The Synthesis of Highly Functionalized Pyrroles: A Challenge in Regioselectivity and Chemical Reactivity

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Dedicated to Prof. Dr. Dr. h.c. Emanuel Vogel on the occasion of his 80th birthday

Abstract: Pyrrole-containing compounds play an eminent role in nature. Since the development of the pyrrole synthesis by Knorr and Paal at the end of the 19th century, the synthesis and study of modified pyrroles has become an active field of chemical research spanning from natural product synthesis, through medicinal chemistry, and on to material science. For example, the synthetic availability of porphyrins and their artificial analogues and isomers in the second half of the last century led to important insights into the function of this prominent molecule in nature. In the last few years, synthetic pyrrole-containing biomacromolecules and intelligent materials such as pyrrole-based conducting polymers have come into focus. All this research requires the efficient synthesis of highly functionalized pyrroles. However, even after more than 100 years since the pioneering work by Paal and Knorr, the synthesis of highly functionalized pyrroles remains challenging. Often, the yields are low and the regioselectivity is only modest. We present here an overview of some recent work in this area, including some of our own research.

1 Introduction

Pyrrole was discovered in the 1830s and finally isolated 150 years ago in 1857 by T. Anderson, through the dry distillation of bone material. Its first synthesis was achieved in 1860 by H. Schwanert. After the elucidation of its structure by A. von Bayer in the 1870s, chemists became increasingly interested in pyrroles and their aromatic properties. Pyrrole is the prototype of a five-membered aromatic heterocycle, even though its aromatic properties are somewhat less than those of thiophene, its sulfur analogue. At the beginning of the 19th century, pyrrole was also identified as an important building block in many natural dyes, such as the porphyrins (including hemoglobin and chlorophyll) and bile pigments.

The deliberate synthesis of substituted pyrroles became possible at the beginning of the 19th century with the pioneering work by Knorr and Paal, who introduced efficient cyclization reactions for the direct synthesis of pyrroles from easily accessed starting materials such as acetoacetates, ketones and amines. Nowadays, a variety of synthetic approaches to substituted pyrroles exists, though their synthesis remains challenging. Often, the yields are rather low and a significant number of byproducts, such as undesired regioisomers, are obtained. Furthermore, pyrroles are susceptible to chemical degradation as they are rather easily oxidized; this further hampers their synthesis and especially their isolation and purification. Thus, even 150 years after its isolation and synthesis, and more than 100 years after the classical pyrrole syntheses were developed, the synthesis of highly substituted pyrroles is anything but straightforward. We present here an overview of some recent work in this area, including some of our own research using pyrroles in supramolecular chemistry. However, we do not intend to provide an exhaustive and complete summary of this synthetic field, but rather to present selected specific examples to highlight some general guidelines and conclusions. The choice of examples is arbitrary and purely subjective.

Most chemical research deals with substituted pyrroles rather than the parent compound itself. The synthesis of such substituted derivatives can be achieved either by substitution reactions using simple pyrroles, or by the choice of appropriate starting materials for direct cyclization into substituted pyrroles. Furthermore, already-substituted pyrroles can be functionalized either by additional substi-
tution or by interconversion of functional groups. All aspects are discussed in this review in a tutorial way, working out the general guidelines (sections 2–5). We then present some specific examples for the synthesis of highly functionalized pyrroles and their application as building blocks for the molecular recognition of anions (section 6). This work is focused on our own research in this field and its purpose is to illustrate some multistep syntheses of pyrroles using modern protecting-group strategies.

2 Monosubstitution of Pyrrole

Pyrrole (1) is an electron-rich heteroaromatic compound and hence its predominant chemical reactivity is its attack by electrophiles and subsequent substitution reaction (Figure 1). In a typical electrophilic aromatic substitution, pyrrole is about \(10^5\) times more reactive than furan, despite its also being more aromatic than furan. The reactivity of pyrrole is comparable to that of an electron-rich benzene derivative such as aniline or phenol. However, pyrrole also contains a polar \(\text{N–H}\) group, and hence is as acidic as a simple alcohol (the \(pK_a\) of pyrrole in aqueous solution is approximately 17.5). Therefore, in a simple pyrrole, there are three possible positions for substitution: the \(\text{N-}\), the \(\alpha\)- and the \(\beta\)-positions. The most important difference in these positions is their proximity to the nitrogen heteroatom that represents the polar center of the ring. Depending on the reaction conditions, substitution is possible in each of these three positions. The regioselectivity of the substitution can, in principle, be controlled by reaction conditions that make use of the specific electronic properties of the pyrrole. If the intrinsic reactivity does not provide the desired regioselectivity, the use of protecting groups to block certain positions can be the method of choice.

2.1 N-Substitution

Substitution at the nitrogen has the largest direct impact on the properties of the pyrrole, as this reaction removes the polar \(\text{N–H}\) and thereby its acid–base properties and capacity as hydrogen-bond donor. Substitution at the pyrrole nitrogen also often destroys its coordination properties; for example, the possibility of introducing a metal into a porphyrin.

As the nitrogen lone pair is part of the aromatic sextet, it is not readily available for reaction with an electrophile. For example, in acidic solutions, protonation occurs preferentially at the carbon atoms of the ring and not at the nitrogen (\(pK_a = –3.8\) for the corresponding protonated form, \(\text{PyrH}^+\)). However, the nitrogen–hydrogen bond is kinetically very labile and undergoes a rapid proton exchange in protic solutions. Therefore, N-substitution of pyrrole can easily be achieved after deprotonation and formation of the corresponding anion. The anion can then be N-alkylated.

Biographical Sketches

Carsten Schmuck is Professor of Organic Chemistry at the University of Würzburg. He studied chemistry and obtained his PhD at the Ruhr University Bochum for work in physical organic chemistry. After a postdoctoral stay at Columbia University in New York with Professor Ronald Breslow, he started his independent academic career at the University of Cologne where he finished his Habilitation in 2001 before moving to his current position in Würzburg in 2002. His main research interests are supramolecular and bioorganic chemistry with a special emphasis on molecular recognition events in aqueous solvents. For this purpose, pyrrole-based guanidinium cations have been developed which are now used for a variety of different applications, such as peptide recognition, organocatalysis, self-assembling nanomaterials, enzyme inhibitors, or nucleic acid sensors.

Daniel Rupprecht studied chemistry and biology in Cologne and obtained his diploma in 2002 working under the guidance of Professor H.-G. Schmalz doing natural product synthesis. He then joined the Schmuck research group, developing artificial receptors for the selective recognition of biologically relevant peptide sequences. He obtained his PhD in 2006 for his work on synthesis and optimization of artificial receptors.
ed or N-acylated in very high yields. In general, N-substitution is the dominant reaction for the sodium or potassium salt of pyrrole and hard electrophiles in dipolar aprotic solvents. For lithium and magnesium salts, significant amounts of α-substitution product are also observed, especially for soft electrophiles such as methyl iodide.

