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One-pot and stereoselective synthesis of 2,3-dihydro-1,5-benzodiazepin-2-one with a phosphanylidene or phosphono-succinate substituent

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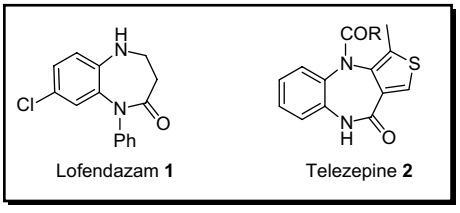
ABSTRACT

The one-pot synthesis of 2,3-dihydro-1,5-benzodiazepins-2-one bearing phosphanylidene (ylide) or phosphono-succinate substituent is described. In this four-component reaction, benzodiazepine derived from condensation of *o*-phenylenediamine and diketene is trapped with the trialkyl phosphite–dialkyl acetylenedicarboxylate zwitterion. In the presence of H_2O, the ylide functional group is hydrolyzed to the corresponding phosphonate. The configuration of the products is selective and only one of the two possible rotamers or diastereomers is formed exclusively in high yield.

1. Introduction

The medicinal value of benzodiazepines is well documented. Benzodiazepines[1] have been an important pharmacophore in the pharmaceutical industry. Some of the therapeutic applications of benzodiazepines include vasopressin antagonists,[2a] HIV reverse transcriptase inhibitors,[2b] and cholecystokinin antagonists.[2c]

In this class of compound, the 1,5-benzodiazepin-2-one is a privileged scaffold and its substructures exhibiting a range of biological activities. Some of them have been clinically used as anxiolytic agents, such as lofendazam **1**[1,3] or as antisecretory agents, such as telenzepine **2**[4] (Scheme 1). In addition, they exhibit activities including interleukin-1β converting enzyme inhibition, delayed rectifier potassium current blocking,[5] and antiarrhythmic activity.[6] They are also found in compounds active against a variety of target types such as protease inhibitors and 7-TM receptors.[7–9] Significantly, less research has been undertaken on the 1,5-benzodiazepin-2-ones, compared to the 1,4-benzodiazepin-2-ones.



Lofendazam **1** Telezepine **2**

Scheme 1.

On the other hand, organophosphorus compounds especially phosphite ylides and phosphonates are well-known biologically active species and are good reagents for transmitting their groups into synthetic intermediates to convert them to target compounds.[10–13]

Synthesis of 1,5-benzodiazepines bearing a phosphite ylide or phosphonate functional group is not only synthetically challenging but also biologically interesting. Thus in continuation of our research on synthesis of important heterocycles with a polar substitution,[14,15] and also synthesis of new organic compound using diketene-based multicomponent reaction,[16–20] we describe our success to obtain an efficient method for one-pot four-component synthesis of phosphanylidene or phosphono-succinate-substituted 1,5-benzodiazepines with high stereoselectivity.

2. Results and discussion

Our new synthetic method leading to the formation of the title compounds is given in Scheme 2. The reaction of 1,5-benzodiazepine-2-one **9**, which is derived from condensation of *o*-phenylenediamine **3** and diketene, with dialkyl acetylenedicarboxylates **4** in the presence of trialkyl phosphite **5** in anhydrous CH_2Cl_2 at ambient temperature produces compound **6**. When the reaction is performed in hydrous CH_2Cl_2, compound **7** is produced (Scheme 2).

Because of restricted rotation around the carbon–carbon double bond resulting from conjugation of the ylide moiety with the adjacent carbonyl group, two rotamers for compound **6** (Scheme 3) were expected,[14] but ^1H, ^{13}C, and ^{31}P NMR spectra at room temperature showed a high percent of one of them, as even some of the corresponding peaks of another rotamer was undistinguishable (Scheme 3), in addition, the signals of the two

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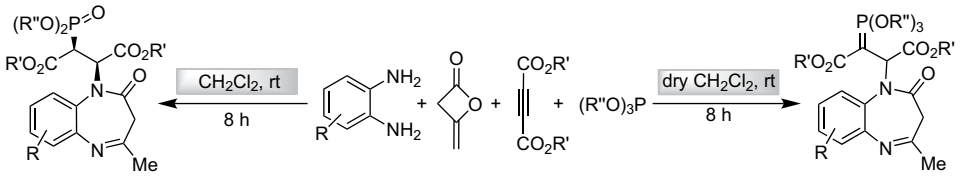
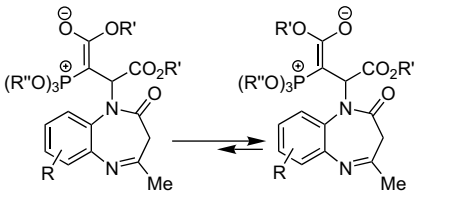


7	R	R'	R''	Yield of **7** %
a	Me	Me	Me	80
b	Me	Et	Me	90
c	Me	Me	Et	90

6	R	R'	R''	Yield of **6** %
a	H	Me	Me	90
b	H	Et	Me	90
c	H	Me	Et	85
d	H	Et	Et	90
e	Me	^{t}Bu	Et	88

Scheme 2.

rotamers did not coalesce at room temperature and thus conversion *Z*-isomer into another is negligible (Scheme 3).



