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Modular $CeCl_3 \cdot 7H_2O$-catalyzed multi-component synthesis of 1,2,3,4-tetrasubstituted pyrroles under microwave irradiation and their further trichloroisocyanuric acid-mediated conversion into 5-sulfenylpyrrole derivatives

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ABSTRACT

A modular, multicomponent synthesis of 1,2,3,4-tetrasubstituted pyrroles promoted by the inexpensive $CeCl_3 \cdot 7H_2O$, is reported. The reaction was carried out under microwave irradiation, affording good yields of products in short time. Scope and limitations were explored and a plausible reaction mechanism is discussed. The resulting heterocycles were smoothly and efficiently converted into their corresponding 5-arylsulfenyl derivatives by reaction with diaryl disulfides and trichloroisocyanuric acid in EtOAc.

1. Introduction

The pyrrole nucleus is the characteristic structural motif of numerous natural (storniamide A, lamellarin P, marinopyrrole B) and synthetic products (Fig. 1).[1] Many polyfunctionalized pyrroles are known to display interesting biological activities, as antilipidemics (atorvastatin, Lipitor®),[2] antioxidants,[3a] and anti-inflammatories.[3b,c] They are also antibacterials,[4a,b] antitumorals,[4c] as well as antifungal,[5a] antitubercular,[5b–d] and central nervous system agents.[6] In addition, pyrroles were observed to inhibit cytokine-mediated diseases[7] and have also found some applications in materials chemistry.[8]

The growing importance and wide usefulness of polysubstituted pyrroles have kept in focus the search of new methods for the efficient synthesis of these heterocycles.

Pyrroles have been prepared by several classical methods,[9a] such as the Barton–Zard,[9b] Hantzsch,[9c,d] Knorr,[10a,b] Trofimov,[10c] Paal-Knorr,[11a,b] and Clauson-Kaas[11c–e] reactions and their modifications. In addition, these heterocycles have also been synthesized by the Huisgen reaction, by transformations involving suitably substituted alkynes and amines,[12] cyclization of *N*-propargylic derivatives,[13a,b] including propargyl aziridines,[13c,d] and through the cyclocondensation of vinyl azides with 1,3-dicarbonyls,[14] among various other alternatives.

However, many of these transformations have important drawbacks, including low yield, the need of multistep operations, the requirement of precious metals or expensive reagents, difficult availability of the starting materials, lack of regiospecificity and narrow functional group compatibility.

Multicomponent reactions (MCRs) are a highly convergent alternative towards complex molecules. Their advantages, in terms of reaction times, yields, and reproducibility, have been repeatedly exploited in various efficient syntheses of heterocyclic compounds.[15] Several MCR approaches towards pyrroles have been described[16] and the subject was repeatedly reviewed.[17]

Lanthanide salts are useful as catalysts and promoters in organic synthesis.[18] Many of them have recently attracted great scientific interest because of their ready availability, low toxicity, and ease of

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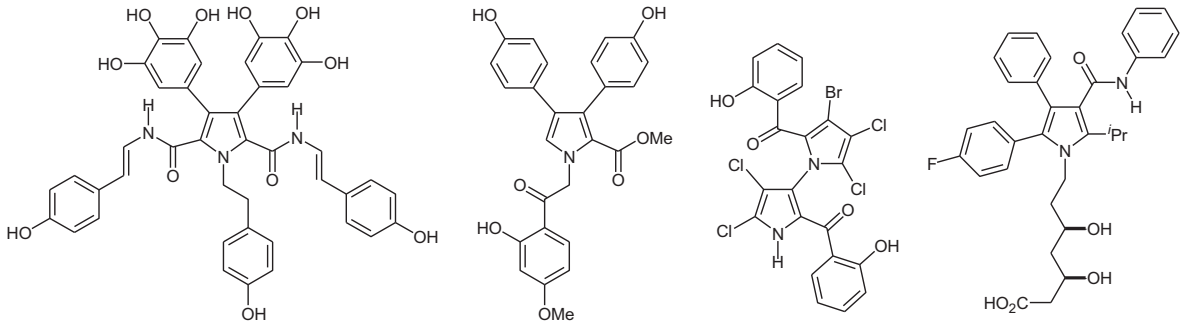


Fig. 1. Examples of relevant natural (storniamide A, lamellarin P, marinopyrrole B) and synthetic (atorvastatin) polysubstituted pyrroles.

handling, as well as for their air and water stability.[19] Among them, cerium compounds have found extensive use in organic synthesis.[20]

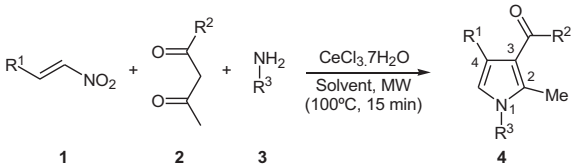
Over the past few years, cerium (III) chloride has emerged as a suitable agent for achieving highly regio- and chemoselective transformations.[21] The salt is an inexpensive, non-toxic, and water-tolerant catalyst, which has been used in its heptahydrate and anhydrous forms, as well as in combination with NaI[22] and as a solid-supported reagent.[23]

Grob and Camenisch[24a] were the first to disclose that pyrroles can be obtained through the reaction of β-enamino carbonyls and nitroalkenes, followed by intramolecular cyclization, but their original protocol was seldom employed as such.[24b–d] However, several variations, including nitroalkane and aldehyde mixtures as β-nitroolefin precursors and reactions of nitroalkenes[25] with dicarbonyl compounds and amines, as β-enamino carbonyl equivalents,[26] have been extensively explored.

In view of our interest in the development of new and cleaner alternatives for classical reactions, promoted by Ce^{III} species,[27] and taking advantage that the enamination of carbonyls mediated by cerium salts,[28] especially $CeCl_3$ has been recently reported, we decided to develop a modular Ce^{III}-mediated MCR for the synthesis of polysubstituted pyrroles.

2. Results and discussion

Therefore, in order to find the optimum reaction conditions (Scheme 1), equimolar amounts of β-nitrostyrene (**1a**), acetylacetone (**2a**) and aniline (**3a**) were submitted to reaction in the presence of 0.3 equiv of $CeCl_3 \cdot 7H_2O$.

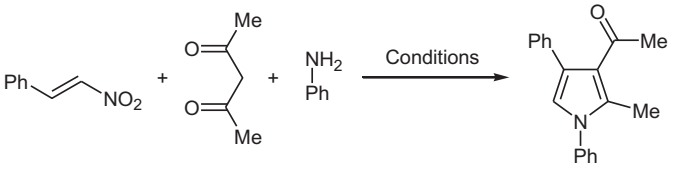


Scheme 1. Proposed MCR synthesis of 1,2,3,4-tetrasubstituted pyrroles.