For example, the N-acetylation of pyrrole (1) can be carried out to provide N-acetyl pyrrole (2) in very high yields of 90% (Scheme 1). In this case, pyrrole is used directly as its potassium salt in refluxing tetrahydrofuran with acetyl chloride as the electrophile. The N-methylation of pyrrole also provides a 99% yield of N-methylpyrrole (3), even with the soft methyl iodide as electrophile, when potassium tert-butoxide in pentane is used as base together with 18-crown-6. For a reversible modification of the nitrogen, protecting groups such as tert-butoxycarbonyl (Boc) or benzoxycarbonyl (Cbz) can be introduced very easily and in good yields. For example, the Cbz protection of pyrrole to 4 occurs in yields of 85%, again using the potassium salt, along with benzyl chloroformate (CbzCl) as the electrophile, in tetrahydrofuran. The reversible N-protection can be crucial for further synthetic modifications at other parts of the pyrrole [an interesting example is given in section 4.3 (see Scheme 22)]. After successful synthesis, the protecting group can then be removed from the nitrogen via hydrogenation (for Cbz) or treatment with a strong acid (for Boc).

Scheme 1 Examples for selective conversion at the N-position into: (a) 2 (potassium pyrrole, THF, AcCl, 90%); (b) 3 (KO-Bu, MeI, 18-crown-6, benzene, 99%), or (c) 4 (potassium pyrrole, THF, CbzCl, 85%).

2.2 α-Substitution

The good yields in the N-substitutions described above depend on the selective deprotonation of the nitrogen, as its hydrogen is the most acidic. This deprotonation converts the nitrogen into the (by far) most nucleophilic center. However, electrophilic attack on pyrrole without prior deprotonation occurs predominantly at the ring carbons rather than at the nitrogen. Even simple protonation gives about 80% protonation at the α-carbon and 20% at the β-carbon. In general, electrophilic attack at the α-position is kinetically preferred over attack at the β-position. This regioselectivity can be rationalized in two different ways: First, the orbital coefficients in the HOMO are larger at C2 and C5 than at C3 or C4. Kinetic attack for reactions with early transition states is therefore expected to occur in the α-position. Second, the σ-complex obtained after addition of the electrophile is more stable for the reaction at C2 than that at C3, as more resonance structures can be formulated. Thus, reactions with late transition states (which resemble that intermediate) should occur preferentially in the α-position, and this is observed experimentally.

One very common type of substitution that allows for versatility in terms of further conversion is the introduction of a carbonyl group. This can be performed by electrophilic aromatic substitution. The standard procedure for this conversion is the Vilsmeier–Haack reaction. For the formylation to α-formylpyrrole (5) with N,N-dimethylformamide and phosphoryl chloride in dichloroethane, a yield of 89% is described, whereas a similar acetylation to α-acetylpyrrole (6) with dimethyl acetamide in benzene provides a 75% yield (Scheme 2). However, the introduction of a carbonyl group is not limited to these reactions. Simple conversion with acetic anhydride or acetyl chloride, even without any further catalyst, also gives 6, but with lower yields and sometimes a product mixture with other regioisomers is obtained. For some of the reactions, there are modern variants with significantly improved yields; for example, a zinc-mediated acetylation was developed recently. For this conversion, pyrrole was treated with acetyl chloride and zinc metal in toluene at room temperature, and provided 6 in 90% yield.

Scheme 2 Some examples for α-carbonylation of pyrrole (1) with good yields of: (a) 5 (DMF, POCl3, C6H5Cl, 89%); (b) 6 (Me2NAC, POCl3, benzene, 75%); and (c) 7 (Cl3CC(O)Cl, Et2O, 96%).

One very interesting compound useful for further synthetic modifications is α-trichloroacylpyrrole (7) (Scheme 2). It can be synthesized from pyrrole by Friedel–Crafts acylation with trichloroacetyl chloride, again without the need for any Lewis acid catalyst; this underlines the increased activity of the electron-rich pyrrole in this type of reaction. Pyrrole 7 is easy to prepare and isolate, and as an activated carbonyl group, the trichloroacetyl functionality can be further converted into a variety of other functional groups such as esters or amides as will be discussed below (section 4.1). The high reactivity of pyroles is often advantageous in that no Lewis acids are required, as these tend to induce polymerization and thereby lead to significantly lower yields.

Another alternative for increasing the yield of α-substitution is the metatation of N-protected pyroles and their subsequent reaction with an electrophile. This also allows for modern palladium-catalyzed cross-coupling reactions. The metatation selectively activates this position for electrophilic attack and no regioisomer is formed. However, as the N-protection is also a kind of substitution, this reaction is discussed in section 3.

2.3 β-Substitution

The product of β-substitution is often the thermodynamically more stable one. Nevertheless, it is generally formed.
only in minor amounts in the case of direct alkylation or acylation of pyrrole. β-Methylpyrrole (8) is usually only a by-product of the α-methylation of pyrrole,15 and the direct β-formylation of pyrrole to form 9 has not been described (Scheme 3). β-Acetlypyrrole (10) was only described as a by-product during the preparation of α-acetylpyrrole (6), but was not isolated.16 In principle, the product distribution can be controlled by the conditions of the reaction. However, to achieve a predominant β-regioselectivity, one has to apply very harsh conditions, such as irradiation of starting materials in the gas phase.17 Under these conditions, a 50% relative yield of β-substitution for methylation of pyrrole with MeFMe+ as electrophile can be achieved (besides 15% α- and 35% N-substitution).

\[
\begin{align*}
1 & \quad (a), (b) \text{ or } (c) \\
8 & \quad R = \text{Me} \\
9 & \quad R = \text{CHO} \\
10 & \quad R = \text{Ac}
\end{align*}
\]

Scheme 3  
Electrophilic substitution in the β-position usually occurs only as a by-product. Reagents and conditions: (a) MeF, γ-radiolysis, gas phase, 50% relative yield, no absolute yield given; (b) direct formylation of pyrrole to β-formylpyrrole (9) has not been described; and (c) 10 (AcOH, AlPW12O40, (CF3O)2O, 7% by GC).

