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Development of novel pyrrole synthesis for the preparation of intermediates of bioactive pyrrole alkaloids

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ABSTRACT

We have developed a novel method for the synthesis of 3,4-diarylpyrrole-2,5-dicarboxylates via α-diazo esters, which are easily obtained from phenylalanine derivatives. Utilizing this method, intermediates of bioactive compounds having the structure of 3,4-diarylpyrrole-2,5-dicarboxylates were synthesized.

In our series of investigations on the reactivity and the utility of α-diazo esters **1**, which are easily available from corresponding α-amino acid esters[1,2], we found that the terminal nitrogen of **1** was readily attacked by nucleophiles, such as aryllithiums, hydride reagents, and phosphines. The addition of aryllithiums to **1** gave aryl hydrazones **2**, the precursor for the Fisher indole synthesis.[2] Aryl hydrazones **2** were converted into indoles **3** under acidic conditions in good yields. Hydride reagents also reacted with **1** to yield hydrazones **4**.[3] Hydrazones **4** in turn could yield 1,3,4-oxadiazin-6-ones **5**, the substrate for the Diels–Alder reaction. The terminal nitrogen of **1** also reacted with phosphines to give aza-ylides **6** that were easily hydrolyzed to furnish **4** (Fig. 1). In this Letter, we report a novel method for the synthesis of 3,4-diarylpyrrole-2,5-dicarboxylates **7** via **4** that were easily obtained from phenylalanine derivatives.

Several 3,4-diarylpyrrole-2,5-dicarboxylates are known for their unique biological activities. For example, polycitone A (**8**) is a natural product that inhibits the activity of retroviral reverse transcriptases and cellular DNA polymerases.[4] Storniamide A (**10**) and permethyl storniamide A (**11**) have multidrug resistance (MDR) reversal activity[5] (Fig. 2). The synthesis of these compounds has been performed by some groups.[6–10] The Piloty–Robinson pyrrole synthesis is a conventional method for the synthesis of pyrroles under vigorous reaction conditions.[11] The condensation of two carbonyl compounds and hydrazine gives azine **12**. It is considered that the isomerization of **12** and its subsequent cyclization furnish pyrrole **7** (Fig. 3). We speculated that hydrazones **4** obtained by our methodology from α-diazo esters **1** could be precur-

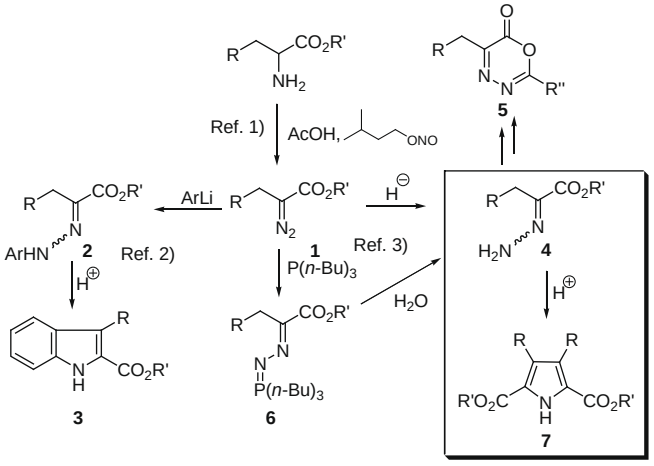

Figure 1.

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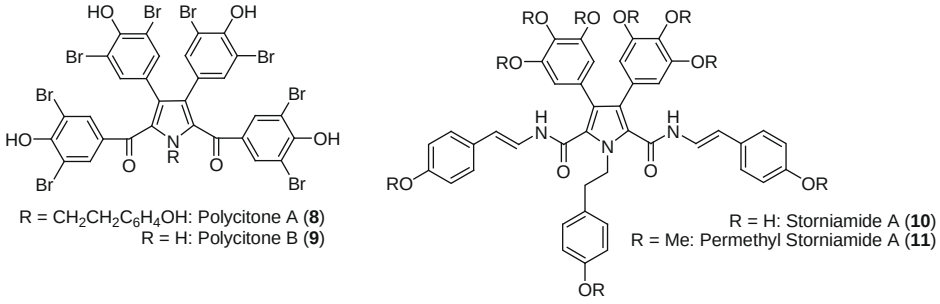


Figure 2.

