Heterocycle Synthesis

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Oligopyrrole Synthesis by 1,3-Dipolar Cycloaddition of Azomethine Ylides with Bissulfonyl Ethylenes**

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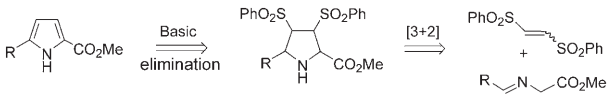
The pyrrole core is a structural motif of particular interest in synthetic and medicinal chemistry, as it is present in a large number of natural products[1] and biologically active compounds.[2] Furthermore, cyclic[3] and linear π-conjugated oligo- and polypyrrolic systems are of growing relevance in materials science, supramolecular chemistry, and nanotechnology. For example, they have found application in anion binding,[4] cation coordination,[5] conducting polymers,[6] liquid crystals,[7] and nonlinear optics.[8]

This wide array of interesting properties has inspired the development of a plethora of procedures for the preparation of differently substituted pyrroles.[9] Methods of synthesis range from the classical Knorr,[10] Paal–Knorr,[11] and Hantzsch[12] strategies to 1,3-dipolar cycloaddition procedures with activated alkynes and alkenes,[13] the dehydrogenation of pyrrolidines,[14] transition-metal-catalyzed coupling,[15] and multicomponent protocols.[16] On the other hand, methods for the construction of α,α′-linked oligopyrroles remain limited. Of particular interest are the Vilsmeier condensation,[17] the Paal–Knorr cyclization,[18] the oxidative coupling of α-unsubstituted pyrroles,[19] Ullmann coupling,[20] and other metal-mediated coupling reactions.[21] However, there is room for improvement in oligopyrrole synthesis, especially in reducing the number of steps in the preparation of the coupling partners and increasing the functional group tolerance and structural scope of the current procedures.

The metal-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with electron-poor alkenes is one of the most convergent and most practical approaches to the synthesis of pyrrolidines substituted with electron-withdrawing groups, in particular with carbonyl-based substituents and nitro groups.[22] Given the excellent ability of sulfones to act as both electron-withdrawing groups and leaving groups,[23] we envisaged that 5-substituted pyrrole-2-carboxylic esters could be prepared readily in a one-pot procedure by the metal-catalyzed 1,3-dipolar cycloaddition of commercially available 1,2-bis(phenylsulfonyl)ethylene[24] with α-iminoesters, followed by in situ aromatization of the bissulfone adduct through the double elimination of the sulfone moieties under basic conditions (Scheme 1).[25] Straightforward conversion of the ester substituent on the pyrrole into a new α-iminoester



Scheme 1. Strategy for the synthesis of pyrroles.

moiety could lead to an iterative approach to the synthesis of α,α′-oligopyrroles and related structures. Herein, we describe the structural versatility of this novel strategy and its efficient application to the synthesis of α,α′-linked bipyrroles, terpyrroles, quaterpyrroles, and pentapyrroles.

On the basis of our recent results on the Cu-catalyzed asymmetric 1,3-dipolar cycloaddition of simple phenyl vinyl sulfone,[26] we chose to study as a model reaction the cycloaddition between *N*-benzylidene glycine methyl ester and *trans*-1,2-bis(phenylsulfonyl)ethylene (**1**) in THF under the catalysis of $[Cu(CH_3CN)_4]PF_6$ (3 mol%) with the ligand PPh_3 (3 mol%) in the presence of the base Et_3N (18 mol%). We were pleased to find that a clean reaction occurred at room temperature, with complete disappearance of the dipolarophile in 5 h, to provide a single bissulfonyl adduct.[27] Interestingly, it was not necessary to isolated this adduct: The addition of DBU[28] to the crude reaction mixture promoted the rapid elimination of the sulfonyl groups with formation of the expected pyrrole **3**, which was isolated in 90% yield (Table 1, entry 1). *cis*-1,2-Bis(phenylsulfonyl)-ethylene (**2**) was also tested as a dipolarophile under the same reaction conditions (Table 1, entry 2). However, this alkene proved to be much less reactive than the *trans* isomer, and the final pyrrole **3** was obtained in only 27% yield after a cycloaddition reaction time of 5 h.

This procedure for the synthesis of pyrrole-2-carboxylic esters by 1,3-dipolar cycloaddition with the bissulfone **1** displays high tolerance with regard to the substitution of the α-iminoester precursor (Table 1). When α-iminoesters with aromatic (Table 1, entries 1, 3, and 4), α,β-unsaturated (entry 5), and aliphatic substituents (entries 6 and 7) were used, the corresponding pyrroles were obtained in good yields (72–93%). Azomethine ylides with furyl (Table 1, entry 8), thienyl (entry 9), and pyrrolyl substituents (entries 10–13) deserve particular attention, as they are of interest for the preparation of oligopyrroles and related structures. Those

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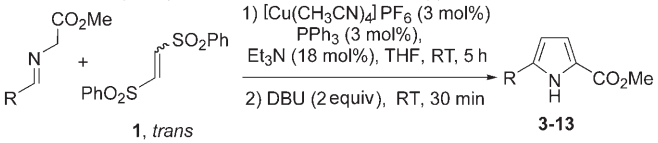
Table 1: One-pot synthesis of 2,5-disubstituted pyrroles.



