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A Three-Step Synthesis of Tetrasubstituted NH-Pyrroles

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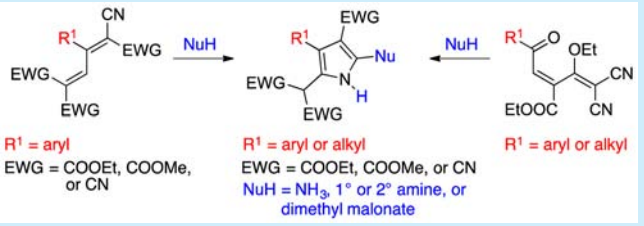
Supporting Information

ABSTRACT: Buta-1,3-dienes appended with electron-withdrawing groups (EWGs), derived from the [2 + 2] cycloaddition−retroelectrocyclization (CA−RE) cascade, react with (predominately) nitrogen-based nucleophiles affording tetrasubstituted 2-amino-NH-pyrroles in moderate to excellent yields with complete regioselectivity. Penta-2,4-dien-1-ones also undergo a similar transformation, providing analogous products and greatly enhancing the substitution of the pyrrole available. Oxidation from pyrrole to pyrrolidinone affords highly colored compounds that experience a strong bathochromic shift of the longest-wavelength absorption band in the UV/vis spectrum upon protonation, with return to the original spectra following neutralization.



Pyrroles with multiple ring substituents are an important class of heterocycles, especially when they can be prepared easily and regioselectively. Of particular interest is the 2-aminopyrrole functionality, which, despite the synthetic challenges associated with its synthesis,[1] is present in a number of bioactive structures.[2] The synthesis of pyrroles has been well established including the versatile Knorr,[3] Paal−Knorr,[4] and Hantzsch[5] reactions; these are, however, not readily adaptable to the synthesis of 2-aminopyrroles or do not provide the regioselectivity required for polysubstituted pyrroles. Attempts to circumvent these problems have focused on multicomponent reactions[6] and metal-catalyzed routes,[7] among others.[8]

A focus of our group has been on the [2 + 2] cycloaddition−retroelectrocyclization (CA−RE) reaction: a "click chemistry"-type transformation[9] for the conversion of electron-rich alkynes into buta-1,3-dienes using electron-poor alkenes.[10] We recently reported the use of ester-containing, tetrasubstituted electron-deficient alkenes in the CA−RE reaction to give buta-1,3-dienes, such as **1**.[11] With the short and easy preparation of these compounds in large quantities, our attention turned to their application in further transformations. Our initial focus was on their ability to act as electrophiles.

With this in mind, we exposed **1** to dimethylamine with heating to afford the tetrasubstituted NH-pyrrole **2a** in 82% yield (Scheme 1). Two-dimensional (2D) NMR spectroscopy allowed for the identification of **2a**; however, ultimate confirmation of the molecular constitution came from X-ray crystallography (see section S3 of the Supporting Information (SI)). Optimization of the reaction conditions showed that a variety of solvents gave similar yields, and little difference was observed between microwave irradiation or conventional heating (see Table S1 in the SI). The preferred conditions include microwave irradiation at 65 °C for 15 min in tetrahydrofuran (THF). Using these conditions, we then explored pyrrole formation with various nucleophiles (Scheme 1). Secondary amines gave the corresponding pyrroles **2b−d** in good yields; however, 1 h of microwave irradiation was required for the reaction of dihexylamine to reach completion. With NH_3 in isopropanol (2.0 M), the 2-NH_2-substituted pyrrole **2e** was obtained in a moderate yield of 53%. By conducting the reaction with cyclopentylamine, *N*-cyclopentylpyrrole **2f** was obtained in 81% yield. This product could be easily identified by ^{1}H NMR through its broad signal at 3.97 ppm for the NH_2 protons, instead of the signal for the pyrrole NH normally seen around 8 ppm. Further structural confirmation was obtained by 2D NMR experiments. Other primary amines afforded the *N*-substituted pyrroles **2g−h**. In these cases, the N atom of the entering nucleophile becomes the pyrrole ring nitrogen.

