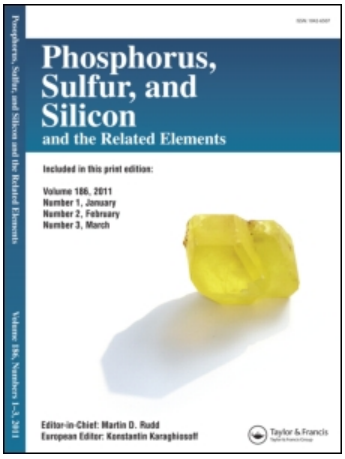

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TRIPHENYLPHOSPHINE-MEDIATED CHEMOSELECTIVE SYNTHESIS OF FUNCTIONALIZED SPIRO-IMIDAZOL-4-ONES

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Stabilized phosphoranes, obtained from the three-component reaction between dialkyl acetylenedicarboxylates and spiro-hydantoins in the presence of triphenylphosphine, undergo a smooth intramolecular Wittig reaction in boiling toluene to produce functionalized spiro-imidazol-4-ones in good yields.

Keywords: Hydantoins; intramolecular Wittig reaction; spiro-imidazol-4-ones; three-component reaction; triphenylphosphine

INTRODUCTION

A number of imidazol-4-one derivatives display a wide range of biological properties, including anticonvulsant,[1] antidepressent,[2] antiinflammatory,[3] antiviral,[4] antitumor,[5] and platelet-inhibitory activities,[6] and are a conspicuous structural feature of several inhibitors of aldose reductase.[7] As part of our study on the development of new routes to heterocyclic and carbocyclic systems,[8–12] we now report on the chemoselective synthesis of functionalized spiro-imidazol-4-ones **4**. Thus, the reaction of spiro-hydantoins and dialkyl acetylenedicarboxylates in the presence of triphenylphosphine leads to phosphoranes **3**, which undergo intramolecular Wittig reaction in boiling toluene to produce **4** in good yields (Scheme 1).

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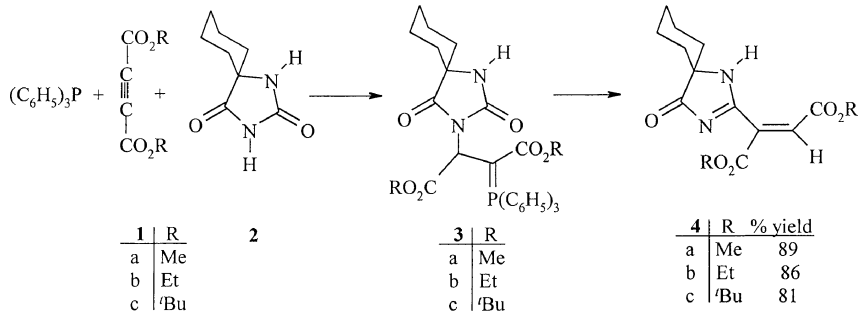


1	R
a	Me
b	Et
c	^{t}Bu

3	R
a	Me
b	Et
c	^{t}Bu

4	R	% yield
a	Me	89
b	Et	86
c	^{t}Bu	81

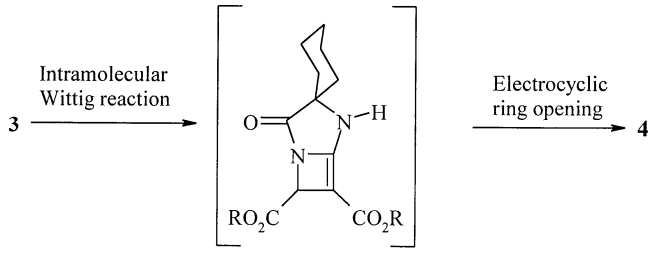
SCHEME 1 Synthesis of functionalized spiro-imidazole-4-ones via phosphorane **3**.

RESULTS AND DISCUSSION

The reaction of dialkyl acetylenedicarboxylates **1** with spiro-hydantoins **2** in the presence of triphenylphosphine at room temperature in ethyl acetate was complete within a few hours, and phosphoranes **3** were produced in good yields.[13] Although these phosphorus ylides are stable at ambient temperature, they undergo a smooth reaction in boiling toluene to produce triphenylphosphine oxide and dialkyl 2-(4-oxo-1,3-diaza-spiro[4.5]dec-2-en-2-yl)but-2-enedioates **4** in good yields (Scheme 1). Structure **4** was assigned to the isolated products on the basis of their elemental analyses, and ^{1}H and ^{13}C NMR spectral data. Thus, the ^{1}H NMR spectrum of each isolated product exhibited a C=CH proton signal at about 6.9–7.1 ppm, which is in agreement with the (*E*) configuration[14] for the vinyl moiety in **4**. Further evidence was obtained from the ^{13}C NMR spectra, which displayed C=CH carbon resonances at about 129–132 ppm and C=N carbon signal at about 154 ppm. Carbon resonances of the NCON and NCO moieties in phosporanes **3** appeared at about 156 and 172 ppm, respectively. In product **4**, the carbon resonance of NCON group was absent, and the carbon resonance of NCO group displayed a peak at about 174 ppm.

