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Facile one-pot preparation of phosphorus ylides from *N*-amino phthalimide derivatives and their intramolecular Wittig reaction

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Abstract: Crystalline phosphorus ylides were obtained in excellent yield from the 1:1:1 addition reaction between triphenylphosphine, dimethyl acetylenedicarboxylate (DMAD) and *N*-amino phthalimide derivatives. These phosphorus ylides undergo a smooth intramolecular Wittig reaction in boiling dioxane to produce isoindole rings in good yield.

Keywords: *N*-Amino phthalimide, Triphenylphosphine, Phosphorus ylide, Intramolecular Wittig reaction.

Introduction

Phosphorus ylides are becoming of increased importance in the synthesis of heterocyclic compounds [1-4]. They have numerous synthetic applications for a wide variety of industrial and biological fields. They are also ideal compounds in many cases due to their simple preparations and high reactivity with a large number of reagents which usually proceed in high yield [5-7].

In this study, we wish to report an efficient route to the synthesis of pyrazolo isoindole derivatives. The reaction of dimethyl acetylenedicarboxylate (DMAD) with *N*-phthalimido amide derivatives in the presence of triphenylphosphine was carried out, and the results are reported (Scheme **1**).

Results and discussion

The reaction of compounds **1a** and **1b** with dimethyl acetylenedicarboxylate (DMAD) in the presence of Ph_3P gave the phosphorus ylides **2a** and **2b.**

The key step in this transformation involves the generation of a zwitterion **2** and protonation of the 1:1 adduct by NH to form a positively charged ion. This positively charged ion is attacked by the nitrogen atom of the conjugate base of the NH acid leading to the formation of a new C-N bond to form a stable phosphorous ylide (**3a, b**). Surprisingly all of our attempts to separate phosphorus ylide **3b** were unsuccessful and it was directly converted to **4b** due to intramolecular Wittig reaction at room temperature. However, compound **3a** needs to be refluxed in toluene to give **4a**.

The proposed structures of ylide **3a** and Wittig products **4a** and **4b** were supported by their spectroscopic data, such as IR, ^{1}H NMR and ^{13}C NMR spectra.

The IR spectrum of **3a** shows two peaks for ester compounds in the region of carbonyl groups. One of the carbonyl groups reveals a strong band at 1618 cm^{-1} which is conjugated with ylide moiety and the nonconjugated carbonyl group appears at about 1746 cm^{-1}.

Since the rotation about the partial double bond in *E* and *Z* isomers is slow on the NMR time scale at ambient temperature (Scheme **2**), the presence of a mixture of the two geometrical isomers for compound **3a** was confirmed by its ^{1}H NMR and ^{13}C NMR spectra.

For example, ^{1}H NMR spectrum of **3a** shows four singlets for methyl hydrogens which indicate the

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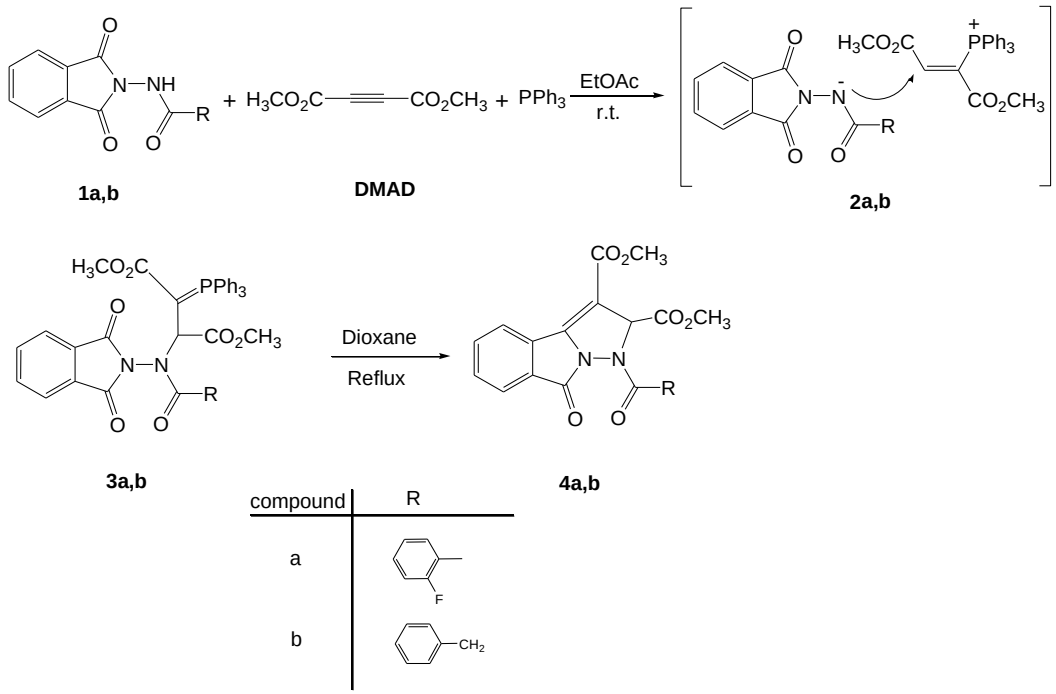
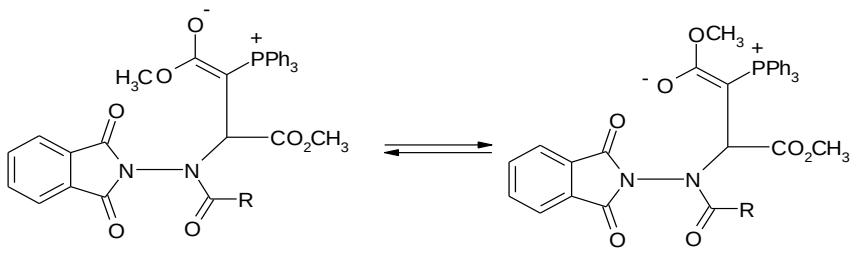
presence of the two isomers. Presence of the ^{31}P-nucleus helps in assignment of this compound by long range spin-spin coupling constants of ^{31}P with ^{1}H and ^{13}C nuclei.