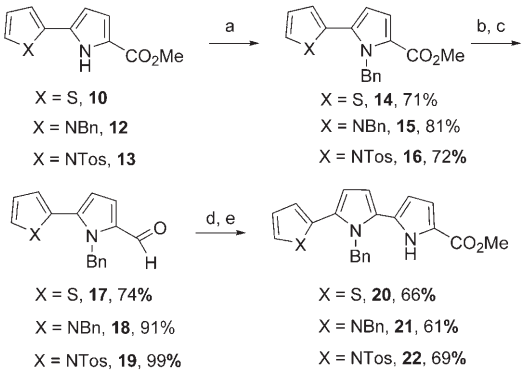
1, *trans*
2, *cis*
3-13

Entry	Bissulfone	R	Product	Yield [%][a]
1	**1**	Ph	**3**	90
2	**2**	Ph	**3**	27
3	**1**	4-(MeO)C_6H_4	**4**	72
4	**1**	3-FC_6H_4	**5**	93
5	**1**	CH=CH–Ph	**6**	88
6	**1**	*t*Bu	**7**	80
7	**1**	cyclohexyl	**8**	86
8	**1**	2-furyl	**9**	72
9	**1**	2-thienyl	**10**	97
10	**1**	2-pyrrolyl	–	–
11	**1**	*N*-Boc-2-pyrrolyl	**11**	67
12	**1**	*N*-Bn-2-pyrrolyl	**12**	78
13	**1**	*N*-Tos-2-pyrrolyl	**13**	61

[a] Yield of the pure product after silica-gel chromatography. Bn = benzyl, Boc = *tert*-butoxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Tos = *p*-toluenesulfonyl.

examined underwent the desired reaction to provide the corresponding α,α′-linked bisheterocycles in good yields (61–92%), except for the substrate with the unprotected pyrrole substituent (Table 1, entry 10).[29]

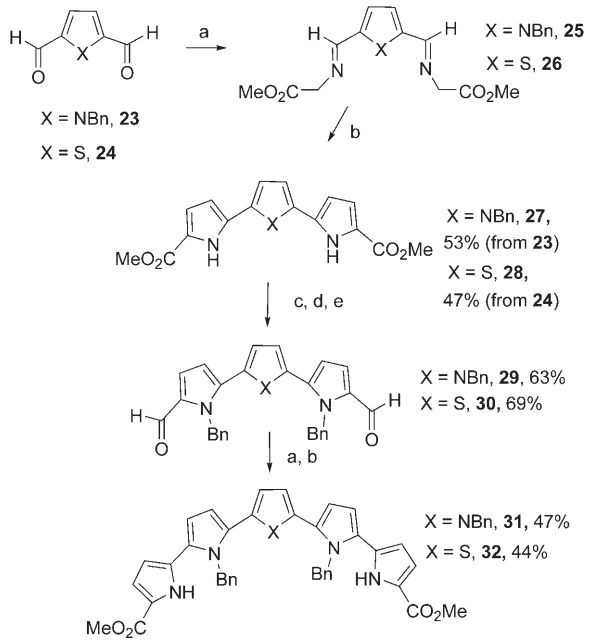
The resulting bipyrroles and related structures serve in turn as substrates for a sequence of reactions in which a further pyrrole ring is constructed to give terpyrroles and analogues (Scheme 2). First, the free NH group of the bipyrroles **12** and **13** and the thienylpyrrole **10** was benzylated under standard conditions (BnBr, NaH, DMF) to provide the protected pyrroles **14**, **15**, and **16**. The resulting bipyrrole (and thienylpyrrole) esters were converted in high yield in a straightforward reduction ($LiAlH_4$)/oxidation (MnO_2) procedure into the corresponding aldehydes **17**, **18**, and **19**, which were condensed with glycine methyl ester to give the key bipyrrole α-iminoesters. These α-iminoesters were isolated and submitted immediately to 1,3-dipolar cycloaddition with the bissulfone **1** under the standard reaction conditions, followed by DBU-promoted desulfonylation in situ. The resulting terpyrroles **21** and **22** and the related compound **20** were obtained after chromatographic purification in good yields of 61–69% (from aldehydes **17**–**19**). This modular approach to the introduction of the pyrrole units allows the selective construction of orthogonally protected terpyrroles, such as **22**, as well as mixed heterocyclic systems, such as the thienylbipyrrole **20**. Furthermore, these terpyrroles could be used as building blocks in the preparation of highly valuable substituted polypyrroles and expanded porphyrins.[3]



Scheme 2. Synthesis of the terpyrroles **21** and **22** and the thienylbipyrrole **20**: a) BnBr, NaH, DMF, room temperature, 12 h; b) $LiAlH_4$, THF, 0°C, 3 h; c) MnO_2, acetone, room temperature, 14 h; d) glycine methyl ester hydrochloride, Et_3N, $MgSO_4$, CH_2Cl_2, room temperature, 15 h; e) **1**, $[Cu(CH_3CN)_4]PF_6$, PPh_3, Et_3N, THF, room temperature, 5 h; then DBU, room temperature, 30 min. DMF = *N*,*N*-dimethylformamide.

