One-Pot Four-Component Synthesis of Tetrasubstituted Pyrroles

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A convenient one-pot four-component synthesis of tetrasubstituted pyrroles was carried out through the reaction of butane-2,3-dione with α-aminophosphorous ylides, obtained *in situ* from the 1:1:1 addition reaction between triphenylphosphine, dialkyl acetylenedicarboxylate, and ammonium acetate.

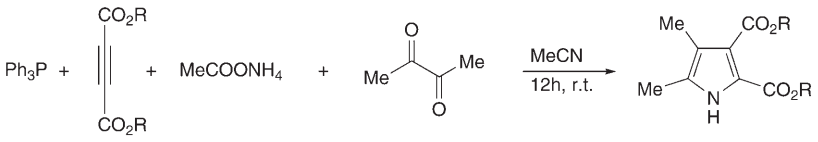
Introduction. – One-pot multicomponent processes combine principles of synthetic efficiency and reaction design, while attracting considerable academic, economic, and ecological interests [1][2]. Among numerous heterocycles synthesized through the multicomponent processes, pyrroles emerge with a great significance [2c]. The pyrrole ring is an important heterocycle in biological systems being incorporated into the porphyrin ring systems of chlorophyll, heme, and vitamin B_{12} [3][4]. Many alkaloids and at least two amino acids, namely proline and hydroxyproline, contain the reduced pyrrole ring (pyrrolidine) [5]. Tetrapyrrole pigments are involved as building blocks in various natural products such as porphobilinogen or bilirubin [6][7]. In particular, 1,2,3,5-tetrasubstituted pyrroles have proven to display antibacterial [8], antiviral (also anti-HIV-1) [9], anti-inflammatory [10], and antioxidant [11] activities, besides inhibiting cytokine-mediated diseases [12]. In addition, pentasubstituted pyrroles are potent hypocholesterolemic agents through the inhibition of HMG-CoA reductase, a key enzyme in the biosynthesis of cholesterol [13]. This feature has driven the search for efficient methods to construct pyrroles. Some of the classical methods such as the *Hantzsch* [14], *Knorr* [15], *Paal–Knorr* [16], *Huisgen* [17], *Trofimov* [18], *Zav'yalov* [19], *Barton–Zard* [20], *Piloty–Robinson* [21], and many other syntheses [22] have been used to produce this valuable heterocycle.

As part of our current studies on the development of new routes in heterocyclic synthesis [23], we report a simple one-pot multicomponent synthesis of 1*H*-pyrrole-2,3-dicarboxylate.

Results and Discussion. – Reaction of Ph_3P with dialkyl acetylenedicarboxylates **1**, in the presence of ammonium acetate in MeCN as a solvent at $-10°$, yielded highly polar α-aminophosphorous ylides **5** within 10 min. Addition of butanedione **2** at room temperature rendered the corresponding dialkyl 4,5-dimethyl-1*H*-pyrrole-2,3-dicarboxylates **3a**–**3d** in 73–91% yield (*Scheme 1*). The structures of compounds **3a**–**3d** were deduced from their elemental analyses, IR, and ^{1}H- and ^{13}C-NMR spectra. The

mass spectrum of **3a** displayed the molecular ion peak at *m*/*z* 211 which was consistent with its molecular formula. The IR spectrum of **3a** revealed the ester C=O absorptions at 1707 and 1661 cm^{-1}, while the absorption of the NH group was at 3265 cm^{-1}. In the ^{1}H-NMR spectrum, the NH proton signal (exchangeable with D_2O) was visible at 9.67 ppm, and two MeO groups were discernible at 3.79 and 3.83 ppm. The ^{13}C-NMR signals for the C=O C-atoms appeared at 161.0 and 166.3 ppm, corresponding to those of the esters.

Scheme 1



1 **2** **3**

Entry	R	Product	Yield [%][a])
a	Me	**3a**	91
b	Et	**3b**	86
c	^{i}Pr	**3c**	73
d	^{t}Bu	**3d**	82

[a]) Yield of isolated products.

