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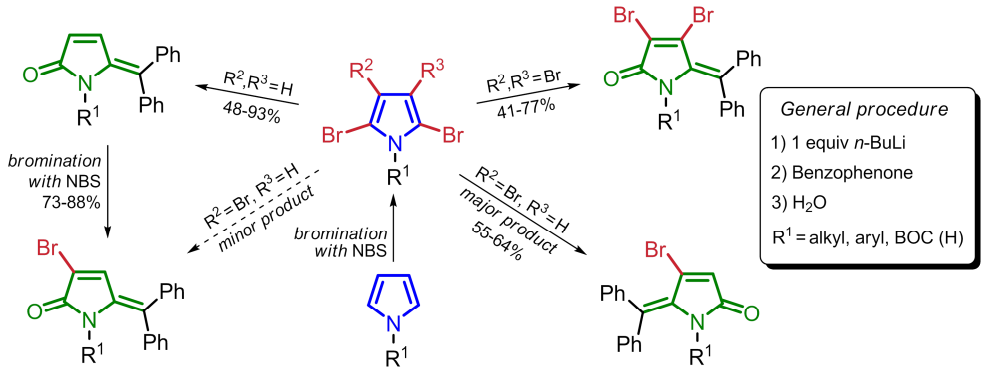

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A novel and convenient method for the preparation of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones; Synthesis and mechanistic study

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ABSTRACT

An efficient, regioselective synthesis has been developed for the preparation of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones from readily available 1*H*-pyrroles by sequential dibromination and selective organometallic bromine/lithium exchange followed by reaction with benzophenone. Comparison of various *N*-substituents was shown to demonstrate the high tolerance of the transformation to functional groups. The structures of the new products were determined by spectroscopic methods and confirmed by single-crystal X-ray diffraction measurement. In addition, theoretical study of the reaction mechanism and selective functionalization of the endocyclic double bond were also presented.

1. Introduction

Over the past decades, numerous research papers have been published describing the versatile methodology for the synthesis of 5-ylidene butenolides.[1-6] 5-Ylidenefuran-2(5*H*)-ones are still important targets for researchers due to their promising biological activities.[3-6] 5-Ylidenepyrrol-2(5*H*)-one structural unit is also found in a number of biologically important natural compounds[7-11] as well as synthetic pharmaceutical molecules.[12-17] Recently, dyes having a 5-ylidenepyrrol-2(5*H*)-one scaffold have also been described as chromophores for dye-sensitized solar cells[18] and electro-optic polymers.[19]

Although 5-ylidene butenolides have been extensively studied, only a few examples are reported for the synthesis of pyrrole analogues. Wittig-type reactions of maleimides[20] and lactamizations of 5-ylidenefuran-2(5*H*)-ones[12,21,22] serve as classical examples of these methods. Due to the growing interest, several new synthetic ways have been published in the last few years.[15,23-32] Among them, cyclization strategies[23-26] mostly catalyzed by transition-metals[27-30] represent new approaches. These generally require the preparation of specific acyclic starting material. Most recently, reductive coupling[33] of succinimides with benzophenone and controlled oxidation techniques[34,35] of 2-alkyl-pyrroles have been developed. Thus, transformations of 5-membered heterocycles to 5-ylidene pyrrolones are valuable alternative methods, however, Kise's reductive coupling[33] requires stoichiometric amount of transition metal and limited to strong Lewis acid tolerant substrates. On the other hand, readily available pyrroles have great synthetic potential,[34,35] although their oxidation usually leads to uncontrolled polymerization and decomposition.[36] Therefore, the development of facile and effective novel methods for the preparation of 5-ylidenepyrrol-2(5*H*)-ones under mild reaction conditions remains a major challenge in organic synthesis.

Recently we have published a highly regioselective bromination method for *N*-substituted 1*H*-pyrroles.[37] Furthermore, we have demonstrated that the halogen atoms of 2,5-dibromo-1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole could be transformed selectively by stepwise organometallic reactions.[37] Bromopyrroles have also great synthetic utility for the preparation of unsaturated γ-lactam structural units. However, 2-bromo-1*H*-pyrroles decompose rapidly after isolation[38] yielding a complex mixture of degradated products, substituted

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2-bromo-5-tosyl-1*H*-pyrrole could be easily transformed to 5-tosyl-1*H*-pyrrol-2(5*H*)-one derivative by acid catalysed reaction.[39] Moreover, oxidation of *N*-substituted 2,5-dibromo-1*H*-pyrrole with concentrated nitric acid leads to the related maleimide structure.[40]

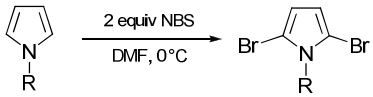
In this paper the convenient synthesis of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones from readily available 1*H*-pyrroles are described. The comparison of various *N*-substituents is shown to demonstrate the high tolerance of the transformation to functional groups. In addition, theoretical study of the reaction mechanism and selective functionalization of the endocyclic double bond are also presented.

2. Results and discussion

2.1. Synthesis of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones

For initial studies of the formation of 5-ylidenepyrrol-2(5*H*)-one structural units from easily accessible pyrroles, a series of *N*-substituted 2,5-dibromo-1*H*-pyrroles were synthesised based on the recently reported method by our group.[37] Aliphatic and various aromatic *N*-substituted dibromo-1*H*-pyrroles (**2a-l**) bearing electron withdrawing or electron donating substituents at different positions of the aromatic rings were prepared, in excellent yields. Moreover *N*-*tert*-butoxycarbonyl protected derivative (**2m**) was also synthesised (Table 1).

Table 1 Synthesis of 2,5-dibromo-1-substituted-1*H*-pyrroles (**2a-m**)[a]



1a-m **2a-m**

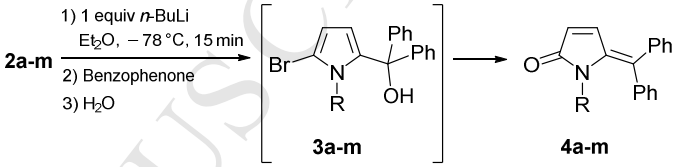
Entry	R group	Product	Yield[b] (%)
1	C_6H_5	**2a**[38]	96
2	4-Me-C_6H_4	**2b**[41]	85
3	2-Et-C_6H_4	**2c**	90
4	2-Et-6-Me-C_6H_3	**2d**	91
5[e]	2-biphenyl	**2e**	88
6	1-naphthyl	**2f**	93
7	2-CF_3-C_6H_4	**2g**[37]	98
8	2-Br-C_6H_4	**2h**	94
9	3-Br-C_6H_4	**2i**	97
10	4-Br-C_6H_4	**2j**	94
11	Benzyl	**2k**[42]	97
12	CH_3	**2l**[38]	86
13	BOC	**2m**[43]	56

[a] The 1-aryl-1*H*-pyrrole derivatives were prepared by Clauson-Kaas pyrrole synthesis[44] following the literature procedures, using 2,5-dimethoxytetrahydrofuran in refluxing acetic acid and commercially available anilines. *N*-Methyl and *N*-*tert*-butoxycarbonyl derivatives were purchased from commercial source.

[b] Isolated yields.

Earlier attempts to prepare diphenyl-(pyrrol-2-yl)-methanol derivatives showed that under acidic conditions water elimination can occur at elevated temperature to produce a corresponding benzoxazepine in good yield[45] Our main goal was to accomplish the efficient combination of this results with the findings that appropriate 2-bromopyrroles can be transformed to 1*H*-pyrrol-2(5*H*)-ones under similar conditions.[46] Therefore, we initiated the organometallic studies using benzophenone as the electrophile. Selective bromine/lithium exchange reaction was performed using 1 equiv of *n*-butyllithium at low temperature followed by the addition of the ketone. LC-MS analysis indicated the formation of the desired bromo alcohol as nearly sole product, however, the first attempt to isolate **3a** has failed. After work-up, visible changes took place in the crude material, its colour slowly altered to dark, and purification by flash column chromatography resulted in a more polar compound as it was expected. Characterisation of the obtained material showed that both of the desired transformations, the elimination of water and the formation of 1*H*-pyrrol-2(5*H*)-one unit were realized simultaneously without any specific additives. Moreover, compound **4a** was obtained in excellent yield (Table 2, entry 2). In addition, the exact structure of **4a** was confirmed by single-crystal X-ray diffraction measurement (Figure 1).

Table 2 Synthesis of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones (**4a-m**)



Entry	R group	Product	Yield[a] (%)
1[b]	C_6H_5	**3a**	72
2	C_6H_5	**4a**	89
3	4-Me-C_6H_4	**4b**	81
4	2-Et-C_6H_4	**4c**	87
5	2-Et-6-Me-C_6H_3	**4d**	80
6	2-biphenyl	**4e**	82
7	1-naphthyl	**4f**	88
8	2-CF_3-C_6H_4	**4g**	92
9	2-Br-C_6H_4	**4h**	70
10	3-Br-C_6H_4	**4i**	90
11	4-Br-C_6H_4	**4j**	93
12	Benzyl	**4k**	69
13	CH_3	**4l**[33]	88
14[c]	BOC → H	**4m**	48

[a] Isolated yields.

[b] The reaction mixture was worked up using basic conditions and **3a** was isolated using preparative RP-HPLC.

[c] Deprotection of *tert*-butyl 2-(diphenylmethylene)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate took place during the transformation, resulting 5-(diphenylmethylene)-1*H*-pyrrol-2-(5*H*)-one (**4m**).

The alcohol intermediate **3a** was presumed to form first in the organometallic reaction, and we were interested in isolating and characterising it. Although the rapid transformation of alcohol **3a** to **4a** was observed, instant reversed phase HPLC separation using slightly basic conditions allowed us to obtain **3a** in pure form (Table 2, entry 1). Immediate characterisation by NMR spectroscopy was carried out successfully, but the elusive **3a** was found to be stable only for a short period of time.

To evaluate the scope of the present reaction, we next investigated a wide range of *N*-substituted 2,5-dibromo-1*H*-pyrroles (Table 2, entries 3-14).

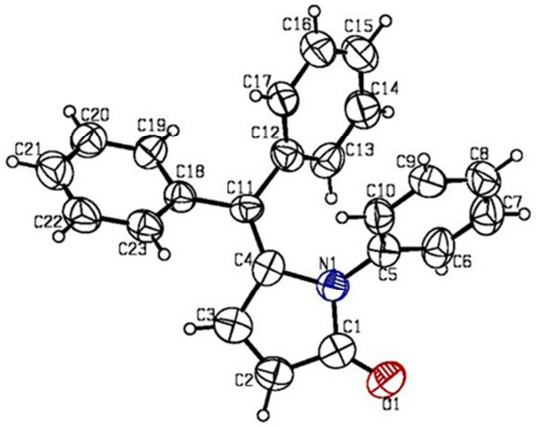


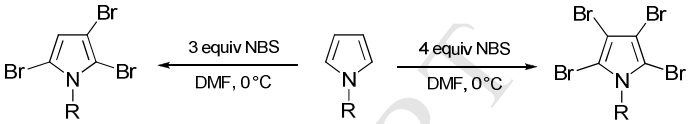
Figure 1 The crystallographically independent molecule in the asymmetric unit of the crystal **4a** with the atomic labelling. Displacement ellipsoids are drawn at the 50% probability level.