Obviously, electrophilic substitution at the β-position is possible but problematic. For example, the gas-phase reaction conditions mentioned above for the synthesis of 8 are certainly not suitable as a general laboratory procedure. One method to circumvent this problem is to rearrange the initially formed α-product to the more stable β-product. For example, β-formylpyrrole (9) can be prepared from the α-isomer 5 by acid-catalyzed rearrangement. For this reaction, 5 is dissolved in a mixture of chloroform and trifluoromethanesulfonic acid (1:1) and heated at reflux temperature for 21 hours. Besides 50% of the starting material 5, the desired β-formylpyrrole (9) is isolated in 30% yield. As one can see at a first glance, these reaction conditions are not appropriate for use with more sensitive pyrrole compounds. Furthermore, polymeric materials are obtained in significant amounts as a byproduct. Thus, this approach is not suited to the general synthesis of more complex compounds.18

3  Disubstitution of Already-Functionalized Pyrroles

Fortunately, the substitution pattern in pyrroles can be controlled by factors other than just the reaction conditions. Another common technique is the introduction of (temporary) substituents which can influence the direction of substitution either by electronic or steric effects.

3.1 Temporary Substituents

The directing effect of a substituent already present in the pyrrole can be illustrated nicely by the formylation reaction. For pyrrole, formylation occurs selectively in the α-position: a 89% yield of 5, without detection of 9, was obtained as already mentioned above.8,13 However, Vilsmeier–Haack formylation of N-tritylpyrrole (11) leads to the β-substituted product, giving up to 6.7 times more of 13 than 12 (Scheme 4) under reaction conditions similar to those used in the formylation of 1.10 Obviously, the sterically demanding trityl group blocks the adjacent α-positions, thereby slowing down electrophilic attack at those carbons. After the reaction, the trityl group can easily be cleaved from the product, making this a very interesting approach for the selective formation of β-substitution products.

\[
\begin{align*}
(a) & \quad R = \text{H} (1) \\
(b) & \quad R = \text{H} (5) > R = \text{H} (9) \\
(c) & \quad \text{R} = \text{CPH}_{3} (11) \quad \text{R} = \text{CPH}_{3} (12) < \text{R} = \text{CPH}_{3} (13)
\end{align*}
\]

Scheme 4  
Regioselectivity of Vilsmeier–Haack formylation depending on the substituent at the N-position. Reagents and conditions: (a) see Scheme 2; (b) PPh3, Br2, DMF, CH2Cl2, reflux, 20 h.

Nevertheless, an 18% total yield for the β-substitution is not satisfactory. However, the following procedure can be used to introduce the formyl group in this position with good regioselectivity and good total yield (Scheme 5). Pyrrole is first protected with the trisopropylsilylethylene (TIPS) group, which can then be brominated with N-bromosuccinimide (NBS), in an excellent yield of 95%, to give exclusively the β-brominated product 15.21 Again, the steric demand of the TIPS group is most likely responsible for this reversal in regiochemistry, as the direct NBS-mediated bromination of pyrrole in tetrahydrofuran at –10 °C provides the α-brominated product in 91% yield.22 Subsequent halogen–metal exchange then allows for the selective functionalization of the β-position, without isomerization. The nucleophilic center of the lithiated pyrrole derived from 15 is exclusively at the desired β-position. Reaction of this carbanion with N,N-dimethylformamide then provides 16 in 82% yield. Subsequent cleavage of the TIPS protecting group provides β-formylpyrrole (9) in an overall yield of 62% from pyrrole (1).23

\[
\begin{align*}
1 & \quad \text{TIPS} \\
14 & \quad \text{TIPS} \\
15 & \quad \text{TIPS} \\
16 & \quad \text{TIPS}
\end{align*}
\]

Scheme 5  
Synthesis of β-formylpyrrole (9) circumventing the problems of poor selectivity and yield observed for direct β-formylation. Reagents and conditions: (a) LDA, TIPSCl, THF, –80 °C; (b) NBS, acetonitrile, reflux; (c) BuLi, THF, –78 °C, DMF; (d) TBAF, THF.
3.2 Permanent Substituents

Organometallic reactions at pyrroles generally require N-protection. In the previous example, the TIPS group served this purpose and allowed for the formation of a stable lithio-pyrrole compound by halogen–metal exchange. If the reactant already bears a substituent at the N-position, this protection is not necessary. The pyrrole is then also accessible for modern cross-coupling reactions as the following example shows (Scheme 6). N-Methylpyrrole (3) can be lithiated directly in the α-position. The lithiation of pyrrole 17 was next converted into the Grignard reagent 18 by transmetalation, and then palladium-catalyzed coupling of 18 with phenyl bromide provides 19 in an excellent 87% overall yield.24

The reversible introduction of a substituent to control the regioselectivity of a second functionalization is mostly limited to the N-protecting groups. However, functional groups that are already present on the ring also have significant effects on the regioselectivity of the disubstitution. In general, electron-releasing substituents in the 2-position direct an incoming electrophile into the 3- or 5-position, whereas electron-withdrawing groups direct the electrophile into the 4- or 5-position. For example, the formylation of methyl pyrrole-2-carboxylate 20 gives a mixture of both the 4- and 5-substituted methyl formylpyrrolecarboxylates 21 and 22 (Scheme 7). The ester group decreases the electron density in the ring, so that the overall reactivity is reduced. Furthermore, attack in the α'-position (C-5) becomes less favorable, as can be seen by the inspection of possible resonance structures for the α-complex, one of which is shown in Scheme 7. The kinetic preference for α-substitution is thereby reduced and one expects an increased amount of the more stable β'-product (substitution at C-4) compared to the reaction with pyrrole (1) as a starting material. Indeed, in the case of the α-methyl ester 20, Vilsmeyer–Haack formylation provided a mixture of both isomers. As both regioisomers can be separated readily using column chromatography this method is a suitable synthesis for both products. Furthermore, the reaction conditions can again influence the product distribution significantly. Several research groups obtained a α/β (21/22) ratio of 1:3, 25 3:26 or 5:227 using only slightly differing reaction conditions. With the right choice of reaction conditions, a yield of up to 60% of the α-substituted product 21 can be achieved, making this route a suitable method for its synthesis against all odds.

How the reaction conditions control the substitution pattern has been investigated extensively for the Friedel–Crafts acylation of 23 (Scheme 8).28 It was found that the substitution pattern for this reaction depends strongly on the Lewis acid catalyst and the temperature. With total yields of 85–99% for all conditions screened, the product distribution differs significantly. Whereas treatment with iron(III) chloride at 0 °C gives an α/β ratio of 1:7.3, the use of zinc chloride at 50 °C provides an inverted product distribution of 1:8.1, in accord with kinetic control that favors the α-substitution (more reactive Lewis acid and lower temperature) and thermodynamic control that favors the β-product (less reactive Lewis acid and higher temperature). Unfortunately, the general reactivity, and therefore the reaction time and overall yield, can become a problem under strictly kinetic control (low temperatures).

