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Diastereoselective synthesis of phosphonate ester through the reaction between activated acetylenic ester and heterocyclic NH compounds with biological activity in the presence of triphenylphosphite

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ABSTRACT

The reaction between dimethyl acetylenedicarboxylate and biological active heterocyclic NH compounds such as 3-methylpyrazole and 3,6-diboromocarbazole in the presence of triphenylphosphite at room temperature led to phosphonate ester 4a-b. The configuration of compounds 4a-b (2S*,3R*)-were determined on the basis of coupling constants emerged from the Karplus equation.

Key words: Diastereoselectivity, Heterocyclic NH compounds; biological activity; Activated acetylenic ester; Triphenylphosphite; Karplus equation.

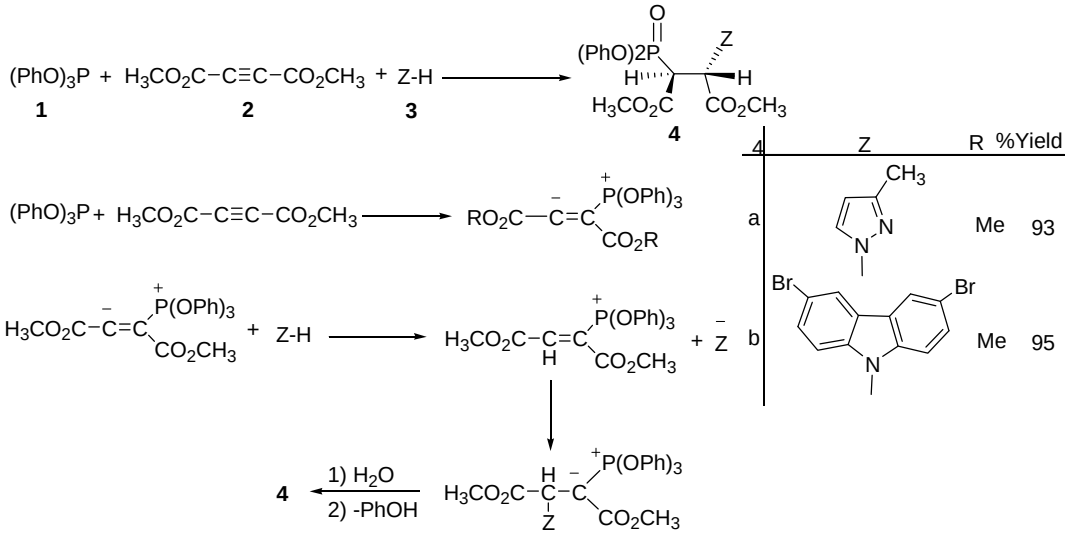
INTRODUCTION

Phosphorus-carbon bond formation[1-15] is an active and important research area, as new reactions are continuously being developed for the preparation of organophosphorus compounds such as phosphinates and phosphonates[16-24]. Over the last few years, the quest for the synthetic efficiency has gained remarkable importance, partly due to the need reduce waste[25]. Given the increasing industrial, biological and synthetic impact of organophosphorus compounds[26-30]. The successful attack by nucleophilic trivalent phosphorus on a carbon atom is facilitated when the latter is part of, or conjugated with, a carbonyl group, or when it is part of an unsaturated bond otherwise activated[27-29]. There are many studies on the reaction between trivalent phosphorus nucleophiles and α, β–unsaturated carbonyl compounds in the presence of a proton source such as alcohol or phenol[31,32]. Previously, the pyrazole and thiazole moieties and their derivatives have been used commercially as pharmaceuticals, pesticides and dyestuffs.[33] Here we wish to report on a simple one-pot synthesis of diastereoselective phosphonate esters 4 through the reaction of biological active heterocyclic NH compounds 3 and dimethyl acetylenedicerboxylate 2 in the presence of triphenylphosphite 1

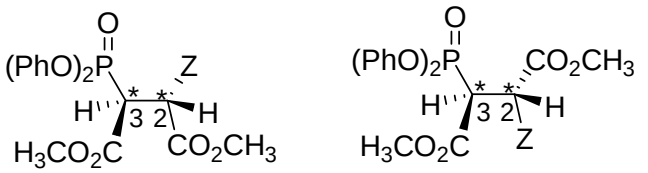
RESULTS AND DISCUSSION

In the current work, we wish to report a simple, short time, neutral, room temperature and high diastereoselective synthesis of phosphonate esters from reaction between triphenylphosphite 1 and acetylenic ester 2 in the presence of heterocyclic NH compounds, such as 3-methylpyrazole and 3,6-diboromocarbazole 3 led to 4 in fairly high yield (see Scheme 1). These reactions were carried out in the mixture of diethyl ether and hexan (2 : 1) as solvent at room temperature and were finished within a few hours. The ^{1}H and ^{13}C NMR spectrum of the crude