At first, the effect of the solvent on the reaction outcome was tested under microwave irradiation (100 °C for 15 min). The results (Table 1) revealed that no reaction was observed in MeOH, MeCN, and glycerol (entries 1–3). On the other hand, running the cyclization under solvent-free conditions (entry 4) gave moderate yields of **4a**, while $MeNO_2$ afforded the best reaction performance (75% yield, entry 5), confirming a solvent influence on the transformation.

Increasing the reaction time in $MeNO_2$ to 20 min did not improve the yields (entry 8), while performing the transformation for 10 min gave only 63% of the product (entry 9). On the other hand, carrying out the reaction at both, 120 °C and 80 °C resulted in comparatively lower yields of the heterocycle (entries 10, 11), whereas use of anhydrous $CeCl_3$ did not improve the efficiency of the transformation (entry 12).

Table 1
Process optimization. Microwave irradiation-assisted synthesis of polysubstituted pyrrole **4a** under different conditions[a]



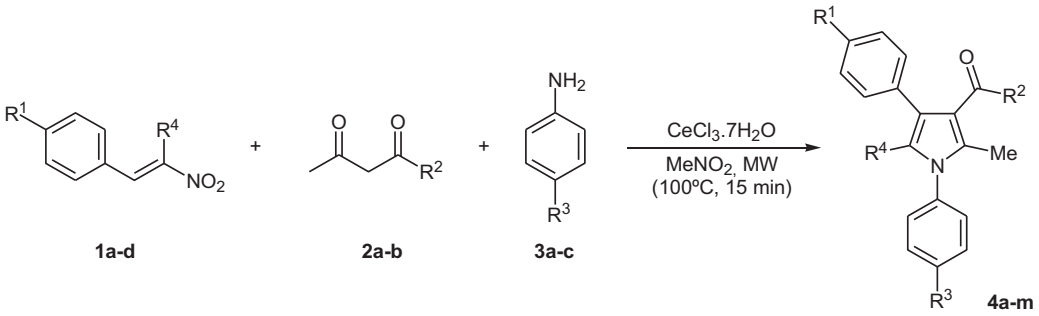
Entry	Catalyst	Solvent	Temp/time (°C/min)	Yield (%)[b]
1	$CeCl_3 \cdot 7H_2O$	MeOH	100/15	—[c]
2	$CeCl_3 \cdot 7H_2O$	MeCN	100/15	—[c]
3	$CeCl_3 \cdot 7H_2O$	Glycerol	100/15	—[c]
4	$CeCl_3 \cdot 7H_2O$	Solvent-free	100/15	48
5	$CeCl_3 \cdot 7H_2O$	$MeNO_2$	100/15	75
6	$CeCl_3 \cdot 7H_2O$	$MeNO_2$	100/15	50[d]
7	$CeCl_3 \cdot 7H_2O$	$MeNO_2$	100/15	58[e]
8	$CeCl_3 \cdot 7H_2O$	$MeNO_2$	100/20	75
9	$CeCl_3 \cdot 7H_2O$	$MeNO_2$	100/10	63
10	$CeCl_3 \cdot 7H_2O$	$MeNO_2$	120/15	65
11	$CeCl_3 \cdot 7H_2O$	$MeNO_2$	80/15	68
12	Anhyd $CeCl_3$	$MeNO_2$	100/15	75
13	$Ce(NO_3)_3 \cdot 6H_2O$	$MeNO_2$	100/15	47
14	$Ce(OTf)_3$	$MeNO_2$	100/15	45
15	CAN	$MeNO_2$	100/15	60

[a] Conditions: Solvent (1 mL), catalyst (0.30 mmol), **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), microwaves irradiation.
[b] After column chromatography.
[c] No reaction.
[d] Employing 0.15 mmol $CeCl_3 \cdot 7H_2O$.
[e] Employing 0.50 mmol $CeCl_3 \cdot 7H_2O$.

The effects of adding different amounts of the promoter was also tested using 0.15–0.50 equiv $CeCl_3 \cdot 7H_2O$ in $MeNO_2$; however, the best result was obtained with 0.30 equiv of the salt at 100 °C (entries 5–7). Other sources of Ce^{III} (nitrate, triflate), as well as $(NH_4)_2Ce(NO_3)_6$ (CAN, a Ce^{IV} derivative),[28e] were also examined as promoters, observing that none of them surpassed the effectiveness of $CeCl_3 \cdot 7H_2O$ (entries 13–15).

With the optimized conditions in hand (entry 5), and in order to establish its scope, the transformation was next extended to the synthesis of other pyrroles with various substituents (Table 2). It was observed that electron-poor aromatics on the β-nitrostyrene side afforded comparatively lower reaction yields (entries 3, 6, 8, and 12) than their counterparts carrying electron-richer aromatic nuclei (entries 1, 2, 4, and 5).

Table 2
The microwaves-assisted and $CeCl_3$-mediated MCR synthesis of polysubstituted pyrroles[a]



1a-d **2a-b** **3a-c** **4a-m**

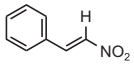
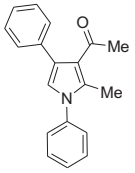
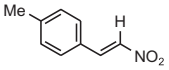
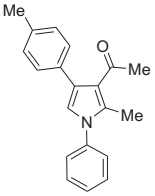
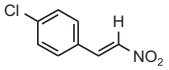
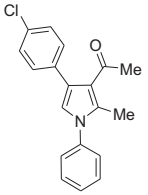
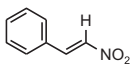
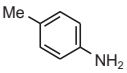
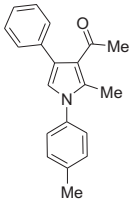
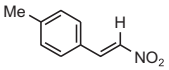
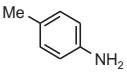
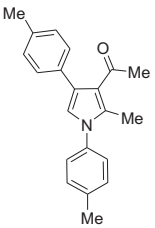
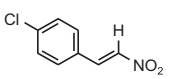
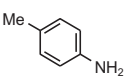
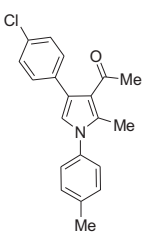
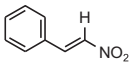
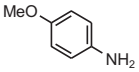
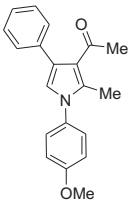
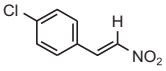
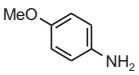
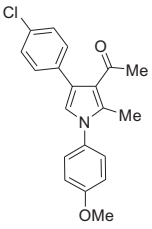
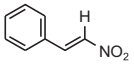
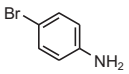
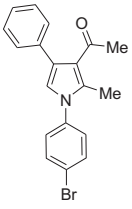
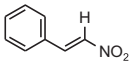
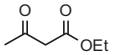
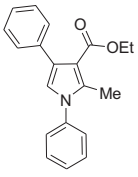
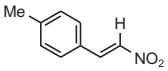
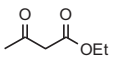
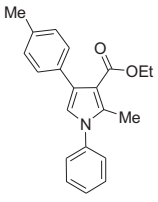
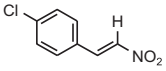
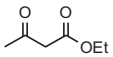
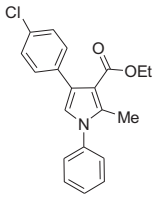
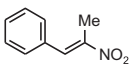
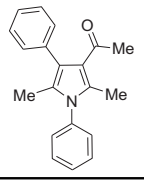
Entry no	β-Nitrostyrene	1,3-Dicarbonyl	Amine	Product	Product no	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**		**4a**	75[29]
2	 **1b**	 **2a**	 **3a**		**4b**	80
3	 **1c**	 **2a**	 **3a**		**4c**	59
4	 **1a**	 **2a**	 **3b**		**4d**	77
5	 **1b**	 **2a**	 **3b**		**4e**	70
6	 **1c**	 **2a**	 **3b**		**4f**	55