Simply allowing the crude products to stand overnight was found to be sufficient for the complete conversions of compounds **3** into **4**. The transformations of both aliphatic and aromatic compounds (**2b-l**) proceeded smoothly providing the corresponding 5-(diphenylmethylene)-1*H*-pyrrol-2-(5*H*)-ones (**4b-l**). Aromatic groups bearing electron donating (**4b-c**) or withdrawing (**4g-j**) functions were equally tolerated, irrespectively of the positions of substituents on the phenyl rings high yields were observed. It is noted, that bromo substituted derivatives have synthetic importance for further functionalizations by coupling reactions, however, the results of the attempts for selective organometallic bromine/lithium exchange is ambiguous. Therefore, the elaborated synthetic strategy was also tested for the synthesis of bromobenzene derivatives **4h-j**. 4-Bromo- and 3-bromobenzene derivatives (**2h** and **2i**) showed good selectivities, the desired products were obtained in excellent yields (Table 2, entries 10 and 11). In the case of the 2-bromobenzene substituted **2j** the transformation into **4j** eventuated in satisfactory results, although the slightly decreased yield (70%) indicated that side reactions had taken place. This observation can be explained by the mechanism of metalation of 1-phenyl-1*H*-pyrrole,[47] the directing effect of the lithium atom in the formed 2-lithiopyrrole derivative could give greater possibility for the bromine/lithium exchange reaction on the benzene ring also.

Another crucial aspect in the synthesis of 5-ylidenepyrrol-2(5*H*)-ones is that most of the published methods for the synthesis of the conjugated scaffold describe exclusively the preparation of *N*-substituted products,[15,23-27,29-32] and fewer studies reported a readily applicable general method with success.[20,33] Therefore, *N*-protected 2,5-dibromo-1*H*-pyrrole (**2m**) was involved in these investigations to develop a route to 5-(diphenylmethylene)-1*H*-pyrrol-2-(5*H*)-one (**4m**). *tert*-Butoxy-carbonyl group was found to be suitable for the protection of pyrrole. Both reactions, the dibromination (Table 1, entry 13) and the bromine/lithium exchange followed by the structural change of the pyrrole ring (Table 2, entry 14), proceeded with moderate yields. Due to the acidic environment during the transformation of the bromo alcohol the removal of the BOC-group was also observed in this case, and the product was isolated in its unprotected form (**4m**).

To further study the scope of the transformation, 2,3,5-tribomo- and 2,3,4,5-tetrabromo-1*H*-pyrroles (**5a-c** and **6a**,**b**) were synthesised using the general method in the presence of 3 or 4 equiv of NBS, respectively (Table 3). The polyhalogenated products were isolated in high yields (71–88%).

Table 3 Synthesis of tribromo- and tetrabromo-1-substituted-1*H*-pyrroles **5a-c** and **6a,b**



5a-c **1a,g,l** **6a,b**

Entry	R group	Product	Yield[a] (%)
1	C_6H_5	**5a**	71
2	2-CF_3-C_6H_4	**5b**	84
3	CH_3	**5c**	75
4	C_6H_5	**6a**	88
5	CH_3	**6b**	81

[a] Isolated yields.

To explore the organometallic bromine/lithium exchange reaction, first the tribomo-1*H*-pyrroles (**5a-c**) were tested using 1 equiv of *n*-butyllithium (Scheme 1, Table 4, entries1-3). Applying the optimal conditions preferred halogen/metal exchanges at the position 2 of the pyrrole rings of **5a-c** were observed and the corresponding 4-bromo compounds (**7a-c**) were isolated in good yields.

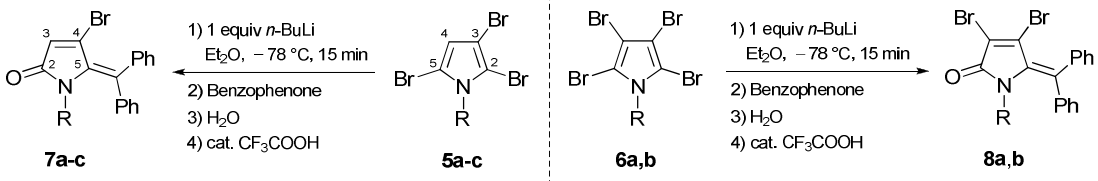
The presence of the regioisomeric 3-bromo derivatives (**9a-c**) in the crude products were also revealed, due to the simultaneous lithiations at the other α-positions. The separation of the regioisomers could easily be accomplished by simple column chromatography resulting the major compounds in pure form In addition, tetrabromo-1*H*-pyrroles (**6a**,**b**) were readily converted to the 3,4-dibromo derivatives (**8a**,**b**, Scheme 1, Table 4, entries 4 and 5).

Table 4 Synthesis of brominated compounds on the endocyclic double bonds **7a-c** and **8a**,**b**

Entry	R group	Product	Yield[a] (%)
1	C_6H_5	**7a**[b]	58
2	2-CF_3-C_6H_4	**7b**	55
3	CH_3	**7c**	64
4	C_6H_5	**8a**	77
5	CH_3	**8b**	41

[a] Isolated yields.

[b] The crude material contained 65% desired product based on ^{19}F NMR measurement.



7a-c **5a-c** **6a,b** **8a,b**

Scheme 1 Synthesis of **7a-c** and **8a-b**.

The intermediate alcohols of **7** and **8** showed somewhat increased stability compared to the unsubstituted compounds (**3**), therefore catalytic amounts of trifluoroacetic acid were added to the crude products to accelerate the completion of the transformations. However, functionalization of the endocyclic double bond was achieved preferably in the position 4 of the ring of **7** by the transformation of the trihalogen derivatives (**5**), we were also insisted on to develop an efficient and selective route to the regioisomeric compounds (**9**). Our goal was accomplished by the bromination of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones (Table 5). Albeit an excess of NBS were required for complete conversions the 3-bromo derivatives (**9a-c**) were formed with excellent regioselectivity and after purification the pure compounds were isolated in high yields.

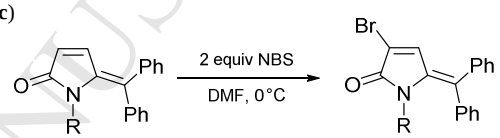
2.2. Mechanistic study on the formation of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones

2.2.1. Proposed reaction mechanism under acidic condition (in the presence of TFA):

In accordance with the experimental results, both the acid and the base catalyzed transformation were studied to gain insight into the formation of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones by G09[48] at B3LYP/6-31G(d,p) level of theory.[49] For the mechanistic study the computed molecules were signed by roman letters. During the exploration of the reaction mechanism under acidic condition, a single trifluoroacetic acid (TFA) molecule was considered as the protonating agent. Under these conditions the protonations of both the pyrrole ring and the alcohol moiety could be presumed.[45,46] Therefore, three different protonation processes were taking into account for the starting material **I** by aqueous TFA, initiating three potential reaction mechanisms (*Route A* in Scheme 2 starting with the protonation of the alcohol moiety; *Route B* and *C* in Scheme 3 starting with the protonation of the pyrrole ring).

Initially, we studied the mechanism strating with water elimination, followed by a specific hydrolysis of the bromopyrrole unit. The proposed reaction mechanism is summarized in *Route A* (Scheme 2). At first formation of hydrogen bonds between the polar groups of the phenylpyrrole derivative and the acid leads to the **Ia**-TFA complex (**IIa**). During this complexation an equilibrium between the TFA dimer and the protonated molecule **IIa** was supposed, resulting in a slightly endothermic process. In the next step, the hydroxyl group is eliminated from the molecule as water *via* the protonation process, providing an unexpectedly stable cationic intermediate (**IIIa**). The corresponding transition state (**TS1a**) energy was found to be moderate (80.4 kJ mol^{-1}). The formed stable cationic intermediate (**IIIa**), represented by two resonance structures, changes its reaction partner from TFA anion – water to two water, slowly reacts with one of the water molecule, involving a well-defined, but high TS (**TS2a**; 116.2 kJ mol^{-1}) and the corresponding intermediate **Va** (–59.6 kJ mol^{-1}). The process finally leads to the product **VIa** through **TS3a** (41.6 kJ mol^{-1}; 101.2 kJ mol^{-1} from **Va**).

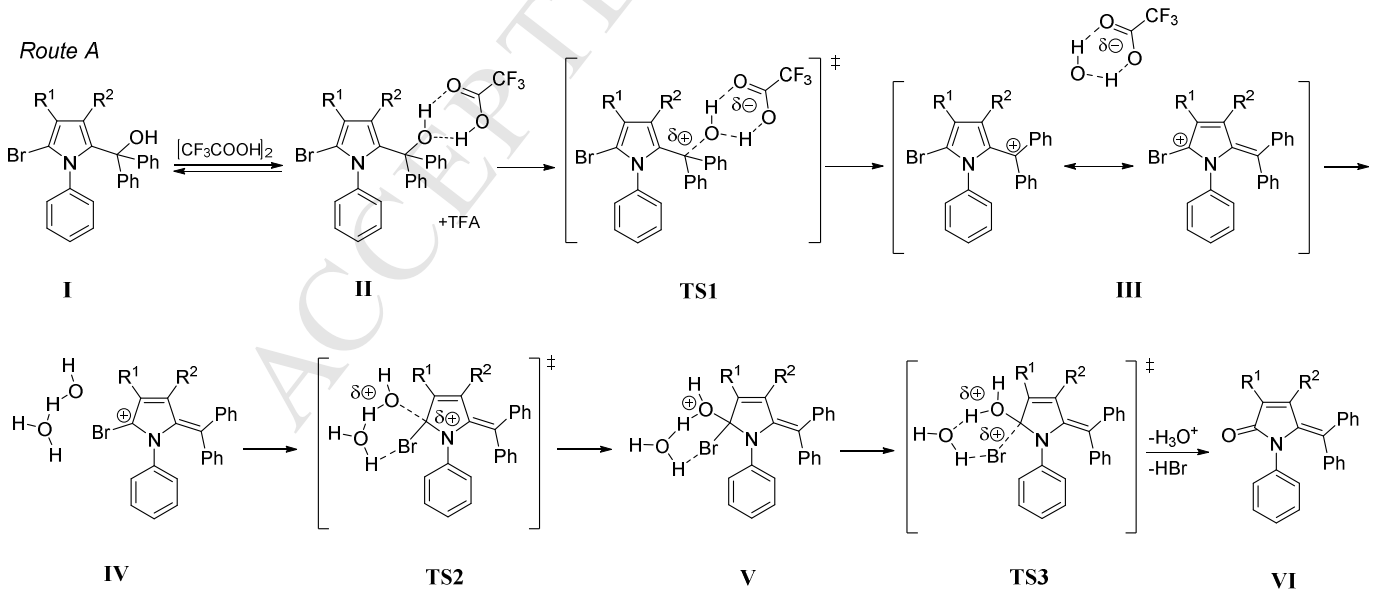
Table 5 Synthesis of 3-bromo-5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones (**9a-c**)



4a,g,l **9a-c**

Entry	R group	Product	Yield[a] (%)
1	C_6H_5	**9a**	82
2	2-CF_3-C_6H_4	**9b**	88
5	CH_3	**9c**	73

[a] Isolated yields.



Scheme 2 The proposed reaction mechanism of the transformation of **I** to **VI** under acidic condition (*Route A*); **a**: R^1,R^2 = H (**Ia ≡ 3a, VIa ≡ 4a**); **b**: R^1 = H,R^2 = Br (**VIb ≡ 7a**); **c**: R^1 = Br,R^2 = H (**VIc ≡ 9a**); **d**: R^1,R^2 = Br (**VId ≡ 8a**); The relating computed enthalpy (Δ*H*) and Gibbs free energy (Δ*G*) values are listed in **Table 6**.

