$FeCl_3$-catalyzed formal [3 + 2] cyclodimerization of 4-carbonyl-1,2-diaza-1,3-dienes

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Abstract: Substituted 1-aminopyrroles are easily accessible by means of iron-catalyzed cascade reaction that requires as starting materials the solely 1,2-diaza-1,3-dienes. Mechanistically, the formal [3 + 2] cyclodimerization is hypothesized to proceed through a [4 + 2] cyclodimerization of 4-substitued 1,2-diaza-1,3-dienes followed by intramolecular ring closure to fused diaziridin-pyrrolines whose successive opening results in a ring contraction process with consequent generation of the pyrrole moiety. The presence of activated hydrogen in the terminal position of the azo-enic moiety is crucial for the success of the synthesis.

Introduction

Pyrroles are one of the most relevant heterocyclic scaffolds that play a prominent role in different branches of chemistry such as biochemistry,[1] medicinal chemistry and drug discovery, or industrial chemistry where they represent useful building blocks in the preparation of polymers,[2] dyes,[3] agrochemicals,[4] corrosion inhibitors,[5] and other widespread chemical products. Few examples are sufficient to fully understand the importance and the strategic role of these simple aromatic nitrogen heterocycles in several biological processes: they are a key structural motif in porphyrins that are the core of chlorophyll, heme, vitamin B12, or bile pigments like bilirubin and biliverdin, as well as they are present in several natural derivatives such as sceptrin,[6] prodigiosin,[7] lamellarin,[8] ryanodine,[9] halitulin.[10] The pyrrole core is also common in natural derivatives of marine origin so much that the definition "marinopyrroles" has been coined. Some of these compounds exhibit strong activity against methicillin-resistant bacteria,[11] and anticancer activity.[12] In addition to the natural products, several pyrroles of synthetic origin display interesting biological activities, as evidenced by the considerable number of pyrrole-derived drugs. Some examples include Atorvastatine, one of the top-selling branded drugs employed as antihyperlipidemic,[13] Sunitinib, used for the treatment of some cancers,[14] Pyrvinium, an efficient anthelmintic agent with promising anticancer activity,[15] Tolmetin, an important non-steroidal anti-inflammatory drug,[16] just to mention a few of the most representative (Figure 1). Then, the high abundance in natural products,[17] the several therapeutic applications,[18] the high request from different areas of the industrial chemistry put the pyrroles into the center of attention of a vast audience of chemists and the development of innovative synthetic methods devoted to their preparation is a very active field of the heterocyclic researches.[19]

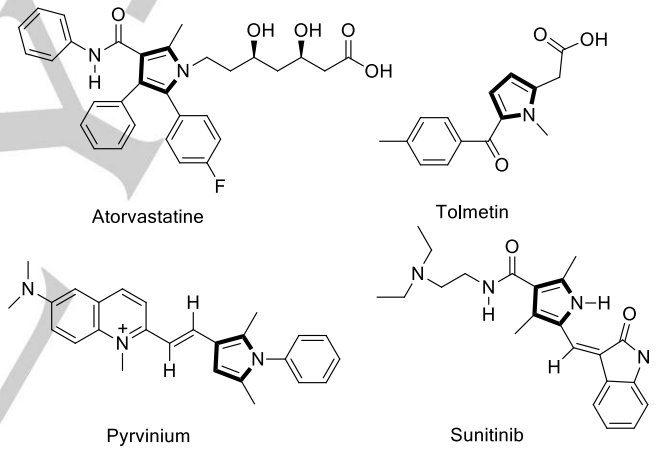


Figure 1. Some representative examples of pyrrole-containing drugs.

However, despite these numerous efforts, the synthetic approaches dedicated to the preparation of fully substituted symmetrical pyrroles remain represented only by sporadic examples.[20] In the design of an innovative synthetic methodology, a primary target to be achieved consists in the development of simple and efficient procedures able to quickly assemble the desired structure. These aspects are correlated to the concept of the "step economy", concerning the development of processes that require the least number of manipulations. The reduction to the fewest number of synthetic steps can translate into both economic and environmental benefits. Avoiding the isolation and the purification of the reaction intermediates, the advantages obtained concern both a saving of time and labor as well as a lower waste of materials such as silica and solvents.[21] Furthermore, procedures that require simple work-up are amenable to automation and/or easily adapted to an eventual scale-up. Over the years, the 1,2-diaza-1,3-butadienes[22] (DDs), also called azoalkenes, have proven to be versatile and multifaceted starting materials for the construction of several