Scheme 3.

The mass spectrum of **6a** showed the molecular ion peak at *m*/*z*=440. The IR spectrum of **6a** showed absorption bands due to the two carbonyl groups at 1738 (CO_2Me) and 1655 cm^{-1} (NCO) and a C=N group at 1627 cm^{-1}. The ^1H NMR spectrum of **6a** exhibited three sharp singlet signals readily recognized as arising from one methyl group of seven-membered ring (δ_H=2.33) and two OMe groups (δ_H=3.48 and 3.83 ppm). The three equivalent OMe groups of phosphite exhibited a doublet at 3.37 ppm ($^3J_{HP}$=12.0 Hz). The methylene protons of the CH_2 moiety are diastereotopic and showed a dd system at δ_H=3.04 and 3.32 ppm ($^2J_{HH}$=11.4 Hz). The doublet resonance at 5.71 ppm is attributed to CHP ($^3J_{HP}$=16.1 Hz). The phenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. 12 singlet and 6 doublet peaks (split with phosphor) in the ^1H decoupled ^{13}C NMR spectrum of **6a** are in agreement with proposed structure. Finally, the structure of **6**, for example, **6c**, was further confirmed by a single crystal X-ray diffraction analysis (Fig. 1).

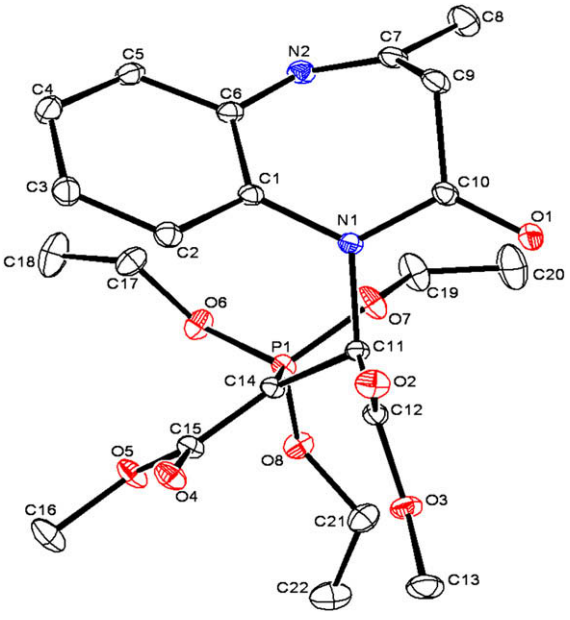
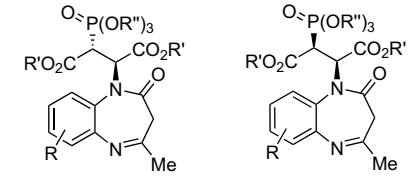


Figure 1. The molecular structure of compound **6c**.

When the reaction was carried in hydrous CH_2Cl_2, only one of the two possible diastereomers (Scheme 4) of **7** was obtained diastereospecifically. The ^1H, ^{13}C, and ^{31}P NMR spectra of the crude product clearly indicated the formation one of the diastereomers in more than 85% yield. Any product other than **7** could not be detected by NMR spectroscopy.



Scheme 4.

Characteristic signals in ^1H NMR spectrum of **7a** is due to the CHCHP=O moiety at 4.40 ($^2J_{HP}$=20.3 Hz, $^3J_{HH}$=10.5 Hz) and 5.15 ppm ($^3J_{HH}$=10.5 Hz, $^3J_{HP}$=3.8 Hz). Partial assignment of these resonances for **6** and **7** derivatives are given in Section 4.

