A Simple Synthesis of 1-Substituted Diethyl Pyrrole-3,4-dicarboxylates

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

A series of 1-substituted diethyl 1*H*-pyrrole-3,4-dicarboxylates **4a** – **o** were prepared in 14 – 93 % yield by acid-catalysed treatment of diethyl 2,3-bis[(*E*,*E*)-(dimethylamino)-methylidene]succinate (**2**) with various aliphatic and (hetero)aromatic primary amines **3a** – **o**. The configuration of the C=C double bonds in the bis-enaminone **2** was determined by ^{1}H NMR and HMBC spectroscopy.

Key words: Pyrroles, Enaminones, Amines, Cyclisations, Heterocycles

Introduction

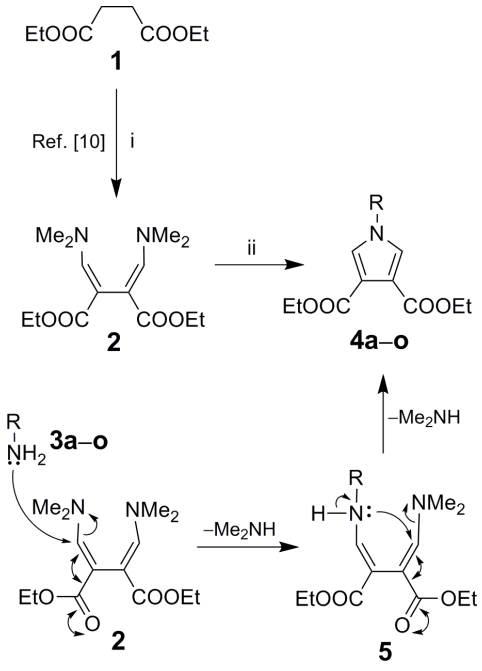
Pyrrole is an important heterocycle because its structure is incorporated in a variety of biologically important compounds, such as heme, chlorophyll, vitamin B_{12}, and bile pigments. Besides, pyrrole and pyrrolidine partial structures occur in numerous natural products and synthetically important compounds [1].

Among numerous syntheses of pyrroles reported so far in the literature, three general methods have to be outlined: a) the Paal-Knorr synthesis of pyrroles from 1,4-dicarbonyl compounds and primary amines (5+1 cyclocondensation approach), b) the Knorr pyrrole synthesis from α-amino ketones and 1,3-dicarbonyl compounds (3+2 cyclocondensation approach), and c) the van Leusen synthesis of pyrroles from tosylmethyl isocyanide (Tosmic) and α,β-unsaturated carbonyl compounds (3+2 cycloaddition approach) [1].

2-Substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones are a group of enamino-masked alkyl α-formylacetates, which are easily available and are versatile reagents in heterocyclic synthesis [2]. In addition to their extensive use in the synthesis of various heterocyclic systems, recent applications of enaminones are mostly oriented towards the preparation of functionalised heterocyclic compounds including natural product analogues [2 – 4] and in combinatorial synthesis of functionalized heterocycles [5]. In this context, pyrrole derivatives have been prepared by intramolecular cyclisation of 2-(2-cyano-vinyl)amino-3-(dimethylamino) propenoates [6], 2-(2-acylvinyl)amino-3-(dimethylamino)-propenoates [7], and trialkyl 1-acylamino-4-(arylamino)-buta-1,3-diene-1,2,3-tricarboxylates [8], and by reactions of 1,2-diaza-1,3-butadienes with 2-acylamino-3-(dimethylamino)-propenoates [9]. Diethyl 2,3-bis[(*E*,*E*)-(dimethylamino)methylidene]succinate (**2**), easily available from diethyl succinate (**1**) [10], seems to be a suitable enaminone-type reagent for a straightforward synthesis of 1-substituted pyrrole-3,4-dicarboxylates **4**. To the best of our knowledge, however, only two reactions of **2** with primary amines have been reported in the literature. In 1983, Kornfeld and Jones synthesised diethyl 1*H*-pyrrole-3,4-dicarboxylate (**4a**) by treatment of **2** with ammonium acetate (**3a**) [11], while 16 years later Townsend and Magawa prepared the *N*-[2-(pyridin-2-yl)ethyl] derivative in an analogous manner [12]. This lack of information was quite intriguing, and we decided to carry out a series of acid-catalysed reactions of bis-enamino succinate **2** [10] with various primary amines **3a** – **o**. Herein, we report the result of this study – a simple and efficient synthesis of 1-substituted-1*H*-pyrrole-3,4-dicarboxylates **4a** – **o**.

