboxylates **8a–g** are achieved, while, starting from 4-alkoxycarbonyl DDs, only dialkyl 5-*N*-(ethanehydrazonoyl)-1-substituted-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i** are produced. The preparation of α,ω-di(*N*-pyrrolyl)alkanes **8h–k** proves that this easy procedure can be successfully employed for further synthetic applications in the construction of more complex systems which are not easily obtainable by other methods.

The advantage of the use of DDs as building blocks in the modelling of pyrroles is the stability and the easy accessibility both of the starting materials as well as of the intermediates. These reactions proceed under mild conditions furnishing interesting new products without complicated work-up procedures. In



Scheme 5. Different approaches for the construction of pyrroles starting from DDs: Route **A** with primary amines and acetylenedicarboxylates; Route **B** with carbonyl compounds; Route **C** with enol silyl derivatives.

particular, the synthesis of the 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates **13a–i** can be conducted also in a one pot mode, avoiding the isolation of the α-aminohydrazone intermediates. Furthermore, all pyrroles here obtained present a large multifunctionality that is difficult to obtain by successive reactions of an unfunctionalized starting skeleton.

Experimental Section

General Remarks

All of the commercially available reagents and solvents were used without further purification. 1,2-Diaza-1,3-dienes **1a–l** were synthesized as a mixture of *E/Z* isomers as previously reported.[27] Solvents were purchased and used without further purification with the exception of THF which was distilled over sodium hydroxide. Melting points were determined on open capillary tubes. Mass spectra EI were made at an ionizing voltage of 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.32 MHz, respectively. All NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm). Proton and carbon spectra were referenced internally to solvent signals, using values of $\delta =$ 2.49 ppm for proton (middle peak) and $\delta = 39.50$ ppm for carbon (middle peak) in DMSO-d_6 and $\delta = 7.26$ ppm for proton and $\delta = 77.00$ ppm for carbon (middle peak) in $CDCl_3$. Coupling constants (J) are given in Hz; the multiplicities were obtained using 135° and 90° DEPT experiments to aid in assignment. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad. All the NH, OH and NH_2 exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μ for column chromatography. Precoated silica gel plates 0.25 mm were employed for analytical thin-layer chromatography and silica gel 60 Å (35–70 μm) for column chromatography. All new compounds shown satisfactory elemental analysis ($C \pm 0.35$; $H \pm 0.30$; $N \pm 0.30$). The chemical name abbreviations of the substituents used are as follows: Me, methyl; Et, ethyl; *t*-Bu, *tert*-butyl; Bn, benzyl; Cy, cyclohexyl; Ph, phenyl; *n*-Bu, normal-butyl. The nomenclature was generated using ACD/IUPAC Name (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON (Canada).

General Procedure for the Synthesis of α-Aminocarbonyl-α-aminohydrazones 3a–i, Bis-α-aminocarbonyl-α-aminohydrazones 3j–n and α-Alkoxycarbonyl-α-aminohydrazones 3o–ab

For the preparation of α-aminocarbonyl-α-aminohydrazones **3a–i** and α-alkoxycarbonyl-α-aminohydrazones **3o–ab**: to a

solution of the 4-aminocarbonyl DDs **1a–e** or 4-alkoxycarbonyl DDs **1g–l** as a mixture of *E*/*Z* isomers[27] (1.0 mmol) in tetrahydrofuran (10 mL), the cyclohexylamine **2a**, the benzylamine **2b**, the *p*-toluidine **2c**, the *p*-anisidine **2d**, or the *n*-butylamine **2g**, (1.0 mmol) was added. The reaction was allowed to proceed under magnetic stirring at room temperature for 2–4 h in the case of **1a–c**, **e**, **g–l** or under reflux for 4 h in the case of **1d**, until the disappearance of the reagents (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **3a–i**, **o–ab** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate (see Supporting Information). With regard to the synthesis of the bis-α-aminocarbonyl-α-aminohydrazones **3j–n**, to a solution of the 4-aminocarbonyl DDs **1b**, **e**, **f** as a mixture of *E*/*Z* isomers[27] (2.0 mmol) in tetrahydrofuran (15 mL), the 1,4-diaminopropane **2e**, or 1,6-diaminohexane **2f** (1.0 mmol) was added dropwise. The reaction was allowed to proceed under magnetic stirring at room temperature for 2–4 h, until the disappearance of the reagents (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **3j–n** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate (see Supporting Information).