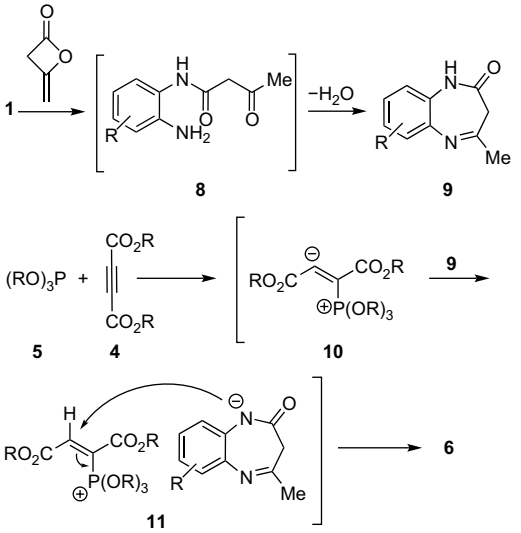
The vicinal proton–proton coupling constant ($^3J_{HH}$) can help, as a function of the torsion angle, to determine the proton position by the Karplus equation.[21] The presence of ^{31}P in **7a–c** helps in the assignment of the signals by long range coupling with ^1H and ^{13}C nuclei. The comparison of observed $^3J_{CP}$ for the C=O group with the desired values indicates the product geometries. It is found that there is only one of the two probable diastereoisomers [(2*R*,3*S*)-**7** or (2*S*, 3*R*)-**7**] in the hydrolysis products.

The vicinal proton–proton coupling constant ($^3J_{HH}$) as a function of the torsion angle can be obtained from the Karplus equation.[21] Typically, J_{gauche} varies between 1.5 and 5 Hz and J_{anti} between 10 and 14 Hz. Observation of $^3J_{HH}$=10.5 Hz for the vicinal protons in compound **7** (see Section 4) indicates an *anti* arrangement for these protons. Since

compound **7** possesses two chirality centers, two diastereoisomers with *anti* H–C–C–H arrangements are possible (see Scheme 4).

The three-bond carbon–phosphorus coupling $^{3}J_{CP}$ depends on configuration, as expected, *transoid* coupling being larger than *cisoid*. The Karplus relation can be derived from the data for organophosphorus compounds with tetra and penta-coordinate phosphorus.[22] The $^{3}J_{CP}$ for the PC–C–C(O) moiety is 17.2, 17.5, and 17.1 Hz, respectively, which corresponds to (2*R*,3*S*)-**7** and its mirror image (2*S*,3*R*)-**7** geometries (Section 4).

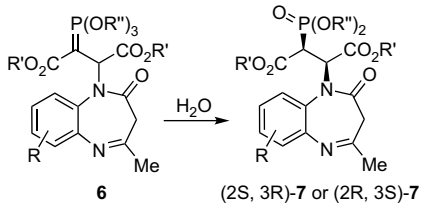
Although the mechanism of the reaction between *o*-phenylenediamine **3**, diketene, and dialkyl acetylenedicarboxylate in the presence of trialkyl phosphite has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 5.



Scheme 5.

At first, reaction of *o*-phenylenediamine and diketene produces intermediate **8**,[16,17,20] which is readily converted to 1,5-benzodiazepine **9** via a condensation reaction (in the separate reaction, structure of **9** was confirmed by ^{1}H NMR spectra).[23] Zwitterion **10**, which is produced from the reaction of trialkyl phosphite and dialkyl acetylenedicarboxylate[15,24–26] is protonated by NH-acid **9**. Then, the positively charged ion **11** might be attacked by the conjugate base of the NH-acid **9** to form corresponding dialkyl 2-(4-methyl-2-oxo-2,3-dihydro-1*H*-1,5-benzodiazepin-1-yl)-3-(1,1,1-trialkoxy-λ^5-phosphanylidene)succinate **6**.

In hydrous CH_2Cl_2, compound **6** is hydrolyzed to corresponding dialkyl 2-(dialkoxyphosphoryl)-3-(4,8-dimethyl-2-oxo-2,3-dihydro-1*H*-1,5-benzodiazepin-1-yl)succinate **7** (Scheme 6).



Scheme 6.

3. Conclusion

In conclusion, we succeeded to synthesis of new class of dihydro-1,5-benzodiazepines with a phosphite ylide or phosphonate functional group with high diastereoselectivity. In addition, the product could have high diversity via various functional groups instead of amine group. High yield and simple purification of products are other advantages of our work. The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

4. Experimental

4.1. General

o-Phenylenediamines, diketene, dialkyl acetylenedicarboxylates, and trialkyl phosphite were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. 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. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.7 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 meshes.

4.2. General procedure

To a magnetically stirred solution of *o*-phenylenediamine derivatives (1 mmol) and diketene (0.08 g, 1 mmol) in anhydrous CH_2Cl_2 for compound **6** and in hydrous CH_2Cl_2 for compound **7** (5 mL) after 4 h was added dialkyl acetylenedicarboxylate (1 mmol) and then trialkyl phosphite (1 mmol) immediately. The reaction mixture was stirred for 4 h. The solvent was removed under reduced pressure and the residue was crystallized in diethyl ether or ethyl acetate.