When $Na_2S{\cdot}9H_2O$ was used in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), the 2-aminothiophene **2i** was isolated in 76% yield with the structure confirmed by X-ray crystallography (see section S3 of the SI). When S_8 was used as the source of sulfur, under more standard Gewald-type conditions,[12] greater amounts of decomposition were observed with **2i** only isolated in 29% yield.

Morpholine gave the unstable product **2j**; however, immediate protection with di-*tert*-butyl dicarbonate (Boc_2O) allowed the isolation of the Boc-protected derivative **2k** in improved yield over two steps.

The generality of our synthetic protocol was further evaluated with other nucleophiles. Imidazole attack required immediate Boc-protection to give **2l** as a stable product. This product exists as a zwitterion as evidenced in the ^{1}H NMR spectrum through the N−H peak at 7.54 ppm and its lack of a malonate C−H, with the corresponding carbon seen at 96.23 ppm in the ^{13}C spectrum. In Me_2SO, substituted malonate esters possess a pK_a-value around 18.0[13] while the pK_a of

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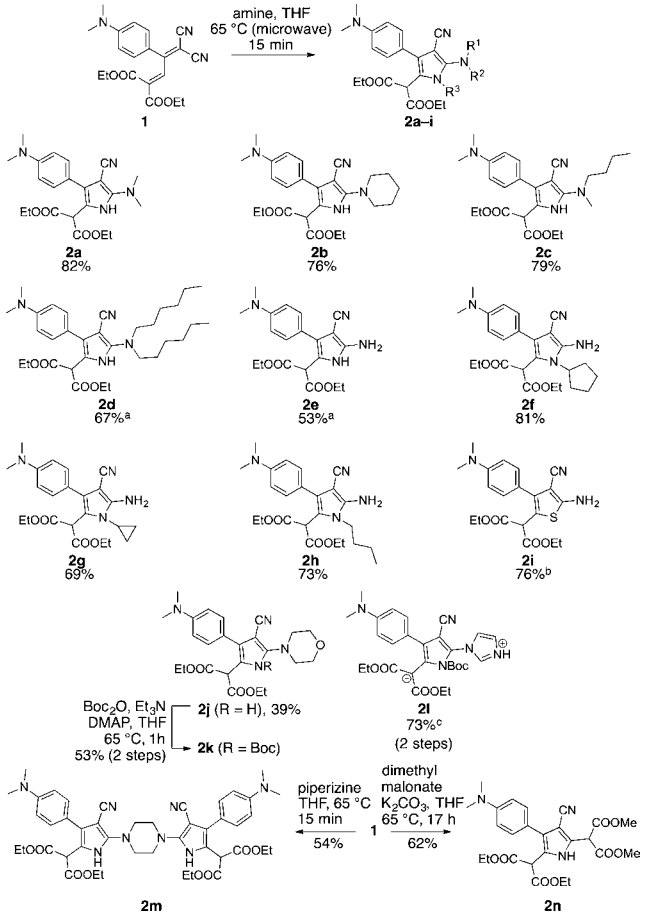
Scheme 1. Synthesis of Pyrroles Using Different Nucleophiles



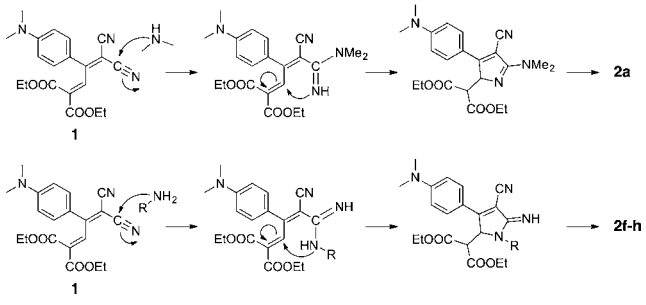
[a]1 h of heating was required. [b]Addition of 1.0 equiv of DABCO and 20 min of conventional heating was required. [c]Protection with Boc_2O was required immediately following pyrrole formation.

imidazole is around 18.6.[14] Dinucleophilic piperazine afforded the dipyrrole species **2m**. Aniline and *N,N*-diphenylamine did not undergo the reaction.