3-[(Aminocarbonyl)hydrazono]-2-(cyclohexylamino)-*N*,*N*-dimethylbutanamide (3a): mp: 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 0.77$–0.94 (m, 6H), 1.23–1.29 (m, 1H), 1.35–1.41 (m, 2H), 1.46–1.52 (m, 1H), 1.54 (s, 3H), 1.93–1.99 (m, 1H), 2.65 (s, 3H), 2.72 (s, 3H), 2.83 (brs, 1H), 3.99 (s, 1H), 5.86 and 6.21 (2 brs, 2H), 9.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 12.4$ (q), 24.7 (t), 24.8 (t), 26.0 (t), 33.1 (t), 33.4 (t), 36.0 (q), 36.9 (q), 54.7 (d), 61.8 (d), 147.9 (s), 159.0 (s), 170.6 (s) ppm; IR (nujol): $\nu_{max} =$ 3422, 3374, 3265, 3204, 1776, 1732, 1676 cm^{-1}; MS: *m/z* (%) = 283 (M^+) (16), 238 (74), 211 (100), 167 (31), 152 (11); anal. calcd. for $C_{13}H_{25}N_5O_2$ (283.37): C 55.10, H 8.89, N 24.71; found: C 55.21, H 8.94, N 24.59.

1,18-Dianilino-*N*,*N*,*N*′,*N*′,4,15-hexamethyl-1,18-dioxo-2,3,6,13,16,17-hexaazaoctadeca-3,15-diene-5,14-dicarboxamide (3l): mp: 165–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): $\delta = 1.23$–1.29 (m, 4H), 1.32–1.42 (m, 4H), 1.76 (s, 6H), 2.35–2.43 (m, 4H), 2.85 (s, 6H), 2.98 (brs, 2H), 3.07 (s, 6H), 4.27 (s, 2H), 6.99 (t, $J = 7.6$ Hz, 2H), 7.29 (t, $J = 7.6$ Hz, 4H), 7.55 (d, $J = 8.4$ Hz, 4H), 8.73 (s, 2H), 9.56 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): $\delta = 12.1$ (q), 26.2 (t), 29.2 (t), 34.8 (q), 36.0 (q), 46.8 (t), 63.8 (d), 118.6 (d), 121.8 (d), 128.1 (d), 138.5 (s), 147.8 (s), 152.9 (s), 169.5 (s); IR (nujol): $\nu_{max} = 3422$, 3374, 3265, 3204, 1776, 1732, 1676 cm^{-1}; MS: *m/z* (%) = 283 (M^+) (16), 238 (74), 211 (100), 167 (31), 152 (11); anal. calcd. for $C_{32}H_{48}N_{10}O_4$ (283.37): C 60.36, H 7.60, N 22.00; found C 60.48, H 7.54, N 21.89.

Ethyl 3-[(aminocarbonyl)hydrazono]-2-(cyclohexylamino)butanoate (3o): mp: 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 1.02$–1.14 (m, 8H), 1.52–1.75 (m, 5H), 1.83 (s, 3H), 2.26–2.33 (m, 1H), 2.60 (brs, 1H), 4.01 (s, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 5.98 (brs, 2H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 13.1$ (q), 14.0 (q), 24.5 (t), 25.7 (t), 33.0 (t), 54.7 (d), 61.2 (t), 64.6 (d), 147.0 (s), 158.4 (s), 171.5 (s); IR (nujol): $\nu_{max} = 3431$, 3389, 3226, 1782, 1751, 1703 cm^{-1}; MS: *m/z* (%) = 284 (M^+) (3), 239 (13), 211 (29), 167 (100), 151 (75); anal. calcd. for $C_{13}H_{24}N_4O_3$ (284.35): C 54.91, H 8.51, N 19.70; found C 54.80, H 8.54, N 19.58.