*4.2.1. Dimethyl 2-(4-methyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)-3-(1,1,1-trimethoxy-λ^5-phosphanylidene) succinate (**6a**)*

White powder, mp=180–182 °C (dec), 0.39 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1738 (CO_2Me), 1655 (NCO), 1627 (C=N), 1510 and 1433 (Ar), 1028 (P–OMe). Anal. Calcd for $C_{19}H_{25}N_2O_8P$ (440.38): C, 51.82; H, 5.72; N, 6.36%. Found: C, 51.85; H, 5.73; N, 6.35%. MS (EI, 70 eV): *m*/*z* (%)=440 (M^+, 54), 426 (77), 353 (31), 343 (43), 215 (100), 203 (15), 145 (39), 133 (48), 77 (44), 43 (12). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=2.33 (3H, s, Me), 3.04 (1H, d, $^{2}J_{HH}$=11.4 Hz, CH_2), 3.32 (1H, d, $^{2}J_{HH}$=11.4 Hz, CH_2), 3.37 (9H, d, $^{3}J_{HP}$=12.0 Hz, $P(OMe)_3$), 3.48 (3H, s, OMe), 3.83 (3H, s, OMe), 5.71 (1H, d, $^{3}J_{HP}$=16.1 Hz, CHC=P), 7.07–7.15 (3H, m, 3CH of Ar), 7.88 (1H, d, $^{3}J_{HH}$=7.8 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=27.1 (Me), 40.4 (d, $^{1}J_{CP}$=222.5 Hz, C=P), 44.0 (CH_2), 50.0 (OMe), 52.5 (OMe), 53.9 (d, $^{2}J_{CP}$=5.4 Hz, $P(OMe)_3$), 59.4 (d, $^{2}J_{CP}$=14.4 Hz, *C*HC=P), 124.7 (CH of Ar), 124.9 (CH of Ar), 125.6 (CH of Ar), 127.3 (CH of Ar), 131.5 (C_{ipso}–NCO), 143.2 (C_{ipso}–N=C), 165.7 (C=N), 165.8 (NCO), 168.5 (d, $^{2}J_{CP}$=20.2 Hz, *C*O_2Me), 171.8 (d, $^{3}J_{CP}$=18.3 Hz, *C*O_2Me). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=57.88 ppm.

4.2.2. Diethyl 2-(4-methyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)-3-(1,1,1-trimethoxy-λ^5-phosphanylidene) succinate (6b)

White powder, mp=176–178 °C (dec), 0.42 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1729 (CO_2Et), 1652 (NCO), 1625 (C=N), 1513 and 1440 (Ar), 1039 (P–OMe). Anal. Calcd for $C_{21}H_{29}N_2O_8P$ (468.44): C, 53.84; H, 6.24; N, 5.98%. Found: C, 53.86; H, 6.23; N, 5.93%. MS (EI, 70 eV): *m*/*z* (%)=468 (M^+, 17), 454 (75), 345 (100), 335 (60), 207 (95), 185 (68), 174 (96), 145 (48), 133 (77), 56 (24). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.07 (3H, t, $^{3}J_{HH}$=7.0 Hz, OCH_2*Me*), 1.28 (3H, t,

$^3J_{HH}$=7.0 Hz, OCH_2Me), 2.33 (3H, s, Me), 3.04 (1H, d, $^2J_{HH}$=11.4 Hz, CH_2), 3.32 (1H, d, $^2J_{HH}$=11.4 Hz, CH_2), 3.38 (9H, d, $^3J_{HP}$=12.0 Hz, $P(OMe)_3$), 3.90–4.05 (2H, m, OCH_2Me), 4.28–4.42 (2H, m, OCH_2Me), 5.68 (1H, d, $^3J_{HP}$=16.6 Hz, CHC=P), 7.05–7.15 (3H, m, 3CH of Ar), 7.93 (1H, d, $^3J_{HH}$=7.7 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.2 (OCH_2Me), 14.9 (OCH_2Me), 27.1 (Me), 40.5 (d, $^1J_{CP}$=222.2 Hz, C=P), 44.0 (CH_2), 53.8 (d, $^2J_{CP}$=5.1 Hz, $P(OMe)_3$), 58.1 (OCH_2Me), 59.5 (d, $^2J_{CP}$=13.8 Hz, *C*HC=P), 61.2 (OCH_2Me), 124.6 (CH of Ar), 124.8 (CH of Ar), 125.5 (CH of Ar), 127.5 (CH of Ar), 131.6 (C_{ipso}–NCO), 143.2 (C_{ipso}–N=C), 165.7 (C=N), 165.8 (NCO), 167.9 (d, $^2J_{CP}$=19.5 Hz, *C*O_2Et), 171.2 (d, $^3J_{CP}$=18.2 Hz, *C*O_2Et). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=59.16 ppm.