Scheme 1. One-pot preparation of phosphorus ylides from *N*-amino phthalimide derivatives and their intramolecular Wittig reaction.



Scheme 2. Rotation about the partial double bond in *E* and *Z* isomers.

Experimental

General Procedure:

Triphenylphosphine, dimethyl acetylene dicarboxylate, toluene, hexane and ethyl acetate were obtained from Merck Chemical Company and used without further purification. Compounds **1a** and **1b** were prepared by reaction of corresponding acid chloride with *N*-aminophthalimide. IR spectra were recorded using KBr pellets on a Bruker IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 400 Avance instrument at 400 and 100 MHz, respectively.

Preparation of ylide 3a and corresponding Wittig product 4a:

To a magnetically stirred solution of triphenylphosphine (0.26 g, 1.00 mmol) and compound **1a** (0.28 g, 1.00 mmol) in ethyl acetate (10 mL) was added dropwise a mixture of DMAD (0.14 g, 1.00 mmol) over 10 min. The reaction mixture was then stirred for 24 h at room temperature. The resulted precipitate was filtered off and washed thoroughly with a mixture of 1:1 hexane-ethyl acetate to give **3a** (62%).

Compound **3a** (0.688 g, 1 mmol) was dissolved in 20 mL of dioxane and refluxed for 5 h. The solvent was removed under reduced pressure and the solid residue was recrystallized from ethanol to give **4a** (58%).

Ylide **3b** directly converted to compound **4b** at room temperature.

Spectral Data:

N-(1, 3-Dioxo-1, 3-dihydro-2H-isoindole-2yl)-2-fluoro benzamide (1a):

White powder, yield 80%, m.p. = 215-219 °C, IR (KBr) (ν_{max}, cm^{-1}): 1696, 1734, 1800 and 3409, ^1H NMR: δ 7.22-7.95 (7H, m, arom), 8.16 (s, 1H, NH) and 8.62 (1H, d, J = 13.3 Hz, arom), ^{13}C NMR: δ 116.7 (d, $^2J_{FC}$ = 24.4 Hz), 118.1 (d, $^2J_{FC}$ = 15.0 Hz), 1124.5, 125.5, 130.4, 133.0, 135.2, 135.5, 161.0 (d, $^1J_{FC}$ = 220 Hz), 162.6 and 165.4.

N-(1, 3-Dioxo-1, 3-dihydro-2H-isoindol-2-yl)-2-phenylacetamide (1b):

White powder, yield 86%, m.p. = 187 °C, IR (KBr) (ν_{max}, cm^{-1}): 1673, 1749 and 1799, ^1H NMR: δ 3.83 (CH_2), 7.29-7.44 (5 H, m, arom), 7.46 (1H, s, NH) and 7.79-7.91 (4H, m, arom), ^{13}C NMR: δ 41.3, 124.0, 127.8, 129.2, 129.6, 130.0, 133.0, 134.7, 164.9 and 169.5.