Table 6 Calculated enthalpy (ΔH, kJ mol^{-1}) and Gibbs free energy (ΔG, kJ mol^{-1}) values for *Route A* mechanism of transformation of **I** to **VI** with different substituents (**a**–**d**); computations were carried out at B3LYP/6-31G(d,p) level of theory with the IEF-PCM solvent model, using the parameter set of DCM.[a]

	$R^1 = R^2 = H$ (**a**)		$R^1 = H$; $R^2 = Br$ (**b**)		$R^1 = Br$; $R^2 = H$ (**c**)		$R^1 = R^2 = Br$ (**d**)	
	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG	ΔH	ΔG
II	19.9	19.5	22.0	23.9	21.2	22.6	22.0	23.9
TS1	80.4	92.1	107.3	123.0	98.6	110.7	94.1	106.2
III	46.3	44.8	61.0	58.1	61.5	59.3	69.6	67.0
IV	32.7	28.4	17.9	24.8	30.0	21.3	15.7	18.2
TS2	116.2	133.0	108.8	127.1	115.9	128.8	106.5	125.4
V	-59.6	-53.0	-48.9	-51.4	-51.6	-51.4	-53.0	-52.2
TS3[b]	41.6	39.2	56.4	54.1	39.8	38.6	40.2	39.4
VI	-72.0	-115.5	-73.4	-115.1	-63.5	-106.7	-66.2	-110.0

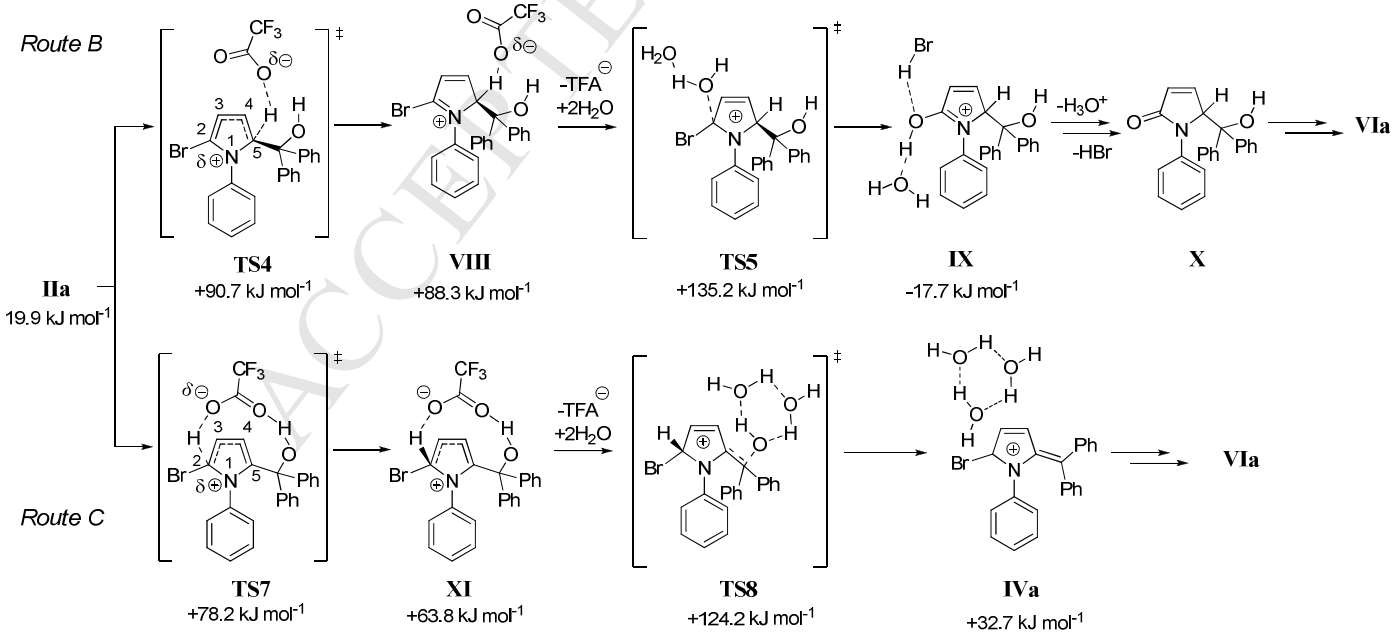
[a] The ΔH(**Ia-d**) values were set as zero points (0 kJ mol^{-1}) during the calculations, respectively.

[b] Estimated values from fixed geometry near to the theoretical transition states.

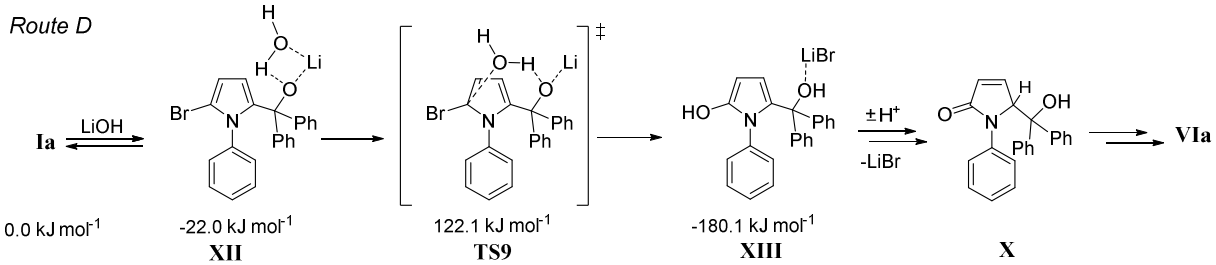
Noteworthy, that the rate determining step of the entire process is the water attack on the α-carbon atom of the heterocyclic ring, which exhibits the highest enthalpy of activation value (**Ia** → **TS2a**; 116.2 kJ mol^{-1}), however, the next Br-elimination step (**Va** → **TS3a**; 101.2 kJ mol^{-1}) also represents significant, but somewhat lower enthalpy value. This highest activation enthalpy, however, does not represent extreme value, allowing relatively fast reaction rate even at room temperature, in agreement with the experimental findings. As can be seen in Table 6, the standard enthalpy of formation of **VIa** [ΔH (**VIa**) – ΔH (**Ia**)] is –72.0 kJ mol^{-1} (solvent model was taking into consideration).

The two monobromo (**Ib** and **Ic**) as well as the dibromo (**Id**) derivatives were also subjected to theoretical investigations (Scheme 1) in order to find the answer to their lower reactivities under acidic conditions compared to the unsubstituted **Ia**, as observed experimentally. Studying the same reaction mechanism (*Route A*) for **Ib**–**Id**, very close enthalpy values were calculated. Decisive difference can be found only for the protonation-water elimination process, where all these transition states exhibited higher enthalpy values by 15–20 kJ mol^{-1} (Table 6, **TS1**, ΔHs). The rate determining steps of the formation of the products (**VIb-d**) reamind the water attack on the α-carbon atom of the heterocyclic ring (**IV**→**V**), however, the higher enthalpy values of **TS1**s can significantly decrease the reaction rate of the transformations. Noteworthy, that the two monobromo derivatives (**IIb** and **IIc**) had larger values, than the dibromo compound (**IId**).

As Lightner's research group showed that the efficient hydrolysis of substituted 2-bromopyrroles could be easily accomplished by TFA yielding 1*H*-pyrrol-2(5*H*)-ones,[46] we were insisted on studying the possibiltiy of this way (Scheme 3). In the case of *Route B* and *C*, the protonations occurred at positions C5 and C2 of the pyrrole rings, respectively. Interestingly, the activation enthalpies of the two carbon protonation processes (**TS4** and **TS6**) showed very close values to the OH-protonation (*Route A*, **TS1**) which make these mechanisms legible on the first sight. However, the cationic intermediates (**VIII** and **XI**) represented quite high instabilities. Moreover, the subsequent steps (**TS5** and **TS8**) possessed larger enthalpy gaps, which were computed for *Route A* (**TS2a**), ranking these mechanisms (*Route B* and *C*) backward.



Scheme 3 The two alternative reaction mechanisms *via Route B* (upper line) and *C* (lower line) for the transformation of **Ia** to **VIa** under acidic condition. The computed enthalpy (ΔH) values are given in kJ mol^{-1} under the related structures. Computations were carried out at B3LYP/6-31G(d,p) level of theory with the IEF-PCM solvent model, using the parameter set of DCM.



Scheme 4 The proposed reaction mechanism under basic condition *via Route D* for the transformation of **Ia** to **VIa**. Computations were carried out at B3LYP/6-31G(d,p) level of theory with the IEF-PCM solvent model, using the parameter set of DCM.

2.2.2. Proposed reaction mechanism under basic condition (in the presence of base):

After the completion of the addition of the ketone, the reaction was quenched with water. The resulting alkaline media could be able to change the reaction mechanism significantly (*Route D* in Scheme 4). In this way, the basic condition allowed intermediate **Ia** to form a complex with LiOH (**XII**), which is able to react with water through a relatively high enthalpy gap (**TS9**, 122.1 kJ mol^{-1}), meanwhile the bromine anion is eliminating from the structure in a parallel way toward the solvent, resulting lithium bromide. In this mechanism, the 122.1 kJ mol^{-1} (**TS9**) represents a considerably high gap, which could allows only a quite slow transformation of **Ia** to **VIa** at room temperature, making possible the safe isolation of **Ia** (≡ **3a** in Table 2) experimentally.

Based on the studied mechanisms and computed energy values for the formation 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones, we concluded that the possibility of the realization of the acid catalyzed *Route A* is much grater than the other studied ways. Moreover, we found that the protonation of the hydroxyl group is depending on the substituents of the pyrrole ring; bromine atom(s) at positions 3 and/or 4 could hinder the protonation-water elimination process decreasing the reaction rate of the transformations significantly, however, the rate determing step of the formation of the products remains the water attack on the α-carbon atom of the heterocyclic rings in all cases.

2.2.3. Systems chemistry analysis

The change of the aromaticity shows interesting evaluation through the reaction, therefore the aromaticity of the central pyrrole ring was examined by aromaticity percentage[50] (in %) and nucleus independent chemical shift[51] (NICS in ppm) methods for **Ia** and **VIa**. From systems chemistry aspect,[52,53] three parameters should be considered in the light of the reaction mechanism, aromaticity (AR, blue),[50,54] olefinicity (OL, red)[55,56] and amidicity (AM, green).[57,58,59] The computed percentage values for these so called *icity* parameters can be easily transformed to their resonance enthalpy values (ΔH_{RE}; eq 1.). The results for the corresponding molecules are summarized in Figure 2.

$$\Delta H_{RE} = \%(\text{icity})/\text{m(icity)} \qquad \text{eq. 1.}$$

where ΔH_{RE} is the resonance enthalpy in kJ mol^{-1}, %(icity) can be the aromaticity(AR), amidicity(AM) or olefinicty(OL) percentage, while m(icity) is the slope of the corresponding icity parameters.[52]

The resonance enthalpies (ΔH_{RE}) are comparable values with enthalpies of formation, moreover, the resonance enthalpies can be added to each other's, in contrast to the non-comparable icity values. Therefore, the transformation of icity parameters to their resonance enthalpies is required for comparison of different values.

In the case of structure **Ia**, only one parameter, the aromaticity is enough to describe the center ring of the molecule, however, **VIa** may require a more sophisticated consideration to describe the detailed structural interactions properly. Structure **VIa** can be analyzed from two aspects. In the first instance the determinant substructure can be composed of two olefinic (OL1, OL2; red) and one amide groups (AM; green), on the other hand it can be considered as only a slightly aromatic, central pyrrole ring (AR; blue number) as well.