Results and Discussion

Diethyl 2,3-bis[(*E*,*E*)-(dimethylamino)methylidene] succinate (**2**) was prepared from diethyl succinate (**1**) and *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent, TBDMAM) according to a modified literature procedure [10]. Heating of the bis-



Scheme 1. Reaction conditions: (i) *tert*-Butoxy-bis(dimethylamino)methane (Bredereck's reagent), reflux (ref. [10]); (ii) R-NH_2 (**3a**–**o**), EtOH-AcOH (2 : 1), reflux.

enaminone **2** with ammonium formate (**3a**), hydroxylamine hydrochloride (**3b**), or 1,1-dimethylhydrazine (**3c**) in a mixture of ethanol and acetic acid for ~1 h afforded the diethyl 1*H*-pyrrole-3,4-dicarboxylates **4a**–**c** in 42–86 % yield. Similarly, reactions of **2** with amino acid derivatives **3d**–**j** proceeded smoothly to give the corresponding 1-alkylated 1*H*-pyrrole-3,4-dicarboxylates **4d**–**j** in 80–93 % yield. Quite expectedly, reactions of **2** with aniline (**3k**) and heteroarylamines **3l**–**o** required longer reaction times (~ 3 h) to achieve a complete conversion of the starting bis-enaminone **2** into the corresponding 1-(hetero)aryl-1*H*-pyrrole-3,4-dicarboxylates **4l**–**o**, which were obtained in 14–80 % yield. The cyclisation of the bis-enamino ester **2** with primary amines **3** can be explained by double substitution of the dimethylamino group, *i. e.* Michael addition of the primary amine **3** to the enaminone **2**, followed by elimination of dimethylamine, leads to the monosubstituted intermediate **5**, which then undergoes the second 1,4-addition-elimination sequence to furnish the pyrrole derivative **4** (Scheme 1, Table 1).

The structures of the novel compounds **4b**–**j** and **4l**–**o** were determined by spectroscopic (NMR, IR, MS) methods and by elemental analyses for C, H, and N. Compounds **4b**–**d**, **4f**–**h**, **4j**, and **4o** were

Table 1. Selected experimental data of diethyl pyrrole-3,4-dicarboxylates **4a**–**o**.

Compound	Ar	Yield (%)
3a, **4a**	H	42
3b, **4b**	OH	85
3c, **4c**	NMe_2	86
3d, **4d**	(*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl	84
3e, **4e**	(*S*)-3-(4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl	86
3f, **4f**	(*S*)-1,5-diethoxy-1,5-dioxopentan-2-yl	93
3g, **4g**	(*S*)-1-methoxy-4-methyl-1-oxopentan-2-yl	90
3h, **4h**	CH_2CH_2COOEt	85
3i, **4i**	CH_2CN	80
3j, **4j**	CH_2COOH	84
3k, **4k**	phenyl	42
3l, **4l**	4-methylpyridin-2-yl	14
3m, **4m**	3-hydroxypyridin-2-yl	37
3n, **4n**	5-methylisoxazol-3-yl	80
3o, **4o**	1*H*-1,2,4-triazol-5-yl	70

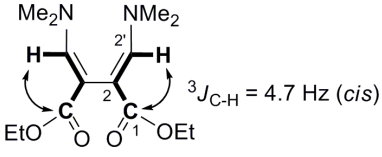


Fig. 1. Structure determination of **2** by HMBC spectroscopy. The double bonds exhibit *E* configuration.

not obtained in analytically pure form. Their identity was confirmed by HRMS and ^{13}C NMR data. The structure of the bis-enaminone **2** was determined by ^1H NMR and HMBC spectroscopy. One set of signals in the ^1H NMR spectrum of compound **2** clearly indicated that compound **2** was symmetrical with the same configuration of both C=C double bonds. The (*E*)-configuration of the exocyclic C=C bonds was confirmed by HMBC spectroscopy on the basis of a long-range coupling constant ($^3J_{C-H}$) between the methylidene proton [*H*–C(2′)] and the carbonyl carbon atom [O=*C*(1)], measured from the antiphase splitting of cross peaks. Generally, the coupling constant $^3J_{C-H}$ for nuclei with *cis*-configuration of the C=C double bond is smaller (2–6 Hz) than for *trans*-oriented nuclei (8–12 Hz) [2, 13]. In compound **2**, the magnitude of the coupling constant, $^3J_{C(1)--H(2')}$ = 5.4 Hz (*cis*), indicated (*E*)-configuration of the C=C double bonds (Fig. 1).