General Procedure for the Synthesis α-Aminocarbonyl-α-(*N*-enamino)-hydrazones 5a–j and Bis-α-aminocarbonyl-α-(*N*-enamino)-hydrazones 5k–p

To a solution of the α-aminocarbonyl α-aminohydrazones **3a–i** (1.0 mmol) in ethanol (20 mL) a stoichiometric amount of the dialkyl acetylenedicarboxylates **4a–c** (1.0 mmol) was added. The reaction mixture was refluxed for 2–4 h until the complete disappearance of the reagents (monitored by TLC). Starting from compounds **3h**, **i**, no reactions were revealed. In the other cases, the solvent was then evaporated under reduced pressure. The products **5a–j** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate. In the case of the α-(*N*-enamino)-hydrazones **5g–j** derived from the benzylamine **2b**, it was possible to separate the *E*, *Z* isomers, while for **5a–f**, derived from the cyclohexylamine **2a**, we have observed the exclusive formation of the *E* isomer (see Supporting Information). With regard to the synthesis of bis-α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5k–p**, to a solution of the bis-α-aminocarbonyl-α-aminohydrazones **3j–n** (1.0 mmol) in ethanol (20 mL) two equivalents of the dialkyl acetylenedicarboxylates **4a**, **b** (2.0 mmol) were added. The reaction mixture was refluxed for 4–7 h until the complete disappearance of the reagents (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **5k–p** are purified by silica gel chromatography (elution mixture: ethyl acetate) and they were crystallized from ethyl acetate (see Supporting Information).

Diethyl (2*E*)-2-({2-[(aminocarbonyl)hydrazono]-1-[(dimethylamino)carbonyl]propyl}(cyclohexyl)amino)but-2-enedioate (5a): mp: 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 0.97$–1.23 (m, 9H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.47–1.54 (m, 2H), 1.71–1.81 (m, 2H), 1.90 (s, 3H), 2.98 (s, 3H), 2.93 (s, 3H), 3.23–3.29 (m, 1H), 3.89–4.06 (m, 2H), 4.18–4.32 (m, 2H), 4.77 (s, 1H), 5.13 (s, 1H), 5.58 and 5.86 (2 brs, 2H), 9.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta =$ 13.8 (q), 14.2 (q), 25.4 (t), 25.8 (t), 26.0 (t), 30.9 (t), 31.1 (t), 35.9 (t), 37.0 (t), 59.1 (t), 61.4 (d), 61.8 (t), 64.0 (d), 91.2 (d), 144.0 (s), 153.1 (s), 157.8 (s), 166.0 (s), 167.4 (s), 167.8 (s); IR (nujol): $\nu_{max} = 3424$, 3200, 1741, 1727, 1704, 1685, 1658 cm^{-1}; MS: *m/z* (%) = 453 ($M^+ + 1$) (1), 408 (3), 378 (48), 349 (11), 334 (41), 306 (8), 262 (100), 239 (22), 193 (53); anal. calcd. for $C_{21}H_{35}N_5O_6$ (453.53): C 55.61, H 7.78, N 15.44; found C 55.72, H 7.91, N 15.51.