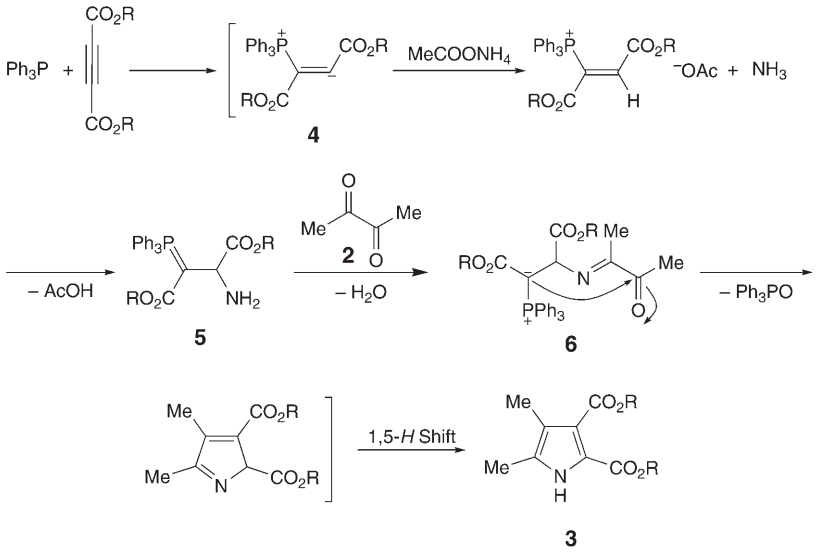
A mechanistic rationale for the reaction may be outlined as follows. The initially formed zwitterionic intermediate **4** [24] from Ph_3P and dialkyl acetylenedicarboxylate is protonated by ammonium acetate, and subsequent *Michael* addition of the conjugate base of NH_3 leads to the α-aminophosphorous ylide **5**. Condensation of the amino group with **2** gives the intermediate **6**. Finally, an intramolecular *Wittig* reaction *via* triphenylphosphine oxide elimination and 1,5-*H* shift leads to the highly substituted 1*H*-pyrrole-2,3-dicarboxylate **3** (*Scheme 2*).

In conclusion, we report a novel one-pot and four-component synthesis of dialkyl 4,5-dimethyl-1*H*-pyrrole-2,3-dicarboxylates **3** of potential synthetic and pharmacological interest. The readily available *in situ* generated phosphorane **5** provides a straightforward route to construct diverse functionalized pyrroles. The present method carries the advantage of being performed under neutral conditions and requiring no activation or modification of the starting materials.

Experimental Part

General. Reagents and solvents used in this work were obtained from *Fluka* (CH-Buchs) and used without further purification. TLC: *Merck silica gel 60 F_{254}* plates, visualization under UV light (254 nm). Column chromatography (CC): silica gel (*Merck* 230–400 mesh). M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR Spectra: at 500.1 and 125.7 MHz, resp., on a *Bruker DRX-500-Avance* FT-NMR instrument with $CDCl_3$ as solvent. MS: *Finnigan-MAT 8430* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses: *Heraeus CHN-O-Rapid analyzer*.

Scheme 2



*General Procedure for the Synthesis of 1*H*-Pyrrole-2,3-dicarboxylates* (exemplified for **3a**). To a soln. of Ph_3P (0.262 g, 1 mmol) and ammonium acetate (0.077 g, 1 mmol) in dry MeCN (3 ml) was added dropwise dimethyl acetylenedicarboxylate (**1**; 0.142 g, 1 mmol) at $-10°$, and the mixture was stirred for 15 min. It was allowed to warm to r.t. After completion of the reaction (TLC), a soln. of *butane-2,3-dione* (**2**; 0.086 g, 1 mmol) in MeCN was added, and the resulting mixture was stirred for 12 h. The solvent was removed *in vacuo*, and the residue was separated by CC (hexane/AcOEt 3 : 1). The solvent was removed under reduced pressure, and the product was recrystallized from MeOH.

*Dimethyl 4,5-Dimethyl-1*H*-pyrrole-2,3-dicarboxylate* (**3a**). Yield 0.19 g (91%). Colorless crystalline solid. M.p. 138–140°. IR (KBr): 3265 (NH); 1707, 1661 (C=O); 1275, 1260 (C–O). ^{1}H-NMR: 2.02 (*s*, Me); 2.17 (*s*, Me); 3.79 (*s*, MeO); 3.83 (*s*, MeO); 9.67 (br. *s*, NH). ^{13}C-NMR: 9.7 (Me); 11.0 (Me); 51.7 (MeO); 51.7 (MeO); 118.4 (C(4)); 118.6 (C(2)); 121.1 (C(3)); 130.0 (C(5)); 161.0 (C(2)–*C*O); 166.3 (C(3)–*C*O). EI-MS: 211 (18), 179 (86), 148 (84), 121 (100), 93 (63), 65 (47), 39 (67). Anal. calc. for $C_{10}H_{13}NO_4$ (211.22): C 56.86, H 6.20, N 6.63; found: C 56.60, H 6.21, N 6.52.

