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A novel method for the synthesis of 3,4-disubstitutedpyrrole-2,5-dicarboxylates from hydrazones derived from α-diazo esters

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ABSTRACT

Hydrazones obtained from α-diazo esters were converted to pyrroles when heated with thionyl chloride in alcohol. Among hydrazones, those substituted with a benzene ring on the β-carbon to the ester are likely to give pyrroles in good yields.

1. Introduction

Nature abounds with compounds containing a pyrrole ring, such as polycitone A,[1] which inhibits retroviral reverse transcriptases and cellular DNA polymerases, and storniamide A,[2] which has multidrug resistance reversal activity. Porphyrin, which is essential for the maintenance of life activity, consists of four pyrroles. Recently, porphyrins have been shown to cleave the DNA chain through their photosensitizing effect. Therefore, interactions between porphyrins and DNA have been studied extensively. In particular, cationic porphyrin TMPyP4 is known to damage DNA and induce apoptosis of cells.[3] It has also attracted much attention from chemical biologists since the late 1990s as it interacts with the G-quadruplex.[4] On the other hand, in the field of functional molecules, a variety of calixpyrroles have been synthesized and their anion binding has been discovered.[5]

During our research on the reactivity of α-diazo esters **1**, which are easily prepared from various α-amino acid esters,[6] we reported a modified synthesis method for polysubstituted indoles by combining the classical Fischer reaction with our new reaction: the facile formation of arylhydrazones by the coupling of **1** and various arylmetal reagents.[7] Fischer indole synthesis was well known to involve a 3,3-sigmatropic rearrangement of hydrazine formed by double bond isomerization of arylhydrazone. The mechanism suggested to us a further application of α-diazo esters, which were thus transformed to polyfunctional pyrroles through a 3,3-sigmatropic rearrangement of divinylhydrazine (Scheme 1).[8] In this paper, we report detailed results on this pyrrole synthesis method.

2. Results and discussion

We first attempted installation of a vinyl group to a terminal nitrogen of an α-diazo ester to obtain vinylhydrazone. However, treatment of **1a** with vinyl magnesium bromide or alkynyl lithiums did not give the desired products (Scheme 2).

This result led us to prepare a diimine, which was expected to isomerize to divinylhydrazine under acidic conditions. Reduction of the α-diazo ester **1a** was carried out according to a previously reported method to give the corresponding hydrazone **2a**.[9] The stereochemistry of the hydrazone **2a** was determined from the chemical shifts in the ^{1}H NMR spectra.[9,10] The signal for the terminal hydrogens on the *syn*-hydrazone amine appeared at a lower field than that for the anti-isomer due to hydrogen bonding with the ester carbonyl group. The subsequent condensation of **2a** with phenylacetaldehyde generated diimine **3** in 78% yield. It was also found that **1a** reacted with 2-butanone when heated in the presence of tributylphosphine to afford diimine **5** directly in 88% yield. Interestingly, treatment of both diimines **3** and **5** with thionyl chloride in EtOH gave the symmetric pyrrole **4a** rather than unsymmetric pyrroles (Scheme 3). The formation of the symmetric pyrrole is explained by beginning with alcoholysis at one C=N bond far from the ester group, by which these diimines revert to

