Convergent Approach to Nonsymmetrical 2,5-Diester Pyrroles

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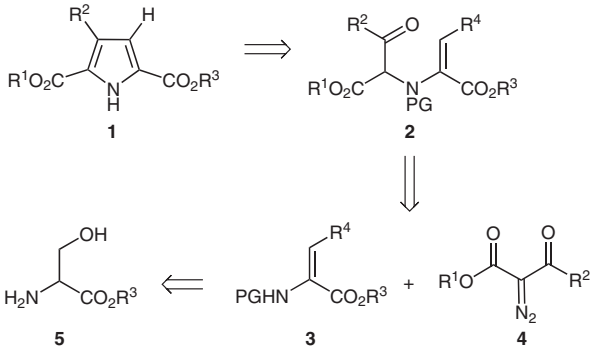
Abstract: A convergent approach towards nonsymmetrical 2,5-diester pyrroles is described. The building blocks can be easily assembled in less than four steps allowing for facile construction of diversity. The synthesis uses a rhodium-catalyzed NH insertion, followed by a one-pot deprotection–condensation to yield the desired pyrroles.

Key words: pyrrole, rhodium catalysis, NH insertion, zinc deprotection, enamine

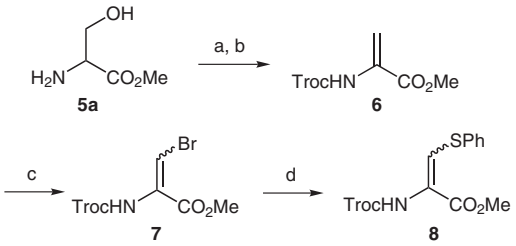
Given their importance in natural and pharmaceutical products,[1] extensive efforts have been targeted to the preparation of pyrroles.[2] However, very few methods allow access to pyrroles bearing two electron-withdrawing groups at the 2- and 5-positions. In most cases, these approaches lead to symmetrical pyrroles.[3] Therefore, the design of a synthesis to access unsymmetrical pyrroles bearing electron-withdrawing groups at the 2- and 5-positions would be of great value.

We envisioned access to 2,5-diester pyrroles bearing a substituent at the 3-position (**1**) via a one-pot deprotection–cyclization of keto enamine **2**. We expected that the deprotection of the enamine would facilitate its cyclization by increasing the electron density on the system.[4] To maximize convergence, **2** would be obtained via a rhodium-catalyzed N–H insertion between readily prepared enamine **3** and diazo **4** (Scheme 1).[5] Enamine **3** can conveniently be prepared from serine.



Scheme 1 Retrosynthetic approach towards pyrroles bearing 2,5-esters

Early on, we realized that the choice of protecting group (PG) on **2** was crucial, since its removal under mild conditions was required during the cyclization. The very acidic conditions required for Boc deprotection led to decomposition and the acetate protecting group proved difficult to remove. The sensitive nature of the enamine **2** led us to consider the use of the Troc group which could be deprotected under buffered conditions. Another key consideration was the nature of R^4. Our original intent was to have $R^4 = H$ which would provide the trisubstituted pyrrole **1**. The general synthesis of the enamine fragments **3** is outlined in Scheme 2.



Scheme 2 Preparation of the Troc-protected enamines substrates. *Reagents and conditions*: a) TrocCl, Et_3N, CH_2Cl_2, 0 °C, 16 h, 93%; b) MsCl, Et_3N, CH_2Cl_2, –30 °C, 16 h, 72%; c) NBS, 16 h, then Et_3N, 2 h, CH_2Cl_2, 20 °C, 68%; d) PhSH, K_2CO_3, MeCN, 20 °C, 1 h, 57%.