heterocyclic frameworks by reactions with nucleophilic agents.[23] In particular, DDs are excellent precursors of pyrroles, and several synthetic pathways with different partners such as enamines,[24] β-dicarbonyl compounds,[25] β-ketosulphones,[26] α-oxophosphoranes,[27] activated nitriles,[28] aldehydes,[29] silyl enol ethers,[30] Danishefsky's dienes,[31] or 1,3-bis(silyloxy)-1,3-butadienes[32] have been developed. DDs can also react with themselves providing tetrahydropyridazines, as reported in two quite recently published papers. In the first one, Lu and Zhou described an elegant catalyst-free self [4 + 2] cycloaddition of *in situ*-generated azoalkenes,[33] while in his interesting work, Suryavanshi reported a [4 + 2] cyclodimerization of *in situ*-generated DDs followed by a C−N bond cleavage (Figure 2a).[34] Both reactions use α-halohydrazones as starting reagents which, by basic treatment, generate the corresponding 4-unsubstituted DDs. These latter compounds are characterized by poor stability and aptitude to give side reactions. Usually 4-unsubstituted DDs cannot be stored even at low temperatures and for this reason they are generated *in situ*. On the contrary, the alkoxy- or the amino-4-carbonyl DDs do not manifest in the time the tendency to give the formation of by-products, usually they require a simple and lean work-up and, last but not least, their chemical behavior is often different from the one exhibited by the 4-unsubstituted DDs. So, motivated by these considerations, we tried to adapt to the 4-substituted DDs the methodologies previously reported by Lu and Zhou,[33] in an attempt to synthesize the corresponding new alkoxy- or amino-4-carbonyl substituted pyridazines. With our great surprise and pleasure, we observed that, in this case, only the formation of fully substituted symmetrical pyrroles occurred through an unexpected formal [3 + 2] cyclodimerization (Figure 2b). Herein, we report full details of this synthesis.

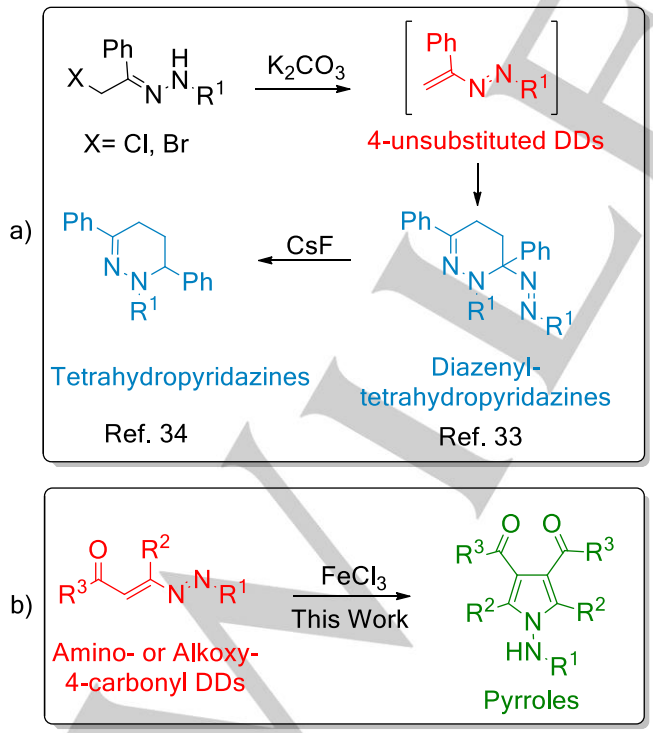
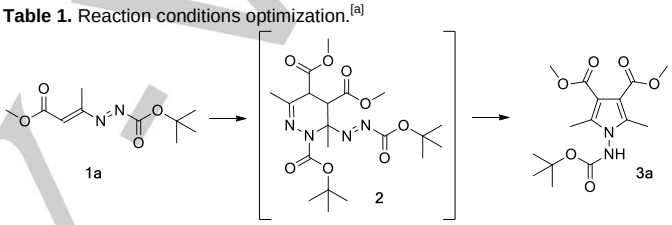


Figure 2. Different regioselectivities in the cyclodimerization of 4-unsubstituted-DDs or alkoxy-/amino-4-carbonyl DDs.