Table 2 (*continued*)

Entry no	β-Nitrostyrene	1,3-Dicarbonyl	Amine	Product	Product no	Yield (%)[b]
7	 **1a**	 **2a**	 **3c**		**4g**	60[29]
8	 **1c**	 **2a**	 **3c**		**4h**	58[29]
9	 **1a**	 **2a**	 **3c**		**4i**	61
10	 **1a**	 **2b**	 **3a**		**4j**	64
11	 **1b**	 **2b**	 **3a**		**4k**	67
12	 **1c**	 **2b**	 **3a**		**4l**	46
13	 **1d**	 **2a**	 **3a**		**4m**	45[30]

[a] The reaction was performed under microwaves (100 W) in the presence of $MeNO_2$ (1 mL), **1a**–**c** (1.0 mmol), **2a**, **b** (1.0 mmol), **3a**–**c** (1.0 mmol), $CeCl_3 \cdot 7H_2O$ (0.30 mmol), unless otherwise noted.

[b] By column chromatography (Hexanes/EtOAc).

The use of a β-ketoester (**2b**) as the 1,3-dicarbonyl component further extended the scope of this method, demonstrating its tolerance to the introduction of various functional groups on positions C-2 and C-3. Despite observing slightly lower yields, good chemoselectivity was achieved, since only the products resulting from the cyclization of the ketone carbonyl moiety were isolated (entries 10–12).

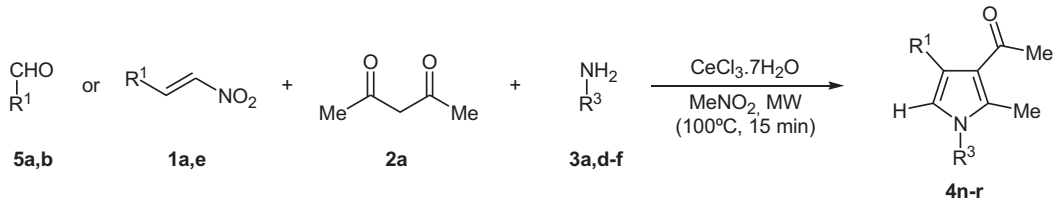
On the other hand, it was verified that cyclic 1,3-dicarbonyl derivatives, such as dimedone, Meldrum's acid and 1,3-cyclo-

hexanedione did not afford the expected reaction products, being unsuitable as replacements of **2a**, **b**. In addition, use of conventional heating at 100 °C afforded similar yields of the heterocyclic products (**4a**, 73%; **4b**, 75%; **4c**, 56%), demonstrating that the transformation can also be run under these conditions, albeit at the expense of longer reaction times (2.5 h for **4a**, **b** and 4 h for **4c**).

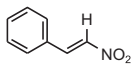
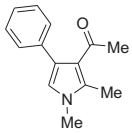
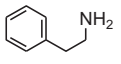
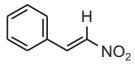
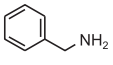
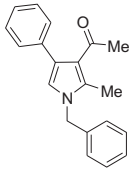
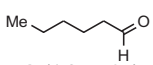
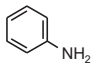
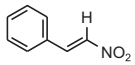
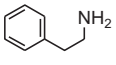
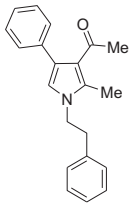
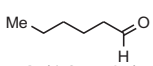
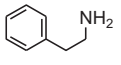
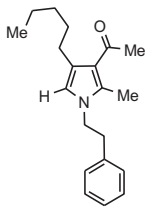
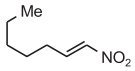
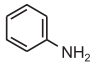
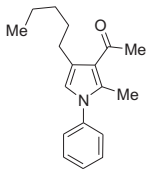
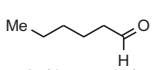
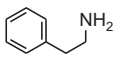
The synthesis of 1,2,3,4,5-pentasubstituted pyrroles was also attempted, employing (*E*)-(2-nitroprop-1-en-1-yl)benzene (**1d**). included the use of aliphatic nitroolefin **1e**[31] and various primary amines, such as methylamine (**3d**) benzylamine (**3e**), and β-phenethylamine (**3f**), with acetylacetone (**2a**) as the 1,3-dicarbonyl component.

As shown in Table 3, when β-nitrostyrene **1a** was subjected to reaction with **2a** and amines **3d**–**f**, the yields of the resulting cyclized products (**4n**–**p**) were lower (23–31%) than those previously observed (entries 1–3).

Table 3
The microwaves-assisted and $CeCl_3$-mediated MCR synthesis of polysubstituted pyrroles. Use of non-aromatic amines and nitroolefins[a]



5a,b **1a,e** **2a** **3a,d-f** **4n-r**

Entry no	β-Nitrostyrene	Amine	Product	Yield (%)[b]	Entry no	Aldehyde	Amine	Product	Yield (%)[b]
1	 **1a**	40% $MeNH_2$ **3d** (2.0 equiv)	 **4n**	23[32]	5	 **5a** (1.2 equiv.)	 **3f** (1.2 equiv.)	**4p**	23[d,34c]
2	 **1a**	 **3e** (1.2 equiv.)	 **4o**	31[33]	6	 **5b** (1.2 equiv.)	 **3a** (1.2 equiv.)	**4q**	No reaction
3	 **1a**	 **3f** (1.2 equiv.)	 **4p**	25[c,34c]	7	 **5b** (1.2 equiv.)	 **3f** (1.2 equiv.)	 **4r**	46[d]
4	 **1e** (1.0 equiv.)	 **3a** (1.1 equiv.)	 **4q**	48	8	 **5b** (1.5 equiv.)	 **3f** (1.5 equiv.)	**4r**	51[d]

[a] The reaction was performed under microwaves (100 W) in the presence of $MeNO_2$ (1 mL), to which the aldehyde or nitroolefin (1.0 mmol), **2a** (1.0 mmol), amine **3a**, **d**–**f** (1.0 mmol), and $CeCl_3 \cdot 7H_2O$ (0.30 mmol) were added, unless otherwise noted.
[b] By column chromatography (Hexanes/EtOAc).
[c] Isolated yields of **4p** were 23% when the mixture was irradiated for 30 min and 43% when 0.60 equiv $CeCl_3 \cdot 7H_2O$ were employed.
[d] The reaction was performed under microwaves (100 W) for 30 min.