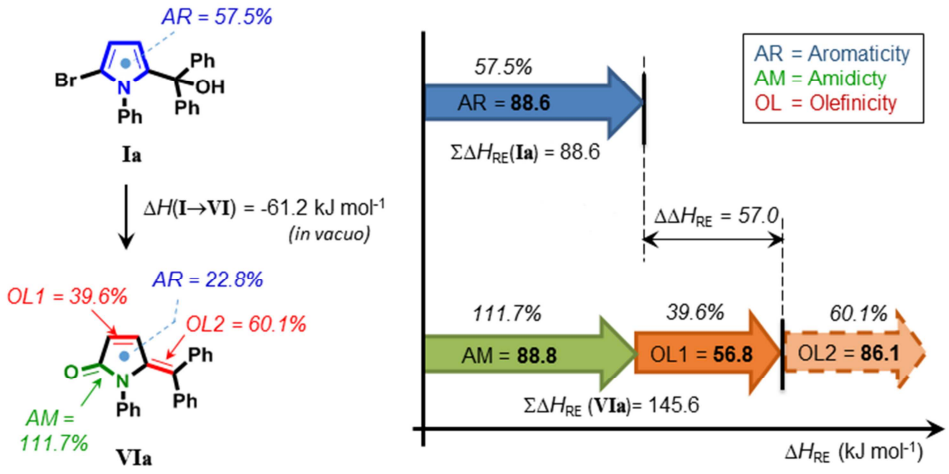


Figure 2 Systems chemistry analysis of the reaction of **Ia** to **VIa**. AR = aromaticity, OL = olefinicity, AM = amidicity in percentage, ΔH_{RE} = resonance enthalpy in kJ mol^{-1}; $\Delta\Delta H_{RE}$ = resonance enthalpy change in kJ mol^{-1}; ΔH(**Ia**→**VIa**) = reaction enthalpy.

Studying only the change of the aromaticity, it can be concluded, that the level of the aromaticity decreases significantly from 57.5% of **Ia** to 22.8% of **VIa**, which gives a quite unfavorable character for the overall process from this aspect. The calculated NICS values for **Ia** and **VIa** confirmed the previous trend. The original –13.2 ppm for **Ia** represents a nice aromaticity, however, the corresponding value is only –2.7 ppm for **VIa**, indicating the weak aromatic character of the product.

Investigating the structure of the product **VIa** from another point of view a more realistic description of the heterocyclic ring could be obtained. A nice cooperation could be recognized between the amide (AM, green) and the olefinic (OL1, red) functional groups, where the amide and the endocyclic double bond of **VIa** intensified each other's icity values (AM = 117.7% and OL1 = 39.6%) due to the fact that their strong conjugation resulted in a slightly aromatic system. In addition, the exocyclic olefin group provides extra electron density to C5, forming the 6-π electron sextet for the ring, resulting in an also high olefinicity value for the exocyclic double bond (OL2 = 60.1%). These olefinicity values (OL1 = 39.6%, OL2 = 60.1%) compared to the relative minimum ($OL_{ethylene}$ = 0%)[55] and maximum ($OL_{allyl\ anion}$ = 100%)[55] values refer to a substantial conjugated nature of the functions. As can be seen in Figure 2, the final of the resonance enthalpy of the heteroycle can be considered for the sum of the endocyclic olefin (OL1) and the amide groups (AM), which provide 145.6 kJ mol^{-1} of resonance enthalpy in summary. The difference between the $\Sigma\Delta H_{RE}$(**VIa**) and $\Sigma\Delta H_{RE}$(**Ia**) is 57.0 kJ mol^{-1}. This value is in a good agreement with the enthalpy gain of the transformation of **Ia** to **VIa** [ΔH (**Ia**) – ΔH (V**Ia**) = 61.2 kJ mol^{-1}], calculated *in vacuo*. These results suggest that the exothermic change in the enthalphy value practically comes from the resonance energy change. In other word, the loss of aromaticity during the transformation of **Ia** to **VIa** is compensated by the resulted new molecular system (aromatic pyrrole → conjugated amide + olefin).

3. Conclusion

In summary, we have demonstrated the new approach of the efficient, regioselective synthesis of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones from readily available 1*H*-pyrroles. Bromo alcohols prepared by sequential dibromination and selective organometallic bromine/lithium exchange followed by reaction with benzophenone proved to be easily transformable intermediates to highly conjugated systems. Comparison of a series of *N*-substituted pyrroles demonstrated the high tolerance of the transformation to functional groups, and single-crystal X-ray diffraction measurement confirmed the structure of the 5-ylidenepyrrolone scaffold. Regioselective mono and difunctionalizations of the endocyclic double bond also shown the versatile usefulness of the elaborated method. Mechanistic study of the reaction mechanism revealed the nature of the process – water elimination followed by hydrolysis of the bromopyrrole unite influenced by acidic additive – and system chemistry analysis suggest that the formation of the conjugated system serves as driving force for the transformation. On the basis of these experimental and mechanistic results this approach could be applied for preparation of highly functionalized divers conjugated systems.

4. Experimental Section

4.1. General

All commercial starting materials were purchased from Sigma-Aldrich Kft. Hungary and Merck Kft. Hungary and were used without further purification. The organometallic reactions were carried out in Schlenk-flasks under a dry nitrogen atmosphere. Solvents were typically freshly distilled or dried over molecular sieves. Diethyl ether was obtained anhydrous by distillation from sodium wire after the characteristic blue colour of the *in situ* generated sodium diphenylketyl had been found to persist. All reactions were monitored by thin-layer chromatography. TLC was carried out on Kieselgel 60 F254 (Merck) aluminium sheets (visualization of the product was made by exposing the plate to UV radiation or by staining it with the aqueous solution of $(NH_4)_6Mo_7O_{24}$, $Ce(SO_4)_2$ and sulfuric acid). Flash column chromatography was performed using a CombiFlash® (Teledyne ISCO). Routine ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained on a Bruker AV 300 or DRX 500 spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) in Hz. Deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS), aceton-d_6 and dimethyl sulfoxide-d_6 (DMSO-d_6) were used as solvents, and signal positions were measured relative to the signals of TMS or solvents (δ_{TMS} = 0 ppm, $\delta_{Acetone}$ = 2.05 ppm, δ_{DMSO} = 2.50 ppm for ^{1}H NMR and δ_{CDCl_3} = 77.0 ppm, $\delta_{Acetone}$ = 29.8 ppm, δ_{DMSO} = 39.4 ppm for ^{13}C NMR). Infrared (IR) spectra were recorded on an appliance type Perkin Elmer 1600 with a Fourier Transformer. Data are given in cm^{-1}. Melting points were determined in capillary tubes, using a Gallenkamp melting point apparatus. High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier XE spectrometer in electrospray ionization (ESI, 2.5 kV) mode, using water (0.035% trifluoroacetic acid)/acetonitrile (0.035% trifluoroacetic acid) as eluent in gradient elution (5%–95% acetonitrile); samples were made up in acetonitrile. The ^{79}Br isotope (M = 78.91834) was used for the calculation and data interpretation of the bromine containing compounds. Single-crystal X-Ray diffraction measurement was accomplished using a Rigaku R-AXIS RAPID diffractometer (graphite monochromator Cu-K_α radiation, λ = 1.54187 Å). CCDC 1017198 (for **4a**) contains the supplementary crystallographic data (including structure factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.2. General procedure for the synthesis of polybrominated 1*H*-pyrrole derivatives[37]

The 1-aryl-1*H*-pyrrole derivatives (**1a-k**) were prepared by Clauson-Kaas pyrrole synthesis[44] following the literature procedures, using 2,5-dimethoxytetrahydrofuran in refluxing acetic acid and commercially available anilines. *N*-Methyl (**1l**) and *N*-*tert*-butoxycarbonyl (**1m**) derivatives were purchased from Sigma-Aldrich Kft. Hungary.

A solution of *N*-bromosuccinimide (NBS, 15.0 mmol, 2.67 g, 2 equiv.) in dry DMF (10 mL) was added dropwise to a stirred solution of 1*H*-pyrrole derivative (**1**, 7.50 mmol) in dry DMF (20 mL) at 0 °C. The mixture was stirred for 30 min after the addition of the solution of NBS was complete. The reaction was monitored by TLC (pure hexane). Hexane (20 mL) and water (60 mL) were added, the phases were separated, and the aqueous phase was washed with hexane (3 × 25 mL). The organic solutions were collected and most part of the solvent was evaporated. The residue was filtered through a short silica column, eluted with hexane and concentrated *in vacuo* to yield pure product. In case of other purification method, it is noted.

For the synthesis of tribrominated products 3 equiv., for the synthesis of tetrabrominated products 4 equiv. of *N*-bromosuccinimide were used.

2,5-Dibromo-1-phenyl-1*H*-pyrrole (2a).[38] The reaction was carried out using 1-phenyl-1*H*-pyrrole (**1a**)[60] as starting material.

TLC was performed in hexane eluent (R_f = 0.40). Pure **2a** is a colourless oil. Yield was 96%; δ_H (300 MHz, $CDCl_3$) 7.54–7.42 (3H, m), 7.34–7.15 (2H, m), 6.31 (2H, s).

2,5-Dibromo-1-(*p*-tolyl)-1*H*-pyrrole (2b).[41] The reaction was carried out using 1-*p*-tolyl-1*H*-pyrrole (**1b**)[61] as starting material. TLC was performed in hexane eluent (R_f = 0.51). Pure **2b** is a colourless oil. Yield was 85%; δ_H (300 MHz, DMSO–d_6) 7.35 (2H, d, *J* 8.0 Hz), 7.16 (2H, d, *J* 8.0 Hz), 6.42 (2H, s), 2.39 (3H, s).

2,5-Dibromo-1-(2-ethylphenyl)-1*H*-pyrrole (2c). The reaction was carried out using 1-(2-ethylphenyl)-1*H*-pyrrole (**1c**)[62] as starting material. TLC was performed in hexane eluent (R_f = 0.44). Pure **2c** is a colourless oil (2.22 g, 90%); ν_{max} (liquid film) 2970, 1515, 1494, 1455, 1421, 1297, 1158 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45 (1H, t, *J* 7.5 Hz), 7.39 (1H, d, *J* 7.0 Hz), 7.31 (1H, t, *J* 7.4 Hz), 7.12 (1H, d, *J* 7.8 Hz), 6.32 (2H, s), 2.31 (2H, q, *J* 7.6 Hz), 1.13 (3H t, *J* 7.6 Hz); δ_C (75 MHz, $CDCl_3$) 143.0, 136.5, 129.8, 129.6, 129.0, 126.4, 112.1 (2C), 102.4 (2C), 23.7, 13.8; HRMS (ESI): MH^+, found 327.9352. $C_{12}H_{12}Br_2N$ requires 327.9336.

2,5-Dibromo-1-(2-ethyl-6-methylphenyl)-1*H*-pyrrole (2d). The reaction was carried out using 1-(2-ethyl-6-methylphenyl)-1*H*-pyrrole (**1d**)[63] as starting material. TLC was performed in hexane eluent (R_f = 0.44). Pure **2d** is a colourless oil (2.34 g, 91%); ν_{max} (liquid film) 3130, 2970, 2934, 2875, 1515, 1472, 1419, 1298 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.40 (1H, t, *J* 7.5 Hz), 7.29 (1H, d, *J* 7.8 Hz), 7.27 (1H, d, *J* 7.6 Hz), 6.48 (2H, s), 2.18 (2H, q, *J* 7.5 Hz), 1.87 (3H, s), 1.09 (3H, t, *J* 7.5 Hz); δ_C (75 MHz, DMSO-d_6) 142.1, 136.6, 134.9, 129.6, 128.0, 126.5, 112.2 (2C), 101.3 (2C), 23.3, 17.0, 13.8; HRMS (ESI): MH^+, found 341.9496. $C_{13}H_{14}Br_2N$ requires 341.9493.