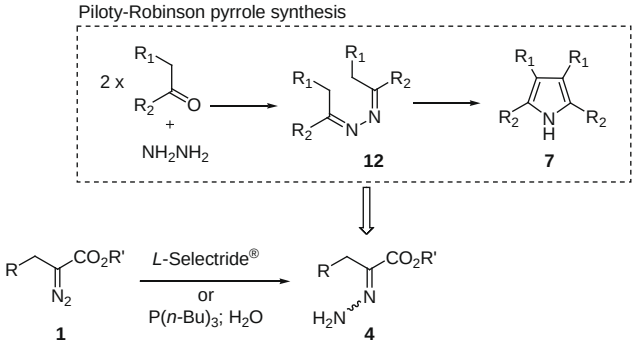


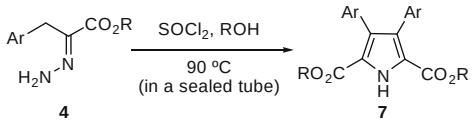
Figure 3.

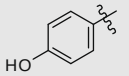
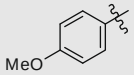
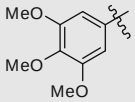
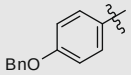
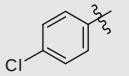
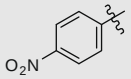
sors for the synthesis of azine **12**. Thus, first, we exposed (*E*)-hydrazone **4a** prepared from α-diazo ester **1a** derived from ethyl phenylalaninate to acidic conditions (heating in a sealed tube with 10 mol equiv of thionyl chloride in ethanol at 90 °C for 45 min) to give azine **12a**. However, the reaction proceeded quickly and pyrrole **7a** was obtained in 94% yield instead of azine **12a** (Scheme 1).[12] (*Z*)-Hydrazone **4a′** or a mixture of both stereoisomers also gave pyrrole **7a** in good yield under the same reaction conditions.

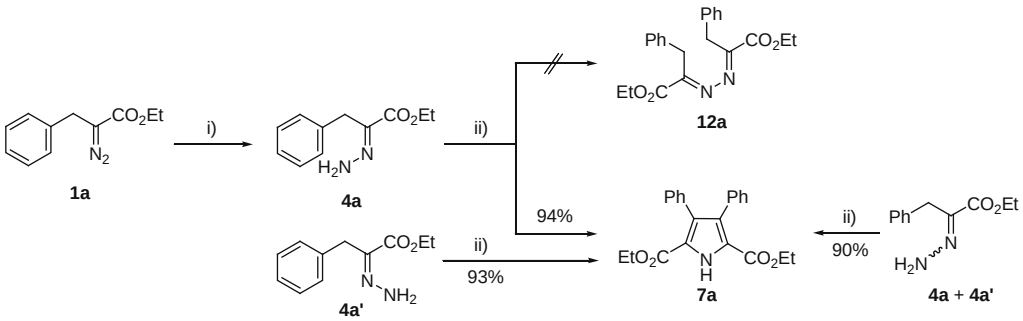
As pyrrole **7a** was obtained in good yield, we examined other substrates (Table 1). Hydrazones **4b–e** derived from tyrosine derivatives gave pyrroles **7b–e** (entries 2–5). Protection of the hydroxyl group was not necessary for a series of reactions (diazotization, reduction, and cyclization). Although hydrazone **4f** derived from 4-chloro phenylalanine gave pyrrole **7f** in good yield, **4g** derived from 4-nitro phenylalanine failed to produce a pyrrole. Hydrazones containing 5-membered heteroaromatic compounds **4h** and **4i** were prepared from corresponding amino acid esters[13] and subjected to cyclization. Unfortunately, no pyrroles could be obtained from these compounds.

