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An Efficient One-pot Synthesis of Dialkyl fumarates Mediated by inyltriphenylphosphonium Salt in the Intramolecular Wittig Reaction

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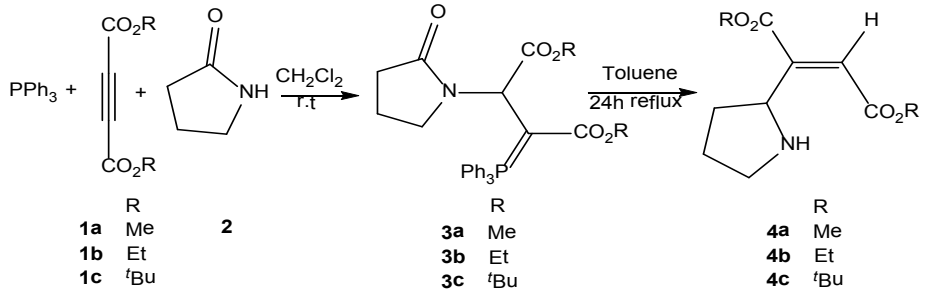
Abstract

An efficient three-component reaction of dialkyl acetylendicarboxylates and 2-Pyrrolidin in the presence of triphenylphosphine produces dialkyl 2-(2-Pyrrolidin-N-yl)-3-(triphenylphosphanylidene)succinate. These phosphoranes undergo mild intramolecular Wittig reaction to produce dialkyl (E)-2-(4,5-dihydro-3H-pyrrol-2-yl)fumarate in excellent yields.

Keywords: Wittig reaction; Dialkyl fumarate; Ph_3P; Acetylenic ester.

1. Introduction

Fumarate was recently investigated to be used the various classes of compounds in pharmaceutical, medical [1], industrial [2] and polymer chemistry [3] which possess biologically significant properties such as anti-cancer [4], superior inhibitors of HIV [5] and an inhibitory effect on parasite-specific [6]. The Wittig reaction is unique of the significant methods for the synthesis of carbon–carbon double bond [7-9]. As part of our current studies on the development of new routes on the way to heterocyclic systems [10-12]. We now design an efficient reaction of dialkyl acetylenedicarboxylates **1** and 2-Pyrrolidin **2** in the presence of Ph_3P, which constitutes a synthesis of yielding dialkyl (*Z*)- and (*E*)- 2-(2-Pyrrolidin-N-yl)-3-(triphenylphosphanylidene)succinate **3**. Stabilized phosphoranes undergo a smooth intramolecular Wittig reaction in boiling toluene to synthesis functionalized dialkyl (E)-2-(4,5-Dihydro-3H-pyrrol-2-yl)fumarate



Scheme 1. Synthesis of compounds 3 and 4.

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4 in good yields (Scheme 1).

2. Results and discussion

The reaction of 2-Pyrrolidin **2** with dialkyl acetylenedicarboxylates **1** in the presence of Ph_3P proceeded at room temperature in CH_2Cl_2, and was complete within a few hours. ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of dialkyl 2-(2-pyrrolidin-N-yl)-3-(triphenylphosphanylidene)succinate **3** (Scheme 1). No other products than **3** could be detected. The structures of compounds **3a–3c** were deduced from their IR, ^1H and ^{13}C NMR spectra. Any initial fragmentation involves loss from, or complete loss of the side chains and scission of the heterocyclic ring system.

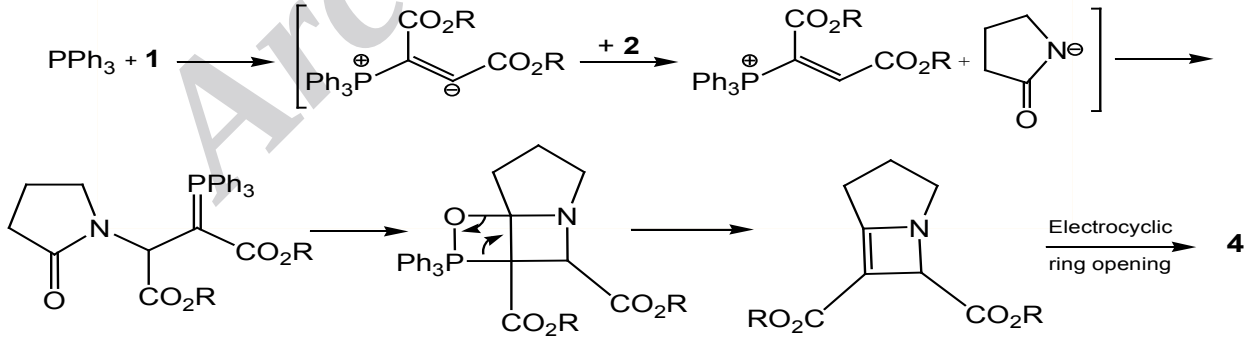
Compound **3** undergoes intramolecular Wittig reaction in boiling toluene to produce the Dialkyl (*E*)-2-(4,5-dihydro-3H-pyrrol-2-yl)fumarate derivative **4**, which undergoes electrocyclic ring opening to produce **4**. The ^1H and ^{13}C NMR spectra of the crude product **4a–4c** clearly indicated the formation of (*E*) isomers. The structures of compounds **4a–4c** were deduced from their elemental analyses and IR, ^1H, and ^{13}C NMR spectra. Although we have not yet established the mechanism of the thermal conversion of **3** to **4** in an experimental manner, a possible explanation is indicated in Scheme 2 on the basis of the well-established chemistry of the Wittig reaction. It is reasonable to assume that compound **4** results from an initial intramolecular Wittig reaction of phosphorane **3** and a subsequent electrocyclic ring opening reaction of the cyclobutene derivative **4.**