1-[(1,1'-Biphenyl)-2-yl]-2,5-dibromo-1*H*-pyrrole (2e). The reaction was carried out using 1-(biphenyl-2-yl)-1*H*-pyrrole (**1e**)[64] as starting material. Methylene chloride (20 mL) and water (60 mL) were added. The phases were separated, the aqueous phase was washed with methylene chloride (3 × 25 mL) and the collected organic solutions were washed with brine (15 mL), dried over sodium sulfate, concentrated in vacuo. The residue was purified by recrystallisation from hexane (10 mL). TLC was performed in hexane eluent (R_f = 0.30). Pure **2e** is a white solid (2.49 g, 88%); m.p. 91–92 °C; ν_{max} (KBr) 3127, 3056, 1504, 1482, 1455, 1420, 1305, 1158 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62–7.42 (3H, m), 7.33–7.21 (4H, m), 7.20–7.12 (2H, m), 6.16 (2H, s); δ_C (75 MHz, $CDCl_3$) 141.6, 138.1, 135.3, 130.9, 130.3, 129.8, 128.6 (2C), 128.0 (2C), 127.9, 127.5, 112.2 (2C), 102.7 (2C); HRMS (ESI): MH^+, found 375.9312. $C_{16}H_{12}Br_2N$ requires 375.9336.

2,5-Dibromo-1-(naphthalen-1-yl)-1*H*-pyrrole (2f). The reaction was carried out using 1-(naphthalen-1-yl)-1*H*-pyrrole (**1f**)[64] as starting material. Methylene chloride (20 mL) and water (60 mL) were added to the reaction mixture. The phases were separated, the aqueous phase was washed with methylene chloride (3 × 20 mL) and the collected organic solutions were washed with brine (15 mL), dried over sodium sulfate, concentrated in vacuo. The residue was purified by recrystallisation from hexane (10 mL). TLC was performed in hexane eluent (R_f = 0.36). Pure **2f** is a white solid (2.44 g, 93%); m.p. 130–131 °C; ν_{max} (KBr) 3127, 3056, 1504, 1420, 1305, 1158 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.00 (1H, d, J 8.3 Hz), 7.94 (1H, d, J 7.8 Hz), 7.62–7.46 (3H, m), 7.42 (1H, d, J 7.2 Hz), 7.16 (1H, d, J 8.1 Hz), 6.42 (2H, s); δ_C (75 MHz, $CDCl_3$) 134.5, 134.0, 131.4, 130.0, 128.2, 127.6, 127.5, 126.8, 125.0, 122.8, 112.4 (2C), 103.5 (2C); HRMS (ESI): MH^+, found 349.9176. $C_{14}H_{10}Br_2N$ requires 349.9180.

2,5-Dibromo-1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole (2g).[37] The reaction was carried out using 1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole (**1g**)[37] as starting material. TLC was performed in hexane eluent (R_f = 0.44). Pure **2g** is a white solid. Yield was 96%; δ_H (300 MHz, DMSO–d_6) 7.99 (1H, d, J 7.5 Hz), 7.90 (1H, t, J 7.5 Hz), 7.83 (1H t, J 7.8 Hz), 7.49 (1H d, J 8.0 Hz), 6.45 (2H, s).

2,5-Dibromo-1-(2-bromophenyl)-1*H*-pyrrole (2h). The reaction was carried out using 1-(2-bromophenyl)-1*H*-pyrrole (**1h**)[65] as starting material. TLC was performed in hexane eluent (R_f = 0.42). Pure **2h** is a white solid (2.68 g, 94%); m.p. 82–83 °C; ν_{max} (KBr) 3127, 1513, 1483, 1439, 1417, 1300 cm^{-1}; δ_H (300 MHz, DMSO–d_6) 7.87 (1H, d, *J* 7.8 Hz), 7.59 (1H, t, *J* 7.4 Hz), 7.55–7.44 (2H, m), 6.45 (2H, s); δ_C (75 MHz, $CDCl_3$) 137.3, 133.3, 131.3, 131.0, 128.1, 124.7, 112.5 (2C), 102.2 (2C); HRMS (ESI): M^+, found 376.8044. $C_{10}H_6Br_3N$ requires 376.8050.

2,5-Dibromo-1-(3-bromophenyl)-1*H*-pyrrole (2i). The reaction was carried out using 1-(3-bromophenyl)-1*H*-pyrrole (**1i**)[65] as starting material. TLC was performed in hexane eluent (R_f = 0.57). Pure **2i** is a white solid (2.62 g, 97%); m.p. 78–80 °C; ν_{max} (KBr) 3068, 1591, 1575, 1514, 1475, 1429, 1295, 1163 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.62 (1H, d, *J* 8.0 Hz), 7.44 (1H, t, *J* 1.8 Hz), 7.37 (1H, t, *J* 8.0 Hz), 7.22 (1H, d, *J* 7.9 Hz), 6.32 (2H, s); δ_C (75 MHz, $CDCl_3$) 138.7, 132.3, 132.2, 130.1, 127.9, 122.1, 112.9 (2C), 102.2 (2C); HRMS (ESI): M^+, found 376.8047. $C_{10}H_6Br_3N$ requires 376.8050.

2,5-Dibromo-1-(4-bromophenyl)-1*H*-pyrrole (2j). The reaction was carried out using 1-(4-bromophenyl)-1*H*-pyrrole (**1j**)[67] as starting material. TLC was performed in hexane eluent (R_f = 0.54). Pure **2j** is a colourless oil (2.68 g, 94%); ν_{max} (liquid film) 3130, 1517, 1489, 1423, 1387, 1308 cm^{-1}; δ_H (300 MHz, DMSO–d_6) 7.77 (2H, d, *J* 8.6 Hz), 7.29 (2H, d, *J* 8.6 Hz), 6.45 (2H, s); δ_C (75 MHz, DMSO–d_6) 136.3, 132.1 (2C), 131.0 (2C), 122.5, 112.7 (2C), 102.0 (2C); HRMS (ESI): M^+, found 376.8046. $C_{10}H_6Br_3N$ requires 376.8050.

1-Benzyl-2,5-dibromo-1*H*-pyrrole (2k).[42] The reaction was carried out using 1-benzyl-1*H*-pyrrole (**1k**)[68] as starting material. TLC was performed in hexane eluent (R_f = 0.54). Pure **2k** is a white solid. Yield was 97%; δ_H (300 MHz, DMSO–d_6) 7.35 (2H, t, *J* 7.1 Hz), 7.27 (1H, t, *J* 6.9 Hz), 7.00 (2H, d, *J* 7.2 Hz), 6.37 (2H, s), 5.24 (2H, m).

2,5-Dibromo-1-methyl-1*H*-pyrrole (2l).[38] The reaction was carried out using 1-methyl-1*H*-pyrrole (**1l**) as starting material. After the general work-up procedure a few drops of triethyl amine were added to the concentrated organic phases. Elution through a short silica column was carried out using hexane (0.1 m/m% TEA) as eluent. In the absence of TEA, after the elution through a short silica column and evaporation of the solvent under reduced pressure the pure material decomposes violently. Taking the stability issue into account the product was immediately transferred into the polar organometallic reaction. Therefore the full characterisation of 2,5-Dibromo-1-methyl-1*H*-pyrrole was missed. TLC was performed in hexane/ethyl acetate = 20/1 eluent (R_f = 0.66). Pure **2l** is a colourless oil. Yield was 86%.

***tert*-Butyl 2,5-dibromo-1*H*-pyrrole-1-carboxylate (2m).**[43] The reaction was carried out using *tert*-butyl 1*H*-pyrrole-1-carboxylate (**1m**) as starting material. TLC was performed in hexane eluent (R_f = 0.24). Pure **2m** is a colourless oil. Yield was 56%; δ_H (300 MHz, DMSO–d_6) 6.44 (2H, s), 1.59 (9H, s).

2,3,5-Tribromo-1-phenyl-1*H*-pyrrole (5a).[38] The reaction was carried out using 1-phenyl-1*H*-pyrrole (**1a**)[60] as starting material. TLC was performed in hexane eluent (R_f = 0.44). Pure **5a** is a colourless oil. Yield was 71%; δ_H (300 MHz, $CDCl_3$) 7.52–7.48 (3H, m), 7.25–7.20 (2H, m), 6.42 (1H, s).

2,3,5-Tribromo-1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole (5b).[37] The reaction was carried out using 1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole (**1b**)[37] as starting material. TLC was performed in hexane eluent (R_f = 0.37). Pure **5b** is a colourless oil. Yield was 84%; δ_H (300 MHz, DMSO-d_6) 8.01 (1H, d, *J* 7.5 Hz), 7.92 (1H, t, *J* 7.2 Hz), 7.84 (1H, t, *J* 7.4 Hz), 7.58 (1H, d, *J* 7.6 Hz), 6.72 (1H, s).

2,3,5-Tribromo-1-methyl-1*H*-pyrrole (5c).[38] The reaction was carried out using 1-methyl-1*H*-pyrrole (**1l**) as starting material. TLC was performed in hexane eluent (R_f = 0.61). Pure **5c** is a colourless oil. Yield was 75%; δ_H (300 MHz, $CDCl_3$) 6.27 (1H, s), 3.61 (3H, s).

2,3,4,5-Tetrabromo-1-phenyl-1*H*-pyrrole (6a).[38] The reaction was carried out using 1-phenyl-1*H*-pyrrole (**1a**)[60] as starting material. TLC was performed in hexane/ethyl acetate = 8/1 eluent (R_f = 0.68). Pure **6a** is a colourless oil. Yield was 88%; δ_H (300 MHz, $CDCl_3$) 7.55–7.48 (3H, m), 7.25-7.19 (2H, m).

2,3,4,5-Tetrabromo-1-methyl-1*H*-pyrrole (6b).[38] The reaction was carried out using 1-methyl-1*H*-pyrrole (**1l**) as starting material. TLC was performed in hexane/ethyl acetate = 8/1 eluent (R_f = 0.59). Pure **6b** is a white solid. Yield was 81%; δ_H (300 MHz, DMSO-d_6) 3.64 (s, 3H).

4.3. General procedure for the synthesis of 5-ylidenepyrrol-2(5*H*)-one derivatives

The corresponding bromo-1*H*-pyrrole derivative (3.00 mmol) was dissolved in dry diethyl ether (10 mL) under dry nitrogen atmosphere and was cooled to –78 °C. A hexane solution of *n*-butyllithium (3.20 mmol, 2.00 mL, 1.6 M) was added dropwise and after 15 min stirring benzophenone (3.30 mmol, 0.60 g) was added to the reaction mixture. After warming up to room temperature the solvent was changed to methylene chloride and water (5 mL) was added into it. The phases were separated and the aqueous phase was washed with methylene chloride (3 × 4 mL) then the collected organic phases were dried over sodium sulfate and concentrated *in vacuo*. The crude product was alloowed to stand overnight for the complition of the transformation to the corresponding 5-ylidenepyrrol-2(5*H*)-one derivative. The resulted dark material was purified by flash column chromatography.

In the cases of 3- and/or 4-bromo substituted derivatives a catalytic amounts of trifluoroacetic acid were added before the dried organic phases were concentrated *in vacuo*. The crude products were allowed to stand overnight for the completions of the transformation to the corresponding 5-ylidenepyrrol-2(5*H*)-one derivatives. The resulted materials were purified by flash column chromatography.

5-(Diphenylmethylene)-1-phenyl-1*H*-pyrrol-2-(5*H*)-one (4a). The reaction was carried out using **2a**[38] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.27). Pure **4a** is a yellow solid (0.86 g, 89%); m.p. 153–155 °C; ν_{max} (KBr) 3050, 1693, 1498, 1369, 1213, 1163 cm^{-1}; δ_H (500 MHz, Acetone-d_6) 7.46–7.40 (3H, m), 7.34–7.27 (2H, m), 7.25 (1H, d, *J* 5.9 Hz), 7.02–6.85 (10H, m), 6.26 (1H, d, *J* 5.9 Hz); δ_C (75 MHz, Acetone–d_6) 171.8, 141.7, 141.3, 139.3, 139.3, 137.4, 132.4 (2C), 131.7 (2C), 130.6, 129.2, 129.0 (2C), 128.5 (2C), 128.4, 128.2 (2C), 128.1 (2C), 126.5, 122.4; HRMS (ESI): MH^+, found 324.1382. $C_{23}H_{18}NO$ requires 324.1388.