However, the β-nitrostyrene **1d** was found to be less reactive than its counterparts **1a**–**c**, and gave a comparatively lower product yield (**4m**, 45%), probably as a result of steric hindrance.

Delightfully, it was also observed that heterocycle **4a** could be generated on a larger scale (5 mmol), under the optimized conditions, without compromising the performance of the transformation (79% isolated yield).

In order to further assess the scope and limitations of this MCR transformation, other reactant combinations were tested. These

Under the optimized conditions, compound **4n** was obtained in 23% yield when 2.0 equiv of aqueous $MeNH_2$ was employed and in 20% yield employing 5.0 equiv of the amine. In the case of **4p**, which was accessed in 25% yield, increasing the irradiation time to 30 min had no effect on the reaction performance (23% yield), while employing 0.60 mmol of the promoter afforded 43% of the heterocycle. These results compared favorably with conventional conditions, which furnished only 13% of the expected pyrrole after heating in an oil bath for 15 h.

Interestingly, comparison of the results consigned in entries 3 and 5 revealed that under an analogous load of promoter the isolated yield of pyrrole **4p** prepared from the preformed β-nitrostyrene **1a** was similar to that observed when this olefinic component was generated in situ from 1.2 equiv of benzaldehyde (**5a**).

On the other side, when the nitroolefin **1e**, derived from hexanal (**5b**), was employed for the reaction with aniline as coupling partner, 48% of pyrrole **4q** was isolated (entry 4). Increasing the amounts of the other reactants (**2a** and **3a**) to 1.5 equiv did not improve the performance of the MCR (45% yield of **4q**), while performing the irradiation for 30 min had a minor deleterious effect on the yield of product. Curiously, however, no reaction product was observed even after irradiating for 60 min when aniline was added as the amino coupling partner and the nitroolefin was prepared in situ from hexanal (**5b**, entry 6).

Contrastingly, using **5b** as model aliphatic aldehyde in the presence of 1.2 equiv of β-phenethylamine (**3f**) afforded 32% pyrrole **4r**, which improved to 46% upon 30 min of irradiation time (entry 7). Moreover, the yield of **4r** increased to 51% when 1.5 equiv of both, aliphatic aldehyde and amine, were employed (entry 8). However, higher excesses of **5b** and **3f** (2.0 equiv each) gave no further improvements (49% of **4r**). These results confirmed that nitroalkene **1e** is being formed under the reaction conditions. They also suggested that the different reaction outcomes should be, at least in part, a result of the properties of the amino component of the MCR.

Mechanisms for analogous transformations leading to pyrroles and related heterocycles have been proposed.[25c,26b,34] The requirement of $CeCl_3 \cdot 7H_2O$ as a promoter is clear, since performing the reaction without the salt, afforded only traces of **4a**. Due to its hardness, the Ce^{III} cation is probably able to activate the carbonyl functionalities of the 1,3-dicarbonyl reactant for a nucleophilic attack, favoring the formation of initial imine and β-enamino carbonyl intermediates.

The plausible role of Ce^{III} in these key steps may also explain the lack of product observed when *p*-nitroaniline was employed as the amine component. This amine is a poor nucleophile and a weak base (pK_a=1.02).[35] Therefore, the initial nucleophilic attack to the 1,3-dicarbonyl compound is strongly disfavored.[35a] The results observed when non-aromatic amines were employed as reaction partners suggest that the outcome of the transformation is also a result of the nucleophilic properties of the amino components of the MCR.[35e]

In view of the easy availability of the 1,2,3,4-tetrasubstituted pyrroles and taking into account our recent experience[36] on the use of trichloroisocyanuric acid (TCCA) for the convenient preparation of 3-sulfenylindoles, the synthesis of their congener 5-sulfanylpyrroles was explored, using TCCA as oxidant.

TCCA is a shelf-stable, inexpensive, and environmentally benign solid, frequently found in commercial products for swimming-pool disinfection,[37] which has been widely used in organic synthesis. Recent examples of its application include oxidation[38] and halogenation[39] reactions, as well as key steps during the total synthesis of many complex structures.[40]

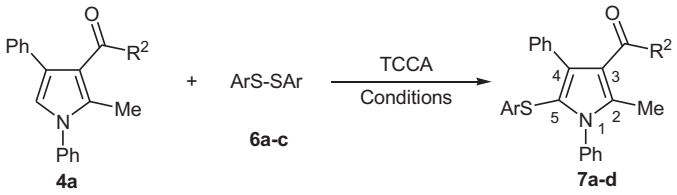
Following the previously described conditions,[36] different alternatives for the sulfenylation of pyrroles were tested (Table 4). It was evidenced that the transformation did not proceed in water (entry 1) and that the observed yields were moderate when it was run in MeCN and THF (entries 2 and 3).

However, the efficiency of the transformation was higher in acetone (entry 4), and EtOAc demonstrated to be the best reaction solvent, furnishing **7a** in 94% yield in a short reaction time (entry 5). Interestingly, only traces of product were obtained when the amount of TCCA was reduced from 1.2 equiv to 0.5 equiv (entry 6).

With the optimized conditions in hand (entry 5), the transformation was also extended to examples with other disulfides and also with ester **4b** (entries 7–9), demonstrating its scope. The progress of the reaction was monitored by GC–MS, which revealed the quick formation of ArSCl and its subsequent consumption during the reaction.