Tetramethyl (2*E*,2*E*′)-2,2′-[hexane-1,6-diylbis({2-[(anilinocarbonyl)hydrazono]-1-[(dimethylamino)carbonyl]propyl}imino)]bisbut-2-enedioate (5n): mp: 164–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): $\delta = 1.15$–1.30 (m, 8H), 2.03 (s, 6H), 2.96 (s, 6H), 3.00 (s, 6H), 3.17–3.30 (m, 4H), 3.65 (s, 6H), 3.90 (s, 6H), 4.75–4.83 (m, 4H), 7.01–7.30 (m, 4H), 7.44 (d, $J = 7.2$ Hz, 4H), 8.12 (s, 2H), 9.72 and 9.75 (2brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): $\delta = 14.0$ (q), 15.2 (q), 26.5 (t), 35.9 (q), 37.0 (q), 48.7 (t), 50.9 (q), 53.1 (q), 65.9 (d), 87.5 (d), 119.0 (d), 123.1 (d), 128.8 (d), 137.9 (s),143.0 (s), 153.8 (s), 154.2 (s), 166.0 (s), 166.4 (s), 167.6 (s); IR (nujol): $\nu_{max} = 3365$, 3276, 1773, 1735, 1712, 1687 cm^{-1}; MS: *m/z* (%) = 666 (13), 594 (7), 522 (35), 463

(67), 404 (52), 379 (82), 320 (100), 261 (34); calcd. for $C_{44}H_{60}N_{10}O_{12}$ (921.01): C 57.38, H 6.57, N 15.21; found C 57.32, H 6.64, N 15.16.

General Procedure for the Synthesis of Dialkyl 1-Substituted-5-aminocarbonyl-1*H*-pyrrole-2,3-dicarboxylates 8a–g and α,ω-Di(*N*-pyrrolyl)alkanes 8h–k

To a solution of the α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5a–j** (1.0 mmol) in dichloromethane (15 mL), a catalytic amount of $Zn(OTf)_2$ (0.2 mmol) was added. The reaction mixture was refluxed for 0.5–0.6 h, until the disappearance of the starting materials (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **8a–g** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate (see Supporting Information). To a solution of the bis-α-aminocarbonyl-α-(*N*-enamino)-hydrazones **5k–p** (1.0 mmol) in dichloromethane (20 mL), a catalytic amount of $Zn(OTf)_2$ (0.4 mmol) was added. The reaction is refluxed for 2–3 h, until the disappearance of the starting materials (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **8h–k** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from ethyl acetate (see Supporting Information).

Diethyl 1-cyclohexyl-5-[(dimethylamino)carbonyl]-4-methyl-1*H*-pyrrole-2,3-dicarboxylate (8a): mp: 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.12–1.26 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.58–1.65 (m, 1H), 1.73–1.82 (m, 3H), 1.89–1.96 (m, 2H), 2.07 (s, 3H), 2.94 (s, 3H), 3.10 (s, 3H), 4.06–4.15 (m, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 10.2 (q), 13.9 (q), 14.2 (q), 24.9 (t), 26.0 (t), 26.3 (t), 31.3 (t), 33.2 (t), 34.7 (q), 38.1 (q), 59.8 (d), 60.1 (t), 61.6 (t), 116.1 (s), 118.8 (s), 126.7 (s), 127.7 (s), 162.9 (s), 164.4 (s), 164.5 (s); IR (nujol): ν_{max} = 1745, 1730, 1640 cm^{-1}; MS: *m/z* (%) = 378 (M^+) (45), 306 (100), 260 (71), 233 (100), 188 (67), 159 (100): anal. calcd. for $C_{20}H_{30}N_2O_5$ (378.46): C 63.47, H 7.99, N 7.40; found C 63.29, H 8.04, N 7.51.