(5-Bromo-1-phenyl-1*H*-pyrrol-2-yl)diphenylmethanol (3a). The reaction was carried out using **2a**[38] as starting material. After the general work-up procedure, the collected organic phases were concentrated under reduced pressure and the residue was purified instantly by preparative RP-HPLC. Gilson pump (333 PUMP); Gilson sampler (GX-281); Detector (UV-VIS-155), Column: Phenomenex, Gemini 250 × 50 mm; 10 µm, C18, 110A, gradient elution (ammonium bicarbonate in water (4 g/L) and acetonitrile). Pure **3a** is a colourless oil (0.87 g, 72%); δ_H (500 MHz, DMSO–d_6) 7.25–7.13 (11H, m), 7.08 (2H, t, *J* 7.5 Hz), 6.81 (2H, d, *J* 7.3 Hz), 6.23 (1H, OH, s), 6.20 (1H, d, *J* 3.9 Hz), 5.52 (1H, d, *J* 3.9 Hz), δ_C (126 MHz, DMSO–d_6) 146.3 (2C), 141.3, 138.9, 130.7 (2C), 128.1, 127.7 (6C), 127.5 (4C), 127.1 (2C), 112.1, 109.3, 105.6, 77.6.

5-(Diphenylmethylene)-1-(*p*-tolyl)-1*H*-pyrrol-2-(5*H*)-one (4b). The reaction was carried out using **2b**[41] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.34). Pure **4b** is a yellow solid (0.82 g, 81%); m.p. 108–110 °C; ν_{max} (KBr) 3042, 2923, 1700, 1552, 1443, 1176 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.47–7.34 (3H, m), 7.26–7.22 (2H, m), 7.18 (1H, d, *J* 5.7 Hz), 7.02–6.88 (3H, m), 6.85–6.75 (6H, s), 6.34 (1H, d, *J* 5.7 Hz), 2.10 (3H, s); δ_C (75 MHz, DMSO–d_6) 170.9, 140.3, 140.2, 137.9, 137.7, 134.8, 133.2, 131.2 (2C), 130.5 (2C), 129.6, 128.3, 128.1 (2C), 128.0 (2C), 127.2, 127.0 (2C), 127.0 (2C), 121.5, 20.3; HRMS (ESI): MH^+, found 338.1549. $C_{24}H_{20}NO$ requires 338.1539.

5-(Diphenylmethylene)-1-(2-ethylphenyl)-1*H*-pyrrol-2-(5*H*)-one (4c). The reaction was carried out using **2c** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.40). Pure **4c** is a yellow solid (0.92 g, 87%); m.p. 115–116°C; ν_{max} (KBr) 2972, 1697, 1491, 1373, 1219, 1161 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.31 (3H, m), 7.25–7.18 (3H, m), 6.97–6.84 (7H, m), 6.83–6.76 (2H, m), 6.31 (1H, d, *J* 5.7 Hz), 2.55 (1H, sex, *J* 7.6 Hz), 2.36 (1H, sex, *J* 7.6 Hz), 1.17 (3H, t, *J* 7.6 Hz); δ_C (75 MHz, $CDCl_3$) 171.9, 141.0, 140.7, 139.6, 138.5, 137.6, 134.5, 131.5 (2C), 130.8, 130.3 (2C), 129.4, 128.3, 128.1 (2C), 128.0, 127.7, 127.5, 127.0 (2C), 125.8, 122.2, 24.0, 13.4; HRMS (ESI): MH^+, found 352.1691. $C_{25}H_{22}NO$ requires 352.1696.

5-(Diphenylmethylene)-1-(2-ethyl-6-methylphenyl)-1*H*-pyrrol-2(5*H*)-one (4d). The reaction was carried out using **2d** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.40). Pure **4d** is a yellow oil (0.88 g, 80%); ν_{max} (liquid film) 3056, 2967, 1701, 1468, 1365, 1217, 1159 cm^{-1}; δ_H (500 MHz, DMSO–d_6) 7.41–7.36 (3H, m), 7.26 (1H, d, *J* 5.9 Hz), 7.18–7.15 (2H, m), 6.96–6.84 (4H, m), 6.80-6.76 (2H, m), 6.74 (2H, t, *J* 7.7 Hz), 6.44 (1H, d, *J* 5.9 Hz), 2.41–2.27 (2H, m), 2.01 (3H, s), 1.05 (3H, t, *J* 7.6 Hz); δ_C (75 MHz, DMSO–d_6) 170.2, 141.3, 140.1, 139.2, 137.1, 136.8, 135.8, 133.5, 130.7 (2C), 129.5, 128.4 (2C), 128.1 (2C), 128.1, 127.6, 127.3, 127.2, 126.8 (2C), 125.2, 122.5, 23.7, 17.8, 13.5; HRMS (ESI): MH^+, found 366.1849. $C_{26}H_{24}NO$ requires 366.1852.

1-[(1,1'-Biphenyl)-2-yl]-5-(diphenylmethylene)-1*H*-pyrrol-2-(5*H*)-one (4e). The reaction was carried out using **2e** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.32). Pure **4e** is a white

solid (0.98 g, 82%); m.p. 174–176 °C; ν_{max} (KBr) 3056, 1694, 1482, 1437, 1368, 1215, 1158 cm^{-1}; δ_H (500 MHz, DMSO–d_6) 7.44–7.34 (4H, m), 7.31–7.26 (1H, m), 7.24 (1H, td, *J* 7.7, 1.4 Hz), 7.19 (2H, t, *J* 7.7 Hz), 7.09 (1H, td, *J* 7.6, 1.2 Hz), 7.04–6.99 (1H, m), 6.96 (2H, t, *J* 7.5 Hz), 6.90–6.85 (3H, m), 6.78 (1H, d, *J* 5.8 Hz), 6.76–6.66 (2H, m), 6.34 (1H, d, *J* 5.8 Hz), 6.31 (2H, d, *J* 7.5 Hz); δ_C (75 MHz, DMSO–d_6) 172.1, 140.2, 139.9, 138.7, 137.8, 137.6, 136.3, 133.4, 131.9, 130.8 (2C), 130.7 (2C), 129.9, 129.6, 128.1 (3C), 127.6, 127.6 (2C), 127.6, 127.3 (2C), 127.2, 127.1, 126.5 (2C), 120.9; HRMS (ESI): MH^+, found 400.1709. $C_{29}H_{22}NO$ requires 400.1696.

5-(Diphenylmethylene)-1-(naphthalen-1-yl)-1*H*-pyrrol-2-(5*H*)-one (4f). The reaction was carried out using **2f** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.40). Pure **4f** is a beige solid (0.99 g, 88%); m.p. 182–184 °C; ν_{max} (KBr) 3098, 3075, 1693, 1404, 1219, 1170 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.75 (1H, d, *J* 8.1 Hz), 7.62 (1H; d, *J* 8.1 Hz), 7.59–7.38 (6H, m), 7.36 (1H, d, *J* 5.9 Hz), 7.27–7.20 (2H, m), 7.19–7.12 (2H, m), 6.74–6.64 (1H, m), 6.57–6.45 (5H, m); δ_C (75 MHz, DMSO–d_6) 171.2, 140.0, 139.9, 138.7, 137.2, 133.2, 132.7, 130.9 (2C), 130.2, 130.0, 129.4 (2C), 128.2, 128.1 (2C), 127.7, 127.3, 127.1, 126.9, 126.1 (3C), 125.6, 124.7, 123.0, 121.9; HRMS (ESI): MH^+, found 374.1526. $C_{27}H_{20}NO$ requires 374.1539.

5-(Diphenylmethylene)-1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrol-2-(5*H*)-one (4g). The reaction was carried out using **2g**[37] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.24). Pure **4g** is a beige solid (1.08 g, 92%); m.p. 182–184 °C; ν_{max} (KBr) 3054, 1701, 1374, 1317, 1159, 1126 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45–7.31 (4H, m), 7.27 (1H, d, *J* 5.9 Hz), 7.24–7.17 (3H, m), 7.15 (1H, d, *J* 7.9 Hz), 7.08 (1H, d, *J* 7.8 Hz), 7.02–6.78 (5H, m), 6.30 (1H, d, *J* 5.8 Hz); δ_C (75 MHz, $CDCl_3$) 172.0, 140.3, 140.2, 139.0, 137.6, 134.0(*J* 1.8 Hz), 132.9, 131.8, 131.3 (2C), 131.2, 130.7 (2C), 128.5, 128.1 (2C), 128.0, 127.9 (*J* 30.9 Hz), 127.7, 127.4 (2C), 127.2 (*J* 4.8 Hz), 123.3 (*J* 273.9 Hz), 121.7; δ_F (282 MHz, $CDCl_3$) –61.04 (3F, s); HRMS (ESI): MH^+, found 392.1254. $C_{24}H_{17}F_3NO$ requires 392.1257.

1-(2-Bromophenyl)-5-(diphenylmethylene)-1*H*-pyrrol-2-(5*H*)-one (4h). The reaction was carried out using **2h** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.28). Pure **4h** is a yellow solid (0.84 g, 70%); m.p. 142–143 °C; ν_{max} (KBr) 3052, 1701, 1477, 1443, 1216, 1161 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.44–7.36 (3H, m), 7.30 (1H, d, *J* 7.8 Hz), 7.26 (1H, d, *J* 5.8 Hz), 7.24–7.18 (2H, m), 7.15 (1H, d, *J* 7.5 Hz), 7.06 (1H, t, *J* 7.5 Hz), 7.00–6.85 (6H, m), 6.42 (1H, d, *J* 5.8 Hz); δ_C (75 MHz, DMSO–d_6) 170.3, 140.0, 139.9, 137.3, 137.1, 135.3, 132.2, 132.0, 131.0 (2C), 129.8 (2C), 129.7, 128.9, 128.3, 128.1 (2C), 128.0 (2C), 127.5, 127.3, 122.5, 121.9; HRMS (ESI): MH^+, found 402.0504. $C_{23}H_{17}BrNO$ requires 402.0488.

1-(3-Bromophenyl)-5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-one (4i). The reaction was carried out using **2i** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 8/1 eluent (R_f = 0.13). Pure **4i** is a yellow solid (1.08 g, 90%); m.p. 139–140 °C; ν_{max} (KBr) 1693, 1588, 1557, 1476, 1364, 1201, 1160 cm^{-1}; δ_H (300 MHz, DMSO–d_6) 7.47–7.36 (3H, m), 7.31–7.25 (2H, m), 7.24 (1H, d, *J* 5.9 Hz), 7.16–7.10 (2H, m), 7.05–6.93 (5H, m), 6.88–6.80 (2H, m), 6.38 (1H, d, *J* 5.8 Hz); δ_C (75 MHz, DMSO–d_6) 170.6, 140.7, 139.9, 137.7, 137.4, 137.1, 131.3 (2C), 130.3 (2C), 130.0, 129.9, 129.2, 128.5, 128.4, 128.1 (2C), 127.7, 127.2 (2C), 126.2, 121.4, 120.2; HRMS (ESI): MH^+, found 402.0475. $C_{23}H_{17}BrNO$ requires 402.0488.