The carbon-based nucleophile dimethyl malonate also underwent the reaction to provide the corresponding pyrrole **2n**. All attempts at pyrrole formation with an oxygen nucleophile (such as EtOH, EtO^-) failed however. Also, the transformation does not occur with phospine-based nucleophiles.

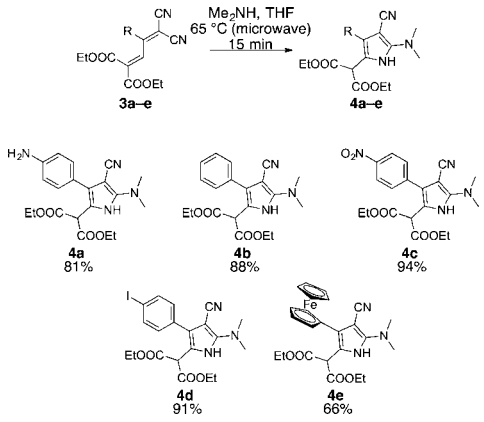
Scheme 2 shows a mechanistic proposal for pyrrole formation, which is outlined in more detail in section S4 in the SI. Amine attack occurs at one of the CN groups to form an amidine, which subsequently reacts with the second electrophilic site to afford the product following tautomerism.

Scheme 2. Proposed Mechanism for Pyrrole Formation



We subsequently investigated which aromatic substitution could be tolerated in the pyrrole-forming reaction (Scheme 3).

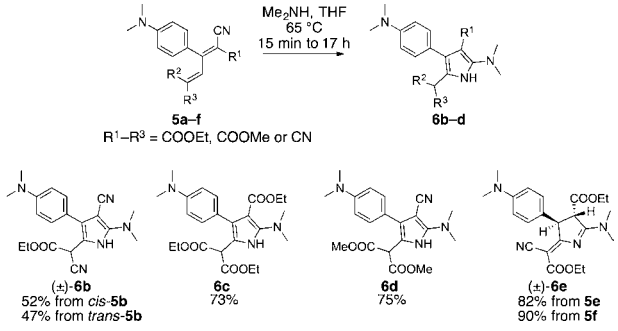
Scheme 3. Synthesis of Pyrroles with Various Aromatic Substituents



Compound **3a** is readily converted to **4a** with the free aniline moiety not posing a problem for the reaction. Similarly, buta-1,3-dienes **3b–d**, prepared by diazonium ion chemistry starting from **3a**,[11] yielded pyrroles **4b–d** in high yields, without substituent effects being noticed. The structures of **4a** and **4c** were confirmed by X-ray crystallography (see section S3 of the SI). Similarly, ferrocenyl substituted pyrrole **4e** could be isolated starting from **3e**.

We next explored the influence of ester vs cyano substitution on pyrrole formation using dimethylamine as the nucleophile (Scheme 4) and differently substituted buta-1,3-dienes **5a–f**. In

Scheme 4. Synthesis of Pyrroles from Different Buta-1,3-dienes



line with previous observations,[15] the tetracyano derivative **5a**[10a] (R^1–R^3 = CN) underwent immediate decomposition upon exposure to dimethylamine with no isolable product formation. The monoester compounds *cis*-**5b** (R^1 and R^2 = CN, R^3 = COOEt) and *trans*-**5b** (R^1 and R^3 = CN, R^2 = COOEt) both underwent pyrrole formation to give (±)-**6b** which was isolated as the racemate. The triester derivative **5c** (R^1–R^3 = COOEt) was also easily transformed into pyrrole **6c** resulting in ester, rather than cyano substitution at the 3-position. The conversion of **5d** (R^1 = CN, R^2 and R^3 = COOMe) into pyrrole **6d** was also demonstrated. When the configurational isomers **5e** (R^1 and R^2 = COOEt, R^3 = CN) and **5f** (R^1 and R^3 =