4.2.3. Dimethyl 2-(4-methyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)-3-(1,1,1-trimethoxy-λ^5-phosphanylidene) succinate (**6c**)

White powder, mp=187–189 °C, 0.41 g, yield 85%. IR (KBr) (ν_{max}, cm^{-1}): 1739 (CO_2Me), 1654 (NCO), 1621 (C=N), 1518 and 1422 (Ar), 1040 (P–OEt). Anal. Calcd for $C_{22}H_{31}N_2O_8P$ (482.46): C, 54.77; H, 6.48; N, 5.81%. Found: C, 54.73; H, 6.46; N, 5.80%. MS (EI, 70 eV): *m*/*z* (%)=482 (M^+, 38), 467 (20), 450 (32), 423 (35), 363 (18), 309 (100), 249 (78), 221 (22), 193 (25), 166 (65), 139 (19), 56 (7). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=0.98 (9H, t, $^3J_{HH}$=7.0 Hz, $P(OCH_2Me)_3$), 2.16 (3H, s, Me), 2.85 (1H, d, $^2J_{HH}$=11.4 Hz, CH_2), 3.16 (1H, d, $^2J_{HH}$=11.4 Hz, CH_2), 3.32 (3H, s, OMe), 3.47–3.53 (6H, m, $P(OCH_2Me)_3$), 3.66 (3H, s, OMe), 5.58 (1H, d, $^3J_{HP}$=16.4 Hz, CHC=P), 6.89–6.99 (3H, m, 3CH of Ar), 7.71 (1H, d, $^3J_{HH}$=7.8 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=15.6 (d, $^3J_{CP}$=7.0 Hz, $P(OCH_2Me)_3$), 27.4 (Me), 41.5 (d, $^1J_{CP}$=222.4 Hz, C=P), 43.9 (CH_2), 49.5 (OMe), 52.3 (OMe), 59.7 (d, $^2J_{CP}$=13.6 Hz, *C*HC=P), 63.7 (d, $^2J_{CP}$=5.3 Hz, $P(OCH_2Me)_3$), 124.4 (CH of Ar), 124.9 (CH of Ar), 125.2 (CH of Ar), 127.1 (CH of Ar), 131.5 (C_{ipso}–NCO), 143.1 (C_{ipso}–N=C), 165.4 (C=N), 165.5 (NCO), 168.6 (d, $^2J_{CP}$=19.6 Hz, *C*O_2Me), 171.8 (d, $^3J_{CP}$=17.9 Hz, *C*O_2Me). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=52.40 ppm.

Crystal data for **7c**: $C_{22}H_{31}N_2O_8P$ (CCDC 695674): MW=482.46, triclinic, space group $P\bar{1}$, a=8.5728(11) Å, b=8.8804(11) Å, c=16.0960(21) Å, α=90.037(2), β=92.860(2), γ=93.971(2)°, V=1220.91(3) Å^3, Z=2, D_c=1.312 mg/m^3, F(000)=512, crystal dimension 0.19×0.29×0.45 mm, radiation, Mo Kα (λ=0.71073 Å), $2.73\leq 2\theta\leq 26.0$, intensity data were collected at 295(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique in the range of $-10\leq h\leq 10$, $-10\leq k\leq 10$, $-19\leq l\leq 19$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 3421 observed reflections with R(int)=0.0281 by a full-matrix least-squares technique converged to R_1=0.052 and WR_2=0.133 [$I>2\sigma(I)$].

4.2.4. Diethyl 2-(4-methyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)-3-(1,1,1-triethoxy-λ^5-phosphanylidene) succinate (**6d**)