Conclusion

Diethyl 2,3-bis[(*E*,*E*)-(dimethylamino)methylidene] succinate (**2**) is an easily available reagent, which can smoothly be reacted with primary amines **3** affording 1-substituted diethyl 1*H*-pyrrole-3,4-dicarb-

oxylates **4**. In most cases, this method affords the pyrroles **4** in very good yields after simple workup. In addition to *N*-alkylation [14] and *N*-arylation [15] of 1-unsubstituted dialkyl 1*H*-pyrrole-3,4-dicarboxylates, this method represents a simple complementary cyclocondensation approach towards the preparation of the title compounds.

Experimental Section

Melting points were determined on a Kofler micro hot stage. The NMR spectra were obtained on a Bruker Avance DPX 300 spectrometer at 300 MHz for ^{1}H and at 75.5 MHz for ^{13}C, using $CDCl_3$ (with TMS as the internal standard) as solvent. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Flash chromatography (FC) was performed on silica gel (Fluka, silica gel 60, 0.04 – 0.06 mm). Diethyl succinate (**1**), *tert*-butoxy-bis (dimethylamino)methane (Bredereck's reagent), and amines **3a** – **o** are commercially available (Sigma Aldrich).

*Diethyl (2E,3E)-2,3-bis[(dimethylamino)methylidene] succinate (**2**)*

This compound was prepared according to a modified literature procedure [12]. A mixture of diethyl succinate (**1**) (10 mL, 60 mmol) and Bredereck's reagent (30 mL, 145 mmol) was refluxed under argon for 9 h. Then, another portion of Bredereck's reagent (5 mL, 24 mmol) was added, and the mixture was refluxed under argon for 9 h. The reaction mixture was evaporated *in vacuo*, the residue was suspended in water (120 mL) and extracted with hexanes (2 × 60 mL). The aqueous phase was evaporated *in vacuo*, the yellow oily residue dissolved in anhydrous diethyl ether (30 mL), and the solution left in a refrigerator for one week. The precipitate was collected by filtration and washed with hexanes to give compound **2**. Yield: 9.55 g (56 %) of yellow crystals; m. p. 70 – 72 °C (from hexanes), ref. [10]: m. p. 70.5 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.20 (6H, t, J = 7.1 Hz, 2 × CH_2CH_3), 2.93 (12H, s, 2 × NMe_2), 4.15 (4H, q, J = 7.1 Hz, 2 × CH_2CH_3), 7.50 (2H, s, 2 × CH).

*Synthesis of 1-substituted diethyl pyrrole-3,4-dicarboxylates **4a** – **o**. General procedures*

*Procedure A. Synthesis of compounds **4b** – **i**, **k**, **n**, **o***

A mixture of bis-enaminone **2** (142 mg, 0.5 mmol), primary amine **3b** – **i**, **k**, **n**, **o** (0.5 mmol), ethanol (2 mL), and acetic acid (1 mL) was heated under reflux for 1 – 3 h. The reaction mixture was cooled, and volatile components were evaporated *in vacuo*. The residue was purified by CC (silica gel, ethyl acetate, column dimensions 10 × 1 cm). Fractions containing the product were combined and evaporated *in vacuo*. **4b** – **i**, **k**, **n**, **o** were prepared in this manner.

*Procedure B. Synthesis of compounds **4a**, **l**, **m***

A mixture of bis-enaminone **2** (142 mg, 0.5 mmol), primary amine **3a**, **l**, **m** (0.5 mmol), ethanol (2 mL), and acetic acid (1 mL) was heated under reflux for 1 – 3 h. The reaction mixture was cooled, and volatile components were evaporated *in vacuo*. The residue was triturated with an appropriate solvent (1.5 mL) and the precipitate collected by filtration to give **4a**, **l**, **m**.