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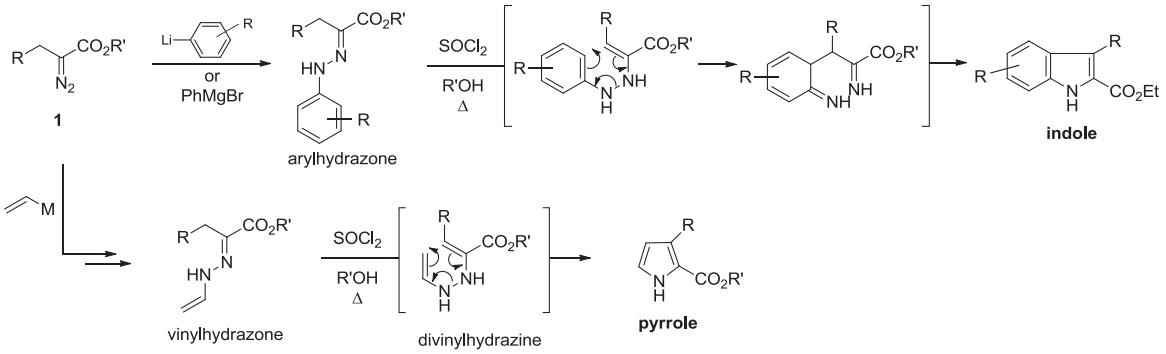
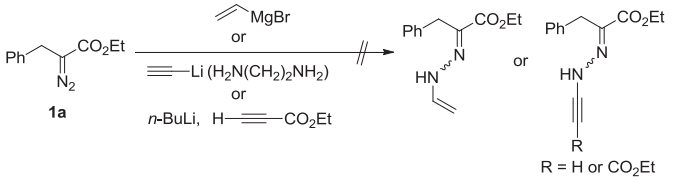
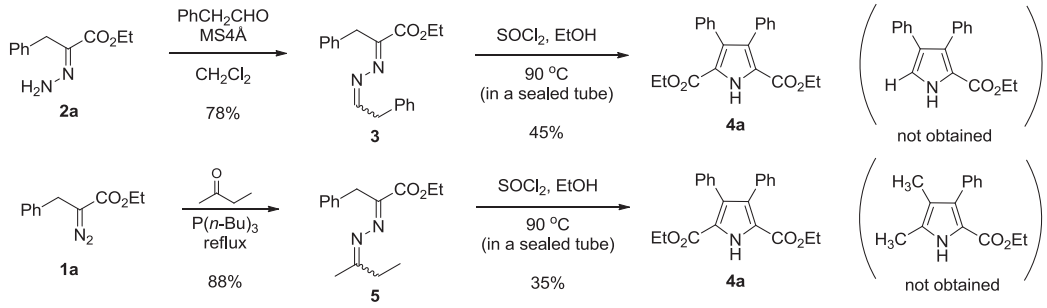


Scheme 1. Plausible mechanism for the synthesis of indole and pyrrole.



Scheme 2. Reactions of alpha-diazo ester with vinyl magnesium bromide or acetylide.

2f with 3,4,5-trimethoxyphenyl produced a polyfunctional pyrrole **4f** in good yield. The reaction of **2g** with a 4-chlorophenyl group also proceeded readily to afford **4g** in fairly good yield. Next, various hydrazones without an aromatic ring at the β-position to the ester were subjected to the same reaction conditions. Among them, only hydrazones **2h** and **2i** derived from benzylcysteine and methionine afforded polyfunctional pyrroles **4h** and **4i** in 60% and 21% yield, respectively. On the other hand, treatment of hydrazones **2j** and **2k**



Scheme 3. Production of symmetrical pyrrole from unsymmetric diimine.

hydrazone **2a**. Subsequently, coupling by two molecules of **2a** concomitant with elimination of N_2H_4 generates the symmetric diimine, so-called azine, which is further converted to **4a** through the same path as the Piloty–Robinson reaction:[11] (i) isomerization to divinyl hydrazine intermediate; (ii) 3,3-sigmatropic rearrangement; (iii) cyclization of diimine intermediate concomitant with elimination of NH_3.

We thus examined the conversion of hydrazone itself into pyrrole under the same conditions, as shown in Table 1. When treated with thionyl chloride in EtOH at 90 °C in a sealed tube, **2a** was converted to **4a** in excellent yield. This remarkable result led us to clarify the scope and limitation of this pyrrole formation using hydrazones having various types of aromatic ring (entries 2–7). The reaction of hydrazones **2b**–**d** derived from tyrosine, benzyl tyrosine and methyl tyrosine, respectively, gave the corresponding pyrroles **4b**–**d** in good yields. Although the yield was unsatisfactory, pyrrole **4e** with a 3,4-dimethoxyphenyl group was also obtained. After the reaction of the hydrazone **2e**, ^{1}H NMR spectra of crude mixture were examined. It contained several byproducts, which were unstable to purify by silica gel column chromatography. Considering from the chart, it seems that aromatic electrophilic substitution occurred inter and intramolecularly and gave complex mixture along with pyrrole **4e**. The reaction of hydrazone derived from benzylserine and leucine under the same conditions resulted in their decomposition.

The reaction of hydrazones **2l**–**n** derived from Cbz-lysine, aspartic acid and glutamic acid are listed in Scheme 4. With its amine at the sixth position from the iminic carbon, **2l** was cyclized to afford the compound **6** in 76% yield. As **2m** and **2n** contain a carbonyl group at the fifth or sixth position from the amine of the hydrazone, intramolecular cyclization occurred faster than intermolecular condensation. It seems that isomerization of the double bond occurred after cyclization and gave **7** from **2m**. Hydrazone **2n** was obtained by reduction of diazo ester **1n** with L-Selectride®. When **1n** was treated with tributylphosphine, cyclic compound **9** was produced in 77% yield.[9] Further, **2n** was gradually cyclized and gave **9** even though it was stored in a refrigerator. When compound **9** was treated with thionyl chloride in ethanol, compound **8** was produced (Scheme 5). Considering these results, product **8** was obtained from **9** via cyclization and subsequent oxidation.