*Diethyl 4,5-Dimethyl-1*H*-pyrrole-2,3-dicarboxylate* (**3b**). Yield 0.21 g (86%). Colorless crystalline solid. M.p. 108–110°. IR (KBr): 3285 (NH); 1702, 1648 (C=O); 1260, 1245 (C–O). ^{1}H-NMR: 1.29 (*t*, $^3J = 7.1$, Me); 1.33 (*t*, $^3J = 7.1$, Me); 2.01 (*s*, Me); 2.16 (*s*, Me); 4.26 (*q*, $^3J = 7.1$, CH_2O); 4.31 (*q*, $^3J = 7.1$, CH_2O); 9.71 (br. *s*, NH). ^{13}C-NMR: 9.5 (Me); 10.9 (Me); 14.2 (2 Me); 60.6 (2 CH_2O); 117.9 (C(4)); 118.6 (C(2)); 121.5 (C(3)); 130.0 (C(5)); 160.8 (C(2)–*C*O); 166.1 (C(3)–*C*O). EI-MS: 239 (14), 193 (79), 164 (16), 148 (45), 121 (100), 93 (39), 65 (35), 42 (59). Anal. calc. for $C_{12}H_{17}NO_4$ (239.27): C 60.24, H 7.16, N 5.85; found: C 60.12, H 7.04, N 5.91.

*Diisopropyl 4,5-Dimethyl-1*H*-pyrrole-2,3-dicarboxylate* (**3c**). Yield 0.20 g (73%). Colorless crystalline solid. M.p. 112–114°. IR (KBr): 3232 (NH); 1705, 1651 (C=O); 1261, 1250 (C–O). ^{1}H-NMR: 1.12 (*d*, $^3J = 6.3$, 2 Me); 1.24 (*d*, $^3J = 6.1$, 2 Me); 2.07 (*s*, Me); 2.25 (*s*, Me); 4.89 (*sept.*, $^3J = 6.3$, CH); 4.99 (*sept.*, $^3J = 6.1$, CH); 9.79 (br. *s*, NH). ^{13}C-NMR: 9.0 (Me); 9.8 (Me); 21.5 (2 Me); 21.5 (2 Me); 21.6 (2 Me); 71.5 (CH); 72.1 (CH); 118.6 (C(4)); 119.2 (C(2)); 121.1 (C(3)); 127.8 (C(5)); 161.7 (C(2)–*C*O); 167.2 (C(3)–*C*O). EI-MS: 267 (4), 226 (6), 183 (18), 165 (100), 147 (26), 121 (83), 93 (71), 65 (33), 42 (61). Anal. calc. for $C_{14}H_{21}NO_4$ (267.32): C 62.90, H 7.92, N 5.24; found: C 62.80, H 7.94, N 5.22.

*Di(*tert*-butyl) 4,5-Dimethyl-1*H*-pyrrole-2,3-dicarboxylate* (**3d**). Yield 0.24 g (82%). Colorless crystalline solid. M.p. 116–118°. IR (KBr): 3295 (NH); 1707, 1658 (C=O); 1280, 1250 (C–O).

^{1}H-NMR: 1.54 (*s*, 3 Me); 1.58 (*s*, 3 Me); 2.03 (*s*, Me); 2.17 (*s*, Me); 9.63 (br. *s*, NH). ^{13}C-NMR: 9.6 (Me); 10.1 (Me); 28.3 (3 Me); 28.4 (3 Me); 80.7 (C); 81.2 (C); 116.9 (C(4)); 119.9 (C(2)); 122.7 (C(3)); 128.6 (C(5)); 160.0 (C(2)–*C*O); 164.9 (C(3)–*C*O). EI-MS: 295 (3), 240 (2), 183 (21), 165 (100), 147 (19), 121 (12), 57 (37), 41 (38). Anal. calc. for $C_{16}H_{25}NO_4$ (295.37): C 65.06, H 8.53, N 4.74; found: C 65.14, H 8.45, N 4.70.

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