Results and Discussion

Our research activities started with the investigation on the behavior of 4-substituted-DDs employing the 1-*tert*-butyl 3,4-dimethyl 1,2-diaza-1,3-diene-1,4-dicarboxylate **1a** as model (Table 1). Initially, according to the procedure reported by Lu and Zhou,[33] or by Suryavanshi,[34] the DD **1a** was treated with potassium carbonate in dichloromethane (DCM). Unfortunately, even refluxing the reaction, the desired tetrahydropyridazine **2** was not formed (Table 1, entry 1) and only a little amount of a degradation product as the corresponding α-oxo-hydrazone was isolated.[35] Since the basic treatment did not provide results, **1a** was successively refluxed in THF, but also in this case, only a little amount of degradation products were formed (Table 1, entry 2). On the other hand, it is well known that Lewis acids are able to catalyze the Diels-Alder reactions,[36] so as further attempt, to a solution of **1a** in dichloromethane at room temperature a catalytic amount (10%) of copper dichloride was added (Table 1, entry 3).

Table 1. Reaction conditions optimization.[a]



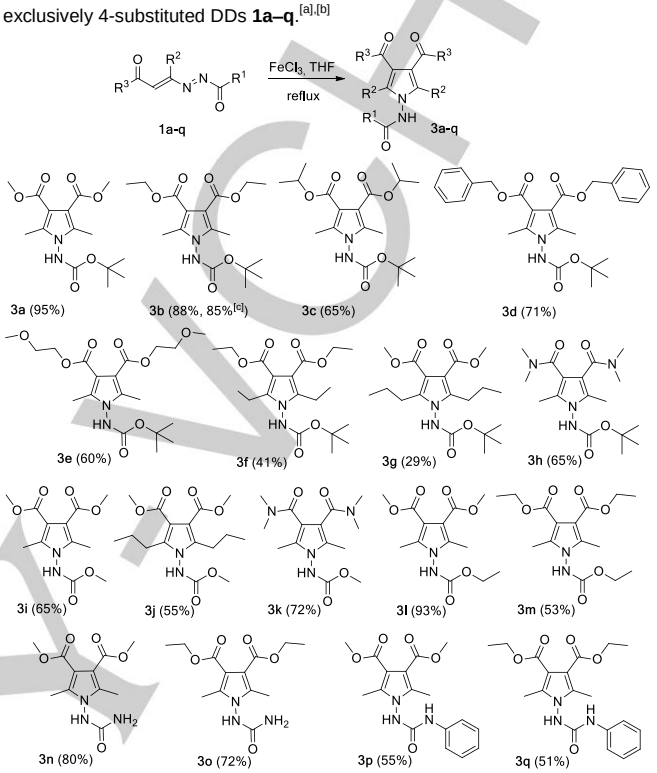
Entry	Solvent	Temperature	Catalyst	Catalyst (%)	Time (h)	Yield **3a** (%)[b]
1[c],[d]	CH_2Cl_2	reflux	K_2CO_3	100	48.0	0
2	THF	reflux	-	-	48.0	0
3[e]	CH_2Cl_2	r.t.	$CuCl_2$	10	72.0	32
4[f]	CH_2Cl_2	r.t.	$CuSO_4$	10	72.0	0
5[e]	CH_2Cl_2	r.t.	$Cu(OTf)_2$	10	72.0	36
6[e]	CH_2Cl_2	r.t.	$Bi(OTf)_3$	10	72.0	18
7[e]	CH_2Cl_2	r.t.	$Yb(OTf)_3$	10	72.0	14
8[e]	CH_2Cl_2	r.t.	$ZnBr_2$	10	72.0	5
9[e]	CH_2Cl_2	r.t.	$TiCl_3$	10	72.0	14
10[e]	CH_2Cl_2	r.t.	$SmCl_3$	10	72.0	17
11[e]	CH_2Cl_2	r.t.	$FeCl_3$	10	72.0	41
12[e]	CH_2Cl_2	r.t.	$FeCl_3 \cdot 6H_2O$	10	72.0	24
13[e]	CH_2Cl_2	reflux	$FeCl_3$	10	72.0	43
14[e]	$CHCl_3$	r.t.	$FeCl_3$	10	72.0	7
15[e]	$CHCl_3$	reflux	$FeCl_3$	10	72.0	28
16[e],[g]	CH_3CN	r.t.	$FeCl_3$	10	72.0	trace
17[e],[g]	CH_3CN	reflux	$FeCl_3$	10	72.0	trace
18[e]	THF	r.t.	$FeCl_3$	10	72.0	50
19[e]	THF	reflux	$FeCl_3$	10	72.0	71
20	THF	reflux	$FeCl_3$	20	24.0	63
21[e]	THF	reflux	$FeCl_3$	5.0	72.0	69
22[e]	THF	reflux	$FeCl_3$	2.5	72.0	48
23[h]	**THF**	**reflux**	**$FeCl_3$**	**5.0+5.0**	**24.0**	**95**

[a] Unless otherwise stated, the reactions were conducted on 0.5 mmol of DD **1a** in 5.0 mL of solvent. [b] Isolated yields of **3a**. [c] 0.46 mmol of **1a** were recovered unreacted. [d] 0.027 mmol of α-oxo-hydrazone were isolated.[34] [e] DD **1a** was not fully converted. [f] The reaction does not occur and a only little amount of α–oxo-hydrazone was obtained.[34]. [g] TLC analysis reveals a complicated reaction profile where only traces of **3a** were detected. [h] To a first

amount of 5% of $FeCl_3$ at the beginning of the reaction, a second portion (5%) was added after 6.0 h and then the reaction was further refluxed for 18.0 h.