The synthesis of pyrrole derivatives containing two different aromatic rings is more difficult. There are two methods to obtain unsymmetric 3,4-diarylpyrroles. The first introduces the different aromatic rings one by one to dibromo or ditriflate pyrrole by a coupling reaction.[12] Lately, as its constructive application, Dauban and Dodd et al. reported one-pot Suzuki–Miyaura couplings

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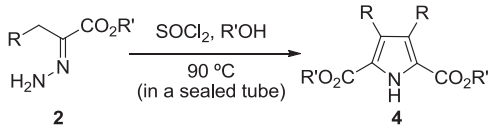
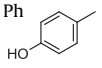
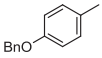
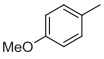
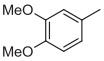
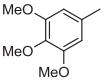
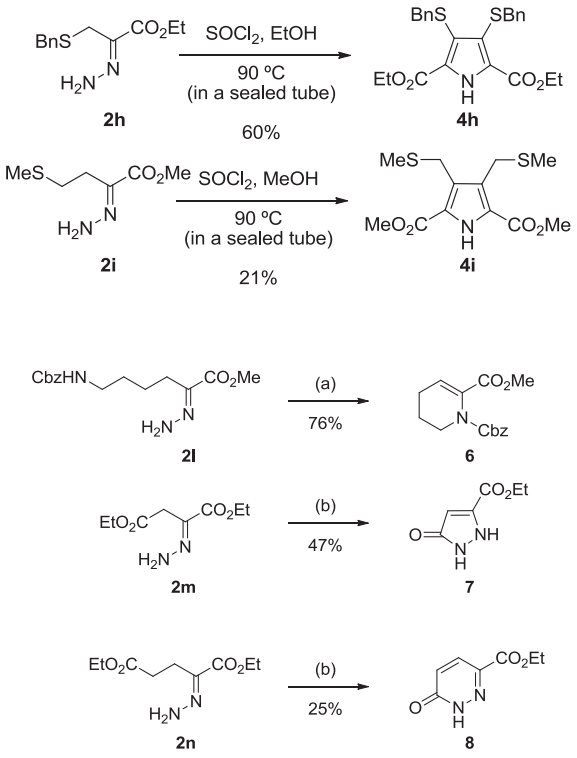
Table 1
Results of cyclization with various hydrazones



2 4

Entry	R		R′	Yield (%)
1	Ph	(**2a**)	Et	94 (**4a**)
2		(**2b**)	Et	79 (**4b**)
3		(**2c**)	Me	74 (**4c**)
4		(**2d**)	Me	79 (**4d**)
5		(**2e**)	Me	37 (**4e**)
6		(**2f**)	Me	66 (**4f**)
7		(**2g**)	Me	80 (**4g**)
8	BnO–	(**2j**)	Me	Complex mixture
9	$(CH_3)_2CH$–	(**2k**)	Et	Complex mixture



Scheme 4. Production of heterocyclic compounds from hydrazones. *Reagents and conditions*: (a) $SOCl_2$, MeOH, 90 °C (in a sealed tube); (b) $SOCl_2$, EtOH, 90 °C (in a sealed tube).

of 3,4-dibromo-1*H*-pyrrole-2,5-dicarboxylate with two kinds of arylboronic acids, generating unsymmetrically substituted pyrrole in moderate yield.[13] A second method is to make 3,4-diarylpyrroles through cyclization of a substrate having aromatic substituents in advance.[14] Steglich et al. reported the synthesis of 3,4-diarylpyrrole-2,5-dicarboxylic acids and their ester derivatives.[15] In their method, pyrrole **4ab** was synthesized from sodium enolate of ethyl 3-(4-hydroxyphenyl) pyruvate, ethyl 3-bromo-3-phenylpyruvate and ammonia in 14% yield. We thus challenged the synthesis of a pyrrole containing two different aromatic rings by using our new method. Treatment of an equivalent mixture of hydrazones **2a** and **2b** with thionyl chloride in EtOH at 90 °C in a sealed tube afforded unsymmetric pyrrole **4ab** in moderate yield along with two symmetric pyrroles (**4a**: 30%; **4b**: 19%) (Scheme 6). There is still room for improvement in synthesizing unsymmetric pyrrole in good yield and further trials are in progress.