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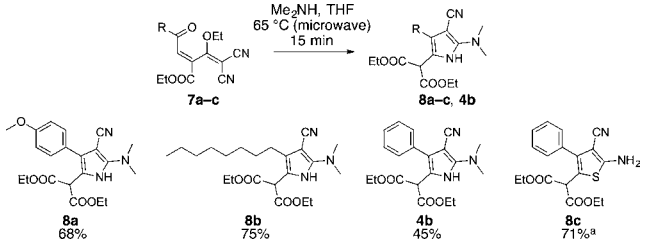
COOEt, R^2 = CN) were reacted with dimethylamine, the same product (±)-**6e** was obtained in high yield. The structure was identified through interpretation of 1D and 2D NMR spectra (for complete assignment of spectra, see section S2 of the SI). There are two aliphatic CH signals at 5.15/55.3 and 3.72/59.3 ppm in the ^{1}H and ^{13}C NMR spectra, respectively, which show a weak vicinal coupling. From the two-dimensional HMBC study (see Figure S52 in the SI), they have cross peaks with the quaternary carbon (128.4 ppm) of the dimethylanilino (DMA) ring and the same C═O (168.0 ppm). The other C═O and CN carbons show no HMBC signals. The DMA and CO_2Et substituents are *trans* leading to a torsion angle of 120° for the two aliphatic hydrogens, agreeing well with the small coupling (J = 1.5 Hz). The two nonanilino NMe moieties appear as separate singlets at 3.10 and 3.42 ppm providing evidence for the conjugation of the NMe_2 group with the imine double bond. Combining these elements suggests the structure assigned to (±)-**6e**. The reason for the formation of this different product is currently unknown.

We recently reported the formation of penta-2,4-dien-1-ones **7a**–**c** (among others) from electron-deficient alkenes and unactivated alkynes.[16] Interestingly, these compounds can also be transformed into tetrasubstituted NH-pyrroles (Scheme 5).

Scheme 5. Synthesis of Pyrroles from Penta-2,4-dien-1-ones



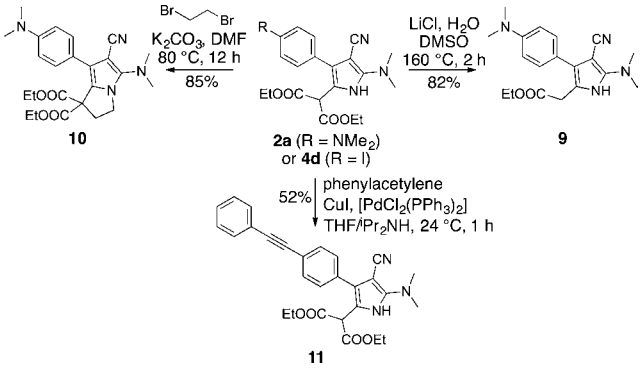
[a]Addition of 1.0 equiv of DABCO and 20 min of conventional heating were required.

When **7a** (R = 4-MeOPh) was exposed to dimethylamine, tetrasubstituted pyrrole **8a** was obtained in 68% yield. Additionally, we were able to show the transformation of **7b** to **8b** (R = C_8H_{17}) whereby an aliphatic substituent was included at the 3-position of the pyrrole. Structural confirmation came by reacting **7c** (R = Ph) under the same conditions to give **4b** already obtained from the buta-1,3-diene reaction. Spectral data confirmed the identity of **4b** obtained from the two different starting materials. In section S4 in the SI, we propose a mechanism of how the penta-2,4-dien-1-ones react with amines to give buta-1,3-dienes which subsequently undergo the pyrrole-forming transformation. The 2-amino-thiophene **8c** could also be obtained from **7c** (R = Ph) using $Na_2S{\cdot}9H_2O$ and DABCO.