Therefore, it can be assumed that ArSCl is the actual active electrophilic species responsible for the transformation. This finding may also explain the stoichiometry of the reaction, because 1.0 mmol TCCA would be capable of forming 3.0 mmol of ArSCl. Interestingly, arylsulfenyl moieties can act as protective groups of the indole nucleus, being easily removed.[41]

Table 4
TCCA-mediated synthesis of 5-sulfenylpyrroles[a]



Entry	Solvent	TCCA (equiv)	Ar	R^2	Time (min)	Prod.	Yield (%)[b]
1	H_2O	1.2	Ph, **6a**	Me, **4a**	60	**7a**	—[c]
2	MeCN	1.2	**6a**	**4a**	60	**7a**	45
3	THF	1.2	**6a**	**4a**	60	**7a**	57
4	Acetone	1.2	**6a**	**4a**	10	**7a**	82
5	EtOAc	1.2	**6a**	**4a**	10	**7a**	94
6	EtOAc	0.5	**6a**	**4a**	10	**7a**	—[d]
7	EtOAc	1.2	*p*-ClPh, **6b**	**4a**	45	**7b**	85
8	EtOAc	1.2	*p*-MeOPh, **6c**	**4a**	30	**7c**	86
9	EtOAc	1.2	**6a**	OEt, **4b**	30	**7d**	87

[a] The reaction was performed with a solution of the pyrrole **4a**, **b** (1.0 mmol), diaryl disulfides **6a**–**c** (0.60 mmol), and TCCA (1.2 equiv) in the given test solvent (2 mL), at room temperature.
[b] By column chromatography (Hexanes/EtOAc).
[c] No reaction.
[d] Only traces of **7a** were detected.

3. Conclusion

In summary, we have developed an operationally simple, modular, and atom-efficient MCR protocol for the chemoselective synthesis 1,2,3,4-tetrasubstituted pyrroles, under microwave irradiation, which can be further extended to afford pentasubstituted heterocycles.

This one-pot process, which exhibited wide generality, is mediated by $CeCl_3 \cdot 7H_2O$ and the substitution pattern on the different positions of the pyrrole ring could be readily controlled through the corresponding starting materials. The products are cleanly obtained in good yields and after short reaction times, resulting in an appealing alternative for accessing highly functionalized pyrroles.

It was also demonstrated that the 1,2,3,4-tetrasubstituted heterocycles could be further efficiently converted into the corresponding 5-arylsulfenyl pyrrole derivatives by treatment with diaryl disulfides and TCCA in EtOAc at room temperature.

4. Experimental section

4.1. General

The ^1H (400 and 200 MHz) and ^{13}C (100 and 50 MHz) NMR spectra were recorded on Bruker DPX 400 and DPX 200 instruments, respectively, using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane or $CHCl_3$, and *J* values are given in Hertz. Elemental analyses were carried out on a Perkin–Elmer 2400 instrument (Central Analítica, IQ–USP, SP). Melting point (mp) determinations

were performed by using an MQAPF-301 instrument and are informed uncorrected.

The mass spectra were obtained in a Shimadzu GC–MS-QP2010 Plus gas chromatograph coupled to a mass detector. The molecular ion and its fragments are described as the relations between their atomic mass and corresponding charge (*m*/*z*), together with their percent relative abundance (%). The gas chromatographies were run on a 30.0 m×0.25 mm RTX-5MS column (Thickness: 0.25 μm). The running conditions were: time: 30 min; injector temperature: 280 °C; initial column oven temperature: 30 °C; linear gradient: 20 °C/min up to 300 °C. Helium (5.4 mL/min; linear velocity: 39.7 cm/s) was employed as carrier gas (Pressure: 68.2 KPa). The high resolution mass spectrum was obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA). Detection of the ions was performed by electrospray ionization, in the positive ion mode.

Solvents were purified and dried before use, according to conventional techniques.[42] All reagents were used as obtained from commercial sources. The reactions were performed in a CEM Discover microwave oven using a 10 mL Pyrex glass tube fitted with a Teflon cap. All the reactions were monitored by thin layer chromatography (TLC) carried out on Whatman-AL SIL G/UV plates. Column chromatography was carried out using silica gel 60 (Aldrich, 230–400 mesh).

4.2. General procedure for the synthesis of polysubstituted pyrroles 4

The β-nitrostyrene (1.0 mmol) was added to a mixture of the amine (1.0 mmol), acetylacetone (**2a**, 1.0 mmol) or ethyl acetoacetate (**2b**, 1.0 mmol) and $CeCl_3 \cdot 7H_2O$ (111 mg, 0.3 mmol) in $MeNO_2$ (1 mL). The reaction mixture was stirred and heated at 100 °C for 15 min in the microwave oven. The reaction progress was monitored by GC–MS. After the specified reaction time, the reaction mixture was extracted with EtOAc (3×10 mL). The organic phase was washed with water and then brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (hexanes/EtOAc, 95:5) to afford the pure products (**4a**–**r**).

*4.2.1. 1-(2-Methyl-1,4-diphenyl-1H-pyrrol-3-yl)ethanone (**4a**).* White solid; mp 104–105 °C (Lit.[29] 105–107 °C). ^{1}H NMR (400 MHz): δ=7.50–7.27 (m, 10H), 6.64 (s, 1H), 2.40 (s, 3H), and 2.07 (s, 3H). ^{13}C NMR (100 MHz): δ=197.4, 138.5, 135.8, 135.1, 129.2, 129.1, 128.9, 128.1, 127.9, 126.6, 126.0, 122.3, 120.4, 30.9, and 12.7. MS (EI): *m*/*z* (%)=275 (M^+, 69), 261 (20), 260 (100), 230 (8), 217 (9), 138 (6), 128 (12), and 77 (20).

*4.2.2. 1-(2-Methyl-1-phenyl-4-p-tolyl-1H-pyrrol-3-yl)ethanone (**4b**).* Yellow solid; mp 104–106 °C. ^{1}H NMR (400 MHz): δ=7.45–7.42 (m, 2H), 7.38–7.35 (m, 1H), 7.30–7.24 (m, 4H), 7.17–7.15 (m, 2H), 6.61 (s, 1H), 2.39 (s, 3H), 2.35 (s, 3H), and 2.07 (s, 3H). ^{13}C NMR (100 MHz): δ=197.4, 138.5, 136.2, 134.9, 132.7, 129.1, 128.9, 128.8, 127.8, 126.0, 125.9, 122.3, 120.2, 30.8, 20.9, and 12.7. MS (EI): *m*/*z* (%)=274 (M^+, 100), 230 (13), 207 (12) 145 (5), 137 (5), 128 (14), 115 (10), 104 (6), and 77 (26). Anal. Calcd (%) for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.63; H, 6.57; N, 4.81.

*4.2.3. 1-(4-(4-Chlorophenyl)-2-methyl-1-phenyl-1H-pyrrol-3-yl)ethanone (**4c**).* Yellow solid; mp 99–101 °C. ^{1}H NMR (200 MHz): δ=7.52–7.40 (m, 3H), 7.36–7.28 (m, 6H), 6.64 (s, 1H), 2.39 (s, 3H), and 2.09 (s, 3H). ^{13}C NMR (50 MHz): δ=197.0, 138.4, 135.3, 134.3, 132.6, 130.3, 129.2, 128.3, 128.1, 126.0, 124.8, 122.3, 120.6, 31.0, and 12.8. MS (EI): *m*/*z* (%)=309 (M^+, 62), 296 (34), 295 (20), 294 (100), 259 (10), 230 (16), 128 (10), and 77 (25). Anal. Calcd (%) for $C_{19}H_{16}ClNO$: C, 73.66; H, 5.21; N, 4.52. Found: C, 73.35; H, 5.17; N, 4.43.