3. Conclusion

A new synthesis method for polyfunctional pyrroles has been found. Various hydrazones obtained from α-diazo esters were converted to the corresponding pyrroles upon treatment with thionyl chloride in alcohol. In particular, hydrazones having an acidic proton on the β-carbon to the ester gave pyrrole derivatives in good yields. These ring formations should proceed through the sequence of coupling of two molecular hydrazones concomitant with elimination of hydrazine, isomerization to divinylhydrazine intermediate, 3,3-sigmatropic rearrangement and cyclization of the diimine intermediate concomitant with elimination of NH_3. This method would be applicable to the polyaromatic systems that are widely found in various drugs and useful materials.

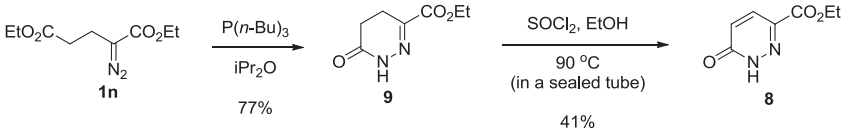
4. Experimental

4.1. General

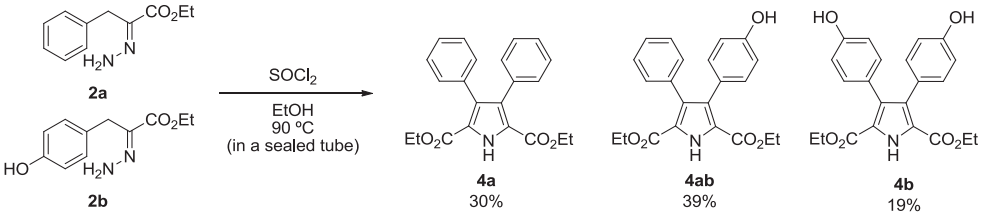
^1H and ^{13}C NMR spectra were recorded on a JEOL JNN-ECX-400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts were expressed in δ parts per million with tetramethylsilane as internal standard (δ=0 ppm) for ^1H NMR. Chemical shifts of carbon signals were referenced to $CDCl_3$ (δ_C=77.0 ppm). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad. IR spectra were recorded on a JASCO FT/IR-4100. Mass spectra were recorded on a JEOL JMS-GCmate II. FAB and ESI-mass spectra were recorded on a JEOL JMS-700. Melting points were determined on a Yanagimoto MP-S3 micro melting point apparatus and were uncorrected.

4.2. Materials

All reagents and solvents were purchased from commercial sources and used without further purification.



Scheme 5. Production of pyridazinone **8**.



Scheme 6. Trial for the synthesis of unsymmetric pyrrole.

4.3. Synthesis of hydrazones

4.3.1. Typical experimental procedure for reduction with L-Selectride®. Diazo ester **1a** (204 mg, 1 mmol) was dissolved in THF (9 ml) and stirred at −68 °C under a nitrogen atmosphere. To this solution was slowly added L-Selectride® (1.0 ml, 1.0 M in THF). The reaction mixture was stirred for 20 min at the same temperature, diluted with saturated NH_4Cl solution and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=2:1) to give **2a** as pale-yellow crystals (172.9 mg, 84%).

4.3.2. Typical experimental procedure for reduction with tributylphosphine. Diazo ester **1a** (427 mg, 2.09 mmol) was dissolved in *i*-Pr_2O (2.1 ml) and stirred at room temperature under a nitrogen atmosphere. To this solution was added tributylphosphine (1.57 ml, 6.27 mmol). The reaction mixture was stirred for 150 min at the same temperature, diluted with ethyl acetate (30 ml) and washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=10:1 to 1:1) to give **2a** (401.5 mg, 93%) and its *Z*-isomer **2a′** (10.1 mg, 2%).

*4.3.2.1. Ethyl (E)-2-hydrazono-3-phenylpropionate (**2a**).* Mp 49–50 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.20 (m, 5H), 6.05 (s, 2H), 4.33 (q, *J*=7.2 Hz, 2H), 3.90 (s, 2H), 1.37 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.16, 137.98, 134.82, 128.96, 128.00, 126.85, 61.40, 30.39, 14.29; IR (KBr) 3386, 1698, 1559 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}N_2O_2$ (M^+) 206.1055, found 206.1053.

*4.3.2.2. Ethyl (Z)-2-hydrazono-3-phenylpropionate (**2a′**).* Mp 67–68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (s, 2H), 7.29–7.18 (m, 5H), 4.14 (q, *J*=7.2 Hz, 2H), 3.70 (s, 2H), 1.22 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.73, 139.23, 130.38, 128.84, 128.13, 126.07, 60.20, 39.48, 13.98; IR (KBr) 3455, 1693, 1676, 1576, 1540, 1211 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}N_2O_2$ (M^+) 206.1055, found 206.1065.