*Procedure C. Synthesis of compound **4j***

A mixture of bis-enaminone **2** (142 mg, 0.5 mmol), glycine (**3j**) (38 mg, 0.5 mmol), ethanol (2 mL), and acetic acid (1 mL) was heated under reflux for 1 h. The reaction mixture was cooled, and volatile components were evaporated *in vacuo*. The residue was suspended in water (10 mL), the suspension made alkaline with solid $NaHCO_3$ and extracted with dichloromethane (20 mL). The aqueous phase was acidified with 1 M hydrochloric acid to pH ~2 and extracted again with dichloromethane (20 mL). The organic phase was dried over anhydrous sodium sulphate, filtered, and the filtrate evaporated *in vacuo* to give **4j**.

*Diethyl 1H-pyrrole-3,4-dicarboxylate (**4a**)*

Compound **4a** was prepared from **2** and ammonium formate (**3a**) (32 mg, 0.5 mmol). Procedure B, reflux for 1 h, trituration with ethanol. Yield: 45 mg (42 %) of a white solid; m. p. 147 – 149 °C, ref. [11]: m. p. 150 – 151 °C. – IR (KBr): ν = 3240, 1710 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (6H, t, J = 7.1 Hz, 2 × CH_2CH_3), 4.38 (4H, q, J = 7.1 Hz, 2 × CH_2CH_3), 7.45 (2H, s, 2-H, 5-H), 9.95 (1H, br s, NH).

*Diethyl 1-hydroxy-1H-pyrrole-3,4-dicarboxylate (**4b**)*

Compound **4b** was prepared from **2** and hydroxylamine hydrochloride (**3b**) (35 mg, 0.5 mmol). Procedure A, reflux for 2 h. Yield: 97 mg (85 %) of a yellowish oil. – IR (NaCl): ν = 3147, 2982, 1724 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.23 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 4.15 (4H, q, J = 7.2 Hz, 2 × CH_2CH_3), 7.39 (2H, s, 2-H, 5-H), 12.20 (1H, br s, OH). – ^{13}C NMR ($CDCl_3$): δ = 14.6, 61.3, 111.7, 124.3, 165.1. – MS (EI): m/z = 227 $[M]^+$. – HRMS (EI): m/z = 227.0801 (calcd. 227.0794 for $C_{10}H_{13}NO_5$, $[M]^+$).

*Diethyl 1-dimethylamino-1H-pyrrole-3,4-dicarboxylate (**4c**)*

Compound **4c** was prepared from **2** and 1,1-dimethylhydrazine (**3c**) (30 mg, 0.5 mmol); Procedure A, reflux for 1 h. Yield: 109 mg (86 %) of a yellowish oil. – IR (NaCl): ν = 3129, 2961, 1734, 1524 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ =

1.32 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 2.80 (6H, s, NMe_2), 4.25 (4H, q, J = 7.2 Hz, 2 × CH_2CH_3), 7.32 (2H, s, 2-H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 14.7, 48.6, 60.6, 114.6, 124.2, 163.8. – MS (EI): *m/z* = 254 $[M]^+$. – MS (FAB): *m/z* = 255 $[M+H]^+$. – HRMS (EI): *m/z* = 254.1276 (calcd. 254.1267 for $C_{12}H_{18}N_2O_4$, $[M]^+$).

*Diethyl 1-[(S)-3-(1H-indol-3-yl)-1-methoxy-1-oxopropan-2-yl]-1H-pyrrole-3,4-dicarboxylate (**4d**)*

Compound **4d** was prepared from **2** and (*S*)-tryptophan methyl ester hydrochloride (**3d**) (127 mg, 0.5 mmol). Procedure A, reflux for 1 h. Yield: 173 mg (84 %) of white crystals; m. p. 23 – 25 °C. – $[\alpha]_D^{22}$ = −11.3 (c = 0.73, $CHCl_3$). – IR (KBr): ν = 3360, 3134, 2981, 1730, 1535 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.32 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 3.51 (2H, m, CH_2CH), 3.76 (3H, s, OMe), 4.27 (4H, q, J = 7.2 Hz, 2 × CH_2CH_3), 4.81 (1H, dd, J = 3.4, 9.4 Hz, CH_2CH), 6.67 (1H, d, J = 2.3 Hz, 2′-H), 7.19 (2H, m, 5′-H, 6′-H), 7.27 (2H, s, 2-H, 5-H), 7.46 (2H, m, 4′-H, 7′-H), 8.05 (1H, br s, NH). – ^{13}C NMR ($CDCl_3$): δ = 14.7, 29.6, 53.4, 60.7, 63.5, 109.2, 111.9, 116.8, 118.3, 120.2, 122.7, 123.6, 127.0, 127.7, 136.5, 163.9, 170.1. – Anal. for $C_{22}H_{24}N_2O_6 \cdot {}^1/_4H_2O$: calcd. C 63.37, H 5.92, N 6.72; found C 63.42, H 6.12, N 6.94. – MS (EI): *m/z* = 412 $[M]^+$. – MS (FAB): *m/z* = 413 $[M+H]^+$. – HRMS (EI): *m/z* = 412.1649 (calcd. 412.1634 for $C_{22}H_{24}N_2O_6$, $[M]^+$).