Conveniently, DL-serine methyl ester is initially protected with a Troc protecting group, followed by a one-pot mesylation–elimination sequence to yield enamine **6**. From this key enamine, we could prepare bromo-substituted enamines **7** and thiophenyl ether **8** to evaluate the effect of substitution pattern on the pyrrole formation chemistry.[6] Literature precedents led us to believe that both these substituents could be removed to access our desired trisubstituted pyrrole **1**.[7] The desired cyclization precursors **2** having $R^4 = H$, Br, and SPh were prepared via rhodium-catalyzed N–H insertion. However, initial attempts at affecting cyclization upon Troc deprotection conditions resulted in decomposition except when using the enamine **2a** (R^4 = SPh). Treating **2a** with excess zinc in THF and 1 N HCl at 60 °C, led to a promising 26% yield of **1a**. Surprisingly, the thiophenol was removed during cyclization. At this moment, we have no direct mechanistic evidence to explain the lost of this moiety, however, literature precedents suggest that it may play a role in the dehydration required to afford the pyrrole.[8]

We then focused our efforts on the optimization of our protocol. The best conditions for the rhodium-catalyzed

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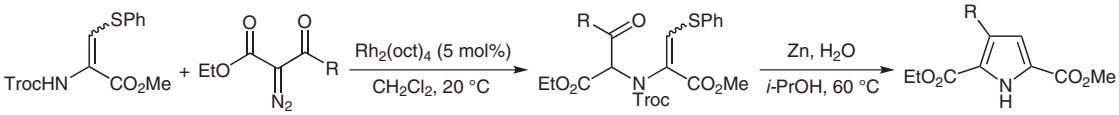
N–H insertion use 5 mol% of $Rh_2(oct)_4$ in dichloromethane at 20 °C in the presence of 1.5 equivalents of diazo **4**. Table 1 outlines the substrate scope of this transformation.

Both electron-rich and electron-poor aryl substituents (entries 1–6), as well as alkyl substituents (entries 7–9) were all well tolerated. Highly stabilized diazo **4h** proved less reactive (entry 8). Extensive development was required to optimize the deprotection–cyclization step.[9] Ultimately, we found that the use of 10 equivalents of zinc, in 2-propanol–water (8:1 ratio), at 60 °C for 24 hours was optimal. Under these conditions, pyrrole **1a**[10] was obtained in 60% yield. Submitting other keto-enamines bearing aryl substituents showed that the electron density on the aryl did not have a significant impact upon cyclization efficiency (Table 1, entries 2–6). Even the strongly withdrawing 4-nitro-substituted keto enamine afforded the pyrrole **1d**, where the nitrogroup is reduced, in respectable yield (Table 1, entry 4). Lower yields were obtained for alkyl-substitued keto enamines (Table 1, entries 7 and 8). However, good yield was achieved for the bulkier isopropyl derived substrate (Table 1, entry 9).

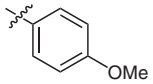
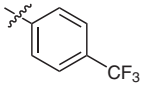
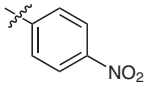
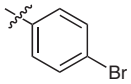
Evaluation of the scope at the 2-position is subject of current evaluation and will be reported in due course. However, we have demonstrated that *tert*-butyl ester at the 2-position can be prepared (in place of the ethyl ester), thus facilitating the differentiation of the two esters on the pyrrole (Equation 1).

In conclusion, we have designed and developed a convergent approach to access nonsymmetrical 2,5-diester pyrroles. The key steps of the synthesis involved a rhodium-catalyzed N–H insertion and a one-pot, zinc-mediated deprotection–cyclization.

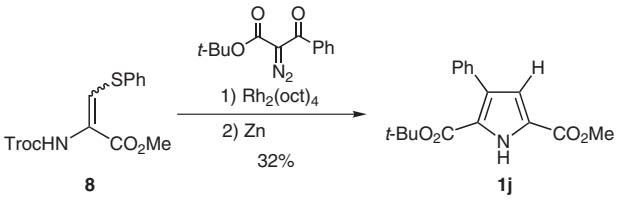
Table 1 Scope for the Rhodium-Catalyzed NH Insertion and Zinc-Mediated Deprotection–Cyclization Sequence



8 **4** (1.5 equiv) **2a–i** **1a–i**

Entry		Diazo **4**		Isolated yield insertion (%)		Isolated yield cyclization (%)
1	**4a**		**2a**	74	**1a**	60
2	**4b**		**2b**	61[a]	**1b**	58
3	**4c**		**2c**	69	**1c**	54
4	**4d**		**2d**	88	**1d**	47[b]
5	**4e**		**2e**	74	**1e**	54
6	**4f**		**2f**	79	**1f**	59
7	**4g**	Me	**2g**	92	**1g**	24
8	**4h**	CF_3	**2h**	58[a]	**1h**	33
9	**4i**	*i*-Pr	**2i**	85[a]	**1i**	52

[a] Conditions: 3 equiv of diazo were used.
[b] The pyrrole-aniline was obtained (reduction of the nitro).