*4.3.2.3. Ethyl (E)-2-hydrazono-3-(4-hydroxyphenyl) propionate (**2b**).* Mp 134–135 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.18 (s, 1H), 7.69 (s, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 6.64 (d, *J*=8.4 Hz, 2H), 4.09 (q, *J*=6.8 Hz, 2H), 3.62 (s, 2H), 1.19 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.47, 155.59, 133.09, 129.21, 126.91, 115.11, 59.78, 39.08, 14.28; IR (KBr) 3441, 1691, 1516 cm^{-1}; HRMS calcd for $C_{11}H_{14}N_2O_3$ (M^+) 222.1004, found 222.1016.

*4.3.2.4. Methyl (E)-2-hydrazono-3-(4-benzyloxyphenyl) propionate (**2c**).* Mp 96.0–96.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.30 (m, 5H), 7.11 (d, *J*=8.8 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 6.03 (s, 2H), 5.02 (s, 2H), 3.85 (s, 3H), 3.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.65, 157.75, 138.14, 136.85, 129.09, 128.55, 127.96, 127.41, 126.78, 115.40, 70.01, 52.51, 29.59; IR (KBr) 3429, 1701, 1510, 1247 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{18}N_2O_3$ (M^+) 298.1317, found 298.1320.

*4.3.2.5. Methyl (E)-2-hydrazono-3-(4-methoxyphenyl) propionate (**2d**).* Mp 63–64 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (d, *J*=8.0 Hz, 2H), 6.81 (d, *J*=8.0 Hz, 2H), 6.04 (s, 2H), 3.84 (s, 3H), 2.06 (s, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.78, 158.63, 138.23, 129.17, 126.59, 114.54, 55.36, 52.63, 29.68; IR (KBr) 3377, 3282, 3209, 1699 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}N_2O_3$ (M^+) 222.1004, found 222.1006.

*4.3.2.6. Methyl (E)-2-hydrazono-3-(3,4-dimethoxyphenyl) propionate (**2e**).* Mp 138–139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.81–6.71 (m, 3H), 6.09 (s, 2H), 3.88 (s, 2H), 3.85 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.67, 149.43, 147.99, 137.89, 126.93, 119.87, 111.39, 111.09, 55.83, 55.81, 52.53, 30.11; IR (KBr) 3402, 3290, 1695 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}N_2O_4$ (M^+) 252.1110, found 252.1103.

*4.3.2.7. Methyl (E)-2-hydrazono-3-(3,4,5-trimethoxyphenyl) propionate (**2f**).* Mp 133.5–134.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.38 (s, 2H), 6.10 (s, 2H), 3.85 (s, 3H), 3.82 (s, 2H), 3.79 (s, 6H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.78, 153.79, 137.50, 136.98, 130.40, 104.93, 60.92, 56.22, 52.70, 30.86; IR (KBr) 3402, 3244, 1698, 1592, 1124 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{18}N_2O_5$ (M^+) 282.1216, found 282.1223.

*4.3.2.8. Methyl (E)-2-hydrazono-3-(4-chlorophenyl) propionate (**2g**).* Mp 62–63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, *J*=8.0 Hz, 2H), 7.12 (d, *J*=8.0 Hz, 2H), 6.06 (s, 2H), 3.84 (s, 3H), 3.83 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.63, 137.14, 133.30, 132.89, 129.50, 129.24, 52.70, 29.72; IR (KBr) 3407, 1708, 1562 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}ClN_2O_2$ (M^+) 226.0509, found 226.0509.

*4.3.2.9. Ethyl (E)-2-hydrazono-3-benzylsulfinyl propionate (**2h**).* Mp 52–53 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.24 (m, 5H), 6.50 (s, 2H), 4.27 (q, *J*=7.2 Hz, 2H), 3.75 (s, 2H), 3.58 (s, 2H), 1.33 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.44, 137.43, 134.40, 128.80, 128.58, 127.38, 61.45, 36.45, 23.88, 14.25; IR (KBr) 3426, 1690, 1551, 1188 cm^{-1}; HRMS (FAB pos.) calcd for $C_{12}H_{17}N_2O_2S$ ($M+H^+$) 253.1011, found 253.1007.

*4.3.2.10. Methyl (E)-2-hydrazono-4-methylsulfinyl butanoate (**2i**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.36 (s, 2H), 3.83 (s, 3H), 2.80 (t, *J*=7.6 Hz, 2H), 2.68 (t, *J*=7.6 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.11, 138.18, 52.27, 29.74, 24.45, 15.79; IR (film) 3410, 3318, 3225, 1705 cm^{-1}; HRMS (EI) calcd for $C_6H_{12}N_2O_2S$ (M^+) 176.0619, found 176.0631.