*Diethyl 1- [(S)-3-(4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl]-1H-pyrrole-3,4-dicarboxylate (**4e**)*

Compound **4e** was prepared from **2** and (*S*)-tyrosine methyl ester hydrochloride (**3e**) (116 mg, 0.5 mmol). Procedure A, reflux for 1 h. Yield: 168 mg (86 %) of white crystals; m. p. 21 – 23 °C. – $[\alpha]_D^{22}$ = −22.8 (c = 1.69, $CHCl_3$). – IR (KBr): ν = 3443, 2984, 1730, 1519 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (6H, t, J = 7.1 Hz, 2 × CH_2CH_3), 3.13 (1H, dd, J = 9.1, 14.1 Hz, 1H of CH_2CH), 3.34 (1H, dd, J = 6.1, 14.1 Hz, 1H of CH_2CH), 3.72 (3H, s, OMe), 4.26 (4H, q, J = 7.1 Hz, 2 × CH_2CH_3), 4.69 (1H, dd, J = 6.1, 9.1 Hz, CH_2CH), 6.72 and 6.83 (4H, 2d, 1 : 1, J = 8.5 Hz, C_6H_4), 7.27 (2H, s, 2-H, 5-H), 7.30 (1H, br s, OH). – ^{13}C NMR ($CDCl_3$): δ = 14.6, 38.9, 53.4, 60.9, 64.8, 116.3, 116.7, 126.5, 127.8, 130.2, 156.3, 164.2, 169.9. – Anal. for $C_{20}H_{23}NO_7$: calcd. C 61.69, H 5.95, N 3.60; found C 61.62, H 6.11, N 3.65. – MS (EI): *m/z* = 389 $[M]^+$. – MS (FAB): *m/z* = 390 $[M+H]^+$. – HRMS (EI): *m/z* = 389.1486 (calcd. 389.1475 for $C_{20}H_{23}NO_7$, $[M]^+$).

*Diethyl 1-[(S)-1,5-diethoxy-1,5-dioxopentan-2-yl]-1H-pyrrole-3,4-dicarboxylate (**4f**)*

Compound **4f** was prepared from **2** and (*S*)-glutamic acid diethyl ester hydrochloride (**3f**) (122 mg, 0.5 mmol). Procedure A, reflux for 1 h. Yield: 185 mg (93 %) of a colourless oil. – $[\alpha]_D^{22}$ = −9.3 (c = 0.38, $CHCl_3$). – IR (NaCl): ν = 3135, 2983, 1736, 1538 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.25, 1.27, 1.34 (12H, 3t, 1 : 1 : 2, J = 7.2 Hz, 4 × CH_2CH_3), 2.33 (4H, m, CH_2CH_2), 4.14, 4.22, 4.29 (8H, 3q, 1 : 1 : 2, J = 7.2 Hz, 4 × CH_2CH_3), 4.74 (1H, dd, J = 4.1, 9.8 Hz, CH_2CH), 7.28 (2H, s, 2-H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 14.4, 14.5, 14.7, 28.2, 30.0, 60.7, 61.3, 61.7, 62.7, 117.3, 127.4, 163.8, 169.3, 172.2. – MS (EI): *m/z* = 397 $[M]^+$. – MS (FAB): *m/z* = 398 $[M+H]^+$. – HRMS (EI): *m/z* = 397.1746 (calcd. 397.1737 for $C_{19}H_{27}NO_8$, $[M]^+$).