In this case, the reaction partially proceeded and its profile was quite complicated as revealed by a TLC analysis. By chromatography, it was possible to recover only two products: the first was detected as the α-oxo-hydrazone[35] while the second one, with our great surprise and pleasure, was identified as the 1-aminopyrrole **3a**. The expected tetrahydropyridazine **2** instead was not isolated. This result has encouraged us to continue our researches and several Lewis acids such as $CuSO_4$, $Cu(OTf)_2$, $Bi(OTf)_3$, $Yb(OTf)_3$, $ZnBr_2$, $TiCl_3$, $SmCl_3$, anhydrous $FeCl_3$, $FeCl_3{\cdot}6H_2O$ were tested (Table 1, entries 4–12). Using $CuSO_4$, no formation of pyrrole **3a** occurred. The other tested catalysts manifested inhomogeneous performances by providing yields of **3a** between 5 and 41%. It is noteworthy that the best result was furnished by anhydrous $FeCl_3$, while the reaction conducted employing its analogous hexahydrate form produced the desired **3a** with a significantly lower yield (41% vs 24%, Table 1 entries 11,12). In the literature there are several examples of effective syntheses of pyrroles or related five membered azacycles based on iron catalysis.[37] This is due to the several inherent advantages of these catalysts such as low and stable cost, excellent functional group tolerance, and relative low toxicity.[38] Subsequently, different solvents were tried both at room temperature as well as under reflux (Table 1, entries 13–19). The tests carried out have shown that the reaction in THF under reflux furnished the best results in terms of yield, although the DD **1a** was not fully converted after 72 hours (Table 1, entry 19). Increasing the catalyst up to 20%, the DD **1a** was fully consumed, but a loss in yield of pyrrole **3a** was observed (Table 1 entry 20). The decrease of the amount of $FeCl_3$ to 5% did not cause a significant loss in yield of **3a** (69%), which however occurred by further lowering the quantity of the catalyst to 2.5% (Table 1 entries 21, 22). Also in these two latter cases, we noticed as also after 72.0 h, an amount of the starting DD **1a** was recovered unreacted. So, we tried two successive additions: to the initial aliquot of catalyst (5%), a further amount (5%) was added after 6 hours from the beginning of the reaction. To our satisfaction, in this case, the DD **1a** was completely converted in 24.0 h and the desired pyrrole **3a** was isolated in 95% yield (Table 1, entry 23). The efficiency and validity of these optimized conditions have been verified employing several DDs with different *N*-protective groups such as esters **1a–m** (R^1 = Me, Et, *t*But), or amides **1n–q** (R^1 = NH_2, NHPh), bearing in 3-position of the azo-ene system alkyl groups of different length (R^2 = Me, Et, *n*-Pr), and functionalized in 4-position with esters **1a–g,i,j,l–q** and amides **1h,k,** (see Table S1, Supporting Information) to tentatively synthesize the corresponding functionalized pyrroles **3a–q**. The adaptability to scale-up and synthetic utility of this method was highlighted conducing a gram-scale synthesis of **3b** that was obtained without loss of yield (85%, Table 2). As described in Table 2, the yields are generally good with the exception of the pyrroles **3f** and **3g** (41% and 29%, respectively). Analyzing the set of the collected data, it is possible to notice how the yields decrease, also in a sensitive way, with the increase of the steric hindrance of the substituents. It is noteworthy that in the reaction of DD **1p** it was possible to isolate by flash chromatography a little amount of the corresponding 1,4,5,6-tetrahydropyridazine **2a** that was quickly characterized by means of the ^{1}H- and ^{13}C-NMR spectroscopy (see Scheme 1d).[39] In particular, the two doublets at 3.51 and 3.99 ppm ascribable to the protons on C4 and C5 and the signal at 83.3 ppm attributable to the C6 of the diazenyl-tetrahydropyridazine are diagnostic for the proposed structure.[33]

Table 2. Substrate scope of the synthesis of pyrroles **3a–q** by employing exclusively 4-substituted DDs **1a–q**.[a],[b]