*4.3.2.11. Methyl (E)-2-hydrazono-3-benzyloxy propionate (**2j**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.27 (m, 5H), 7.05 (s, 2H), 4.61 (s, 2H), 4.48 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.93, 137.04, 133.06, 128.54, 128.19, 128.09, 72.68, 63.57, 52.32; IR (film) 3424, 3310, 3229, 2951, 2862, 1694, 1566, 1441 cm^{-1};

HRMS (FAB pos.) calcd for $C_{11}H_{15}N_2O_3$ ($M+H^+$) 223.1083, found 223.1108.

*4.3.2.12. Ethyl (E)-2-hydrazono-4-methyl pentanoate (**2k**).* ^1H NMR ($CDCl_3$, 400 MHz) δ 6.03 (s, 2H), 4.28 (q, J=7.2 Hz, 2H), 2.37 (d, J=7.6 Hz, 2H), 2.03 (septet, J=7.2 Hz, 1H), 1.35 (t, J=7.2 Hz, 3H), 0.96 (d, J=6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.20, 140.23, 61.13, 32.60, 25.88, 22.88, 14.29; IR (film) 3412, 1701, 1140 cm^{-1}; HRMS calcd for $C_8H_{16}N_2O_2$ (M^+) 172.1212, found 172.1210.

*4.3.2.13. Methyl (E)-2-hydrazono-6-benzyloxycarbonylamino hexanoate (**2l**).* ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.28 (m, 5H), 6.21 (s, 2H), 5.08 (s, 2H), 4.86 (br s, 1H), 3.78 (s, 3H), 3.28 (q, J=6.4 Hz, 2H), 2.50 (t, J=8.0 Hz, 2H), 1.56 (q, J=6.4 Hz, 2H), 1.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.53, 156.99, 138.55, 136.51, 128.51, 128.13, 127.93, 66.72, 52.20, 39.48, 30.15, 22.99, 20.80; IR (film) 3410, 3318, 2947, 2862, 1708, 1535, 1443, 1207 cm^{-1}; HRMS calcd for $C_{15}H_{21}N_3O_4$ (M^+) 307.1532, found 307.1532.

*4.3.2.14. Ethyl (E)-2-hydrazono succinate (**2m**).* Mp 85.5–86.0 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.60 (s, 2H), 4.31 (q, J=7.2 Hz, 2H), 4.17 (q, J=7.2 Hz, 2H), 3.63 (s, 2H), 1.36 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.80, 164.31, 132.26, 61.69, 61.65, 31.50, 14.30, 14.06; IR (KBr) 3410, 3298, 1716, 1697 cm^{-1}; HRMS (FAB pos.) calcd for $C_8H_{15}N_2O_4$ (M^+) 203.1032, found 203.1033.

*4.3.2.15. Ethyl (E)-2-hydrazono glutarate (**2n**).* ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68 (s, 2H), 4.28 (q, J=7.2 Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 2.74 (t, J=6.4 Hz, 2H), 2.62 (t, J=6.4 Hz, 2H), 1.35 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.11, 164.77, 138.44, 61.13, 61.08, 30.69, 19.09, 14.28, 14.07; IR (film) 3418, 2986, 2932, 1720 cm^{-1}; HRMS calcd for $C_9H_{16}N_2O_4$ (M^+) 216.1110, found 216.1094.

4.4. Synthesis of pyrroles

*4.4.1. Typical experimental procedure for pyrrole **4a**.* Hydrazone **2a** (176.1 mg, 0.85 mmol) was dissolved in ethanol (2 ml) in a sealed tube. To this solution was slowly added thionyl chloride (0.62 ml, 8.50 mmol) diluted in ethanol (3 ml) at 0 °C and stirred for 45 min at 90 °C. After cooling to room temperature, the reaction mixture was slowly poured into saturated aqueous $NaHCO_3$ solution (30 ml) and extracted with ethyl acetate (10 ml) three times. 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 **4a** as colourless crystals (145.5 mg, 94%).

*4.4.1.1. Diethyl 3,4-bis(4-phenyl)-1H-pyrrole-2,5-dicarboxylate (**4a**).* Mp 151–151.8 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.86 (br s, 1H), 7.21–7.16 (m, 6H), 7.15–7.09 (m, 4H), 4.22 (q, J=8.0 Hz, 4H), 1.17 (t, J=8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 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 calcd for $C_{22}H_{21}NO_4$ (M^+) 363.1471, found 363.1477.