*Diethyl 1-[(S)-1-methoxy-4-methyl-1-oxopentan-2-yl]-1H-pyrrole-3,4-dicarboxylate (**4g**)*

Compound **4g** was prepared from **2** and (*S*)-leucine methyl ester hydrochloride (**3g**) (99 mg, 0.5 mmol). Procedure A, reflux for 1 h. Yield: 152 mg (90 %) of a colourless oil. – $[\alpha]_D^{23}$ = 12.0 (c = 0.38, $CHCl_3$). – IR (NaCl): ν = 3133, 2959, 1738, 1537 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.93 (6H, d, J = 6.8 Hz, Me_2CH), 1.34 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 1.43 (1H, m, Me_2CH), 1.95 (2H, m, CH_2CH), 3.74 (3H, s, OMe), 4.29 (4H, q, J = 7.2 Hz, 2 × CH_2CH_3), 4.62 (1H, dd, J = 7.2, 8.7 Hz, CH_2CH), 7.29 (2H, s, 2-H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 14.7, 21.8, 23.0, 24.9, 41.6, 53.3, 60.7, 61.2, 117.0, 127.2, 163.9, 170.6. – MS (EI): *m/z* = 339 $[M]^+$. – MS (FAB): *m/z* = 340 $[M+H]^+$. – HRMS (EI): *m/z* = 339.1691 (calcd. 339.1682 for $C_{17}H_{25}NO_6$, $[M]^+$).

*Diethyl 1-(3-ethoxy-3-oxopropyl)-1H-pyrrole-3,4-dicarboxylate (**4h**)*

Compound **4h** was prepared from **2** and β-alanine ethyl ester hydrochloride (**3h**) (77 mg, 0.5 mmol). Procedure A, reflux for 1 h. Yield: 109 mg (85 %) of white crystals; m. p. 64 – 66 °C. – IR (KBr): ν = 3132, 2982, 1732, 1542 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.25, 1.33 (9H, 2t, 1 : 2, J = 7.2 Hz, 3 × CH_2CH_3), 2.77 (2H, t, J = 6.9 Hz, CH_2COOEt), 4.16 (2H, q, J = 7.2 Hz, CH_2CH_3), 4.19 (2H, t, J = 6.9 Hz, CH_2N), 4.28 (4H, q, J = 7.2 Hz, 2 × CH_2CH_3), 7.23 (2H, s, 2-H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 14.5, 14.7, 36.2, 45.9, 60.6, 61.6, 116.9, 128.0, 163.9, 170.6. – MS (EI): *m/z* = 311 $[M]^+$. – MS (FAB): *m/z* = 312 $[M+H]^+$. – HRMS (EI): *m/z* = 311.1377 (calcd. 311.1369 for $C_{15}H_{21}NO_6$, $[M]^+$).

*Diethyl 1-cyanomethyl-1H-pyrrole-3,4-dicarboxylate (**4i**)*

Compound **4i** was prepared from **2** and aminoacetonitrile hydrochloride (**3i**) (47 mg, 0.5 mmol). Procedure A, reflux for 1 h. Yield: 101 mg (80 %) of white crystals; m. p. 99 – 102 °C. – IR (KBr): ν = 3138, 2984, 2196, 1731, 1289 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.34 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 4.30 (4H, q, J = 7.2 Hz, CH_2CH_3), 4.84 (2H, s, CH_2CN), 7.30 (2H, s, 2-H, 5-H). – Anal. for $C_{12}H_{14}N_2O_4$:

calcd. C 57.59, H 5.64, N 11.19; found C 57.87, H 5.90, N 11.01.

*2-(3,4-Bis(ethoxycarbonyl)-1H-pyrrol-1-yl)acetic acid (**4j**)*

Compound **4j** was prepared from **2** and glycine (**3j**) (38 mg, 0.5 mmol). Procedure C, reflux for 1 h. Yield: 113 mg (84 %) of white crystals; m. p. 105 – 107 °C. – IR (KBr): ν = 3135, 2983, 1723, 1544 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.32 (6H, 2t, J = 7.2 Hz, 2 × CH_2CH_3), 4.28 (4H, q, J = 7.2 Hz, 2 × CH_2CH_3), 4.62 (2H, s, CH_2N), 5.95 (1H, br s, COOH), 7.26 (2H, s, 2-H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 14.6, 51.1, 61.1, 116.8, 129.7, 164.8, 169.9. – MS (EI): *m/z* = 269 $[M]^+$. – HRMS (EI): *m/z* = 269.0909 (calcd. 269.0899 for $C_{12}H_{15}NO_6$, $[M]^+$).

*Diethyl 1-phenyl-1H-pyrrole-3,4-dicarboxylate (**4k**)*

Compound **4k** was prepared from **2** and aniline (**3k**) (47 mg, 0.5 mmol). Procedure A, reflux for 3 h. Yield: 62 mg (42 %) of white crystals; m. p. 46 – 48 °C, lit. [16] m. p. 48 °C. – IR (KBr): ν = 1721, 1689 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.34 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 4.38 (4H, q, J = 7.2 Hz, CH_2CH_3), 7.40 (5H, s, Ph), 7.65 (2H, s, 2-H, 5-H).