White powder, mp=141–143 °C, 0.46 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1737 (CO_2Et), 1652 (NCO), 1626 (C=N), 1517 and 1440 (Ar), 1040 (P–OEt). Anal. Calcd for $C_{24}H_{35}N_2O_8P$ (510.52): C, 56.46; H, 6.91; N, 5.49%. Found: C, 56.51; H, 6.89; N, 5.48%. MS (EI, 70 eV): *m*/*z* (%)=510 (M^+, 32), 464 (18), 437 (25), 337 (100), 263 (21), 235 (25), 207 (18), 179 (28), 166 (30), 107 (14), 65 (5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.04 (3H, t, $^3J_{HH}$=7.0 Hz, OCH_2Me), 1.10 (9H, t, $^3J_{HH}$=7.2 Hz, $P(OCH_2Me)_3$), 1.22 (3H, t, $^3J_{HH}$=7.0 Hz, OCH_2Me), 2.27 (3H, s, Me), 2.98 (1H, d, $^2J_{HH}$=11.4 Hz, CH_2), 3.27 (1H, d, $^2J_{HH}$=11.4 Hz, CH_2), 3.56–3.67 (6H, m, $P(OCH_2Me)_3$), 3.84–4.00 (2H, m, OCH_2Me), 4.21–4.26 (2H, m, OCH_2Me), 5.67 (1H, d, $^3J_{HP}$=16.9 Hz, CHC=P), 6.99–7.11 (3H, m, 3CH of Ar), 7.87 (1H, d, $^3J_{HH}$=7.2 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=14.1 (OCH_2Me), 14.9 (OCH_2Me), 15.7 (d, $^3J_{CP}$=7.1 Hz, $P(OCH_2Me)_3$), 27.4 (Me), 41.5 (d, $^1J_{CP}$=221.1 Hz, C=P), 44.0 (CH_2), 57.9 (OCH_2Me), 59.9 (d, $^2J_{CP}$=13.8 Hz, *C*HC=P), 61.0 (OCH_2Me), 63.5 (d, $^2J_{CP}$=5.0 Hz, $P(OCH_2Me)_3$), 124.5 (CH of Ar), 124.9 (CH of Ar), 125.2 (CH of Ar), 127.3 (CH of Ar), 131.7 (C_{ipso}–NCO), 143.1 (C_{ipso}–N=C), 165.5 (C=N), 165.6 (NCO), 168.2 (d, $^3J_{CP}$=19.6 Hz, *C*O_2Et), 171.3 (d, $^2J_{CP}$=16.8 Hz, *C*O_2Et). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=53.77 ppm.

4.2.5. Di(tert-butyl) 2-(4,8-dimethyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)-3-(1,1,1-triethoxy-λ^5-phosphanylidene) succinate (**6e**)

White powder, mp=145–147 °C, 0.5 g, yield 88%. IR (KBr) (ν_{max}, cm^{-1}): 1733 ($CO_2{}^t$Bu), 1655 (NCO), 1620 (C=N), 1522 and 1418 (Ar), 1037 (P–OEt). Anal. Calcd for $C_{29}H_{45}N_2O_8P$ (580.65): C, 59.99; H, 7.81; N, 4.82%. Found: C, 59.98; H, 7.82; N, 4.81%. MS (EI, 70 eV): *m*/*z* (%)=580 (M^+, 36), 566 (9), 465 (12), 409 (17), 337 (15), 281 (19), 191 (23), 174 (16), 132 (100), 107 (12), 57 (35). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=1.16 (3H, t, $^3J_{HH}$=7.0 Hz, $P(OCH_2Me)_3$), 1.35 (9H, s, CMe_3), 1.52 (9H, s, CMe_3), 2.30 (3H, s, Me), 2.39 (3H, s, Me), 3.02 (1H, d, $^2J_{HH}$=11.3 Hz, CH_2), 3.32 (1H, d, $^2J_{HH}$=11.3 Hz, CH_2), 3.60–3.68 (6H, m, $P(OCH_2Me)_3$), 5.54 (1H, d, $^3J_{HP}$=16.7 Hz, CHC=P), 7.06–7.20 (3H, m, 3CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=15.8 (d, $^3J_{CP}$=7.5 Hz, $P(OCH_2Me)_3$), 27.4 (Me), 27.9 (Me), 28.1 (CMe_3), 28.8 (CMe_3), 41.7 (d, $^1J_{CP}$=218.8 Hz, C=P), 60.7 (d, $^2J_{CP}$=13.7 Hz, *C*HC=P), 63.0 (d, $^2J_{CP}$=4.5 Hz, $P(OCH_2Me)_3$), 76.7 (*C*Me_3), 80.4 (*C*Me_3), 121.8 (CH of Ar), 124.9 (CH of Ar), 126.1 (CH of Ar), 131.9 (C_{ipso}–NCO), 139.7 (C_{ipso}–Me), 143.0 (C_{ipso}–N=C), 165.3 (C=N), 165.7 (NCO), 167.6 (d, $^2J_{CP}$=18.3 Hz, *C*$O_2{}^t$Bu), 169.9 (d, $^3J_{CP}$=17.6 Hz, *C*$O_2{}^t$Bu). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=54.87 ppm.