1-(4-Bromophenyl)-5-(diphenylmethylene)-1*H*-pyrrol-2-(5*H*)-one (4j). The reaction was carried out using **2j** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.40). Pure **4j** is a yellow solid (1.12 g, 93%); m.p. 101–103 °C; ν_{max} (KBr) 3074, 1695, 1487, 1363, 1209, 1155 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.47–7.38 (3H, m), 7.30–7.24 (2H, m), 7.23 (1H, d, *J* 5.9 Hz), 7.17 (2H, d, *J* 8.6 Hz), 7.08–6.94 (3H, m), 6.92 (2H, d, *J* 8.6 Hz), 6.83 (2H, d, *J* 7.0 Hz), 6.37 (1H, d, *J* 5.9 Hz); δ_C (75 MHz, DMSO–d_6) 170.6, 140.6, 139.9, 137.7, 137.5, 135.1, 131.2 (2C), 130.5 (2C), 130.4 (2C), 129.9, 129.1 (2C), 128.4, 128.1 (2C), 127.5, 127.2 (2C), 121.5, 118.4; HRMS (ESI): MH^+, found 402.0489. $C_{23}H_{17}BrNO$ requires 402.0488.

1-Benzyl-5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-one (4k). The reaction was carried out using **2k**[42] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.40). Pure **4k** is a yellow solid (0.70 g, 69%); m.p. 135–137 °C; ν_{max} (KBr) 3061, 3027, 1687, 1448, 1363, 1129 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.35–7.20 (6H, m), 7.11–7.07 (3H, m), 7.06 (1H, d, *J* 5.8 Hz), 7.04–7.01 (2H, m), 6.97 (2H, d, *J* 7.6 Hz), 6.56–6.52 (2H, m), 6.29 (1H, d, *J* 5.8 Hz), 4.59 (2H, s); δ_C (75 MHz, $CDCl_3$) 173.4, 140.6, 140.2, 138.7, 138.0, 137.5, 131.4 (2C), 131.2 (2C), 131.1, 128.5, 128.3, 128.0 (2C), 127.9 (4C), 126.7, 126.2 (2C), 122.2, 45.0; HRMS (ESI): MH^+, found 338.1536. $C_{24}H_{20}NO$ requires 338.1539.

5-(Diphenylmethylene)-1-methyl-1*H*-pyrrol-2(5*H*)-one (4l).[33] The reaction was carried out using **2l**[38] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.16). Pure **4l** is a pale yellow solid (0.69 g, 88%); m.p. 116–117 °C; ν_{max} (KBr) 1684, 1592, 1542, 1442, 1422, 1137 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43–7.30 (6H, m), 7.28–7.15 (4H, m), 7.02 (1H, d, *J* 5.8 Hz), 6.20 (1H, d, *J* 5.8 Hz), 2.71 (3H, s); δ_C (75 MHz, $CDCl_3$) 173.0, 140.5, 139.7, 139.2, 138.7, 131.5 (2C), 131.0 (2C), 129.6, 128.5, 128.3, 128.2 (2C), 128.1 (2C), 122.7, 30.2; HRMS (ESI): MH^+, found 262.1218. $C_{18}H_{16}NO$ requires 262.1232.

5-(Diphenylmethylene)-1*H*-pyrrol-2-(5*H*)-one (4m). The reaction was carried out using **2m**[43] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.11). Pure **4m** is a white solid (0.36 g, 48%); m.p. 174–176 °C; ν_{max} (KBr) 3259, 3046, 1683, 1444, 1334, 1209 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 9.84 (1H, br s), 7.45–7.31 (6H, m), 7.23 (2H, d, *J* 6.9 Hz), 7.19–7.11 (2H, m), 7.02 (1H, d, *J* 5.4 Hz), 6.23 (1H, d, *J* 5.5 Hz); δ_C (75 MHz, DMSO–d_6) 172.1, 139.2, 138.5, 137.6, 136.6, 130.8 (2C), 130.2 (2C), 128.4 (2C), 128.1 (2C), 127.9 (2C), 126.5, 124.6; HRMS (ESI): MH^+, found 248.1072. $C_{17}H_{14}NO$ requires 248.1070.

4-Bromo-5-(diphenylmethylene)-1-phenyl-1*H*-pyrrol-2(5*H*)-one (7a). The reaction was carried out using **5a**[38] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 8/1 eluent (R_f = 0.18). Pure **7a** is a yellow solid (0.70 g, 58%); m.p. 167–168 °C; ν_{max} (KBr) 3115, 3044, 1772, 1533, 1508, 1443, 1349, 1295, 1150 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.43 (1H, t, *J* 7.3 Hz), 7.38 (2H, t, *J* 7.4 Hz), 7.24 (1H, s), 7.03–6.94 (5H, m), 6.91 (3H, t, *J* 7.4 Hz), 6.88–6.77 (3H, m), 6.57 (1H, s); δ_C (126 MHz, $CDCl_3$) 169.1, 139.6, 139.4, 136.5, 136.2, 134.4, 132.5 (2C), 131.4 (2C), 131.0, 129.4, 128.4, 128.2 (2C), 128.1 (2C), 127.4 (2C), 127.2 (2C), 126.6, 126.3; HRMS (ESI): MH^+, found 402.0473. $C_{23}H_{17}BrNO$ requires 402.0494.

4-Bromo-5-(diphenylmethylene)-1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrol-2(5*H*)-one (7b). The reaction was carried out using **5b**[37] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.32). Pure **7b** is a yellow solid (0.78 g, 55%); m.p. 108–109°C; ν_{max} (KBr) 1704, 1542, 1454, 1316, 1266, 1125 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.44–7.28 (5H, m), 7.21–6.93 (7H, m), 6.91–6.79 (1H, m), 6.74–6.63 (1H, m), 6.59 (1H, s); δ_C (75 MHz, $CDCl_3$) 169.0, 139.3, 139.2, 136.9, 134.5, 133.7 (d, *J* 1.7 Hz), 133.3, 132.8, 131.8, 131.4, 131.2, 130.9, 130.7, 129.2, 128.3, 128.1, 128.0 (2C), 127.9 (2C), 127.4 (q, *J* 30.5 Hz), 127.2 (q, *J* 4.6 Hz), 126.8, 123.3 (d, *J* 273.8 Hz). δ_F (282 MHz, $CDCl_3$) –60.82; HRMS (ESI): MH^+, found 470.0380. $C_{24}H_{16}BrF_3NO$ requires 470.0367.

4-Bromo-5-(diphenylmethylene)-1-methyl-1*H*-pyrrol-2(5*H*)-one (7c). The reaction was carried out using **5c**[38] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.27). Pure **7c** is a yellow solid (0.65 g, 64%). m.p. 145–146 °C; ν_{max} (KBr) 2921, 1675, 1559, 1445, 1420, 1362, 1317, 1101 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43–7.31 (6H, m), 7.22–7.12 (4H, m), 6.48 (1H, s), 2.67 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.3, 140.3, 139.6, 137.6, 132.8, 132.5 (2C), 131.3 (2C), 129.2, 129.1, 129.0, 128.3 (2C), 128.2 (2C), 127.6, 31.4; HRMS (ESI): MH^+, found 340.0317. $C_{18}H_{15}BrNO$ requires 340.0337.

3,4-Dibromo-5-(diphenylmethylene)-1-phenyl-1*H*-pyrrol-2(5*H*)-one (8a). The reaction was carried out using **6a**[38] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 8/1 eluent (R_f = 0.16). Pure **8a** is a yellow solid (1.11 g, 77%); m.p. 184–185 °C; ν_{max} (KBr) 3056, 1708, 1596, 1539, 1490, 1445, 1357, 1296, 1104 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.45 (1H, t, *J* 7.4 Hz), 7.39 (2H, t, *J* 7.5 Hz), 7.25 (2H, d, *J* 8.3 Hz), 7.03–6.96 (5H, m), 6.95–6.90 (3H, m), 6.86 (2H, d, *J* 7.2 Hz); δ_C (126 MHz, $CDCl_3$) 164.7, 139.8, 139.4, 136.2, 135.7, 134.7, 132.4 (2C), 131.5 (2C), 130.3, 129.6, 128.6, 128.3 (2C), 128.2 (2C), 127.5 (2C), 127.2 (2C), 126.6, 121.5; HRMS (ESI): MH^+, found 479.9592. $C_{23}H_{16}Br_2NO$ requires 479.9599.

3,4-Dibromo-5-(diphenylmethylene)-1-methyl-1*H*-pyrrol-2(5*H*)-one (8b). The reaction was carried out using **6b**[38] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 8/1 eluent (R_f = 0.16). Pure **8b** is a yellow solid (0.51 g, 41%); m.p. 199–200 °C; ν_{max} (KBr) 3053, 1699, 1570, 1472, 1443, 1358, 1295, 1269, 1110, 1011 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.47–7.31 (6H, m), 7.23–7.14 (4H, m), 2.74 (3H, s); δ_C (75 MHz, $CDCl_3$) 165.9, 140.1, 139.7, 136.8, 133.2, 132.4 (2C), 131.3 (2C), 129.5, 129.2, 128.5 (2C), 128.4, 128.3 (2C), 122.1, 32.6; HRMS (ESI): MH^+, found 417.9428. $C_{18}H_{14}Br_2NO$ requires 417.9442.

4.4. General procedure for the bromination of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones

A solution of *N*-bromosuccinimide (NBS, 5.00 mmol, 0.89 g) in dry DMF (5 mL) was added dropwise to a stirred solution of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-one derivative (**4**, 2.50 mmol) in dry DMF (10 mL) at 0 °C. The mixture was stirred for overnight at room temperature after the addition of the solution of NBS was complete. The reaction was monitored by TLC (hexane/ethyl acetate). Ethyl acetate (10 mL) and water (30 mL) were added, the phases were separated, and the aqueous phase was washed with ethyl acetate (3 × 10 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

3-Bromo-5-(diphenylmethylene)-1-phenyl-1*H*-pyrrol-2(5*H*)-one (9a). The reaction was carried out using **4a** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 8/1 eluent (R_f = 0.26). Pure **9a** is a yellow solid (0.82 g, 82%); m.p. 178–179 °C; ν_{max} (KBr) 3057, 1726, 1702, 1493, 1443 1372, 1197, 1078 cm^{-1}; δ_H (300 MHz, Acetone-d_6) 7.51–7.42 (3H, m), 7.40 (1H, s), 7.38–7.28 (2H, m), 7.09–6.88 (10H, m); δ_C (75 MHz, Acetone-d_6) 166.7, 141.3, 139.5, 138.9, 137.6, 137.1, 132.4 (2C), 132.2, 131.8 (2C), 129.5, 129.1 (2C), 128.7, 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.0, 115.5; HRMS (ESI): MH^+, found 402.0487. $C_{23}H_{17}BrNO$ requires 402.0494.

3-Bromo-5-(diphenylmethylene)-1-(2-(trifluoromethyl)phenyl)-1*H*-pyrrol-2(5*H*)-one (9b). The reaction was carried out using **4g** as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.40). Pure **9b** is a yellow solid (1.03 g, 88%); m.p. 164–165 °C; ν_{max} (KBr) 1709, 1496, 1454, 1373, 1315, 1141 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.31 (5H, m), 7.24–7.13 (4H, m), 7.08 (1H, d, *J* 7.6 Hz), 6.99–6.83 (5H, m); δ_C (75 MHz, $CDCl_3$) 166.7, 140.0, 138.4, 137.4, 133.6 (d, *J* 1.5 Hz), 132.7, 132.0, 131.9, 131.3 (2C), 130.7 (2C), 128.8, 128.3 (4C), 128.0, 127.8 (q, *J* 30.9 Hz), 127.5 (2C), 127.2 (q, *J* 4.5 Hz), 123.2 (q, *J* 273.9 Hz), 115.1; δ_F (282 MHz, $CDCl_3$) -60.93 (3F, s); HRMS (ESI): MH^+, found 470.0365. $C_{24}H_{16}BrF_3NO$ requires 470.0367.