*4.2.4. 1-(2-Methyl-4-phenyl-1-p-tolyl-1H-pyrrol-3-yl)ethanone (**4d**).* Yellow solid; mp 108–110 °C. ^{1}H NMR (200 MHz): δ=7.38–7.28 (m, 6H), 7.25–7.17 (m, 3H), 6.63 (s, 1H), 2.40 (s, 3H), 2.39 (s, 3H), and 2.07 (s, 3H). ^{13}C NMR (50 MHz): δ=197.5, 138.0, 136.1, 136.0, 135.3, 129.8, 129.2, 128.2, 126.7, 126.0, 125.9, 122.3, 120.6, 31.0, 21.0, and 12.8. MS (EI): *m*/*z* (%)=289 (M^+, 56), 275 (21), 274 (100), 230 (11), 206 (10), 128 (14), 91 (17), 77 (7), and 65 (14). Anal. Calcd (%) for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.95; H, 6.62; N, 4.82.

*4.2.5. 1-(2-Methyl-1,4-di-p-tolyl-1H-pyrrol-3-yl)ethanone (**4e**).* Yellow solid; mp 94–96 °C. ^{1}H NMR (200 MHz): δ=7.27–7.13 (m, 8H), 6.59 (s, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H), and 2.08 (s, 3H). ^{13}C NMR (50 MHz): δ=197.3, 137.8, 136.1, 136.0, 135.0, 132.8, 129.6, 129.0, 128.7, 125.9, 125.7, 122.2, 120.3, 30.8, 20.9, 20.8, and 12.6. MS (EI): *m*/*z* (%)=303 (M^+, 64), 289 (22), 288 (100), 253 (14), 244 (14), 208 (15), 207 (72), 133 (11), 128 (15), 115 (12), 96 (12), 91 (18), and 73 (25). Anal. Calcd (%) for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.18; H, 7.09; N, 4.61.

*4.2.6. 1-(4-(4-Chlorophenyl)-2-methyl-1-p-tolyl-1H-pyrrol-3-yl)ethanone (**4f**).* White solid; mp 105–107 °C. ^{1}H NMR (200 MHz): δ=7.31–7.25 (m, 6H), 7.19–7.15 (m, 2H), 6.61 (s, 1H), 2.40–2.38 (m, 6H), and 2.09 (s, 3H). ^{13}C NMR (50 MHz): δ=197.0, 138.1, 135.8, 135.6, 134.4, 132.5, 130.3, 129.8, 128.2, 125.8, 124.7, 122.1, 120.7, 30.9, 20.9, and 12.7. MS (EI): *m*/*z* (%)=323 (M^+, 23), 310 (14), 308 (44), 281 (34), 253 (19), 209 (14), 208 (21), 207 (100), 191 (16), 133 (15), 96 (17), 91 (10), 77 (2), and 73 (35). Anal. Calcd (%) for $C_{20}H_{18}ClNO$: C, 74.18; H, 5.60; N, 4.33. Found: C, 74.02; H, 5.77; N, 4.24.

*4.2.7. 1-(1-(4-Methoxyphenyl)-2-methyl-4-phenyl-1H-pyrrol-3-yl)ethanone (**4g**).* Yellow solid; mp 88–90 °C (Lit.[29] 90–91 °C). ^{1}H NMR (200 MHz): δ=7.37–7.27 (m, 5H), 7.21 (d, *J*=8.8, 2H), 6.96 (d, *J*=8.8, 2H), 6.61 (s, 1H), 3.82 (s, 3H), 2.37 (s, 3H), and 2.07 (s, 3H). ^{13}C NMR (50 MHz): δ=197.3, 159.1, 135.9, 135.4, 131.3, 129.1, 128.1, 127.2, 126.6, 125.8, 122.0, 120.7, 114.2, 55.3, 30.9, and 12.6. MS (EI): *m*/*z* (%)=305 (M^+, 70), 291 (21), 290 (100), 263 (8), 218 (8), 153 (5), 128 (8), and 77 (9).

*4.2.8. 1-(4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-2-methyl-1H-pyrrol-3-yl)ethanone (**4h**).* Yellow solid; mp 116–118 °C (Lit.[29] 117–119 °C). ^{1}H NMR (200 MHz): δ=7.36–7.30 (m, 4H), 7.22 (d, *J*=8.9, 2H), 6.97 (d, *J*=8.9, 2H), 6.61 (s, 1H), 3.84 (s, 3H), 2.36 (s, 3H), and 2.09 (s, 3H). ^{13}C NMR (50 MHz): δ=196.8, 159.1, 135.7, 134.4, 132.4, 131.1, 130.3, 128.2, 127.2, 124.5, 121.8, 120.8, 114.3, 55.3, 30.9, and 12.6. MS (EI): *m*/*z* (%)=339 (M^+, 12), 324 (21), 281 (36), 253 (20), 209 (14), 208 (21), 207 (100), 191 (16), 133 (14), 96 (17), and 73 (35).

*4.2.9. 1-(1-(4-Bromophenyl)-2-methyl-4-phenyl-1H-pyrrol-3-yl)ethanone (**4i**).* Yellow solid; mp 136–137 °C. ^{1}H NMR (200 MHz): δ=7.58 (d, *J*=8.5, 2H), 7.36–7.34 (m, 5H), 7.18 (d, *J*=8.5, 2H), 6.62 (s, 1H), 2.39 (s, 3H), and 2.06 (s, 3H). ^{13}C NMR (50 MHz): δ=197.4, 137.4, 135.4, 134.9, 132.3, 129.0, 128.1, 127.5, 126.7, 126.4, 122.5, 121.7, 120.1, 30.8, and 12.7. MS (EI): *m*/*z* (%)=355 (M^+, 62), 340 (95), 338 (100), 258 (14), 230 (29), 202 (5), 137 (15), 128 (23), 115 (7), 77 (10), and 76 (13). Anal. Calcd (%) for $C_{19}H_{16}BrNO$: C, 64.42; H, 4.55; N, 3.95. Found: C, 64.44; H, 4.63; N, 3.89.

*4.2.10. Ethyl 2-methyl-1,4-diphenyl-1H-pyrrole-3-carboxylate (**4j**).* Yellow oil. ^{1}H NMR (200 MHz): δ=7.41–7.39 (m, 2H), 7.35–7.32 (m, 2H), 7.29–7.24 (m, 3H), 7.20–7.18 (m, 3H), 6.61 (s, 1H), 4.13 (q, *J*=7.0, 2H), 2.41 (s, 3H), and 1.08 (t, *J*=7.0, 3H). ^{13}C NMR

(50 MHz): δ=165.2, 138.5, 136.0, 135.3, 129.0, 128.9, 128.9, 127.5, 127.1, 126.4, 125.8, 120.4, 111.5, 58.8, 13.6, and 12.1. MS (EI): *m/z* (%)=305 (M^+, 100), 276 (42), 260 (37), 258 (31), 230 (26), 217 (10), 128 (13), and 77 (28). Anal. Calcd (%) for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.41; H, 6.27; N, 4.27.