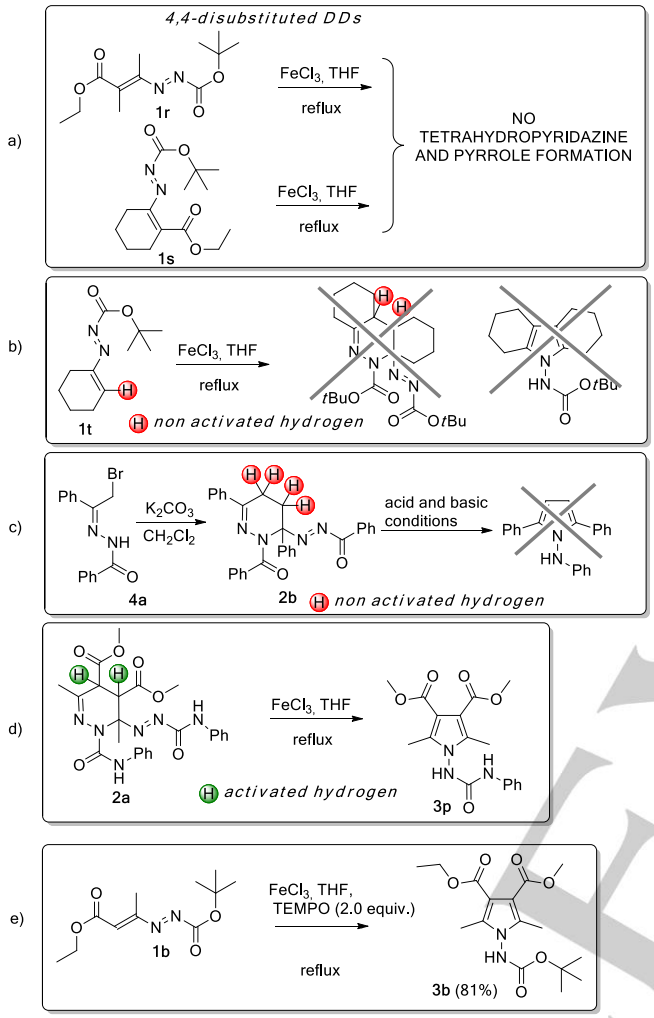
[a] Reaction conditions: **1** (1.0 mmol), $FeCl_3$ (0.05 mmol), THF, 10.0 mL, reflux 6.0 h, then to the crude other $FeCl_3$ (0.05 mmol) was added and the reaction was further refluxed for 18.0–24.0 h. [b] Isolated yields. [c] **3b** (1.202 g) was obtained starting from 8.0 mmol of **1b**.

In order to obtain information on the mechanistic details, some experiments were conducted (Scheme 1). Obviously, 4,4-disubstituted DDs, lacking hydrogen, are not able to supply the final pyrroles **3**, as evidenced in the case of the DDs **1r,s** (Scheme 1a).[40] The same behavior was noted using the cyclic DD **1t**,[41] a stable compound that can be easily handled and stored for a long time (Scheme 1b).[42]

Also the isolated 3,4-unsubstituted-tetrahydropyridazine **2b** obtained from the *N*'-(2-chloro-1-phenylethylidene)benzohydrazide **4a** according to the Zhou's procedure is not able to supply the corresponding pyrrole both by acid or basic treatments (Scheme 1c, and Table S2 Supporting Information).[43] On the contrary, the treatment under the optimized conditions of the isolated tetrahydropyridazine 3,4-dicarboxylate **2a** furnished the corresponding 1-aminopyrrole **3p** in 87% yield (Scheme 1d). The set of collected data clearly indicates that the presence of activated hydrogens originally located in position four of the azo-ene system of the starting DDs **1** is determinant for the success of the reaction. Based on these evidences, a plausible mechanism can involve an initial [4 + 2] cycloaddition in which one DD acts as a diene and a second one as a dienophile: this aza-Diels-Alder reaction produces the diazenyl-tetrahydropyridazine-3,4-dicarboxylates **2** accordingly to what previously observed by Lu and Zhou[33] or by Suryavanshi (Scheme 2).[34] In this case, the role of the Lewis