Dimethyl-2-[(1, 3-dioxo-1, 3-dihydro-2H-isoindol-2-yl) (2fluorobenzoyl) amino]-3-(1, 1, 1-triphenyl phosphoranylidene) succinate (3a):

White powder, yield 62%, m.p. = 185 °C, IR (KBr) (ν_{max}, cm^{-1}): 1618, 1673, 1746, 1768, 2939 and 3062. Major isomer (*Z*) (80%): ^1H NMR: δ 3.17 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.44 (1H, d, 20.3 Hz, P=C-CH)* and 6.91-7.79 (46 H, m, arom)*, ^{13}C NMR: δ 41.3 (d, $^1J_{PC}$ = 135.0 Hz)*, 49.9 and 52.9 (2 OCH_3), 61.9 (d, $^2J_{PC}$ = 18.0 Hz)*, 116.3 (d, $^2J_{FC}$ = 21.5 Hz)*, 123.7, 123.8 (d, $^2J_{FC}$ = 12.5 Hz)*, 124.5, 126.7 (d, $^1J_{PC}$ = 92.7 Hz, C^{ipso}), 127.7, 129.2 (d, $^3J_{PC}$ = 12.4 Hz, C^{meta}), 130.3 (C^{para}), 132.5 (d, $^2J_{PC}$ = 9.8 Hz, C^{ortho}), 133.8, 134.3, 135.1, 161.0 (d, $^1J_{FC}$ = 226.2 Hz, C-F)*, 164.7 (C=O), 166.1 (C=O), 171.3 (d, $^2J_{PC}$ = 15.8 Hz, C=O ester)* and 171.5 (C=O ester).

Minor isomer (*E*) (20%): ^1H NMR: δ 2.81 (3H, s, OCH_3) and 3.89 (3H, s, OCH_3), ^{13}C NMR: δ 49.3 and 52.7 (2 OCH_3), 124.0, 127.6, 128.9 (d, $^3J_{PC}$ = 12.2 Hz, C^{meta}), 130.5 (C^{para}), 131.4, 132.4 (d, $^2J_{PC}$ = 9.3 Hz, C^{ortho}), 133.6, 134.4, 135.2, 165.4 (C=O), 167.5 (C=O) and 170.9 (C=O ester). (* for two geometrical isomers).

Dimethyl-1-(2-fluorobenzoyl)-8-oxo-2, 8-dihydro-1H-pyrazolo [5, 1-a] isoindole-2, 3-dicarboxylate (4a):

Yellow powder, Yield 58%, m.p. = 164 °C, IR (KBr) (ν_{max}, cm^{-1}): 1652, 1703 and 1748, ^1H NMR: δ 3.77 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.79 (1H, s, CH) and 7.13-8.45 (8H, m, arom), ^{13}C NMR: δ 52.7 and 53.6 (2OCH_3), 72.7 (CH), 103.1, 116.8 (d, $^2J_{FC}$ = 21.3 Hz) 120.9 (d, $^2J_{FC}$ = 14.9 Hz), 124.8, 125.0 (d, $^4J_{FC}$ = 3.3 Hz), 127.2, 127.5, 127.6, 131.3, 133.3 (d, $^3J_{FC}$ = 10.4 Hz), 134.6 (d, $^3J_{FC}$ = 5.8 Hz), 147.8, 158.5, 160.3 (d, $^1J_{FC}$ = 336.5 Hz), 167.7 and 168.0.

Dimethyl-8-oxo-1-(2-phenylacetyl)-2, 8-dihydro-1H-pyrazolo [5, 1-a] isoindole-2, 3-dicarboxylate (4b):

Yellow powder, yield 71%, m.p. = 185 °C, IR (KBr) (ν_{max}, cm^{-1}): 1655, 1705 and 1747, ^1H NMR: δ 3.80 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.07 (d, $^2J_{HH}$ = 16.4 Hz), 4.24 (d, $^2J_{HH}$ = 16.4 Hz), 6.14 (1H, s, CH) and 7.20-8.42 (9H, m, arom), ^{13}C NMR: δ 40.6 (CH2), 52.4 and 53.3 (2OCH_3), 71.2 (CH), 103.8, 124.4, 126.7, 127.2, 127.5, 128.6, 129.3, 132.7, 132.8, 133.2, 133.4, 147.00, 159.8, 162.2, 167.9 and 174.8.

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