The ^1H and ^{13}C NMR spectra of the ylides **3a–3c** are consisted with the presence of two diastereoisomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the partial double bond in the (*E*)-**3** and (*Z*)-**3** geometrical isomers (Scheme 3) is slow on the NMR time scale at ambient temperature [13-14].

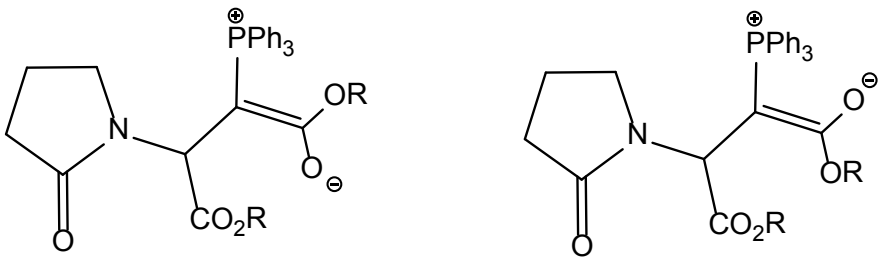
(*Z*)-**3**; Minor
(*E*)-**3**; Major

3. Experimental

Acetylenic esters **1** and Ph_3P were obtained from Fluka and were used without further purification. 2-Pyrrolidin **2** were prepared by known methods [15]. Melting points were measured on an Electrothermal 9001; apparatus. The experimental data were in good agreement with the calculated values. ^1H and ^{13}C NMR spectra ($CDCl_3$) were measured with



Scheme 2. A plausible mechanism for the formation of compounds **3** and **4**.



Scheme 3. (*E*)- and (*Z*)-stereoisomers of compound **3**.

a Bruker DRX-400 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Aldrich silica gel 70-230 mesh.

General procedure for the preparation of phosphorus ylides 3

To a stirred solution of 2 mmol of **1** and 2 mmol of **2** in 5 mL of CH_2Cl_2 was added drop wise a solution of 0.52 g of Ph_3P (2 mmol) in **2** of CH_2Cl_2 at room temperature over 10 min. After 12 h stirring at r.t., the product was filtered and washed with cold ether.

Dimethyl 2-(2-pyrrolidin-N-yl)-3-(triphenylphosphanylidene)succinate (3a)

White powder; mp: 216-219°C; yield: 0.74 g (76%); IR (KBr) (ν_{max}/cm^{-1}): 1743 (C=O), 1437 (C=C). Major isomer (*E*)-**3a** (58%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.04 (2 H, m, CH_2), 2.23 (2 H, t, CH_2-C=O), 2.39 (2 H, t, CH_2-N), 3.10 (3 H, s, MeO), 3.72 (3 H, s, MeO), 4.70 (1 H, d, $^3J_{PC}$=18.8 Hz, *CH*), 7.47–7.65 (15 H, m, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.1 (CH_2), 35.1 (CH_2-C=O), 37.6 (CH_2-N), 44.6 (d, $^1J_{PC}$=156 Hz, P=*C*), 49.0 (d, $^2J_{PC}$=17 Hz, P=C-CH), 49.3 (MeO), 50.4 (MeO), 125.7-133.6 (18 C, C_6H_5), 171.5 (d, $^3J_{PC}$=10 Hz, C=O), 172 (d, $^2J_{PC}$=16 Hz, C=O), 173.9 (CH_2C=O); ^{31}PNMR (162 MHz, $CDCl_3$): δ=23.93 (Ph_3P^+-C). Minor isomer (*Z*)-**3a** (42%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.02 (2 H, m, CH_2), 2.22 (2 H, t, CH_2-C=O), 2.37 (2 H, t, CH_2-N), 3.52 (3H, s, MeO), 3.70 (3H, s, MeO), 4.68 (1 H, d, $^3J_{PC}$=17.5 Hz, CH), 7.47–7.65 (15 H, m, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.0 (CH_2), 35.0 (*CH*$_2$ -C=O), 37.5 (*CH*$_2$-N), 42.5 (d, $^1J_{PC}$=140 Hz, P=C), 48.3 (MeO), 50.2 (MeO), 50.5 (d, $^2J_{PC}$=13 Hz, P=C-*CH*), 125.7-133.6 (18 C Arom), 171 (d, $^2J_{PC}$=16 Hz, C=O), 171.5(d, $^3J_{PC}$=11.5 Hz, C=O), 173.09 (*CH*$_2$-C=O); ^{31}PNMR(162 MHz, $CDCl_3$): 24.43 (Ph_3P^+-C).

