

A FACILE ONE-POT SYNTHESIS OF FUNCTIONALIZED N-HYDROXYPYRROLE MEDIATED BY VINYL- TRIPHENYLPHOSPHONIUM SALT[☆]

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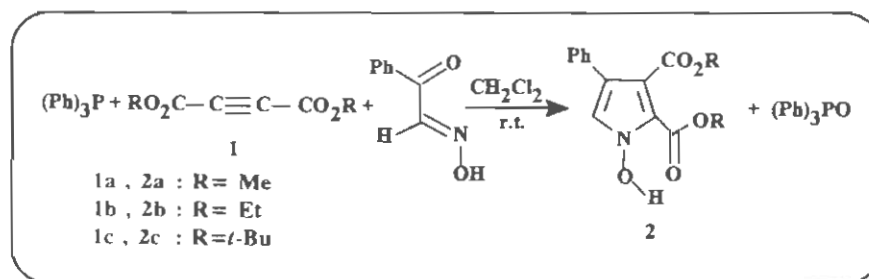
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ABSTRACT: Protonation of the reactive intermediates generated in the reaction between dialkyl acetylenedicarboxylates and triphenylphosphine by isonitrosoacetophenone leads to vinyltriphenylphosphonium salts, which undergo intramolecular Wittig reaction to produce dialkyl 4-phenyl-N-hydroxypyrrole-2,3-dicarboxylates in moderate yields.

KEY WORDS: N-Hydroxypyrroles, Intramolecular, Wittig reaction, Triphenylphosphine, Acetylenic ester, Isonitrosoacetophenone.

Functionalized pyrroles are important heterocycles and many naturally occurring pyrroles are known to possess biological activity [1]. There are many studies on the synthesis of the pyrrole ring structure [1-4]. Among the large family of pyrroles, several efforts have been focussed on the pyrrole-carboxylates [5]. Recently, we have described a

method for heterocyclic synthesis using a novel approach to vinylphosphonium salts [6,7]. We here report a facile synthetic route to N-hydroxypyrroles having an unsubstituted α -position, such as **2**, using intramolecular Wittig reaction [8,9]. Thus, reaction of acetylenic esters **1** with isonitrosoacetophenone in the presence of triphenylphosphine leads to the

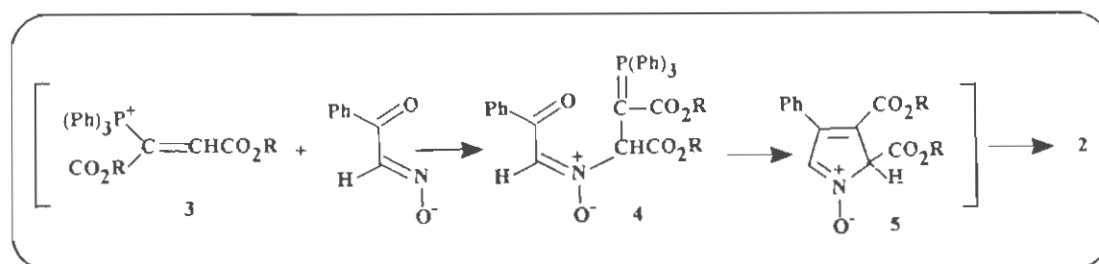


[☆] Dedicated to Professor Abbas Shafiee on the occasion of his 60th birthday.

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corresponding *N*-hydroxypyrroles **2**.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles [8-15] it is reasonable to assume that pyrrole **2** result from initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the 1:1 adduct, followed by attack of nitrogen atom of the anion of isonitrosoacetophenone to vinyltriphenylphosphonium cation **3** to generate yield **4**. Attack of phosphorane **4** on the benzoyl carbonyl in a normal intramolecular Wittig reaction would lead to the amine oxide **5** which is a tautomer of **2**.

Structure **2** was assigned to the isolated addition-cyclization products on the basis of their elemental analysis and ^1H NMR, ^{13}C NMR and mass spectral data as well as from the IR spectra which exhibited strong OH bonds. The mass spectra of compounds **2a-c** displayed molecular ion peaks at $m/z = 275$, 303 and 359 , respectively. Initial fragmentations involve loss of the pyrrole side chains.

The ^1H NMR spectrum of **2a** displayed three single sharp lines arising from methoxy ($\delta = 3.77$ and 3.92 ppm) and methine ($\delta = 7.10$ ppm) protons along with a fairly complex multiplet in the aromatic region. The OH group exhibited a fairly broad peak at $\delta = 11.8$ ppm, indicating extensive intramolecular hydrogen-bond formation with the vicinal carbonyl group [16]. The ^{13}C NMR spectrum of **2a** showed twelve distinct resonances in agreement with the pyrrole structure. Partial assignments of these resonances are given in Experimental.

The ^1H and ^{13}C NMR spectra of **2b** and **2c** are similar to those of **2a**, except for the ester groups which exhibit characteristic signals with appropriate chemical shifts (see Experimental).

The structural assignments made on the basis of the NMR spectra of compounds **2a-c** were supported

by measurement of their IR spectra. A noteworthy feature of the IR spectra is the carbonyl absorption (1675 - 1718 cm^{-1}) for these compounds. Conjugation with the heterocyclic ring and intramolecular hydrogen-bond formation with the OH group appear to be plausible factors in the reduction of the wavenumbers of the carbonyl absorption bands [16].