*4.4.1.2. Diethyl 3,4-bis(4-hydroxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**4b**).* Mp 227–228 °C; ^1H NMR (CD_3OD, 400 MHz) δ 6.88 (d, J=8.8 Hz, 2H), 6.60 (d, J=8.8 Hz, 2H), 4.17 (q, J=7.2 Hz, 2H), 1.15 (t, J=7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 162.43, 157.27, 133.20, 132.67, 126.34, 123.18, 115.06, 61.61, 14.35; IR (KBr) 3526, 3402, 3271, 1697, 1481, 1427, 1296, 1242 cm^{-1}; HRMS calcd for $C_{22}H_{21}NO_6$ (M^+) 395.1369, found 395.1367.

*4.4.1.3. Dimethyl 3,4-bis(4-benzyloxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**4c**).* Mp 172–173 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.79 (br s, 1H), 7.45–7.30 (m, 10H), 7.05 (d, J=8.4 Hz, 4H), 6.84 (d, J=8.4 Hz, 4H), 5.02 (s, 4H), 3.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.75, 157.83, 136.98, 131.93, 131.20, 128.51, 127.91, 125.35, 121.08, 113.79, 69.87, 51.75; IR (KBr) 3263, 1703, 1212 cm^{-1}; HRMS calcd for $C_{34}H_{29}NO_6$ (M^+) 547.1995, found 547.1994.

*4.4.1.4. Dimethyl 3,4-bis(4-methoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**4d**).* Mp 198–199 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.79 (br s, 1H), 7.04 (d, J=8.8 Hz, 4H), 6.76 (d, J=9.2 Hz, 4H), 3.77 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.76, 158.50, 131.89, 131.25, 125.08, 121.08, 112.88, 55.05, 51.73; IR (KBr) 3348, 1705 cm^{-1}; HRMS calcd for $C_{22}H_{21}NO_6$ (M^+) 395.1369, found 395.1365.

*4.4.1.5. Dimethyl 3,4-bis(3,4-dimethoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**4e**).* Mp 171–171.5 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.80 (br s, 1H), 6.74 (m, 4H), 6.62 (d, J=1.2 Hz, 2H), 3.86 (s, 6H), 3.80 (s, 6H), 3.64 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.75, 148.04, 147.88, 131.25, 125.37, 123.40, 121.07, 114.32, 110.29, 55.74, 51.83; IR (KBr) 3310, 1721, 1682, 1535, 1466, 1319, 1250 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{25}NO_8$ (M^+) 455.1580, found 455.1566.

*4.4.1.6. Dimethyl 3,4-bis(3,4,5-trimethoxyphenyl)-1H-pyrrole-2,5-dicarboxylate (**4f**).* Mp 168.0–168.5 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.85 (br s, 1H), 6.36 (s, 4H), 3.81 (s, 12H), 3.64 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 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.

*4.4.1.7. Dimethyl 3,4-bis(4-chlorophenyl)-1H-pyrrole-2,5-dicarboxylate (**4g**).* Mp 182–183 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.90 (br s, 1H), 7.19 (d, J=8.0 Hz, 4H), 7.02 (d, J=8.0 Hz, 4H), 3.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.54, 133.36, 132.13, 131.10, 130.18, 127.93, 121.48, 52.05; IR (KBr) 2952, 1710, 1297, 1247 cm^{-1}; HRMS calcd for $C_{12}H_{13}N_3O_2$ (M^+) 403.0378, found 403.0378.

*4.4.1.8. Diethyl 3,4-bis(benzylsulfinyl)-1H-pyrrole-2,5-dicarboxylate (**4h**).* ^1H NMR ($CDCl_3$, 400 MHz) δ 9.84 (br s, 1H), 7.23–7.10 (m, 10H), 4.31 (q, J=7.2 Hz, 4H), 3.96 (s, 4H), 1.37 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.22, 137.78, 128.98, 128.15, 126.93, 126.60, 126.07, 61.39, 40.49, 14.26; IR (film) 3271, 1705, 1273 cm^{-1}; HRMS calcd for $C_{24}H_{25}NO_4S_2$ (M^+) 455.1225, found 455.1225.

*4.4.1.9. Dimethyl 3,4-bis(methylsulfinyl)-1H-pyrrole-2,5-dicarboxylate (**4i**).* Mp 91–92 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.50 (br s, 1H), 4.06 (s, 4H), 3.91 (s, 6H), 2.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.67, 127.44, 122.38, 51.85, 26.48, 15.21; IR (KBr) 3321, 1697, 1282, 1273 cm^{-1}; HRMS calcd for $C_{12}H_{18}NO_4S_2$ ($M+H^+$) 304.0677, found 304.0647.