Another possibility for increasing the regioselectivity of electrophilic attack is for the undesired position to be blocked by substituents. The nitration of pyrrole can be used as an example (Scheme 9). In general, nitration is a low-yielding reaction owing to the harsh reaction conditions that have to be applied.29 We observed that the direct nitration of 20 leads to a yield of only 10% of 26 and 7% of the C-4 regioisomer.30 One of the problems of the direct nitration of pyrrole is the limited stability of the products under the oxidative reaction conditions.31 Pyrroles are electron-rich compounds which are quite easily oxidized. If both β-positions are blocked, as in the 3,4-dimethylpyrrole 27, the yield is increased to 40% of 28. The methyl substituents make the pyrrole more susceptible to electrophilic substitution.
philic substitution as well as to oxidation. As the significantly increased yield demonstrates, the former aspect dominates in this case.

This general influence of an electron-donating substituent can also be seen for the nitration of 2-methylpyrrole (3). The product distribution remains similar to that for the nitration of 20, which lacks any electron-donating substituent, but the total yield is significantly increased. After nitration of 3, 25% yield of α-product 29 and 14% yield of β-product 30 are obtained (Scheme 10).32 This observation, too, can be explained by the increased stability of the product (the absence of the NH prevents the formation of the anion which is even more easily oxidized than the parent pyrrole). Again, the reactivity of the starting material towards electrophilic substitution is larger.

The subtlety of the effects of a substituent and the changes it causes in terms of regioselectivity and reactivity can be seen for the nitration of the trichloroacetylpyrrole 7 (Scheme 11). The electron-withdrawing properties of this substituent deactivate the ring and promote 4-substitution in the same way as mentioned above for the methyl ester 20 (see Scheme 7). Thus, a predominant β'-substitution can be achieved and the formation of 7 gives mainly 4-formyl-2-trichloroacetylpyrrole (31) in 75% yield.33 In contrast to this observation, the nitration of 7 leads to a surprisingly high yield of 61% of α'-nitropyrrrole 32. Subsequent hydrolysis of the trichloroacetyl group to the methyl ester can be achieved in 97% yield, and makes this route the method of choice for synthesis of 26 by circumventing the less effective direct nitration of the α-methoxycarbonylpyrrole (20) mentioned in Scheme 9.30

All these examples show that pyrrole chemistry is often controllable, but not always predictable, as in general more than one factor has to be considered. Hence, empirical guidelines can be deduced based on experimental ob-

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Scheme 9  α-Nitration of pyroles. Reagents and conditions: (a) HNO₃, Ac₂O, −15 °C, 10%; (b) pentylnitrite, Et₂O, r.t. The increased yield can be explained by the blocking of the competing substitution at the β-position, as well as by the higher reactivity of the activated pyrrole.

Scheme 10  N-Methylation leads to significantly increased yields in nitration reactions. Reagents and conditions: (a) HNO₃, Ac₂O, T < 5 °C, 25% 29 and 14% 30.

Scheme 11  An electron-withdrawing substituent in the α-position favors subsequent substitution at the β-position. Nevertheless, this is a suitable starting material for the synthesis of 26. Reagents and conditions: (a) (dichloromethoxy)methane, AlCl₃, CH₂Cl₂, MeNO₂, −20 °C; (b) HNO₃, Ac₂O, −40 °C; (c) NaOMe, MeOH, reflux.

4  Interconversion of Substituents

If the direct introduction of the desired substituent is not feasible (owing to its instability under the reaction conditions or an unfavorable regiochemistry), the interconversion of functional groups might be the method of choice. Once a substituent has been installed in the desired position, its further conversion can most often be performed without isomerization and without a change in the substitution pattern.

4.1 Transformations Involving Carbonyl Groups

The aldehyde function in 21 represents the most reactive carbonyl group and can be converted in a versatile manner (Scheme 12). Oxidation with potassium permanganate provides the corresponding acid 33 in a very good yield of 75%.34 Reduction with sodium borohydride to the alcohol also takes place selectively at the aldehyde function, without affecting the ester, and 34 can be obtained in good yields.35 For a similar compound, the direct reductive amination of the aldehyde function with sodium cyanoborohydride and valine was reported to provide the corresponding secondary amine in a very good yield of 78%.36

Scheme 12  Selective oxidation and reduction of the aldehyde is possible. Reagents and conditions: (a) KMnO₄, acetone–H₂O (1:1); 40 °C; (b) NaBH₄, THF or MeOH.
Pyrrole dicarboxylates of the type 33 are versatile in synthesis. An example from our work is the synthesis of 35 (Scheme 13), a standard building block for the synthesis of supramolecular binding motifs for the recognition of carboxylates. The alcoholysis of trichloroacetylpyrrole 7 with sodium benzylate provides the benzyl ester 36 in a 91% yield. Vilsmeier–Haack formylation of 36 then gives 37, which can be oxidized to carboxylic acid 38 with potassium permanganate. PyBOP-mediated coupling with Boc-guanidine provides the benzyl ester 35. The overall five-step yield of 31% can be considered as excellent for a compound with such a high degree of functionalization, and demonstrates that this kind of pyrrole chemistry is compatible with modern orthogonal protective groups, for example the use of the tert-butoxycarbonyl and the benzyl ester groups in the same synthesis.

Scheme 13  Synthesis of 35. Reagents and conditions: (a) NaOBN, BnOH, CH2Cl2, r.t., 1 h, 91%; (b) PCl3, DMF, DCE, r.t., 27 h, 63%; (c) K2MnO4, acetone–H2O (1:1), 40 °C, 67%; (d) Boc-guanidine, PyBOP, NMM, DMF, 84%; (e) H2, Pd/C, MeOH, 95%.

4.2 Radical α-Halogenation

Another versatile possibility for the further interconversion of substituents is their functionalization via radical reactions. For this kind of reaction, too, an effective distinction between the α- and β-positions is possible. For example, an α-methyl group can be reacted selectively in the presence of one or more β-methyl groups. Through radical reaction, the methyl at the α-position can be chlorinated up to three times without affecting the β-substituents. This is a surprisingly good regioselectivity, because each chlorination deactivates the α-position for the next radical reaction (chlorine atoms are electrophilic radicals which prefer electron-rich carbon–hydrogen bonds). However, if there is any unsubstituted ring position, halogenation occurs at the ring carbons before the methyl group is attacked. For example, sulfuryl chloride or elemental bromine can convert pyrrole into the tetrahalopyrroles, and N-bromosuccinimide gives the 2-bromopyrrole. This limits the methodology to the halogenation of fully substituted pyrroles, that is to say pyrroles with no ring hydrogens.

The preference for radical reaction in the α-position can be explained by considering that the radical obtained through H-abstraction from the α-methyl group is much better stabilized by resonance than the radical formed from a β-methyl group. The degree of oxidation can be controlled simply by the amount of added chlorination reagent. Sulfuryl chloride is easy to handle and is the reagent of choice because it is a liquid at room temperature and can be quantified easily. The chlorinated products can be isolated if needed, but are often very sensitive to nucleophilic attack and are therefore directly converted into the desired products by alcoholysis or aqueous work-up, for example. For a choice of possible products, see Scheme 14.