3-Bromo-5-(diphenylmethylene)-1-methyl-1*H*-pyrrol-2(5*H*)-one (9c). The reaction was carried out using **4l**[33] as starting material. Flash column chromatography was performed in hexane/ethyl acetate = 4/1 eluent (R_f = 0.40). Pure **9c** is a yellow solid (0.62 g, 73%); m.p. 139–140 °C; ν_{max} (KBr) 2948, 1697, 1590, 1489, 1465, 1444, 1363, 1177, 1133, 1102 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43–7.31 (6H, m), 7.25–7.15 (4H, m), 7.13 (1H, s), 2.76 (3H, s); δ_C (75 MHz, $CDCl_3$) 167.7, 140.1, 138.8, 138.0, 136.7, 131.4 (2C), 131.0 (2C), 130.5, 128.8, 128.7, 128.3 (2C), 128.3 (2C), 116.0, 31.4; HRMS (ESI): MH^+, found 340.0321. $C_{18}H_{15}BrNO$ requires 340.0337.

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Supplementary data

Supplementary data including the copies of NMR spectra, XRD crystallographic data of **4a** and detailes of computational methods can be found in the online version, at http://dx.doi.org/.

References and notes

1. Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707-6738.
2. Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679-718.
3. Liu, G.-Z.; Guan, Y.-B.; Wu, Y.; Liu, H.-M. *Journal of Chemistry* **2013**, 1-8.
4. Zhang, R.; Chan, D.; Jessica, S.; Iskander, G.; Black, D.; Kumar, N. *Arkivoc* **2009**, 102-115.
5. Fáková, H.; Pour, M.; Kuneš, J.; Šenel, P. *Tetrahedron Lett.* **2005**, *46*, 8137-8140.
6. Schmidt-Leithoff, J.; Brückner, R. *Helv. Chim. Acta* **2005**, *88*, 1943-1959.
7. Liras, P. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 1023-1030.
8. Bermejo, F. A.; Rico-Ferreira, R.; Bamidele-Sanni, S.; García-Granda, S. *J. Org. Chem.* **2001**, *66*, 8287-8292.
9. Cardellina, J. H.; Moore, R. E. *Tetrahedron Lett.* **1979**, *20*, 2007-2010.
10. Falk, H.; Grubmayr, K.; Herzig, U.; Hofer, O. *Tetrahedron Lett.* **1975**, *16*, 559-562.

11. Celmer, W. D.; Solomons, I. A. *J. Am. Chem. Soc.* **1955**, *77*, 2861-2865.
12. Ho, K. K. K.; Chen, R.; Willcox, M. D. P.; Rice, S. A.; Cole, N.; Iskander, G.; Kumar, N. *Biomaterials* **2014**, *35*, 2336-2345.
13. Birru, W.; Fernley, R. T.; Graham, L. D.; Grusovin, J.; Hill, R. J.; Hofmann, A.; Howell, L.; James, P. J.; Jarvis, K. E.; Johnson, W. M.; Jones, D. A.; Leitner, C.; Liepa, A. J.; Lovrecz, G. O.; Lu, L.; Nearn, R. H.; O'Driscoll, B. J.; Phan, T.; Pollard, M.; Turner, K. A.; Winkler, D. A. *Bioorg. Med. Chem.* **2010**, *18*, 5647-5660.
14. Li, B.; Lyle, M. P. A.; Chen, G.; Li, J.; Hu, K.; Tang, L.; Alaoui-Jamali, M. A.; Webster, J. *Bioorg. Med. Chem.* **2007**, *15*, 4601-4608.
15. Adhikari, R.; Jones, D. A.; Liepa, A. J.; Nearn, R. H. *Aust. J. Chem.* **2005**, *58*, 882-890.
16. Arai, K.; Sato, M. **1997**, WO9732847.
17. Goh, W. K.; Iskander, G.; Black, D. S.; Kumar, N. *Tetrahedron Lett.* **2007**, *48*, 2287-2290.
18. Bürckstümmer, H.; Kronenberg, N. M.; Meerholz, K.; Würthner, F. *Org. Lett.* **2010**, *12*, 3666-3669.
19. Wang, L.; Bo, S.; Liu, J.; Zhen, Z.; Liu, X. *Polymer Science, Ser. B* **2012**, *54*, 297-305.
20. Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567-2579.
21. Yamada, K.; Kato, T.; Hirata, Y. *J. Chem. Soc. D* **1969**, 1479-1480.
22. Klopfleisch, M.; Seidel, R. A.; Görls, H.; Richter, H.; Beckert, R.; Imhof, W.; Reiher, M.; Pohnert, G.; Westerhausen, M. *Org. Lett.* **2013**, *15*, 4608-4611.
23. Cherry, K.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L.; Abarbri, M. *Tetrahedron Lett.* **2004**, *45*, 2063-2066.
24. Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229-3231.
25. Yoshimatsu, M.; Machida, K.; Fuseya, T.; Shimizu, H.; Kataoka, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1839-1843.
26. Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Chem. Heterocycl. Compd.* **1987**, *23*, 1070-1076.
27. Hou, W.; Zhou, B.; Yang, Y.; Feng, H.; Li, Y. *Org. Lett.* **2013**, *15*, 1814-1817.
28. Grigg, R. D.; Schomaker, J. M.; Timokhin, V. *Tetrahedron* **2011**, *67*, 4318-4326.
29. Saito, T.; Sugizaki, K.; Osada, H.; Kutsumura, N.; Otani, T. *Heterocycles* **2010**, *80*, 207-211.
30. Wuckelt, J.; Döring, M.; Langer, P.; Beckert, R.; Görls, H. *J. Org. Chem.* **1999**, *64*, 365-372.
31. Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1994**, *59*, 7910-7914.
32. Fiorenza, M.; Reginato, G.; Ricci, A.; Taddei, M.; Dembech, P. *J. Org. Chem.* **1984**, *49*, 551-553.
33. Kise, N.; Kinameri, S.; Sakurai, T. *Tetrahedron Lett.* **2013**, *54*, 6944-6948.
34. Kancharla, P.; Lu, W.; Salem, S. M.; Kelly, J. X.; Reynolds, K. A. *J. Org. Chem.* **2014**, *79*, 11674-11689.
35. Howard, J. K.; Hyland, C. J. T.; Just, J.; Smith, J. A. *Org. Lett.* **2013**, *15*, 1714-1717.
36. Kang, H. C.; Geckeler, K. E. *Polymer* **2000**, *41*, 6931-6934.
37. Faigl, F.; Mátravölgyi, B.; Deák, S.; Holczbauer, T.; Czugler, M.; Balázs, L.; Hermecz, I. *Tetrahedron* **2012**, *68*, 4259-4266.
38. Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221-2225.
39. Sabido, P.; Lightner, D. *Monatsh. Chem.* **2014**, *145*, 775-789.
40. Wang, S.; Hong, W.; Ren, S.; Li, J.; Wang, M.; Gao, X.; Li, H. *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 4272-4276.
41. Hildebrandt, A.; Lang, H. *Dalton Trans.* **2011**, *40*, 11831-11837.
42. Choi, D.-S.; Huang, S.; Huang, M.; Barnard, T. S.; Adams, R. D.; Seminario, J. M.; Tour, J. M. *J. Org. Chem.* **1998**, *63*, 2646-2655.
43. Chen, W.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 6025-6026.
44. Elming, N.; Clauson-Kaas, N. *Acta Chem. Scand.* **1952**, *6*, 867-874.
45. Faigl, F.; Tárkányi, G.; Fogassy, K.; Tepfenhardt, D.; Thurner, A. *Tetrahedron* **2008**, *64*, 1371-1377.
46. Brower, J. O.; Lightner, D. A.; McDonagh, A. F. *Tetrahedron* **2001**, *57*, 7813-7827.
47. Faigl, F.; Schlosser, M. *Tetrahedron* **1993**, *49*, 10271-10278.
48. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, X.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09; Gaussian Inc., Wallingford CT, **2009**.
49. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5656.
50. Mucsi, Z.; Viskolcz, B.; Csizmadia, I. G. *J. Phys. Chem. A* **2007**, *111*, 1123-1132.
51. Schleyer, P. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317-6318.
52. Mucsi, Z.; Chass, G. A.; Csizmadia, I. G. *J. Phys. Chem. B* **2009**, *113*, 10308-10314.
53. Mucsi, Z.; Porcs-Makkay, M.; Simig, Gy.; Csizmadia, I. G.; Volk, B. *J. Org. Chem.* **2012**, *77*, 7282-7290.
54. Mucsi, Z.; Körtvélyesi, T.; Viskolcz, B.; Csizmadia, I. G.; Novák, T.; Keglevich, G. *Eur. J. Org. Chem.* **2007**, 1759-1767.
55. Mucsi, Z.; Chass, G. A.; Viskolcz, B.; Csizmadia, I. G. *J. Phys. Chem. A* **2009**, *113*, 7953-7962.
56. Novak, T.; Mucsi, Z.; Balazs, B.; Keresztely, L.; Blasko, G.; Nyerges, M. *Synlett* **2010**, *16*, 2411-2414.
57. Mucsi, Z.; Tsai, A.; Szori, M.; Chass, G. A.; Viskolcz, B.; Csizmadia, I. G. *J. Phys. Chem. A* **2007**, *111*, 13245-13254.
58. Pilipecz, M.; Mucsi, Z.; Varga, T.; Scheiber, P.; Nemes, P. *Tetrahedron* **2008**, *64*, 5545-5550.
59. Mucsi, Z.; Chass, G. A.; Csizmadia, I. G. *J. Phys. Chem. B* **2008**, *112*, 7885-7893.
60. Wu, P.; Zhang, J.; Meng, Q.; Nare, B.; Jacobs, R. T.; Zhou, H. *Eur. J. Med. Chem.* **2014**, *81*, 59-75.
61. La Regina, G.; Bai, R.; Coluccia, A.; Famiglini, V.; Pelliccia, S.; Passacantilli, S.; Mazzoccoli, C.; Ruggieri, V.; Sisinni, L.; Bolognesi, A.; Rensen, W. M.; Miele, A.; Nalli, M.; Alfonsi, R.; Di Marcotullio, L.; Gulino, A.; Brancale, A.; Novellino, E.; Dondio, G.; Vultaggio, S.; Varasi, M.; Mercurio, C.; Hamel, E.; Lavia, P.; Silvestri, R. *J. Med. Chem.* **2014**, *57*, 6531-6552.
62. Faigl, F.; Vas Feldhoffer, B.; Thurner, A. *Synth. Commun.* **2006**, *36*, 2841-2849.
63. Faigl, F.; Vas-Feldhoffer, B.; Kubinyi, M.; Pál, K.; Tárkányi, G.; Czugler, M. *Tetrahedron: Asymmetry* **2009**, *20*, 98-103.
64. Paillet-Loilier, M.; Fabis, F.; Lepailleur, A.; Bureau, R.; Butt-Gueulle, S.; Dauphin, F.; Delarue, C.; Vaudry, H.; Rault, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3753-3757.
65. Liu, H.; Duan, T.; Zhang, Z.; Xie, C.; Ma, C. *Org. Lett.* **2015**, *17*, 2932-2935.
66. Lee, D. H.; Lee, S. G.; Jung, D. I.; Hahn, J. T. *Asian J. Chem.* **2013**, *25*, 501-504.
67. Castro, M. C. R.; Belsley, M.; Fonseca, A. M. C.; Raposo, M. M. M. *Tetrahedron* **2012**, *68*, 8147-8155.
68. Richards, J. J.; Reed, C. S.; Melander, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4325-4327.