*4.4.1.10. Diethyl 3-(4-hydroxyphenyl)-4-phenyl-1H-pyrrole-2,5-dicarboxylate (**4ab**).* Mp 186.0–186.4 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.85 (br s, 1H), 7.20–7.18 (m, 3H), 7.13–7.11 (m, 2H), 6.99–6.95 (m, 2H), 6.66–6.62 (m, 2H), 4.25 (q, J=7.2 Hz, 2H), 4.22 (q, J=7.2 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H), 1.16 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.56, 160.53, 155.05, 133.21, 132.02, 131.39, 131.32, 130.84, 127.23, 126.81, 124.83, 121.49, 121.38, 114.38, 60.85, 14.06, 13.94; IR (KBr) 3348, 3210, 1690, 1474, 1435, 1296, 1250 cm^{-1}; HRMS calcd for $C_{22}H_{21}NO_6$ (M^+) 379.1420, found 379.1419.

4.5. Synthesis of heterocyclic compounds in Schemes 4 and 5

4.5.1. Experimental procedure for compounds in Scheme 4. Hydrazone was dissolved in alcohol in a sealed tube. To this solution was slowly added thionyl chloride diluted in the same alcohol at 0 °C

and stirred for 45 min at 90 °C. After cooling to room temperature, the reaction mixture was slowly poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate three times. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give heterocyclic compounds.

*4.5.1.1. 1,2-(4H)-Pyridinedicarboxylic acid,5,6-dihydro-2-methyl 1-(phenylmethyl) ester (**6**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.37 (m, 5H), 6.08 (t, J=3.6 Hz, 1H), 5.14 (s, 2H), 3.66 (t, J=5.6 Hz, 2H), 3.54 (br s, 3H), 2.24 (dt, J=6.8, 3.6 Hz, 2H), 1.83 (quint, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.10, 153.98, 135.74, 132.31, 128.42, 128.14, 128.12, 123.14, 67.91, 51.86, 43.62, 22.83, 22.61; IR (film) 1713, 1396, 1335, 1273, 1258, 1234 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1158, found 275.1157.

*4.5.1.2. Ethyl 2,5-dihydro-5-oxo-1H-pyrazole-3-carboxylate (**7**).* Mp 185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.21 (s, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.43, 161.39, 134.28, 92.90, 62.28, 14.12; IR (KBr) 3356, 1720, 1504, 1443, 1381, 1281 cm^{-1}; HRMS (EI) calcd for $C_6H_8N_2O_3$ (M^+) 156.0535, found 156.0532.

*4.5.1.3. Ethyl 3-pyridazinone-6-carboxylate (**8**).* Mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, J=10 Hz, 1H), 7.04 (d, J=10 Hz, 1H), 4.46 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.12, 161.43, 137.51, 132.55, 129.92, 62.51, 14.15; IR (KBr) 2847, 1713, 1288, 1142 cm^{-1}; HRMS (EI) calcd for $C_7H_8N_2O_3$ (M^+) 168.0535, found 168.0528.

*4.5.2. Experimental procedure for compound **9**.* Diazo ester **1n** (285 mg, 1.33 mmol) was dissolved in i-Pr_2O (1.3 ml) and stirred at room temperature under a nitrogen atmosphere. To this solution was added tributylphosphine (1.00 ml, 3.95 mmol). The reaction mixture was stirred for 60 min at the same temperature, diluted with ethyl acetate (30 ml) and washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=6:1 to 1:1) to give **9** (175 mg, 77%) and its Z-hydrazone **2n′** (18.4 mg, 6%).

*4.5.2.1. Ethyl 6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylate (**9**).* Mp 133–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.10 (s, 1H), 4.36 (q, J=7.2 Hz, 2H), 2.93 (t, J=8.4 Hz, 2H), 2.57 (t, J=8.4 Hz, 2H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.88, 162.94, 142.89, 62.20, 25.69, 21.02, 14.11; IR (KBr) 1713, 1624, 1288, 1202 cm^{-1}; HRMS (EI) calcd for $C_7H_{10}N_2O_3$ (M^+) 170.0691, found 170.0692.

*4.5.3. Experimental procedure for compound **8** from **9**.* The compound **9** (103.5 mg, 0.61 mmol) was slowly added thionyl chloride (0.440 ml, 6.10 mmol) diluted in ethanol (4 ml) and stirred for 60 min at 90 °C in a sealed tube. After cooling to room temperature, the reaction mixture was slowly poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate three times. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=1:2) to give the compound **8** (41.9 mg, 0.25 mmol, 41%).

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