Scheme 14  Radical chlorination at the α-position and subsequent alcoholysis or hydrolysis (R2 = any residue but H). Reagents: (a) n = 1–3, 1–3 equiv SO2Cl2; (b) n = 1, H2O, 41; (c) n = 1, R1OH, 42; (d) n = 2, H2O, 43; (e) n = 2, R1OH, 44; (f) n = 3, H2O, 45; (g) n = 3, R1OH, 46.

The oxidation of the α-methyl group with one equivalent of sulfuryl chloride to obtain the corresponding alcohol 41 is described in the literature to take place without isolation of the intermediate monochloride. Nevertheless, this is not a procedure often used because the direct oxidation of an α-methylpyrrole to an alcohol can be achieved more easily with lead tetraacetate or iron(III). Of greater interest is the use of other nucleophiles for quenching the α-chlorinated product. The α-methylpyrrole 47 can be chlorinated selectively in the α-position (Scheme 15) despite its having alkyl functions, that are also susceptible to radical reactions, in both β-positions (see below). Direct alcoholysis of monochloride 48 to form ether 49 occurs...
readily while warming in ethanol. However, the use of 48 as electrophile for other attacking nucleophiles is also of great interest. Nucleophilic attack of a second pyrrole, as in the formation of the dipyrole 50, gives a yield of 55%. This is surprisingly good with regard to the fact that the attaching pyrrole (3-ethoxycarbonyl-4-methylpyrrole) has three nucleophilic centers (the NH and two different α-positions). 50 is a key intermediate in the total synthesis of chlorophyll a.47

The next level of oxidation, from methyl to aldehyde, can also be achieved by lead tetraacetate as well as sulfuryl chloride.48 For oxidation to the aldehyde, methylpyrrole 51 was reacted with two equivalents of sulfuryl chloride to provide dichloride 52 (Scheme 16). Although there is a second methyl group in the β-position, and the first chlorination deactivates the α-position to the subsequent chlorination, this reaction gives a 67% yield of the α,α-dichlorinated product. This indicates that the relative activation of the α-position by the electron-donating properties of the pyrrole nitrogen is significantly stronger than the deactivation by the inductive effect of the first chloro substituent. Aldehyde 53 can then be obtained in an excellent yield by hydrolysis of the dichloride.49

Selective oxidation of the α-methyl group to the trichloride (i.e., carboxylic acid oxidation level) is also possible. Due to the very high electrophilicity of this kind of compound (three electron-withdrawing substituents in the side chain), the trichloride is normally not isolated but instead converted directly, to an acid derivative, for example. An illustration of this is the chlorination of 54 followed by hydrolysis that provides the acid 55 in 80% yield (Scheme 17).52

This method can also be used to obtain, directly, acetal 44 (Scheme 14) which is of interest as a protected version of the aldehyde. There are some examples for such protected α-aldehyde pyrroles described in literature, and these are most often N-protected as well. However, they are normally not synthesized via alcoholsysis of the corresponding dichloride and are therefore not discussed here.50 A similar alcoholsysis of an α-dichloromethyl group to the α-dimethoxyacetal was performed with an indole derivative in 91% yield using sodium methoxide as the nucleophile.51 In general, direct acetal formation from the dichloride remains a synthetic challenge because alcoholsysis of the dichloride releases two equivalents of hydrochloric acid which can cause hydrolysis of the acetal or polymerization of the pyrrole. To prevent these side reactions, careful control of the reaction conditions is necessary and the acid has to be trapped effectively. Unfortunately, not every compound survives treatment with base.

Scheme 16 α-Oxidation to aldehyde 53 via the dichloride. Reagents and conditions: (a) 2 equiv SO2Cl2, AcOH, 50 °C, 30 min; (b) H2O, EtOH, reflux.

Scheme 17 Oxidation of α-methylpyrrole 54 to acid 55. Reagents and conditions: (a) SO2Cl2, Et2O, CH2Cl2, 10 min, reflux; (b) H2O, acetone, NaHCO3, 80% overall yield.

The major problem in the synthesis of α-pyrrolecarboxylic acids is their sensitivity to acid-induced decarboxylation. During the hydrolysis of the trichloride, three equivalents of hydrochloric acid are released, and these have to be quenched effectively. For this purpose, a wide range of reaction conditions (variation of solvent, base, etc.) have been described in the literature, but no standard procedure that works for any compound has been established.53 Normally, for each specific compound, the best reaction conditions have to be established empirically. On the other hand, the ease of decarboxylation of α-pyrrolecarboxylic acids can be utilized advantageously, for the synthesis of pyrroles without substitution in this α-position. If the carboxylic acid group remains from the ring synthesis (see below) or was needed as a directing group for the introduction of another substituent, it can easily be removed afterwards by acidic decarboxylation. This is exemplified in the synthesis of 58 (Scheme 18). The starting material 56 bears electron-donating methyl groups which increase the general tendency of pyrrole carboxylic acids to undergo decarboxylation. The benzyl ester can be cleaved by hydrogenolysis, and the resulting acid 57 is so sensitive to decarboxylation that it has to be stored at −20 °C. Stirring with trifluoroacetic acid (which is still less acidic than the hydrochloric acid released during hydrolysis of the trichloroacetyl group to the carboxylic acid) then decarboxylates 57 to provide 58 in a high yield of 83%.54 There are even α-pyrrolecarboxylic acids described in the literature whose intrinsic acidity is sufficient to induce self-decarboxylation at higher temperatures.55 Often they decarboxylate in solution upon warming, or in the solid state at their melting points. In this regard, an α-carboxylic acid group can be considered as a cleavable protecting group.

There are various methods to circumvent the problem of α-decarboxylation if the acid is the desired target.
aqueous work-up. The α-pyrrole aldehyde is much more stable under acidic conditions than is the corresponding carboxylic acid. After its isolation, the aldehyde can then be oxidized in a second step, selectively and under mild conditions, to the acid. This has already been shown above for the oxidation of 37 (see Scheme 13). Another route to avoid producing the free acid under the given reaction conditions is to perform a direct alcoholysis of the trichloride intermediate to the ester instead of the aqueous work-up that leads to the acid. Chlorination of 58 followed by methanolysis provides 59 in a 69% yield (Scheme 19). If the acid is needed, it can then be released, for example, by basic saponification of the methyl ester. The deprotonated carboxylate released after basic cleavage of the ester is much more stable towards decarboxylation than is the free acid.

\[ \text{Scheme 19 Oxidation to the carboxylate. Reagents and conditions:} \]
\[ \text{(a) SO}_2\text{Cl}_2, \text{CCl}_4, \text{0 °C, 8 h; (b) MeOH, NaOAc, 50 °C, 5 h, 69% overall yield.} \]