Although we have not yet established the mechanism of formation of **4** in an experimental manner, a possible explanation is proposed in Scheme 2. Ylides **3** undergo intramolecular Wittig reaction to produce the fused bicyclic intermediates **5**, which apparently isomerize under the reaction conditions employed to produce **4** in good yields. Compound **3** has two carbonyl groups, namely the NCO and NCON, available for intramolecular Wittig reaction. However, only the NCON carbonyl group participates in the intramolecular Wittig reaction. This chemoselectivity arises from higher nucleophilic reactivity of the NCON carbonyl

group toward ylenic carbon compared to the carbonyl group of the NCO moiety. Another reason for less reactivity of the NCO carbonyl group may be the steric hindrance imposed by the $(CH_2)_5$ moiety adjacent to C-5.



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SCHEME 2 Proposed mechanism for conversion of phosphorane **3** to compound **4**.

In conclusion, the present method features the advantages that the reaction can be performed under neutral conditions and the starting materials and reagents can be mixed without any modifications. The procedure described here provides an acceptable method for preparation of highly functionalized imidazol-4-ones.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. These data were in good agreement with the calculated ones. IR spectra were measured on a Shimadzu IR 460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. The mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Triphenylphosphine and dialkyl acetylenedicarboxylates were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Phosphoranes **3a–c** have been reported.[13]

The typical process for the preparation of **dimethyl 2-(4-oxo-1,3-diaza-spiro[4.5]dec-2-en-2-yl)but-2-enedioate 4a** is described as an example. A magnetically stirred mixture of 0.57 g phosphorane **3a** (1 mmol) in 30 ml of toluene was refluxed for 12 h. The solvent was removed under reduced pressure, the solid residue was washed with

2×5 ml of cold diethyl ether, and the product was obtained as colorless crystals; m.p. 167–169°C. IR (KBr) (ν_{max}, cm^{-1}): 3210 (N—H), 1707, and 1738 (C=O). Anal. Calcd. for $C_{14}H_{18}N_2O_3$ (294.3): C, 57.13; H,6.16; N, 9.52. Found: C, 57.2; H, 6.2; N, 9.6. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.3–1.9 (10H, m, $5CH_2$), 3.71 and 3.83 (6H 2*s*, $2CH_3$), 7.04 (1H, *s*, C—H), 7.87 (1H, *s*, NH).^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.5, 24.6, and 33.4 ($5CH_2$), 52.3 and 53.3 ($2CH_3$), 62.8 ($C(CH_2)_2$), 128.7 (CH), 131.4 (*C*=CH), 154.1 (C=N), 162.3 and 163.0 (2 OC=O), 174.5 (NC=O).

Diethyl 2-(4-oxo-1,3-diaza-spiro[4.5]dec-2-en-2-yl)but-2-enedioate 4b. Colorless crystals, m.p. 161–163°C. IR (KBr) (ν_{max}, cm^{-1}): 3205 (N—H), 1710 and 1735 (C=O). Anal. Calcd. for $C_{16}H_{22}N_2O_3$ (322.4): C, 59.61; H, 6.88; N, 8.69%. Found: C, 59.6; H, 6.9; N, 8.7. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.27 (3H *t*, $^3J_{HH} = 7.0$ Hz, CH_3), 1.30 (3H *t*, $^3J_{HH} = 7.0$ Hz, CH_3), 1.4–1.9 (10H, m, 5 CH_2), 4.19 (2H *q*, $^3J_{HH} = 7.0$ Hz, CH_2), 4.28 (2H *q*, $^3J_{HH} = 7.0$ Hz, CH_2), 7.05 (1H, *s*, CH), 7.49 (1H, *s*, N—H).^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.0 and 14.1 (2 CH_3), 21.5, 24.6, and 33.3 (5 CH_2), 61.4 and 62.6 (2 OCH_2), 62.7 ($C(CH_2)_2$), 128.8 (CH), 131.2 (*C*=CH), 154.4 (C=N), 161.7 and 162.6 (2 OC=O), 174.4 (NC=O).

Dibuthyl 2-(4-oxo-1,3-diaza-spiro[4.5]dec-2-en-2-yl)but-2-enedioate 4c. Colorless crystals, m.p. 154–156°C. IR (KBr) (ν_{max}, cm^{-1}): 3213 (N—H), 1713 and 1745 (C=O). Anal. Calcd. for $C_{20}H_{30}N_2O_3$ (378.5): C, 63.47; H, 7.99; N, 7.40. Found: C, 63.5; H, 8.0; N, 7.4. ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.47 and 1.50 (18 H, 2*s*, $C(CH_3)_3$), 1.4–1.9 (10 H, m, 5 CH_2), 6.90 (1H, *s*, CH), 7.87 (1H, *s*, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 21.7, 24.4, and 33.4 (5 CH_2), 27.8 and 27.9 (2 $C(CH_3)_3$), 52.3 and 53.3 (2 CH_3), 62.7 ($C(CH_2)_2$), 129.8 (CH), 132.0 (*C*=CH), 154.5 (C=N), 160.9 and 161.1 (2 OC=O), 174.3 (NC=O).

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