Diethyl 2-(2-pyrrolidin-N-yl)-3-(triphenylphosphanylidene) succinate (3b)

Yellow powder; mp: 210-213°C; yield: 0.76 g (74%); IR (KBr) (ν_{max}/cm^{-1}): 1747 (C=O), 1493 (C=C). Major isomer (*E*)-**3b** (68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.5 (3 H, t, $^3J_{HH}$ =7.0 Hz, Me), 1.28 (3 H, t, $^3J_{HH}$=7.0 Hz, Me), 2.06 (2 H, m, CH_2), 2.33 (2 H, t, CH_2 -C=O), 2.37 (2 H, t, CH_2-N), 3.92 (2 H, q, CH_2O), 4.52 (2 H, q, CH_2O), 5.43 (1 H, d, $^3J_{PC}$=16.5 Hz, CH), 7.33–7.72 (15 H, m, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.8 (Me), 14.5 (Me), 18.3 (CH_2), 35.2 (*CH*$_2$-C=O), 37.5 (CH_2-N), 37.7 (d, $^1J_{PC}$=132 Hz, P=C), 57.6 (CH_2O), 63.0 (d, $^2J_{PC}$=18.0 Hz, CH), 61.2 (CH_2O), 128.7-143.5 (18 C Arom), 169.9 (d,$^3J_{PC}$=14 Hz, C=O), 170.1 (d, $^2J_{PC}$=16 Hz, C=O), 173.9 (*CH*$_2$C=O). Minor isomer (*Z*)-**3b** (32%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.39 (3 H, t, $^3J_{HH}$ =7.0 Hz, Me), 1.37 (3 H, t, $^3J_{HH}$=7.0 Hz, Me), 2.08 (2 H, m, CH_2), 2.33 (2 H, t, CH_2-C=O), 2.39 (2 H, t, CH_2-N), 3.92 (2 H, q, CH_2O), 4.05 (2 H, q, CH_2O), 5.31 (1 H, d, $^3J_{PC}$=15.5 Hz, CH), 7.33–7.72 (15 H, m, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.8 (Me), 14.3 (Me), 18.2 (CH_2), 35.1 (*CH*$_2$-C=O), 37.6 (CH_2-N), 36.7 (d, $^1J_{PC}$=130 Hz, P=C), 57.6 (CH_2O), 60.0 (d, $^2J_{PC}$=17.0 Hz , CH), 60.3 (CH_2O), 128.7-143.5 (18 C Arom), 168.9 (d,$^3J_{PC}$=14 Hz, C=O), 170.4 (d, $^2J_{PC}$=16 Hz , C=O), 174.9 (*CH*$_2$C=O).

Di-tert-butyl 2-(2-pyrrolidin-N-yl)-3-(triphenylphosphanylidene)succinate (3c)

Withe powder; mp: 206-209°C; yield: 0.91 g (80%); IR (KBr) (ν_{max}/cm^{-1}): 1747 (C=O), 1492 (C=C). major isomer (E)-**3**c (74%); ^{1}H NMR (400 MHz, CDC1$_3$): δ=1.03 (9 H, s, 3 Me), 1.54 (9 H, s, 3 Me), 2.17 (2 H, m, CH_2), 2.35 (2 H, t, CH_2-C=O), 2.47 (2 H, t, CH_2-N), 5.41 (1 H, d, $^3J_{PC}$=17 Hz, CH), 7.43–7.92 (15 H, m, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.3 (CH_2), 27.1 (3 Me), 28.4 (3 Me), 34.7 (*CH*$_2$-C=O), 38.5 (CH_2-N), 38.7 (d, $^1J_{PC}$=135 Hz, P=C), 64.0 (d, $^2J_{PC}$=18.0 Hz, CH), 74.5 (*C*Me$_3$), 74.8 (*C*Me$_3$), 169.4 (d,$^2J_{PC}$=18 Hz, C=O), 170.5 (d, $^2J_{PC}$=13 Hz, C=O), 172.7 (CH_2C=O). Minor isomer (*E*)-**3c** (26%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.04 (9 H, s, 3