### 4.3 Radical β-Halogenation

If there is no free ring hydrogen and both α-positions are unreactive toward radical reactions, the β-position can also be reacted selectively. A relevant example is shown in Scheme 20. In pyrrole 60, both β-methyl groups can be oxidized selectively to produce the dibromide 61 in good yields using N-bromosuccinimide as the brominating reagent.

\[ \text{Scheme 20 Radical halogenation of the β-position. Reagents and conditions: (a) NBS, AIBN, CCl}_4, \text{reflux, 2.5 h, quantitative yield.} \]

The resulting dibromide can then be used as an electrophile in further reactions. We used it, for example, to adjust the solubility of pyrroles without affecting their acid–base or coordination properties. As an illustration of this, in order to enhance the water solubility of a certain pyrrole, triethylene glycol side chains were introduced by treatment of dibromide 61 with triethylene glycol under basic conditions. The best reaction conditions were found to be heating a solution of 61 in triethylene glycol to reflux for 24 hours in the presence of triethylamine as a co-solvent. Work-up of the reaction had to be carried out carefully because of possible product loss owing to its good water solubility. Therefore, the yield can be increased significantly by avoiding aqueous work-up and purifying the crude reaction mixture directly after evaporation of the solvent by means of reverse-phase column chromatography. By this method, the yield of 62 can be increased from <45% after aqueous work-up to 64% (Scheme 21).

\[ \text{Scheme 21 Mediation of solubility properties by modification in the β-position. Triethylene glycol chains enhance the solubility in aqueous media, whereas the hexyl chains mediate solubility in polar solvents. Reagents and conditions: (a) triethylene glycol, Et}_3\text{N, 100 °C, 24 h; (b) TFA, r.t., 1 h, then n-hexan-1-ol, toluene, Et}_3\text{N, reflux, 20 h.} \]

To mediate the solubility of pyrroles in organic solvents, n-hexyl side chains can be introduced into the molecule, again using nucleophilic substitution but this time with hexanol as the reaction partner. Surprisingly, this reaction did not work well with the diester under the same conditions that allowed the introduction of the triethylene glycol chains. However, after acidic cleavage of the tert-butyl ester in 61, both bromines can be substituted by n-hexanol to provide 63 in 85% yield (Scheme 21). Dibromide 61 can also be used to incorporate the pyrrole into a cyclic scaffold. One example is the reaction of two equivalents of 61 with 1,2,4,5-tetrahydroxybenzene as the nucleophile, as shown in Scheme 22. This reaction is an illustrative example of the need for temporary N-protection of the starting material. Reaction of the free pyrrole 61 with 1,2,4,5-tetrahydroxybenzene does not provide any of the desired product 64; only decomposition is observed. If the pyrrole is used as the N-Boc-protected derivative 65, the reaction gives a yield of 38%. This is a considerably good result, especially considering that, besides the desired trans product 66, the cis derivative forms in similar yield and thus results in a cyclization yield of around 70% for both isomers. Furthermore, polymer formation and 1,3-disubstitution (to form a nine-membered
instead of an eight-membered ring) can occur as a side reaction, thereby lowering the yield.

In the examples presented so far, the β-position of the pyrrole has been used in the reactions as the electrophilic center. However, a nucleophilic group at the β-position may sometimes be needed for further reactions. The interconversion of the halogen in the β-position into the corresponding alcohol can be performed as mentioned above for the hydrolysis of an α-methyl chloride. The dibromide 67 is hydrolyzed under basic aqueous conditions to the diol 68 in an excellent yield (Scheme 23).56b

To obtain the amine, which is an even better nucleophile, the bromine can be substituted first by azide. Subsequent catalytic hydrogenation then provides the amine which can be used in further reactions. This reaction cascade was carried out in the synthesis of 71 from 69 (Scheme 24).59

4.4 Regioselective Transesterification

As already mentioned, the possibility of distinguishing between the α- and β-positions in electrophilic substitution reactions has its origin in the higher electron-density in the α-position which favors the attack of an electrophile at this position. The different electron densities at the α- and β-positions can also be exploited to achieve selective functional group interconversion. If there is an ester attached to the heterocycle, the electron-donating effect of the heterocycle deactivates this ester for basic hydrolysis or transesterification reactions. This effect is again more pronounced in the α- than in the β-position. For this reason, an ester in the α-position is more strongly deactivated toward nucleophilic attack than it is in the β-position, and even more so than a normal alkyl ester. An interesting example of this effect is the possibility of selective basic cleavage of one of the two ethyl esters in 72 (Scheme 25). The ester in the side chain is a normal alkyl ester which can be cleaved under basic conditions in an excellent yield without affecting the deactivated α-pyrrole ester. Once hydrolysis is achieved, the resulting carboxylic acid is deprotonated and the carboxylate is inert towards further nucleophilic attack. Basic hydrolysis is, therefore, not an equilibrium reaction, in contrast to the base-induced transesterification. This may explain why a similar selective transesterification of the side chain carboxylate in 72 failed, instead resulting in significant formation of the corresponding dibenzyl carboxylate. The transesterification required much longer reaction times to achieve significant conversion, so that the less reactive α-ester group also started to react.

However, once the saponification of the ester in the side chain is performed, the ester group in the α-position can be further reacted through transesterification under basic conditions, as shown in Scheme 25 for the synthesis of 74. Finally, the side-chain carboxylic acid in 74 can again be converted into any other ester after activation; for example, using PyBOP or another modern coupling reagent and reaction with an alcohol. This procedure even works for alcohols of very low nucleophilicity, as demonstrated by the formation of the tert-butyl ester in 75.60

Scheme 22 Conversion with the unprotected pyrrole 61 as well as with the protected derivative 65. Reagents and conditions: (a) DMSO, Cs2CO3, r.t., 3 h.

Scheme 23 Conversion of the bromide to the alcohol at the β-position. Reagents and conditions: (a) H2O, acetone, K2CO3.

Scheme 24 Conversion of the bromide to the corresponding amine. Reagents and conditions: (a) NaN3, 63%; (b) H2, Pd/C, MeOH, 68%.

Scheme 25 Selective interconversion of functional groups starting from diethylpyrrole dicarboxylate 72. Reagents and conditions: (a) NaOH, H2O, EtOH, 60 °C, 3.5 h; (b) NaOBr, BrOH, 100 °C, 6 h, reflux; (c) oxalyl chloride, CH2Cl2, DMF, r.t., 2 h, KOt-Bu, r-BuOH, 40 °C, 6 h.
This example again shows how the electronic properties of the pyrrole influence the reactivity of the different ring positions, which can then be exploited for the selective synthesis of highly functionalized pyrroles.