product clearly indicated the formation of phosphonate esters 4a-b. Any products other than 4a-b could not be detected by NMR spectroscopy. The structures of compounds 4a-b were confirmed by ^{1}H, ^{13}C, ^{31}P NMR, mass spectrometry, IR and elemental analysis. The mass spectra of compounds 4a-b displayed molecular ion peaks at appropriate values, which were consistent with 1:1:1 adducts of heterocyclic NH compounds, DMAD and triphenylphosphite. The 300 MHz ^{1}H NMR spectra of compound 4a displayed three sharp lines (δ= 2.23, 3.74 and 3.80) arising from methyl and methoxy protons along with signals for methine protons at δ= 4.64 ppm (1H, $^{2}J_{PH}$=21.2 Hz, $^{3}J_{HH}$=10.9 Hz) and δ= 5.74 ppm (1H, $^{3}J_{PH}$=8.7 Hz, $^{3}J_{HH}$=10.9 Hz) which appear as two doublet of doublet, respectively, for the O=P-C*H*-CH and O=P-CH-C*H* groups. The vicinal proton-proton coupling constant ($^{3}J_{HH}$) as a function of the torsion angle can be obtained from the Karplus equation.[34] Typically, J_{gauche} varies between 1.5 and 5 Hz and J_{anti} between 10 and 14 Hz. Observation of $^{3}J_{HH}$=10.9 Hz for the vicinal protons in compound 4a (see Experimental section) indicates an anti arrangement for these protons. Since compound 4a possess two stereogenic center, two diastereoisomers with anti HCCH arrangements are possible. The three-bond carbon-phosphorus coupling, $^{3}J_{CP}$, depends on configuration, as expected, transoid coupling being larger than cisoid ones. The Karplus relation can be derived from the data for organophosphorus compound with tetra and pentavalent phosphorus.[35] The observation of $^{3}J_{CP}$ of 18.3 Hz for the ester C=O group (see Experimental section), is in a good agreement with the 2S*,3R*-4a and its mirror image 2R*,3S*-4a geometries (Scheme 2). Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of 4a, it helps in assignment of the signals by long-range couplings with the ^{1}H and ^{13}C nuclei (see Experimental section). The ^{1}H and ^{13}C NMR spectra of 4b is similar to those of 4a, except for the ester groups, which exhibited



Scheme 1



Scheme 2

characteristic resonances with appropriate chemical shifts (see Experimental section). The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds 4a-b were supported by the IR spectra. (see Experimental section).

In conclusion, we have prepared novel diastereoselective phosphonate esters using a one-pot reaction between triphenylphosphite and dimethyl acetylenedicarboxylate in the presence of heterocyclic NH compounds such as 3-methylpyrazole and 3,6-diboromocarbazole. The present method, carries the advantage that, not only the reaction is performed under neutral conditions, but also the substances can be mixed without any activation or modifications.

EXPERIMENTAL

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer respectively. Also, the ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained from a BRUKER DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1, 121.5, and 75.5 MHz respectively. In addition, the mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. Dimethyl acetylenedicarboxylate, triphenlphosphite, 3-methylpyrazole and 3,6-diboromocarba- zole were purchased from Fluka, (Buchs, Switzerland) and used without further purifications.

