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

Luka Škrlep, Andreja Čerček-Hočevar, Renata Jakše, Branko Stanovnik, and Jurij Svete

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, P. O. Box 537, 1000 Ljubljana, Slovenia

Reprint requests to Prof. Jurij Svete. Fax: +386 1 2419 220. E-mail: jurij.svete@fkkt.uni-lj.si

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*Dedicated to Professor Gerhard Maas on the occasion of his 60$^{th}$ 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

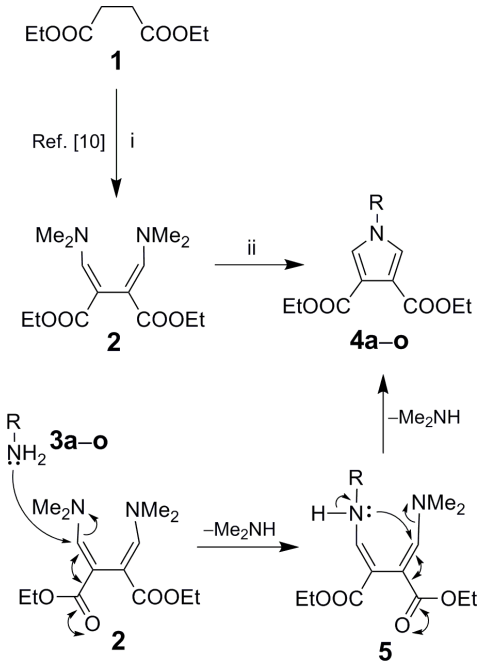
Pyrrole is an important heterocycle because its structure is incorporated in a variety of biologically important compounds, such as heme, chlorophyll, vitamin $B_{12}$, and bile pigments. Besides, pyrrole and pyrrolidine partial structures occur in numerous natural products and synthetically important 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 $\alpha$-amino ketones and 1,3-dicarbonyl compounds (3+2 cyclocondensation approach), and c) the van Leusen synthesis of pyrroles from tosylmethyl isocyanide (Tosmic) and $\alpha,\beta$-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 $\alpha$-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 |

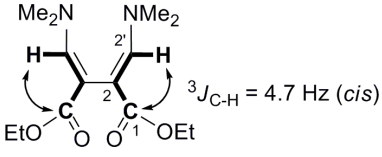



Fig. 1. Structure determination of **2** by HMBC spectroscopy. The double bonds exhibit *E* configuration.

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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 3240, 1710 cm$^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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): $\nu$ = 3147, 2982, 1724 cm$^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 3129, 2961, 1734, 1524 cm$^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ =

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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 3360, 3134, 2981, 1730, 1535 $cm^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 3443, 2984, 1730, 1519 $cm^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 3135, 2983, 1736, 1538 $cm^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 3133, 2959, 1738, 1537 $cm^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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 $\beta$-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): $\nu$ = 3132, 2982, 1732, 1542 $cm^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 3138, 2984, 2196, 1731, 1289 $cm^{-1}$. – $^1$H NMR ($CDCl_3$): $\delta$ = 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): $\nu$ = 3135, 2983, 1723, 1544 $cm^{-1}$. – $^1H$ NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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): $\nu$ = 1721, 1689 $cm^{-1}$. – $^1H$ NMR ($CDCl_3$): $\delta$ = 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): $\nu$ = 1718, 1690 $cm^{-1}$. – $^1H$ NMR ($CDCl_3$): $\delta$ = 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): $\nu$ = 3340, 1720, 1695 $cm^{-1}$. – $^1H$ NMR ($CDCl_3$): $\delta$ = 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): $\nu$ = 3348, 1730, 1697, 1620 $cm^{-1}$. – $^1H$ NMR ($CDCl_3$): $\delta$ = 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): $\nu$ = 2980, 1740 $cm^{-1}$. – $^1H$ NMR ($CDCl_3$): $\delta$ = 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 ($CDCl_3$): $\delta$ = 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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