The reactions described herein represent a simple and efficient entry into the synthesis of functionalized pyrroles which provide potential utility in organic synthesis. Further investigation of the present method will be required to establish its utility and scope.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analysis for C, H and N was performed using a Heracus CHN-O-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrophotometer. ^1H and ^{13}C NMR spectra were measured with JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionization potential of 70 eV. Isonitrosoacetophenone and dialkyl acetylenedicarboxylates were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of dimethyl 4-phenyl-*N*-hydroxypyrrole-2,3-dicarboxylate (**2a**); General procedure

To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol) and isonitrosoacetophenone (0.298 g, 2 mmol) in dichloromethane (10 mL) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.284 g, 2 mmol) in dichloro-

methane (2 mL) at -5°C over 10 minutes. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 hours. The solvent was removed under reduced pressure and the viscous residue was purified by silica gel (Merck silica gel 60, 230-400 mesh) column chromatography using ethyl acetate-hexane (1:2) as eluent. The solvent was removed under reduced pressure and colorless crystals of dimethyl 4-phenyl-*N*-hydroxypyrrole-2,3-dicarboxylate (**2a**, 0.25 g, mp $83-84^{\circ}\text{C}$, 45%) were collected by filtration.

IR(KBr): ν_{max} (cm^{-1}), 1718 and 1702 (C=O), 1202 and 1182 (C-O).

^1H NMR(CDCl_3): δ (ppm), 3.77 and 3.92 (6H, 2s, 2 CH_3O), 7.10(1H, s, N-CH), 7.2-7.4(5H, m, C_6H_5), 11.8(1H, br s, O-H...O=C).

^{13}C NMR(CDCl_3): δ (ppm), 52.33 and 52.49(2 OCH_3), 114.18, 115.08, 118.21 and 120.41 (pyrrole, C4, C3, CH and C2, respectively), 127.13 (*para*-CH, Ph), 172.66 and 128.56 (*ortho*- and *meta*-CH, Ph), 132.99 (*ipso*-C, Ph), 163.13 and 166.06 (2C=O).

MS: m/z (%), 275(M^+ , 48), 243(M^+ - CH_3OH , 48), 196 (M^+ -2 CH_3O -OH, 100).

Calc. for $\text{C}_{14}\text{H}_{11}\text{NO}_5$ (275.26): C, 61.09, H, 4.76, N, 5.09 %; found: C, 61.3, H, 4.7, N, 5.0 %.

Diethyl 4-phenyl-*N*-hydroxypyrrole-2,3-dicarboxylate (**2b**)

Colorless crystals, 0.35 g, 58%, mp $105-107^{\circ}\text{C}$; yield: 58%.

IR(KBr): ν_{max} (cm^{-1}), 1709 and 1687 (C=O), 1271 and 1251(C-O).

^1H NMR(CDCl_3): δ (ppm), 1.24 and 37 (6H, 2t, $J = 7.2$ Hz, 2 CH_3), 4.27 and 4.39 (4H, 2q, $J = 7.2$ Hz, 2 CH_2), 7.10(1H, s, N-CH), 7.2-7.4(5H, m, C_6H_5), 11.9(1H, s, O-H...O=C).

^{13}C NMR(CDCl_3): δ (ppm), 14.01 and 14.03 (2 CH_3), 61.45 and 61.90(2 CH_2), 113.20, 115.40, 117.56 and 120.17 (pyrrole, C4, C3, CH and C2, respectively), 127.13(*para*-CH, Ph), 127.74 and 128.51(*ortho*- and *meta*-CH, Ph), 133.08(*ipso*-C, Ph), 163.41 and 165.57 (2C=O).

MS: m/z (%), 303(M^+ , 35), 257(M^+ - $\text{C}_2\text{H}_5\text{OH}$, 12), 229 (M^+ -2 $\text{CH}_2=\text{CH}_2-\text{H}_2\text{O}$, 12), 185(M^+ -2 $\text{CH}_2=\text{CH}_2-\text{CO}_2-\text{H}_2\text{O}$, 47), 196(M^+ -2 $\text{CH}_3\text{CH}_2\text{O}$ -OH, 100).

Calc. for $\text{C}_{16}\text{H}_{17}\text{NO}_5$ (303.32): C, 63.36, H, 5.65, N,

4.62%; found: C, 64.1, H, 5.5, N, 4.8%.

Di-*t*-butyl 4-phenyl-*N*-hydroxypyrrole-2,3-dicarboxylate (**2c**)

Colorless crystals, 0.50 g, yield: 70%, mp $112-114^{\circ}\text{C}$. IR(KBr): ν_{max} (cm^{-1}), 1708 and 1675 (C=O), 1289 and 1251(C-O).

^1H NMR(CDCl_3): δ (ppm), 1.35 and 1.58 (18H, 2s, 2 *t*-Bu), 6.98(1H, s, N-CH), 7.2-7.4(5H, m, C_6H_5), 12.3(1H, br, s, O-H...O=C).

^{13}C NMR(CDCl_3): δ (ppm), 27.85 and 28.30(6 CH_3 of 2 *t*-Bu), 81.36 and 84.36(2C of 2 *t*-Bu), 113.78, 116.71, 116.73 and 120.13 (pyrrole, C4, CH, C3, and C2, respectively), 129.93(*para*-CH, Ph), 128.11 and 128.51 (*ortho*- and *meta*-CH, Ph), 133.69(*ipso*-C, Ph), 163.49 and 163.78(2C=O).

MS: m/z (%), 361(M^+ +2, 6), 247(M^+ -2 $\text{Me}_2\text{C}=\text{CH}_2$, 100), 229(M^+ -2 $\text{Me}_2\text{C}=\text{CH}_2-\text{H}_2\text{O}$, 84).

Calc. for $\text{C}_{20}\text{H}_{25}\text{NO}_5$ (359.43): C, 66.84, H, 7.01, N, 3.90%, found: C, 66.7, H, 7.0, N, 3.7%.

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