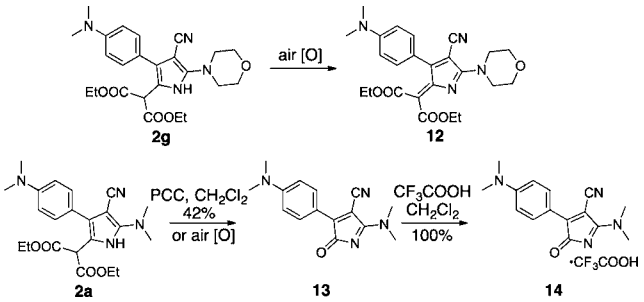
Next we conducted an initial exploration on how these pyrroles could be further manipulated (Scheme 6). Krapcho decarboxylation[17] of **2a** occurred under standard conditions without the need for N–H protection, affording the decarboxylated product **9** in high yield. Cyclization of **2a** with 1,2-dibromoethane gave the aryl-appended bicyclic structure **10**. Sonogashira cross-coupling of aryl iodide **4d** led to **11** without the need for a protecting group.

Some of the pyrrole products started to decompose, particularly when in solution and exposed to air. We investigated these processes in more detail (Scheme 7). When morpholine-substituted pyrrole **2g** was left in dichloro-

Scheme 6. Further Functionalization of Pyrroles



Scheme 7. Oxidation of Pyrroles



methane solution open to air, it underwent an oxidation process to give azafulvene **12**. More interestingly, the oxidation product of **2a** underwent further hydrolysis to afford the purple-colored, push–pull substituted 2-azacyclopentadienone **13**. To further explore the properties of this product, we prepared larger quantities of **13** by oxidation with pyridinium chlorochromate (PCC). The UV/vis spectrum of pyrrolidine **13** shows a strong longest-wavelength band with λ_{max} = 545 nm (ε = 18 700 M^{-1} cm^{-1}) and a second band with vibrational fine structure around 400 nm (Figure 1). These absorptions differ

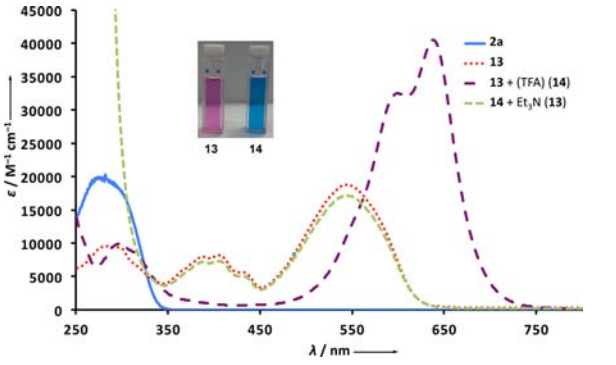


Figure 1. UV/vis spectra of compounds **2a**, **13**, **13** following treatment with TFA affording **14**, and following reneutralization with Et_3N fully regenerating **13**. Inset: actual color of compounds **13** and **14**.

dramatically from those of pyrrole **2a** which shows a single higher-energy band at λ_{max} = 280 nm (ε = 19 800 M^{-1} cm^{-1}). When **13** was treated with trifluoroacetic acid (TFA), it underwent a color change from purple to blue (Figure 1, inset). The color change was reflected in the UV/vis spectrum with a bathochromic shift of the longest-wavelength band to two maxima at 638 and 599 nm and an approximate doubling of the

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extinction coefficient to 40 500 and 32 500 M^{-1} cm^{-1}, respectively. These observations were shown to be the result of reversible protonation. Reneutralization with triethylamine regenerated the original purple color and UV/vis spectrum of **13**. Compound **14** could be isolated as a blue solid; however, the site of protonation could not yet be identified.

In summary, we report a simple one-step synthesis of tetrasubstituted NH-pyrroles from readily available starting materials (22 examples). Variation of substituents can be achieved by altering the starting material, which is easily accessible from the CA−RE reaction, or by using a different reacting nucleophile. Air oxidation of the pyrroles led to highly colored products, which showed interesting reversible color changes upon protonation with TFA. This report shows how products readily derived from CA−RE reactions can be transformed into compounds of greater complexity and additional chemical utility. Future work will detail the further transformations that can occur with these products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00890.

Experimental procedures, full characterization of new compounds, copies of ^{1}H and ^{13}C NMR spectra, and X-ray data (PDF)
Crystallographic data for compound **2a** (CIF)
Crystallographic data for compound **2i** (CIF)
Crystallographic data for compound **4a** (CIF)
Crystallographic data for compound **4c** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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