Equation 1 Preparation of the pyrrole bearing a *tert*-butyl ester at 2-position

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

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(9) Optimization of the deprotection–cyclization involved screening for organic solvents, aqueous solvent (pH 1–14 buffer), metal used, quantity of zinc, temperature, and reaction time.

(10) **General Procedure for the Synthesis of Compounds 2a–i**
To a stirred solution of **8** (1.70 mmol) and $Rh_2(oct)_4$ (0.085 mmol) in CH_2Cl_2 (4 mL) at 20 °C was added a solution of **4** (3.40 mmol) in CH_2Cl_2 (2 mL) over a period of 20 min. The mixture was stirred for 1 h; gas evolution was observed. The reaction mixture was partitioned between CH_2Cl_2 and a sat. $NaHCO_3$ solution, back extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Purification by flash chromatography (silica gel, 230–400 mesh; Merck) using hexanes–EtOAc yielded **2** as a pure product.
Methyl 2-{(1-Ethoxy-1,3-dioxo-3-phenylpropan-2-yl)[(2,2,2-trichloroethoxy)carbonyl]amino}-3-(phenylthio)acrylate (2a)
^{1}H NMR (400 MHz, acetone-d_6): δ = 8.12 (br, 1 H), 7.58–7.51 (m, 2 H), 7.53–7.45 (m, 3 H), 7.45–7.39 (m, 2 H), 7.38–7.30 (m, 2 H), 7.30–7.24 (m, 2 H), 4.83 (s, 2 H), 3.78 (q, *J* = 7.1 Hz, 2 H), 3.60 (s, 3 H), 0.79 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, acetone-d_6): δ = 165.9, 165.0, 159.8, 153.3, 149.7, 134.7, 133.7, 131.6, 131.1, 130.0, 129.7, 129.6, 128.1, 114.9, 112.3, 96.7, 75.2, 61.9, 52.1, 13.8 ppm. IR (neat): 3311 (br), 2982, 1715, 1439, 1268, 1179, 1128, 1034, 732. ESI-HRMS: *m/z* calcd for $C_{24}H_{22}Cl_3NNaO_7S$ [M + Na]: 598.0049; found: 598.0044.
General Procedure for the Synthesis of Compounds 1a–i
To a stirred solution **2** (0.35 mmol) in 2-PrOH (3.5 mL) and H_2O (0.627 mL, 35 mmol) was added zinc (228 mg, 3.5 mmol). Mixture was heated to 60 °C and stirred for 24 h. The suspension was filtered on Celite, then concentrated under vacuum. Purification by flash chromatography (silica gel, 230–400 mesh; Merck) using hexanes–EtOAc yielded **1** as a pure product.
2-Ethyl 5-Methyl 3-Phenyl-1*H*-pyrrole-2,5-dicarboxylate (1a)
^{1}H NMR (400 MHz, acetone-d_6): δ = 11.43 (br, 1 H), 7.69–7.65 (m, 2 H), 7.42–7.39 (m, 3 H), 7.30 (s, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 3.81 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, acetone-d_6): δ = 164.2, 161.3, 141.7, 131.9, 130.6, 129.5, 128.5, 123.3, 118.8, 114.7, 60.2, 51.8, 14.5 ppm. IR (neat): 3706 (br), 3306, 2973, 1692, 1467, 1249, 1143, 1035, 757, 687. ESI-HRMS: *m/z* calcd for $C_{15}H_{16}NO_4$ [M + H]: 274.1074; found: 274.1077.