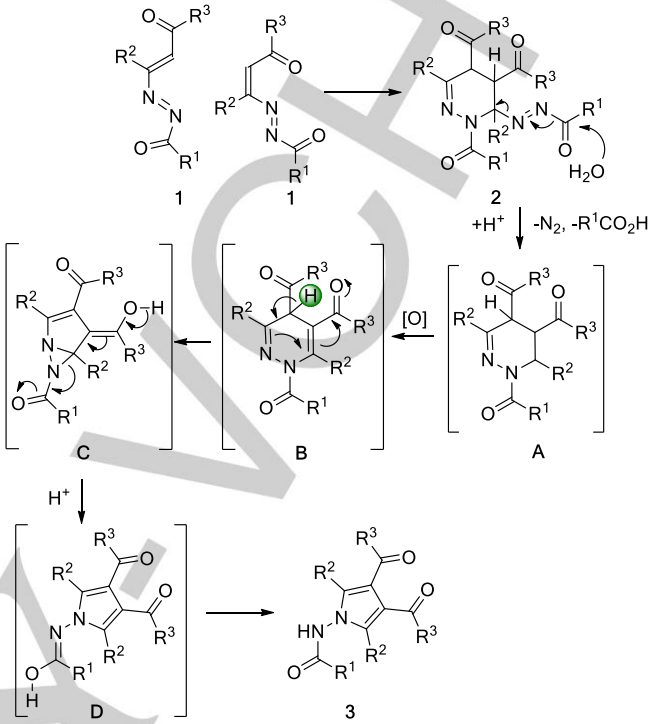
acid is crucial, as confirmed by the lack of reactions in the absence of catalyst (Table 1, entry 2).[44] The azo group combined with the presence of electron withdrawing groups such as esters and amides, makes the DDs electron deficient dienes.[22]

Scheme 1. Control experiments.



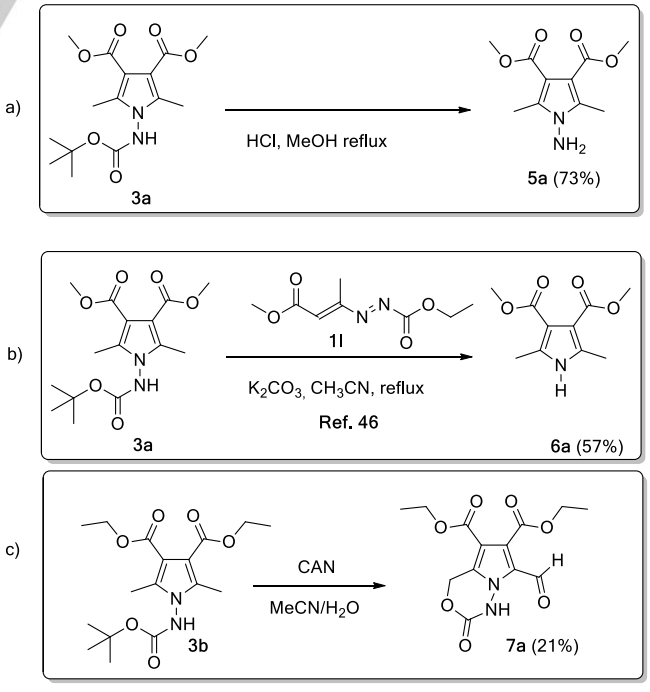
It is known as the catalytic activity of Lewis acid affects the dienes in the inverse electron demand Diels−Alder reaction (IEDDA reaction) favoring the cycloaddition.[45] Similarly to the behavior observed by Suryavanshi the C−N bond cleavage is probably due to a regioselective nucleophilic attack to the acyl carbonyl group of the diazenyl-tetrahydropyridazine **2** which triggers the nitrogen elimination with consequent formation of an unstable carbanion that is readily protonated to produce the intermediate **A**.[34] In the reaction medium probably the $FeCl_3$ degrades making necessary the addition of a second portion of the catalyst during the course of the reaction.[46] An alternative way for the formation of **A** that involves a radical mechanism, as observed by Stephanidou-Stephanatou on similar systems, can be excluded since the reaction was not suppressed if TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), as radical-trapping reagent, was added (Scheme 1e).[47] The successive spontaneous oxidation leads to the 1,4-dihydropyridazine intermediate **B**. The elimination of H(4), activated by the ester function, triggers the internal aza-Michael-addition of the N(2) onto the C(6), producing the diaziridin-pyrrolinic intermediate **C**. The keto-enolic tautomerism causes the opening of the diaziridine nucleus, resulting in ring contraction and generation of the pyrrole **D**.[48] The final tautomeric process determines the formation of the products **3**.

Scheme 2. Plausible reaction mechanism.



The structure of pyrroles **3** was confirmed by NMR comparison with the spectroscopic data of the same compounds obtained by means of different procedures,[49] as well as by the hydrolysis of the amide BOC (**5a**, Scheme 3a), or by N–N bond cleavage (**6a**, Scheme 3b).[50]

Scheme 3. Synthetic transformations of **3**.