*4.2.11. Ethyl 2-methyl-1-phenyl-4-p-tolyl-1H-pyrrole-3-carboxy late (**4k**).* Yellow oil. ^{1}H NMR (200 MHz): δ=7.44–7.24 (m, 7H), 7.14–7.10 (m, 2H), 6.65 (s, 1H), 4.18 (q, *J*=7.1, 2H), 2.43 (s, 3H), 2.34 (s, 3H), and 1.15 (t, *J*=7.1, 3H). ^{13}C NMR (50 MHz): δ=165.6, 138.7, 136.1, 135.5, 132.3, 129.1, 128.9, 128.1, 127.8, 126.4, 126.0, 120.4, 111.5, 59.2, 20.9, 14.0, and 12.5. MS (EI): *m/z* (%)=319 (M^+, 100), 290 (36), 274 (29), 244 (16), 230 (15), 141 (4), 128 (9), and 77 (17). Anal. Calcd (%) for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.85; H, 6.58; N, 4.27.

*4.2.12. Ethyl 4-(4-chlorophenyl)-2-methyl-1-phenyl-1H-pyrrole-3-carboxylate (**4l**).* White solid; mp 84–86 °C. ^{1}H NMR (200 MHz): δ=7.49–7.36 (m, 3H), 7.33–7.26 (m, 6H), 6.68 (s, 1H), 4.19 (q, *J*=7.1, 2H), 2.44 (s, 3H), and 1.16 (t, *J*=7.1, 3H). ^{13}C NMR (50 MHz): δ=165.5, 138.7, 136.8, 134.0, 132.0, 130.5, 129.3, 128.1, 127.6, 126.2, 125.3, 120.8, 111.4, 59.5, 14.1, and 12.6. MS (EI): *m/z* (%)=339 (M^+, 100), 310 (40), 294 (41), 267 (9), 258 (8), 229 (31), 128 (9), and 77 (30). Anal. Calcd (%) for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34; N, 4.12. Found: C, 70.64; H, 5.35; N, 4.05.

*4.2.13. 1-(2,5-Dimethyl-1,4-diphenyl-1H-pyrrol-3-yl)ethanone (**4m**).* Reddish solid; mp 113–116 °C (Lit.[30] 114–115 °C). ^{1}H NMR (200 MHz): δ=7.56–7.44 (m, 3H), 7.42–7.23 (m, 7H), 2.29 (s, 3H), 1.95 (s, 3H), and 1.85 (s, 3H). ^{13}C NMR (50 MHz): δ=197.4, 137.4, 136.7, 134.9, 130.4, 129.4, 128.5, 128.1, 128.1, 126.6, 126.5, 122.0, 121.7, 30.9, 13.0, and 11.1. MS (EI): *m/z* (%)=289 (M^+, 72), 274 (100), 230 (16), 144 (9), 128 (10), 102 (3), and 77 (30).

*4.2.14. 1-(1,2-Dimethyl-4-phenyl-1H-pyrrol-3-yl)ethanone (**4n**).* Yellow oil.[31] ^{1}H NMR (400 MHz): δ=7.32–7.30 (m, 2H), 7.29–7.26 (m, 2H), 7.21–7.20 (dd, *J*=7.4 and 1.5, 1H), 6.43 (s, 1H), 3.51 (s, 3H), 2.45 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz): δ=195.7, 139.2, 135.5, 129.2, 127.9, 126.4, 125.5, 122.4, 120.0, 31.9, 31.0, 30.0, 27.4, 22.6, 14.0, and 13.6. MS (EI): *m/z* (%)=213 (M^+, 73), 198 (100), 128 (18), 98 (12), and 77 (6). HRMS Found *m/z* 214.1223; $C_{14}H_{16}NO$ [$(M+H)^+$] requires *m/z* 214.1226.

*4.2.15. 1-(1-Benzyl-2-methyl-4-phenyl-1H-pyrrol-3-yl)ethanone (**4o**).* Brown solid, mp: 51–54 °C (Lit.[32] 52–54 °C). ^{1}H NMR (400 MHz): δ=7.35–7.30 (m, 6H), 7.28–7.23 (m, 2H), 7.07 (d, *J*=7.3, 2H), 6.52 (s, 1H), 5.03 (s, 2H), 2.42 (s, 3H), and 2.02 (s, 3H); ^{13}C NMR (100 MHz): δ=197.4, 136.5, 136.3, 135.1, 129.3, 128.9, 128.1, 127.8, 126.6, 126.6, 125.9, 122.0, 120.0, 50.2, 31.0, and 11.5; MS (EI): *m/z* (%)=289 (M^+, 58), 274 (61), 153 (2), 91 (100), and 77 (2).

*4.2.16. 1-(2-Methyl-1-phenethyl-4-phenyl-1H-pyrrol-3-yl)ethanone (**4p**).* White solid; mp: 86–88 °C.[34c] ^{1}H NMR (400 MHz): δ=7.35–7.23 (m, 8H), 7.09 (d, *J*=6.6, 2H), 6.39 (s, 1H), 4.05 (t, *J*=7.5, 2H), 3.00 (t, *J*=7.2, 2H), 2.38 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz): δ=197.4, 137.6, 136.4, 134.8, 129.4, 128.7 (2C), 128.1, 126.9, 126.6, 125.8, 121.6, 119.4, 48.0, 37.5, 30.9, and 11.3; MS (EI): *m/z* (%)=303 (M^+, 100), 288 (76), 198 (58), 105 (46), and 77 (19). HRMS Found *m/z* 304.1708; $C_{21}H_{22}NO$ [$(M+H)^+$] requires *m/z* 304.1696.

*4.2.17. 1-(2-Methyl-4-pentyl-1-phenyl-1H-pyrrol-3-yl)ethanone (**4q**).* Yellow oil. ^{1}H NMR (400 MHz): δ=7.46–7.43 (m, 2H), 7.40–7.36 (m, 1H), 7.26–7.23 (m, 2H), 6.48 (s, 1H), 2.71 (t, *J*=7.2, 2H), 2.47 (s, 3H) 2.37 (s, 3H), 1.62 (quintet, *J*=7.2, 2H), 1.43–1.31 (m, 4H), 0.92–0.88 (t, *J*=7.2, 3H). ^{13}C NMR (100 MHz): δ=195.7, 139.2, 135.5, 129.2, 127.9, 126.4, 125.5, 122.4, 120.0, 31.9, 31.0, 30.0, 27.4, 22.6, 14.0, 13.6. MS (EI): *m/z* (%)=269 (M^+, 62), 254 (26), 213 (100), 197 (40), 103 (19), and 77 (35). HRMS Found *m/z* 292.1672; $C_{18}H_{23}NNaO$ [$(M+Na)^+$] requires *m/z* 292.1672.