Me), 1.64 (9 H, s, 3 Me), 2.19 (2 H, m, CH_2), 2.37 (2 H, t, CH_2-C=O), 2.45 (2 H, t, CH_2-N), 5.45 (1 H, d, $^3J_{PC}$=17, CH), 7.43–7.92 (15 H, m, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.3 (CH_2), 28.1 (3 Me), 29.4 (3 Me), 35.7 (*CH_2*-C=O), 36.5 (CH_2-N), 37.7 (d, $^1J_{PC}$=132 Hz, P=C), 64.0 (d, $^2J_{PC}$=16 Hz, CH), 73.6 (*C*Me_3), 73.9 (*C*Me_3), 169.6 (d,$^2J_{PC}$=18 Hz, C=O), 170.9 (d, $^2J_{PC}$=13 Hz, C=O), 172.9 (CH_2*C*=O).

General procedure for conversion of 3 to 4

A solution of 1 mmol of **3a-c** in 20 mL of toluene was refluxed for 24 h. The solvent was removed under reduced pressure and the yellowish oil was separated from triphenylphosphine oxide using cold Et_2O. The solvent was removed under reduced pressure and the residue was separated by silica column chromatography (Merck 230-400 mesh) using hexane/ethyl acetate as eluent.

Dimethyl (E)-2-(4,5-dihydro-3H-pyrrol-2-yl) fumarate (4a)

Yellow oil; yield: 0.16 g (79%); IR (KBr) (ν_{max}/cm^{-1}): 3478 (NH), 1493 (C=C), 1765 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ =1.66 (1 H, s, NH), 1.32 (2 H, m, *CH_2*-CH_2-NH), 2.18 (2 H, dt, *CH_2*-CH), 2.47 (2 H, t, *CH_2*-NH), 3.72 (1 H, t, *CH*-NH), 3.76 (3 H, s, MeO), 3.83 (3 H, s, MeO), 6.76 (1 H, s, C=CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.6 (CH_2), 26.2 (CH_2), 45.3 (CH_2-NH), 50.2 (CH-NH), 52.7 (MeO), 53.9 (MeO), 127.5 (*CH*=C), 152 (C), 162.2 (C=O), 162.9 (C=O).

Diethyl (E)-2-(4,5-dihydro-3H-pyrrol-2-yl 2,) fumarate (4b)

Yellow oil; yield: 0.17 g (73%); IR (KBr) (ν_{max}/cm^{-1}): 3338 (NH), 1495 (C=C), 1782 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.38 (3H , t, Me), 1.41 (3 H , t, Me), 1.49 (2 H, m, *CH_2*-CH_2-NH), 1.67 (1 H, s, NH), 2.38 (2 H, dt, *CH_2*-CH), 2.44 (2 H, t, *CH_2*-NH), 3.74 (1 H, t, *CH*-NH), 4.31 (2 H, q, CH_2O), 4.28 (2 H, q, CH_2O), 6.77 (1 H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.2 (Me), 15.8 (Me), 25.9 (CH_2), 27.5 (CH_2), 46.2 (*CH_2*-NH), 54.2 (CH-NH), 63.0 (CH_2O), 65.3 (CH_2O), 132.5 (*CH*=C), 162 (C), 169.2 (C=O), 172.9 (C=O).

Di-tert-butyl (E)-2-(4,5-dihydro-3H-pyrrol-2-yl)fumarate (4c)

Yellow oil; yield: 0.22 g (75%); IR (KBr) (ν_{max}/cm^{-1}): 3437 (NH), 1484 (C=C), 1772 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.42 (9 H, s, 3 Me), 1.49 (9 H, s, 3 Me), 1.51 (2 H, m, *CH_2*-CH_2-NH), 1.87 (1 H, s, NH), 2.42 (2 H, dt, *CH_2*-CH), 2.64 (2 H, t, *CH_2*-NH), 3.63 (1 H, t, CH-NH), 6.97 (1 H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.9 (CH_2), 27.2 (CH_2), 27.9 (3 Me), 28.8 (3 Me), 48.5 (CH_2-NH), 52.2 (CH-NH), 73.7 (*C*Me_3), 74.2 (*C*Me_3), 138.5 (*CH*=C), 142 (C), 170.2 (C=O), 171.9 (C=O).

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