These evidences further corroborates the occurred ring contraction and excludes unequivocally the possible six-membered structure for derivatives **3**. An example of the synthetic utility of the products **3** is represented by the construction of an unprecedented bicyclic-fused derivative such as the pyrrolo[1,2-*d*][1,3,4]oxadiazine **7a**. The treatment of pyrrole **3b** with CAN in a mixture of acetonitrile/water induces the selective oxidation of the methyl groups.[51] The reaction proceeds through the preliminary formation of the alcohol that in turn gives a nucleophilic attack onto the carbammate function producing the oxadiazine nucleus. The other methyl, instead, is oxidized to formyl group (Scheme 3c).

Conclusion

In summary, we have developed an unusual and practical $FeCl_3$-catalyzed formal [3 + 2] cyclodimerization of 4-substituted DDs for the preparation of fully substituted symmetric 1-aminopyrroles. The key steps of this sequence involved a "ring-closure-ring-opening" process that determines a cycle contraction. The ring closure is triggered by the loss of the activated proton, originally located in the terminal position of the azo-ene system of the 4-amino- or 4-alkoxy-carbonyl-DDs. As demonstrated, the replacement of the *in situ* generated 4-unsubstituted DDs with the 4-substituted-ones is *crucial* for the success of the whole sequence that leads to the pyrrole formation. This strategy makes simplicity its main strength, and it was demonstrated to efficiently proceed since it can be easily scaled up.

Experimental Section

General procedure for the synthesis of 1,4,5,6-tetrahydropyridazine 2a and 1-aminopyrroles 3a–q.

To a solution of 1,2-diaza-1,3-dienes **1a–q** (1.0 mmol)[41] in tetrahydrofuran (10.0 mL), $FeCl_3$ (0.05mmol) was added and the mixture was refluxed. After 6.0 h a second aliquot of $FeCl_3$ (0.05 mmol) was added to the solution that was refluxed for other 18.0–24.0 h until the complete disappearance of the starting 1,2-diaza-1,3-dienes **1a–q** (TLC monitoring). Then, the solvent was removed *in vacuo*; the so-formed 1-aminopyrroles **3a–q** were purified by silica gel column chromatography using cyclohexane/ethyl acetate mixtures as eluent and then were crystallized from ethyl acetate/petroleum ether. In the case of the reaction of 1,2-diaza-1,3-diene **1p** it was possible to isolate the corresponding diazenyl-1,4,5,6-tetrahydropyridazine **2a** by stopping the reflux after 2.0 h from the first addition of $FeCl_3$ (0.05 mmol). In this case, the solvent was evaporated under *vacuo* and the crude was chromatographed very quickly to obtain the pure compound **2a**.

General procedure for the conversion of diazenyl 1,4,5,6-tetrahydropyridazine 2a to 1-aminopyrrole 3p.

To a solution of diazenyl 1,4,5,6-tetrahydropyridazine **2a** (0.2 mmol), in tetrahydrofuran (3.0 mL) $FeCl_3$ (0.01mmol) was added and the mixture was refluxed until the complete disappearance of the starting 1,4,5,6-tetrahydropyridazine **2a** (2.5 h, TLC monitoring). Then, the solvent was removed in *vacuo*; the so-formed 1-aminopyrrole **3p** was purified by silica gel column chromatography using cyclohexane/ethyl acetate mixtures as eluent.

General procedure for the synthesis of 1-amino-1H-pyrrole 5a.

The dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **3a** (0.3 mmol) was dissolved in 15.0 mL of methanol and then 0.15 mL of HCl 37 % was added. The reaction was refluxed for 2 h (controlling reaction progress by TLC). The reaction mixture was then neutralized by addition of Na_2CO_3, anhydrified with Na_2SO_4. Successively, the solution was filtered, and the crude was concentrated under reduced pressure. Product **5a** was isolated by chromatography on silica gel column using cyclohexane/ethyl acetate mixtures as eluent and purified by crystallization from ethyl acetate.

General procedure for the synthesis of 1*H*-pyrrole 6a.[50]

To a magnetically stirred solution of dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **3a** (0.5 mmol) in MeCN (10.0 mL), the DD **2l** (1.0 mmol) and K_2CO_3 (1.5 mmol) were added and the reaction mixture was refluxed for 1 hour, until the TLC analysis revealed the disappearance of the starting reagent **3** and the formation of 1*H*-pyrrole **6a**. After the filtration of K_2CO_3, the solvent was removed in *vacuo*; the so-formed product **6a** was purified by silica gel column chromatography using cyclohexane/ethyl acetate mixtures as eluent and then was crystallized from ethyl acetate/petroleum ether.