Preparation of (2S*,3R*)-Dimethyl-2-(3-methylpyrazole-1-yl)-3-(diphenoxyphosphonato)-butanedioate (4a). To a magnetically stirred solution of triphenylphosphite (0.31g, 1mmol) and 3-methylpyrazole (0.08g, 1mmol) in diethyl ether/ hexan (10ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.14g, 1mmol) in diethyl ether (5ml) at -10 °C over 10 min. After approximately 10 hours stirring at room temperature, the solvent was removed under reduced pressure and product washed with cold diethyl ether (2×5µL). White powder, %93, m.p 125-127 °C, IR (KBr) (λ_{max}, cm^{-1}): 1740 and 1715 (C=O), 1270 (P=O). Ms, (m/z, %): 458 (M^+, 3), 427 (M-OCH_3, 33), 399 (M-CO_2CH_3, 45), 365 (M-Ph, 19), 377 (M-$C_4H_5N_2$, 9), 93 (OPh, 15), 77 (Ph, 100). Anal. Calcd for $C_{21}H_{21}N_2O_7P$ (458): C, 57.64; H, 5.02; N, 6.11, Found: C, 57.56; H, 4.95; N, 6.18. ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 2.23 (CH_3), 3.73 and 3.80 (6H, 2s, 2OC*H*$_3$), 4.64 (1H, dd, $^{2}J_{PH}$=21.2 Hz, $^{3}J_{HH}$=10.9 Hz, P-C*H*-CH), 5.74 (1H, dd, $^{3}J_{PH}$=8.7 Hz, $^{3}J_{HH}$=10.9 Hz, P-CH-C*H*), 6.05 -7.56 (13H, m, H_{aro}). ^{13}C NMR (75.5 MHz, δ, $CDCl_3$): 13.60 (CH_3), 47.93 (d, $^{1}J_{CP}$=134.6 Hz, P-*C*H), 53.28 and 53.42 (2S, 2O*C*H$_3$), 61.72 (d, $^{2}J_{CP}$=3.5 Hz, P-C-*C*H), 106.06 (1C, $C_3H_3N_2$), 120.16 and 120.37 (2d, $^{3}J_{PC}$= 4.8 Hz C_{ortho} of $2C_6H_5$), 125.40 and 125.49 (C_{para} of $2C_6H_5$), 129.69 and 129.80 (C_{meta} of $2C_6H_5$), 132.98 (1C , $C_3H_3N_2$), 149.70 and 150.45 (2d, $^{2}J_{CP}$=9.6 Hz ,C_{ipso} of $2C_6H_5$), 150.46 (1C, $C_3H_3N_2$), 166.85 (d, $^{2}J_{CP}$=6.0 Hz, C=O), 167.74 (d, $^{3}J_{CP}$=18.3 Hz, C=O). ^{31}P NMR (121.5 MHz, δ, 10.38 [s, $(PhO)_2P(=O)$].

(2S,3R)-Dimethyl-2-(3,6-diboromocarbazole-1-yl)-3-(diphenoxyphosphonato)- butanedioate (4d)

White powder, %95, m.p 163-165 °C, IR (KBr) (ν_{max}, cm^{-1}): 1748 and 1720 (C=O), 1271 (P=O).MS, (m/z, %): 701 (M^+, 33), 642 (M-CO_2CH_3, 38), 608 (M-OPh, 29), 377 (M-$C_{12}H_6Br_2N_2$, 15), 77 (Ph, 100). Anal. Calcd for $C_{25}H_{23}N_2O_7P$ (701): C, 51.36; H, 3.42; N, 1.99, Found: C, 51.49; H, 3.36; N, 2.07. ^{1}H NMR (300.1 MHz, δ, $CDCl_3$): 3.61 and 3.89 (6H, 2s, 2OC*H*$_3$), 4.73 (1H, dd, $^{2}J_{PH}$=21.1 Hz, $^{3}J_{HH}$=11.8 Hz, P-C*H*-CH), 6.27 (1H, dd, $^{3}J_{PH}$=7.9 Hz, $^{3}J_{HH}$=11.8 Hz, P-CH-C*H*), 6.38 -8.08 (16H, m, H_{aro}). ^{13}C NMR (75.5 MHz, δ, $CDCl_3$): 45.55 (d, $^{1}J_{CP}$=136.9 Hz, P-*C*H), 53.56 and 53.64 (2S, 2O*C*H$_3$), 55.80 (d, $^{2}J_{CP}$=3.9 Hz, P-C-*C*H), 111.30, 111.99, 112.41, 113.46 and 113.66 (5C, $C_{12}H_6Br_2N$), 119.07 and 119.77 (2d, $^{3}J_{PC}$= 3.5 Hz C_{ortho} of $2C_6H_5$), 123.04, 123.09, 123.72. 123.85 and 125.12 (5C , $C_{12}H_6Br_2N$), 125.40 and 125.33 (C_{para} of $2C_6H_5$), 129.40 (1C , $C_{12}H_6Br_2N$), 129.57 and 129.60 (C_{meta} of $2C_6H_5$), 129.64 (1C , $C_{12}H_6Br_2N$), 149.12 and 149.58 (2d, $^{2}J_{CP}$=9.1 Hz ,C_{ipso} of $2C_6H_5$), 166.72 (d, $^{2}J_{CP}$= 6.3 Hz, C=O), 168.84 (d, $^{3}J_{CP}$=19.5 Hz, C=O). ^{31}P NMR (121.5 MHz, δ, 9.83 [S, $(PhO)_2P$=O].

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