4.2.6. Dimethyl 2-(dimethoxyphosphoryl)-3-(4,8-dimethyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)succinate (**7a**)

White powder, mp=127–129 °C, 0.37 g, yield 85%. IR (KBr) (ν_{max}, cm^{-1}): 1732 (CO_2Me), 1670 (NCO), 1634 (N=C), 1513 and 1428 (Ar), 1287 (P=O). Anal. Calcd for $C_{19}H_{25}N_2O_8P$ (440.38): C, 51.82; H, 5.72; N, 6.36%. Found: C, 51.81; H, 5.75; N, 6.39%. MS (EI, 70 eV): *m*/*z* (%)=440 (M^+, 32), 349 (23), 331 (51), 299 (38), 221 (43), 199 (47), 188 (72), 146 (100), 109 (49), 77 (30), 65 (24). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=2.37 (3H, s, Me), 2.38 (3H, s, Me), 2.93 (1H, d, $^2J_{HH}$=11.8 Hz, CH_2), 3.28 (1H, d, $^2J_{HH}$=11.8 Hz, CH_2), 3.50 (6H, d, $^3J_{HP}$=11.8 Hz, $P(OMe)_2$), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 4.40 (1H, dd, $^2J_{HP}$=20.3 Hz, $^3J_{HH}$=10.5 Hz, CHC*H*P), 5.15 (1H, dd, $^3J_{HP}$=3.8 Hz, $^3J_{HH}$=10.5 Hz, C*H*CHP), 7.07 (1H, d, $^3J_{HH}$=7.9 Hz, CH of Ar), 7.11 (1H, s, CH of Ar), 7.34 (1H, d, $^3J_{HH}$=7.9 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=20.7 (Me), 28.0 (Me), 43.3 (CH_2), 45.5 (d, $^1J_{CP}$=130.0 Hz, CHCHP), 52.9 (d, $^2J_{CP}$=5.5 Hz, $P(OMe)_2$), 53.0 (OMe), 53.0 (OMe), 53.3 (d, $^2J_{CP}$=5.5 Hz, $P(OMe)_2$), 62.0 (d, $^2J_{CP}$=5.1 Hz, *C*HCHP), 121.4 (CH of Ar), 126.5 (CH of Ar), 126.9 (CH of Ar), 133.0 (C_{ipso}–NCO), 135.5 (C_{ipso}–Me), 140.3 (C_{ipso}–N=C), 164.4 (C=N), 168.2 (NCO), 168.5 (d, $^2J_{CP}$=7.7 Hz, *C*O_2Me), 169.9 (d, $^3J_{CP}$=17.2 Hz, *C*O_2Me). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=21.84 ppm.

4.2.7. Diethyl 2-(dimethoxyphosphoryl)-3-(4,8-dimethyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)succinate (**7b**)

White powder, mp=141–143 °C, 0.42 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1735 (CO_2Et), 1677 (NCO), 1641 (N=C), 1511 and 1432 (Ar), 1280 (P=O). Anal. Calcd for $C_{21}H_{29}N_2O_8P$ (468.44): C, 53.84; H, 6.24; N, 5.98%. Found: C, 53.81; H, 6.23; N, 5.95%. MS (EI, 70 eV): *m*/*z* (%)=468 (M^+, 45), 377 (24), 331 (100), 299 (59), 249 (23), 199 (61), 188 (60), 172 (26), 159 (23), 145 (60), 91 (24), 81 (29), 59 (19). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=0.96 (3H, t, $^3J_{HH}$=7.0 Hz, OCH_2Me), 1.03 (3H, t, $^3J_{HH}$=7.0 Hz, OCH_2Me), 2.36 (3H, s, Me), 2.38 (3H, s, Me), 2.93 (1H, d, $^2J_{HH}$=12.0 Hz, CH_2), 3.27 (1H, d, $^2J_{HH}$=12.0 Hz, CH_2), 3.79 (6H, d, $^3J_{HP}$=11.7 Hz, $P(OMe)_2$), 3.80–4.11 (4H, m, 2 OCH_2Me), 4.38 (1H, dd, $^2J_{HP}$=20.3 Hz, $^3J_{HH}$=10.6 Hz, CHC*H*P), 5.16 (1H, dd, $^3J_{HH}$=10.6 Hz, $^3J_{HP}$=4.1 Hz, C*H*CHP), 7.06 (1H, d, $^3J_{HH}$=8.0 Hz, CH of Ar), 7.10 (1H, s, CH of Ar), 7.35 (1H, d, $^3J_{HH}$=8.0 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=15.8 (OCH_2Me), 15.8 (OCH_2Me), 20.6