General procedure for the synthesis of diethyl 7-formyl-2-oxo-2,4-dihydro-1*H*-pyrrolo[1,2-*d*][1,3,4]oxadiazine-5,6-dicarboxylate 7a starting from pyrrole 3a.

The dimethyl 1-((*tert*-butoxycarbonyl)amino)-2,5-dimethyl-1*H*-pyrrole-3,4-dicarboxylate **3a** (0.3 mmol) was dissolved in 9.0 mL of a mixture of acetonitrile/water (8:1 v/v) and then cerium(IV) ammonium nitrate was added (2.4 mmol). The reaction was refluxed for 5 h (controlling reaction progress by TLC). The reaction mixture was cooled to r.t., concentrated under vacuum, washed with H_2O (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with H_2O (2 × 10 mL), brine (10 mL), and dried over $NaSO_4$. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a short silica column (cyclohexane-ethyl acetate).

Acknowledgements

The authors thank Dr. Giada Maraia for her precious advices and Dr. Anna Maria Gioacchini who competently performed the mass spectra.

Keywords: Cyclization • Domino reactions • Michael addition • Pyrroles • Ring contraction.

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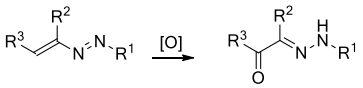

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[40] DDs **1r,s**, treated under the optimized reaction conditions, provided only a complicated reaction profile, from which it was not possible to isolate even the corresponding tetrahydropyridazine **2**.

[41] DD **1t** can be isolated as pure product by chromatographic column and stored at -20 °C for several years. For the general preparation procedure of DDs, please see: L. Preti, O. A. Attanasi, E. Caselli, G. Favi, C. Ori, P. Davoli, F. Felluga, F. Prati, *Eur. J. Org. Chem.* **2010**, 4312-4320.

[42] The reaction profile is quite complicate, and only by-products were isolated.

[43] The isolated 2,3,4,5-tetrahydropyridazine **2b** was treated both under the optimized reaction conditions as well with several bases at room temperature or under reflux (Table S2, Supporting Information). In all cases, the reactions did not provide pyrrole.

[44] Recently it was demonstrated as the aza-Diels−Alder reaction of nonactivated dienes and imines was catalyzed through the action of the ionpaired Lewis acid catalyst $[FeCl_2]^+[FeCl_4]^-$ generated by the in situ disproportionation of $FeCl_3$. The uniquely high reactivity of $[FeCl_2]^+[FeCl4]^-$ was attributed to both the highly Lewis acidic$[FeCl_2]^+$ and thermodynamically stable $FeCl_4^-$ acting as an ion-paired catalyst: R. Tomifuji, K. Maeda, T. Takahashi, T. Kurahashi, S. Matsubara *Org. Lett*. **2018**, *20*, 7474-7477.

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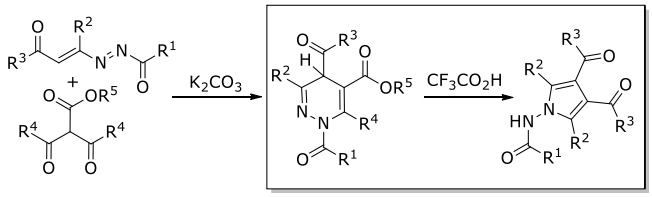

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[50] Recently we proposed a base-promoted N-N bond cleavage, by means of a Michael type addition/E1cb elimination sequence, assisted by DDs on a series of *N*-amino-heterocycles, to obtain exclusively the corresponding *N*H-free heteroring derivatives. G. Mari, G. Favi, S. Santeusanio, F. Mantellini, L. De Crescentini, *Org. Chem. Front.* **2019**, *6*, 3408-3414.

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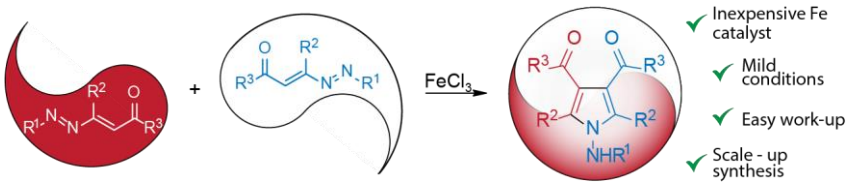

The 1,2-diaza-1,3-diene's cyclodimerization that provides symmetrically fully substituted 1-amino pyrroles through an unusual formal [3+2] reaction is investigated. The study has demonstrated as the presence of electron withdrawing groups onto the terminal carbon atom of the azo-ene system is crucial for the success of the reaction. The synthesis occurs with complete regioselectivity and requires a very easy work-up procedure.