To accelerate the construction process for the synthesis of higher order oligoheterocycles, we next explored whether the 1,3-dipolar cycloaddition could be used to generate two pyrrole rings in a one-pot procedure from a bis(α-iminoester) as a precursor to bisazomethine ylide. This (1+2) and (1+2+2) approach from *N*-benzylpyrrole-2,5-dicarbaldehyde (**23**) and thiophene-2,5-dicarbaldehyde (**24**) is illustrated in Scheme 3.

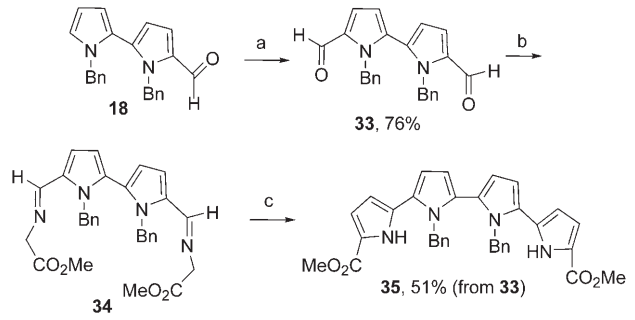
The pyrrole dialdehyde **23**[30] was condensed with excess glycine methyl ester, and the resulting crude bisimine **25** was treated immediately with excess bissulfone **1** under the usual conditions of Cu catalysis, followed by DBU. The expected symmetrical terpyrrole **27** was obtained as the main product in 53% yield from **23** along with a minor amount of the bipyrrole aldehyde (11%) that results from monocycloaddition with hydrolysis of the second imine unit. The terpyrrole diester was converted efficiently into the N-protected terpyrrole dialdehyde **29** in the three steps developed for the iterative (2+1) strategy (N benzylation followed by reduction



Scheme 3. Synthesis of the pentaheterocycles **31** and **32**: a) glycine methyl ester hydrochloride, Et_3N, EtOH, SiO_2, ultrasound, room temperature, 2 h; b) **1**, $[Cu(CH_3CN)_4]PF_6$, PPh_3, Et_3N, CH_2Cl_2, 4-Å molecular sieves, room temperature, 5 h; then DBU, room temperature, 30 min; c) BnBr, NaH, DMF, room temperature, 12 h; d) $LiAlH_4$, THF, 0°C, 3 h; e) MnO_2, acetone, room temperature, 14 h.

of the ester groups and alcohol oxidation with MnO_2). The terpyrrole dialdehyde **29** was then used as a substrate for the simultaneous construction of two pyrrole rings via the corresponding bis(α-iminoester) to provide the pentapyrrole **31** as the main product in 47% yield from **29**. The quaterpyrrole aldehyde that results from monocycloaddition was also isolated as a minor product (12%). As a demonstration of the generality of this novel method for the synthesis of α,α′-linked oligopyrroles, the trisheterocycle **28** (47%) and pentaheterocycle **32** (44% yield[31] from the dialdehyde **30**) were obtained by the same reaction sequence from the thiophene dialdehyde **24**.

Finally, to complement these syntheses of oligopyrroles with an odd number of pyrrole units, we applied a similar (2+2) construction strategy to the synthesis of oligopyrroles with an even number of pyrrole units, such as quaterpyrroles (Scheme 4). Vilsmeier formylation ($POCl_3$, DMF)[32] of the



Scheme 4. Synthesis of the quaterpyrrole **35**: a) $POCl_3$, DMF, 0°C→RT, 12 h; b) glycine methyl ester hydrochloride, Et_3N, EtOH, SiO_2, ultrasound, room temperature, 2 h; c) **1**, $[Cu(CH_3CN)_4]PF_6$, PPh_3, Et_3N, CH_2Cl_2, 4-Å molecular sieves, room temperature, 5 h; then DBU, room temperature, 30 min.

previously prepared bipyrrole aldehyde **18** provided the symmetrical bipyrrole dialdehyde **33** (76% yield), a suitable substrate for the construction of two further pyrrole rings. Thus, the formation of the bis(α-iminoester) **34**, followed by 1,3-dipolar cycloaddition with **1** and DBU-promoted desulfonylation, afforded the quaterpyrrole **35** in 51% yield.[33]

In summary, the 1,3-dipolar cycloaddition of commercially available *trans*-bis(phenylsulfonyl)ethylene (**1**) with azomethine ylides derived from α-iminoesters, followed by DBU-promoted elimination of the sulfonyl groups in situ, constitutes a very practical and general approach to the synthesis of 2,5-disubstituted pyrroles. Through the straightforward conversion of the ester moiety of the pyrrole unit into a new α-iminoester functionality, this procedure can be applied iteratively to the synthesis of α,α′-linked oligopyrroles and related oligoheterocycles. A number of sequences of pyrrole-ring construction ((1+1), (2+1), (1+2), (2+2), and (1+2+2)) have been developed for the efficient preparation of a range of bi-, ter-, quater-, and pentapyrroles.

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