*Diethyl 1-(4-methylpyridin-2-yl)-1H-pyrrole-3,4-dicarboxylate (**4l**)*

Compound **4l** was prepared from **2** and 2-amino-3-hydroxypyridine (**3l**) (47 mg, 0.5 mmol). Procedure B, reflux for 3 h, trituration with cyclohexane-diisopropyl ether. Yield: 20 mg (14 %) of white crystals; m. p. 86 – 88 °C. – IR (KBr): ν = 1718, 1690 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.38 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 2.48 (3H, s, 4′-Me), 4.40 (4H, q, J = 7.2 Hz, CH_2CH_3), 7.15 (1H, dd, J = 3.2, 5.4 Hz, 5′-H), 7.80 (1H, d, J = 3.2 Hz, 3′-H), 8.05 (2H, s, 2-H, 5-H), 8.45 (1H, d, J = 5.4 Hz, 6′-H). – Anal. for $C_{16}H_{18}N_2O_4$: calcd. C 63.56, H 6.00, N 9.27; found C 63.49, H 5.97, N 9.44.

*Diethyl 1-(3-hydroxypyridin-2-yl)-1H-pyrrole-3,4-dicarboxylate (**4m**)*

Compound **4m** was prepared from **2** and **3m** (55 mg, 0.5 mmol). Procedure B, reflux for 3 h, trituration with water. Yield: 98 mg (64 %) of white crystals; m. p. 140 – 143 °C. – IR (KBr): ν = 3340, 1720, 1695 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.27 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 4.25 (4H, q, J = 7.2 Hz, CH_2CH_3), 7.21 – 7.68 (2H, m, 5′-H, 6′-H), 8.07 (1H, dd, J = 2.2, 5.3 Hz, 4′-H), 8.15 (2H, s, 2-H, 5-H), 11.03 (1H, br s, OH). – Anal. for $C_{15}H_{16}N_2O_5$: calcd. C 59.21, H 5.30, N 9.21; found C 59.49, H 5.09, N 9.17.

*Diethyl 1-(5-methylisoxazol-3-yl)-1H-pyrrole-3,4-dicarboxylate (**4n**)*

Compound **4n** was prepared from **2** and 3-amino-5-methylisoxazole (**3n**) (49 mg, 0.5 mmol). Procedure A, reflux for 5 h. Yield: 117 mg (80 %) of white crystals; m. p. 79 – 81 °C. – IR (KBr): ν = 3348, 1730, 1697, 1620 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.35 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 2.50 (3H, s, 5′-Me), 4.35 (4H, q, J = 7.2 Hz, CH_2CH_3), 7.28 (1H, s, 4′-H), 7.30 (2H, s, 2-H, 5-H). – Anal. for $C_{14}H_{16}N_2O_5$: calcd. C 57.53, H 5.52, N 9.58; found C 57.90, H 5.38, N 9.84.

*Diethyl 1-(1H-1,2,4-triazol-5-yl)-1H-pyrrole-3,4-dicarboxylate (**4o**)*

Compound **4o** was prepared from **2** and 5-amino-1*H*-1,2,4-triazole (**3o**) (42 mg, 0.5 mmol). Procedure A, reflux for 1.5 h. Yield: 97 mg (70 %) of white crystals; m. p. 170 – 173 °C. – IR (KBr): ν = 2980, 1740 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.28 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 4.22 (4H, q, J = 7.2 Hz, 2 × CH_2CH_3), 7.88 (2H, s, 2-H, 5-H), 8.68 (1H, s, 3-H), 14.35 (1H, br s, NH). – ^{13}C NMR ($CDCl_3$): δ = 14.6, 61.1, 117.9, 126.2, 144.0, 157.0, 164.3. – Anal. for $C_{12}H_{14}N_2O_4 \cdot {}^1/_4H_2O$: calcd. C 50.97, H 5.17, N 19.81; found C 51.43, H 5.32, N 19.09. – MS (EI): *m/z* = 278 $[M]^+$. – HRMS (EI): *m/z* = 278.1024 (calcd. 278.1016 for $C_{12}H_{14}NO_6$, $[M]^+$).

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