*4.2.18. 1-(2-Methyl-4-pentyl-1-phenethyl-1H-pyrrol-3-yl)ethanone (**4r**).* Yellow oil. ^{1}H NMR (400 MHz): δ=7.29–7.20 (m, 3H), 7.04 (d, *J*=6.6, 2H), 6.22 (s, 1H), 3.97 (t, *J*=7.2, 2H), 2.94 (t, *J*=7.3, 2H), 2.62 (t, *J*=7.4, 2H), 2.39 (s, 3H), 2.30 (s, 3H), 1.57–1.50 (m, 2H), 1.35–1.32 (m, 4H), and 0.90 (t, *J*=6.8, 3H). ^{13}C NMR (100 MHz): δ=195.6, 137.8, 135.1, 128.7, 128.6, 126.8, 124.8, 121.2, 118.4, 47.9, 37.5, 31.8, 30.9, 30.1, 27.5, 22.5, 14.0, and 12.0. MS (EI): *m/z* (%)=297 (M^+, 83), 254 (39), 241 (96), 150 (96), 105 (100), and 76 (28). HRMS Found *m/z* 320.1982; $C_{20}H_{27}NNaO$ [$(M+Na)^+$] requires *m/z* 320.1985.

4.3. General procedure for the synthesis of 5-sulfenylpyrroles 7

A solution of the diaryl disulfide (**6**, 0.6 mmol) in EtOAc (2 mL) was treated with TCCA (0.4 mmol, 1.2 equiv) and the reaction was stirred at room temperature until it became colorless. Then, the 1,2,3,4-tetrasubstituted pyrrole (**4**, 1.0 mmol) was added. The mixture was further stirred at room temperature for the specified time while being monitored by TLC and GC–MS. When all the starting material had disappeared, the reaction was diluted with EtOAc (3×10 mL) and brine (1 mL); the organic phase was separated and successively washed with water (20 mL) and saturated brine (20 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (hexanes/EtOAc, 95:5) to afford pure products (**7a**–**d**).

*4.3.1. 1-(2-Methyl-1,4-diphenyl-5-(phenylthio)-1H-pyrrol-3-yl)ethanone (**7a**).* White solid; mp 145–147 °C. ^{1}H NMR (200 MHz): δ=7.24–7.14 (m, 8H), 6.97–6.89 (m, 5H), 6.66–6.61 (m, 2H), 2.22 (s, 3), and 1.86 (s, 3H). ^{13}C NMR (50 MHz): δ=197.2, 139.2, 138.0, 136.8, 135.4, 134.2, 130.3, 129.3, 128.7, 128.5, 128.4, 128.1, 127.4, 126.6, 125.4, 123.0, 118.4, 31.0, and 13.7. MS (EI): *m/z* (%)=383 (M^+, 29), 382 (100), 340 (49), 289 (8), 258 (33), 188 (3), 152 (13), 128 (20), and 77 (45). Anal. Calcd (%) for $C_{25}H_{21}NOS$: C, 78.30; H, 5.52; N, 3.65. Found: C, 78.11; H, 5.59; N, 3.74.

*4.3.2. 1-(5-((4-Chlorophenyl)thio)-2-methyl-1,4-diphenyl-1H-pyrrol-3-yl)ethanone (**7b**).* White solid; mp 167–168 °C. ^{1}H NMR (200 MHz): δ=7.37–7.26 (m, 8H), 7.07–7.03 (m, 4H), 6.66 (d, *J*=8.4, 2H), 2.33 (s, 3H), and 1.96 (s, 3H). ^{13}C NMR (50 MHz): δ=197.1, 139.4, 136.6, 136.6, 135.2, 134.4, 131.3, 130.2, 129.2, 128.9, 128.7, 128.3, 128.1, 127.7, 127.6, 123.1, 117.8, 31.0, and 13.7. MS (EI): *m/z* (%)=417 (M^+, 100), 401 (27), 376 (24), 374 (62), 289 (10), 261 (12), 258 (33), 152 (17), 128 (26), and 77 (41). Anal. Calcd (%) for $C_{25}H_{20}ClNOS$: C, 71.84; H, 4.82; N, 3.35. Found: C, 71.74; H, 4.97; N, 3.43.

*4.3.3. 1-(5-((4-Methoxyphenyl)thio)-2-methyl-1,4-diphenyl-1H-pyrrol-3-yl)ethanone (**7c**).* White solid; mp 100–102 °C. ^{1}H NMR (200 MHz): δ=7.44–7.31 (m, 8H), 7.04–7.00 (m, 2H), 6.65–6.54 (m, 4H), 3.71 (s, 3H), 2.30 (s, 3H), and 1.96 (s, 3H). ^{13}C NMR (50 MHz): δ=197.2, 158.3, 138.7, 136.9, 135.7, 133.3, 130.6, 129.8, 129.4, 128.7, 128.6, 128.1, 127.9, 127.3, 122.9, 120.2, 114.2, 55.2, 30.9, and 13.6. MS (EI): *m/z* (%)=413 (M^+, 100), 371 (82), 290 (18), 229 (10), 128 (16), 102 (5), and 77 (28). Anal. Calcd (%) for $C_{26}H_{23}NO_2S$: C, 75.52; H, 5.61; N, 3.39. Found: C, 75.39; H, 5.75; N, 3.43.

*4.3.4. Ethyl 2-methyl-1,4-diphenyl-5-(phenylthio)-1H-pyrrole-3-carboxylate (**7d**).* Yellow oil. ^{1}H NMR (200 MHz): δ=7.35–7.26 (m, 8H), 7.09–6.98 (m, 5H), 6.79–6.75 (m, 2H), 4.10 (q, *J*=7.1, 2H), 2.36 (s, 3H), and 1.01 (t, *J*=7.1, 3H). ^{13}C NMR (50 MHz): δ=165.1, 139.9, 138.2, 136.8, 135.0, 134.6, 130.1, 128.59, 128.6, 128.4, 128.4, 127.1, 126.6,

126.3, 125.2, 118.2, 112.6, 59.4, 13.8, and 13.3. MS (EI): m/z (%)=413 (M^+, 100), 384 (5), 340 (26), 287 (5), 230 (13), 128 (14), and 77 (31). HRMS Found m/z 436.1323; $C_{26}H_{23}NNaO_2S$ [$(M+Na)^+$] requires m/z 436.1342.

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