5 Direct Synthesis of Substituted Pyrroles via Cyclization Reactions

The direct introduction of a functional group into the pyrrole has already been discussed, as have some subsequent functional group interconversions. However, most substitution patterns can also be achieved by choosing suitable starting materials for the direct synthesis of a substituted pyrrole through classical cyclization reactions. This is often a more convenient way to synthesize a specifically substituted pyrrole, and there are several different approaches for this purpose. All of these can be applied very well to the synthesis of substituted pyrroles and the substitution pattern can be controlled by the choice of starting material and the type of cyclization reaction.

In principle, there are several different modes of how to build a pyrrole using classical polar condensation reactions. The most common of these are shown in Figure 2 and differ in the retrosynthetic cleavage of the heterocycle. For each of these cyclization types, a large variety of different modifications have been developed in addition to the classical examples. Thus it is again difficult to predict which synthetic approach will be the best for a given pyrrole and, often, practical issues, such as availability of starting materials or isolation and purification requirements, might dictate which reaction is finally used. Furthermore, there is a number of more modern reactions available (a few examples are shown below), but these are often hampered by their being limited to very specific substitution patterns or by the availability of starting materials. Hence the focus here is on the more traditional condensation reactions.

![Figure 2](image) Various methods for the retrosynthetic cleavage of a pyrrole.

5.1 Knorr, Paal–Knorr and Hantzsch Reactions

The most prominent example, the classical Knorr reaction, provides a pyrrole after condensation of a ketone with an α-amino ketone, which is often generated by in situ reduction of an oxime. This reaction is an example of the retrosynthetic cleavage of type 1 in Figure 2. The synthesis of 78 (Scheme 26) is a highly efficient example of this reaction. Condensation of the α-amino ketone 76 with ketone 77 occurs rapidly in ethanol at room temperature. Despite the high degree of functionalization of both start-
compound of choice, whereas for an N-substituted pyrrole, the corresponding primary amine is used. For example, for the synthesis of N-methylated pyrrole 84, 1,4-diketone 82 was treated with methylamine (83) at room temperature to obtain 84 in an excellent 85% yield (Scheme 28).63

5.2 **Modified Knorr Reactions**

Another widespread modification of the Knorr synthesis is the cyclization mode 3 illustrated in Figure 2. In this reaction, a β-diketone is reacted with an α-amino carbonyl compound. In contrast to the conventional Knorr reaction, where both reactants contribute two carbon atoms to the heterocycle (C2+C2 mode), in this case, three carbon atoms originate from the 1,3-dicarbonyl compound and the amino compound provides only one carbon atom in addition to the nitrogen (C3+C1 mode). As an example of this method, the synthesis of compound 87 (a precursor of 60, Scheme 20) is presented in Scheme 29.64 The β-diketone 85 is treated with α-amino carbonyl compound 86. One of the ethoxycarbonyl groups in 86 is cleaved off after cyclization and therefore does not appear in the resulting pyrrole 87. This functional group does not have to be an ester but can also be an acetyl group, as shown in another example below (Scheme 31).

The three methyl groups in 87 can be distinguished using selective radical reactions in the α-position (e.g. halogenation) for further functionalization of this molecule as discussed in section 4. Discrimination between the two β-positions is not possible, even though they differ slightly in their electronic properties. If two different functional groups in the β-positions are required, 1,3-dicarbonyl compounds with an appropriate substitution pattern must be used as starting materials for the cyclization. One example is the synthesis of diester 72 (Scheme 30). In this case, the amino compound is synthesized by in situ reduction of 89 (compare 86).65 The resulting amine then attacks one of the ketone functions of 88 and subsequent cyclocondensation provides pyrrole 72 in 75% yield.

In diester 72, each of the functional groups in the four positions of the pyrrole can be addressed selectively even though not necessarily in any desired order. The two methyl groups differ in their reactivity towards radical substitution reaction, and the two ester groups in their susceptibility to nucleophilic attack, as described above. However, using suitable starting materials for the cyclization, pyroles of type 72 can be prepared with two different ester groups. The advantage of functional group variation before cyclization is the often-easier purification of the starting materials which are of lower molecular weight and sometimes less polar. In most cases, they can be purified by distillation, which simplifies the scale-up of the reaction when compared to column chromatography of the product pyroles. Thus, by correct choice of starting materials, the desired substitution pattern can be achieved directly after cyclization to the pyrrole. This is demonstrated in Scheme 31 by the synthesis of 92. We were able to show that, for this cyclization, three steps can be performed subsequently in one pot, thereby significantly facilitating scale-up and purification of the final pyrrole 92.69 In the first step, 91 is treated with sodium nitrite to provide the β-diketo-α-oxide (synthetic equivalent to 89) which is then reduced, in situ, by zinc, and the resulting amine undergoes the modified Knorr reaction with 90 to give pyrrole 92 in an overall yield of 32%. This is a very good yield for this kind of reaction, and using this synthetic method, 92 was prepared in multigram quantities and required only one final purification step by crystallization.

As mentioned before, for this modified Knorr synthesis, the α-amino carbonyl compound does not have to result from a diester.66 Here, an acetooacetate is used for the in situ oxime preparation and reduction. This leads to an acetyl group which is eventually cleaved off under the basic conditions during the synthesis. In 92, both carboxylates can be hydrolyzed selectively by acidic cleavage of the tert-butyl ester, or basic cleavage of the methyl ester.

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5.3 Other Pyrrole Syntheses

Pyrroles can also be synthesized according to the cyclization mode 4 shown in Figure 2. In this case, the β-carbon atoms are provided by an α-diketone and the α-carbons and the pyrrole nitrogen come from an α,α’-diacetylated amine. This method allows for the easy synthesis of various 3,4-disubstituted pyrroles. An example is outlined in Scheme 32 for the synthesis of 95. The α-dicarbonyl 93 is reacted under basic conditions with secondary amine 94 to provide pyrrole 95 in a good yield (61%). This synthesis can also be used for the preparation of β-alkyl- or β-aryl-substituted pyrroles.

As mentioned before, it may be interesting to have nucleophilic centers in the β-position of a pyrrole. To achieve this, the interconversion of the bromide in the β-position, as already discussed, can be used; however, this synthetic route requires further reaction steps after pyrrole synthesis. The preparation of 95 in Scheme 32 is thus an interesting example of how to obtain the desired functionality (in this case, a nucleophilic group in the β-position of the pyrrole) directly, again through the intelligent choice of starting materials.

The synthesis of pyrroles is not limited to the classical polar condensation reactions presented so far. In recent times, a variety of approaches based on pericyclic reactions has also been developed. Unfortunately, these syntheses are often limited to few examples with very specific substitution patterns. Furthermore, these are sometimes difficult to scale up. Nevertheless, one example is discussed here to illustrate the approach. An interesting pyrrole synthesis based on a 1,3-dipolar cycloaddition is the preparation of 98 (Scheme 33). Irradiation of aziridine 97 provides the corresponding azomethine ylide, in situ, which undergoes a cycloaddition with 96 to provide pyrrole 98 in 95% yield. Even though this special synthesis is both smart and efficient, the method is limited to rather specific conditions and requires substituents in the aziridine reactant that stabilize the dipolar intermediate in the [3+2] cycloaddition. Therefore, this method is of less importance to pyrrole synthesis in general, and is more of mechanistic interest.