(Me), 28.1 (Me), 43.4 (CH_2), 45.5 (d, $^1J_{CP}$=130.5 Hz, CHCHP), 52.7 (OCH_2Me), 53.2 (OCH_2Me), 62.1 (d, $^2J_{CP}$=5.0 Hz, *C*HCHP), 62.6 (d, $^2J_{CP}$=6.6 Hz, P($OCH_2Me)_2$), 63.0 (d, $^2J_{CP}$=6.6 Hz, P($OCH_2Me)_2$), 121.5 (CH of Ar), 126.6 (CH of Ar), 126.7 (CH of Ar), 133.2 (C_{ipso}–NCO), 135.4 (C_{ipso}–Me), 141.6 (C_{ipso}–N=C), 164.4 (C=N), 168.3 (NCO), 168.8 (d, $^2J_{CP}$=7.3 Hz, CO_2Et), 170.0 (d, $^3J_{CP}$=17.5 Hz, CO_2Et). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=18.80 ppm.

*4.2.8. Diethyl 2-(diethoxyphosphoryl)-3-(4,8-dimethyl-2-oxo-2,3-dihydro-1H-1,5-benzodiazepin-1-yl)succinate (**7c**)*

White powder, mp=147–149 °C, 0.44 g, yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1727 (CO_2Et), 1671 (NCO), 1641 (N=C), 1525 and 1480 (Ar), 1282 (P=O). Anal. Calcd for $C_{23}H_{33}N_2O_8P$ (496.49): C, 55.64; H, 6.70; N, 5.64%. Found: C, 55.67; H, 6.72; N, 5.66%. MS (EI, 70 eV): *m*/*z* (%)=497 (M^++1, 100), 496 (M^+, 75), 451 (24), 423 (24), 377 (39), 359 (97), 313 (58), 285 (22), 199 (64), 188 (64), 145 (60), 81 (15), 65 (6). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H=0.94 (3H, t, $^3J_{HH}$=7.0 Hz, OCH_2*Me*), 1.04 (3H, t, $^3J_{HH}$=7.0 Hz, OCH_2*Me*), 1.26 (3H, t, $^3J_{HH}$=7.1 Hz, P(OCH_2*Me*)$_2$), 1.33 (3H, t, $^3J_{HH}$=7.1 Hz, P(OCH_2*Me*)$_2$), 2.36 (3H, s, Me), 2.38 (3H, s, Me), 2.92 (1H, d, $^2J_{HH}$=12.0 Hz, CH_2), 3.27 (1H, d, $^2J_{HH}$=12.0 Hz, CH_2), 3.76–3.81 (1H, m, O*C*H_2Me), 3.87–3.92 (1H, m, O*C*H_2Me), 3.96 (2H, q, $^3J_{HH}$=7.1 Hz, O*C*H_2Me), 4.18–4.29 (4H, m, P(O*C*H_2Me)$_2$), 4.36 (1H, dd, $^2J_{HP}$=20.4 Hz, $^3J_{HH}$=10.6 Hz, CHC*H*P), 5.13 (1H, dd, $^3J_{HP}$=4.0 Hz, $^3J_{HH}$=10.6 Hz, C*H*CHP), 7.05 (1H, d, $^3J_{HH}$=7.9 Hz, CH of Ar), 7.09 (1H, s, CH of Ar), 7.37 (1H, d, $^3J_{HH}$=8.0 Hz, CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C=13.9 (OCH_2*Me*), 13.9 (OCH_2*Me*), 15.7 (d, $^3J_{CP}$=6.5 Hz, P(OCH_2*Me*)$_2$), 15.8 (d, $^3J_{CP}$=6.5 Hz, P(OCH_2*Me*)$_2$), 20.6 (Me), 28.1 (Me), 43.4 (CH_2), 45.6 (d, $^1J_{CP}$=129.8 Hz, CHCHP), 61.7 (OCH_2Me), 62.2 (d, $^2J_{CP}$=5.4 Hz, *C*HCHP), 62.2 (OCH_2Me), 62.4 (d, $^2J_{CP}$=6.9 Hz, P($OCH_2Me)_2$), 62.8 (d, $^2J_{CP}$=6.2 Hz, P($OCH_2Me)_2$), 121.5 (CH of Ar), 126.5 (CH of Ar), 126.7 (CH of Ar), 133.3 (C_{ipso}–NCO), 135.2 (C_{ipso}–Me), 141.6 (C_{ipso}–N=C), 164.5 (C=N), 168.2 (NCO), 168.4 (d, $^2J_{CP}$=8.1 Hz, CO_2Et), 169.5 (d, $^3J_{CP}$=17.1 Hz, CO_2Et). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ_P=18.97 ppm.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.091.

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