Tetramethyl 1,1′-hexane-1,6-diylbis{5-[(dimethylamino)-carbonyl]-4-methyl-1*H*-pyrrole-2,3-dicarboxylate} (8j): mp: 142–144 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 1.02–1.26 (m, 4H), 1.41–1.56 (m, 4H), 2.04 (s, 6H), 2.84 (s, 6H), 2.95 (s, 6H), 3.75 (s, 6H), 3.83–3.92 (m, 2H), 3.96 (s, 6H), 4.04–4.13 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 9.8 (q), 24.6 (t), 27.6 (t), 33.8 (q), 37.3 (q), 45.5 (t), 51.4 (q), 53.2 (q), 116.5 (s), 117.5 (s), 125.2 (s), 128.5 (s), 160.4 (s), 161.1 (s), 163.7 (s); IR (nujol): ν_{max} = 3393, 3243, 1782, 1721, 1702, 1674 cm^{-1}; MS: *m/z* (%) = 618 (M^+) (6), 559 (12), 486 (38), 456 (67), 428 (52), 355 (100), 297 (43), 238 (53); anal. calcd. for $C_{30}H_{42}N_4O_{10}$ (618.68): C 58.24, H 6.84, N 9.06; found C 58.42, H 6.78, N 8.95.

General Procedure for the Synthesis of 4-Hydroxy-1*H*-pyrrole-2,3-dicarboxylates 13a–i

To a solution of the α-alkoxycarbonyl-α-aminohydrazones **3o–ab** (1.0 mmol) in chloroform (20 mL) a stoichiometric amount of the dialkyl acetylenedicarboxylates **4a**, **b** (1.0 mmol) was added. The reaction mixture was refluxed for 5.0–7.0 h until the complete disappearance of the reagents (monitored by TLC). Starting from compounds **3o**, **p**, **w**, **x** no reactions were revealed. In the other cases, the solvent was then evaporated under reduced pressure. The products **13a–i** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from diethyl ether (see Supporting Information).

General Procedure for the One-Pot Synthesis 4-Hydroxy-1*H*-pyrrole-2,3-dicarboxylates 13a–i

To a solution of 4-alkoxycarbonyl DDs **1g–l** as a mixture of *E*/*Z* isomers[27] (1.0 mmol) in chloroform (10 mL), the benzylamine **2b** (1.0 mmol) or the *n*-butylamine **2g** was added. The reaction was allowed to proceed under magnetic stirring at room temperature for 2–4 h, until the disappearance of the reagents (monitored by TLC). To the mixture 1.2 equivalents of dialkyl acetylenedicarboxylates **4a**, **b** were then added and the crude solution was refluxed for 4–11 h until the complete disappearance of the reagents (monitored by TLC). The solvent was then evaporated under reduced pressure. The products **13a–i** were purified by silica gel chromatography (elution mixture: ethyl acetate/cyclohexane) and they were crystallized from diethyl ether (See Supporting Information).

Diethyl 5-[*N*-(aminocarbonyl)ethanehydrazonoyl]-1-benzyl-4-hydroxy-1*H*-pyrrole-2,3-dicarboxylate (13a): mp: 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.13 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.19 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 4.83 (brs, 2H), 5.48 (s, 2H), 6.95 (d, J = 8.4 Hz, 2H), 7.20–7.30 (m, 3H), 8.42 (s, 1H), 8.51 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.8 (q), 14.2 (q), 14.6 (q), 50.0 (t), 60.8 (t), 61.8 (t), 102.9 (s), 115.9 (s), 125.6 (s), 127.2 (d), 128.6 (s), 128.8 (s), 138.0 (s), 139.7 (s), 147.7 (s), 157.3 (s), 161.4 (s), 166.1 (s); IR (nujol): ν_{max} = 3381, 3278, 3167, 1737, 1669 cm^{-1}; MS: *m/z* (%) = 416 (M^+) (4), 370 (40), 343 (57), 325 (62), 252 (100), 207 (32), 179 (41), 134 (16), 106 (83); anal. calcd. for $C_{20}H_{24}N_4O_6$ (416.43): C 57.68, H 5.81, N 13.45; found C 57.76, H 5.75, N 13.49.

Supporting Information

Experimental details and spectroscopic characterization of all compounds are given in the Supporting Information.

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