Then, we examined the synthesis of intermediates that can lead to bioactive compounds **8**, **9**, and **11** (Scheme 2). 4-Methoxy

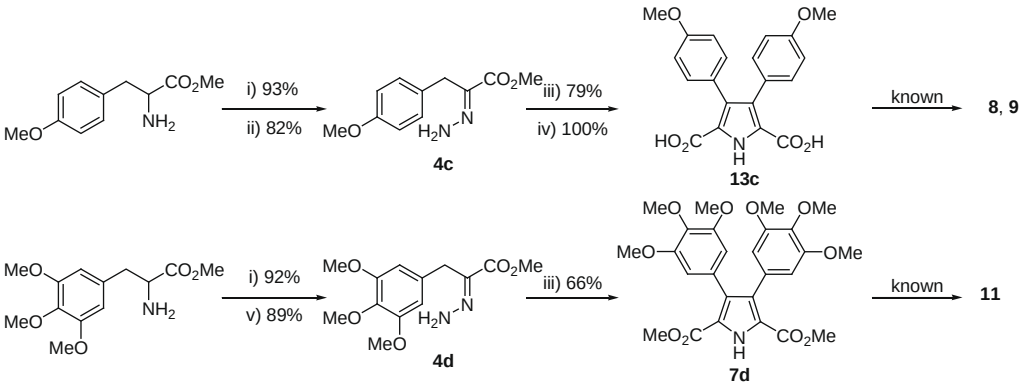
Table 1



Entry	Ar		R	Yield (%)
1	Ph	(**4a**)	Et	94 (**7a**)
2		(**4b**)	Me	79 (**7b**)
3		(**4c**)	Me	79 (**7c**)
4		(**4d**)	Me	66 (**7d**)
5		(**4e**)	Et	74 (**7e**)
6		(**4f**)	Me	80 (**7f**)
7		(**4g**)	Me	0
8		(**4h**)	Me	0
9		(**4i**)	Me	0

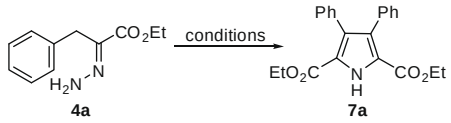


Scheme 1. Reagents and conditions: (i) $P(n\text{-}Bu)_3$, IPE, 93%; and (ii) $SOCl_2$, EtOH, 90 °C (in a sealed tube).



Scheme 2. Reagents and conditions: (i) isoamyl nitrite, AcOH, $CHCl_3$, 70 °C; (ii) P(*n*-Bu)$_3$, IPE; (iii) $SOCl_2$, EtOH, 90 °C (in a sealed tube); (iv) aq KOH, MeOH; and (v) L-selectride®, THF.

Table 2



Entry	Conditions	Yield (%)
1	$SOCl_2$ (×10), EtOH	94
2	$SOCl_2$ (×5), EtOH	91
3	$SOCl_2$ (×2.5), EtOH	63
4	$SOCl_2$, THF	0
5	AcCl, EtOH	84
6	AcOH	0[a]
7	0.5 M aq HCl, EtOH	3
8	36% aq HCl, EtOH	8
9	98% H_2SO_4, EtOH	12
10	85% H_3PO_4, EtOH	0[b]
11	46% HBr, EtOH	8[c]
12	TFA, CH_2Cl_2	26

[a] (*Z*)-Hydrazone was isolated in 19% yield. Starting material was recovered in 67% yield.
[b] Starting material was recovered in 31% yield.
[c] Starting material was recovered in 5% yield.

tyrosine was esterified with methanol and subjected to diazotization. The resulting diazo ester was reduced to hydrazone **4c**, and **4c** was heated in a sealed tube under acidic conditions to give pyrrole **7c** in good yield. Hydrolysis of **7c** gave corresponding carboxylic acid **13c**,[14] the synthetic intermediate of **8** and **9**.[7c] The same conversions were applied to 3,4,5-trimethoxy tyrosine obtained by known procedures[15] to yield pyrrole **7d**,[16] the intermediate of **11**.[6]