Another interesting method for pyrrole synthesis is the use of p-toluenesulfonyl methyl isocyanide (TosMIC; 100), which can react with a Michael system to give a β,β’-disubstituted pyrrole. If benzyl butenoate 99 is used, pyrrole 101 can be obtained in a good yield of 68% (Scheme 34). This method can be an alternative for the direct cyclization to highly β-functionalized compounds, but is limited to pyrroles without α-substitution.

6 Application of Highly Functionalized Pyrroles in Supramolecular Chemistry

Even though most of the synthetic methods described above are rather old (the classical Knorr and Paal–Knorr condensation reactions go back more than 100 years), they are still used today in a variety of research fields, such as natural product synthesis, medicinal chemistry, supramolecular chemistry, and materials science. Therefore, we present here a few examples of multistep syntheses of highly functionalized pyrroles from our own research in this area.

We use cationic guanidiniocarbonyl pyrroles as building blocks for anion recognition or self-assembling zwitterions. A very useful key intermediate is compound 35, the synthesis of which is described above (section 4.1). Starting from this compound, the artificial arginine analogue 103 was synthesized by reaction of the carboxylic acid group in 35 with amine 102 (Scheme 35). This can be performed by activation of the carboxylate with PyBOP and subsequent conversion with the nucleophilic amine of 102.
The Boc group can then be removed from the guanidine moiety by acidic cleavage. The cationic guanidinocarbonyl pyrrole can then be used for the selective recognition of oxoanions, especially carboxylates. The binding strength results from the cooperation of the ionic interaction and the hydrogen bonds (Figure 3). Additional interaction of the receptor side chain (R1 in 104) with the carboxylate side chain (R2 in 105) then ensure a selectivity of recognition towards a specified carboxylate coordination target. The synthetic introduction under mild conditions of sensitive side chains into the molecule is a current challenge.

One point of interest is if, and how, the direction of the amide bond in the 5-position of the pyrrole affects the coordination properties of such cationic guanidinocarbonyl pyroles. To investigate this question, a guanidinocarbonyl pyrrole building block with an amide bond in the same position, but with inverted direction, has been prepared. For this purpose, 2-nitro-5-methoxycarbonyl pyrrole (26) was used. Interestingly, this compound is accessible in good yields by nitration of α-trichloroacetetyl pyrrole (7) and subsequent hydrolysis as discussed above, but not via direct nitration of the methyl ester. Pyrrole 26 is then reduced to the amine 106; this can be performed in quantitative yield by palladium-catalyzed hydrogenation at 40 °C (Scheme 36). N-Acetylation with subsequent hydrolysis of the methyl ester then gives carboxylic acid 108, which can be coupled with Boc-guanidine using PyBOP. The resulting compound 109 possesses the same pyrrole moiety as 104, except that the direction of the amide bond is inverted.30

A problem often encountered while working with such highly functionalized pyroles is their inadequate solubility, especially in aqueous solvents. As both α-positions are already substituted and essential for anion binding in these compounds, the physical properties can only be tuned via modification at the β-positions. For maximum effect, a symmetric approach aiming for twofold substitution of both β-positions is desirable. A suitable starting material is therefore the 3,4-bis(triethylene glycol)-substituted compound 62, which was obtained from the dibromide as described above. Transesterification of the ethyl to the corresponding benzyl ester in the 5-position, followed by acidic cleavage of the tert-butyl ester in the 2-position, provides 110 (Scheme 37). This carboxylic acid can then be further reacted using modern coupling reagents such as 2-(6-chloro-1H-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU) to give 111. The terminal hydroxyl groups of the triethylene glycol substituents can then be protected as silyl ethers to remove their nucleophilicity which might otherwise cause unwanted side reactions later on. Hydrogenation of the benzyl ester provides building block 113, which is completely analogous to 35 but with the protected triethylene glycol substituents in both β-positions. After coupling of this carboxylic acid, the protective groups (TBS and Boc) can be cleaved under relatively mild conditions. By this method, any triethylene glycol analogue of the guanidinocarbonyl pyrrole 35 is synthetically accessible.57

For some applications, this building block may have to be bound covalently via the β-position to another moiety; for example, in the formation of polymers or for immobilization for chromatographic purposes. Therefore, it may be desirable to be able to convert the guanidinocarbonyl pyrrole in the northern moiety at only one position. This means that the use of a symmetrically substituted compound, like the β-bromomethylpyrrole 61, would not be suitable. However, pyrrole tricarboxylates like 114 offer a synthetic solution to this challenge. Starting from 92, directly obtained after modified Knorr pyrrole synthesis, the selective α-oxidation by sulfonyl chloride can be carried out (Scheme 38). Carboxylic acid 114 can then be activated again using HCTU and Cbz-protected guanidine as nu-

**Scheme 35** Use of the pyrrole building block 35 for standard peptide-bond formation. Reagents and conditions: (a) n = 1–4, PyBOP, NMM, DMF.

**Scheme 36** Preparation of pyrrole building block 109 with an inverted amide bond, starting from 2-nitro-5-methoxycarbonylpyrrole (26). Reagents and conditions: (a) H2, Pd/C, MeOH, 40 °C; (b) Ac2O, CHCl3, 18 h, 60 °C; (c) LiOH, MeOH, 80 °C; (d) Boc-guanidine, PyBOP, NMM, DMF, r.t.

**Figure 3** Recognition of carboxylates 105 by guanidinio carbonyl pyroles 104.
cleophile. The resulting compound 115 is a completely orthogonally protected precursor for a variety of different guanidinocarbonyl pyroles. The protective groups can be cleaved in any desired sequence by hydrogenation (Cbz), basic (methyl ester) or acidic (tert-butyl ester) cleavage, allowing for maximum flexibility for further synthesis.\(^7\)

7 Conclusion

The various examples discussed in this review demonstrate that, even today, the synthesis of highly functionalized pyroles remains a synthetic challenge in terms of regioselectivity and chemoselectivity. Even 100 years after the classical methods for pyrrole synthesis – which are still the methods of choice today – were developed, one is often confronted with unexpected problems when trying to synthesize a specific pyrrole derivative. However, empirical guidelines based on a large number of experimental observations can help in planning the synthesis so that, in combination with modern protecting group strategies, even highly functionalized pyroles can be obtained in good yields nowadays. This subsequently allows for this fascinating heterocycle to be used in a wide range of applications.

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