To clarify the mechanism of this reaction, several acidic conditions were next examined using hydrazone **4a** (Table 2). We conjectured that anhydrous hydrogen chloride generated from thionyl chloride and alcohol would work as a proton source to promote the reaction. At this stage, the reaction mechanism can be represented as depicted in Figure 4. Two molecules of hydrazone **4a** were condensed with the loss of hydrazine salt to yield symmetric azine **12a**. Azine **12a** was isomerized with the aid of acid, and 3,3-sigmatropic rearrangement led to cyclization immediately under heating with the loss of ammonium salt. When the cyclization was accomplished in THF with thionyl chloride, no pyrrole was obtained at all because no hydrogen chloride was produced. Furthermore, the combination of acetyl chloride and ethanol also gave pyrrole **7a** in good yield. Although hydrogen chloride seemed to be an essential factor, aqueous hydrochloric acid hardly promoted the reaction (entries 7 and 8). Also, sulfuric acid and phosphoric acid were not suitable (entries 9 and 10). Acetic acid promoted only the isomerization of the hydrazone **4a** to give **4a′** in 19% yield, and 67% of the starting material was recovered. Hydrobromide in acetic acid produced a small amount of pyrrole **7a**. Thus, the combination of thionyl chloride and alcohol is the best condition. Although the yield scarcely decreased when the amount of thionyl chloride was reduced to 5 mol equiv (91%), use of 2.5 mol equiv of thionyl chloride severely lowered the yield (63%). Further studies aimed at developing a novel method for the synthesis of pyrroles from other α-diazo esters derived from a variety of α-amino acid esters are in progress.

In conclusion, we have developed a novel method for the synthesis of 3,4-diarylpyrrole-2,5-dicarboxylates via α-diazo esters that are easily obtained from phenylalanine derivatives. Our method is milder than the Piloty–Robinson pyrrole synthesis, and pyrroles are obtained in good yields.

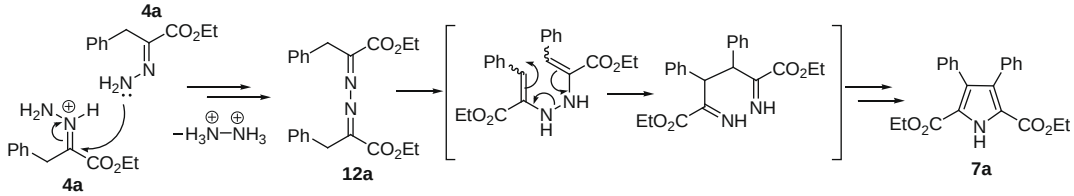


Figure 4.

Acknowledgments

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12. *Typical experimental procedure for the synthesis of pyrrole* **7a**: Hydrazone **4a** (176.1 mg, 0.85 mmol) was dissolved in ethanol (2 mL) in a sealed tube. To this solution, thionyl chloride (0.62 mL, 8.50 mmol) diluted in ethanol (3 mL) was slowly added at 0 °C, and the mixture was stirred for 45 min at 90 °C. After cooling to room temperature, the reaction mixture was slowly poured into saturated $NaHCO_3$ (30 mL) and extracted with ethyl acetate (10 mL) thrice. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to give **7a** as colorless crystals (145.5 mg, 94%). Recrystallization from ethyl acetate and hexane afforded colorless needles, mp (151–151.8 °C). Data for **7a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 7.21–7.16 (m, 6H), 7.15–7.19 (m, 4H), 4.22 (q, 4H, J = 8.0 Hz), 1.17 (t, 6H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.55, 133.14, 131.46, 130.93, 127.34, 127.00, 121.64, 60.97, 14.09; IR (KBr) 3325, 1703, 1302, 1242 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{21}NO_4$ (M^+) 363.1471, found 363.1477.
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14. The spectral data for **13c** exhibited properties that were identical to those reported by Gupton et al.[9b] Data for **13c**: mp 199–200.5 °C (DMSO) (lit.[9b] 200–202 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (br s, 1H), 6.92 (d, J = 8.0 Hz, 4H), 6.69 (d, J = 8.0 Hz, 4H), 3.68 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.01, 158.25, 132.31, 130.23, 126.54, 122.66, 113.12, 55.36; IR (KBr) 3413, 1675, 1245 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{17}NO_6$ (M^+) 367.1056, found 367.1054.
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16. The spectral data for **7d** exhibited properties that were identical to those reported by Boger et al.[6] Data for **7d**: mp 168.0–168.5 °C ($CHCl_3$–hexane) (lit.[6] 153–155 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (br s, 1H), 6.36 (s, 4H), 3.81 (s, 12H), 3.64 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.71, 152.44, 137.34, 131.22, 128.19, 121.10, 108.50, 60.98, 56.15, 52.04; IR (KBr) 3276, 2942, 1702, 1239, 1125 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{29}NO_{10}$ (M^+) 515.1791, found 515.1750.