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A Facile Route to 1,5-Benzodiazepin-2-yl-phosphonates via Ytterbium Chloride-Catalyzed Three-Component Reaction

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ABSTRACT: *1,5-Benzodiazepin-2-yl-phosphonates were facilely synthesized via a one-pot three-component condensation of o-diaminobenzene, 1,3-diketone and diethyl phosphite in the presence of a catalytic amount of ytterbium chloride under mild reaction conditions*. © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:89–95, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20573

INTRODUCTION

α-Amino phosphonate and its derivatives are an important class of compounds widely used in the biochemical field, the pharmaceutical field, and the field of metal complexation as well [1–7]. Among these compounds, the azaheterocyclic phosphonates occupy an important position because of the already presented and well-promised biological activities of them [8–14]. Thus, the methods for the synthesis of this type of compounds have attracted and are still attracting special attention of organic synthetic chemists. Many research groups dedicated their efforts to this direction, which resulted in a vast diversity of synthetic pathways [15]. However, from the viewpoint of the ring size of azaheterocycle, there were very few papers describing the synthetic routes toward the seven-membered or fused seven-membered azaheterocyclic phosphonates [16–18]. In another respect, benzodiazepine and its derivatives are well known to possess a number of useful biological properties and proved to be of considerable importance and interest to the medicinal field [19–22]. Encouraged by the valuable properties of α-amino phosphonates and benzodiazepines provided, we conceived the idea of developing efficient methods for the synthesis of benzodiazepine-based phosphonates, with a hope of finding novel seven-membered azaheterocyclic phosphonates as lead compounds in the further research on bioactive materials.

The most straightforward and efficient way of synthesizing α-amino phosphonate is the one-pot condensation of carbonyl compound, amine and phosphite, usually catalyzed by Lewis acid. In continuation of our studies on lanthanide halide catalyzed carbon–nitrogen bond-forming reactions [23–26], we investigated the effectiveness of lanthanide chlorides, which are readily available and economical, as Lewis acid-type catalysts for the three-component reaction of *o*-diaminobenzene, 1,3-diketone, and phosphite that would provide a novel,

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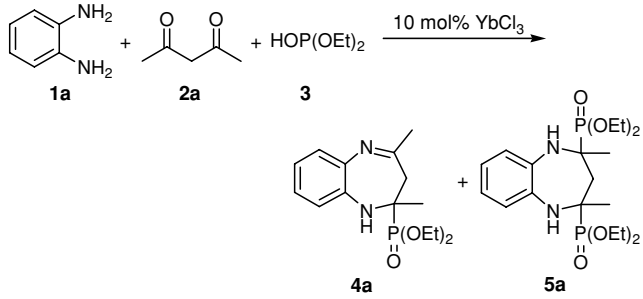
rapid, and efficient route toward 1,5-benzodiazepin-2-yl-phosphonate. Herein, we wish to report our preliminary results.

RESULTS AND DISCUSSION

At the outset, the reaction of *o*-diaminobenzene (**1a**), pentane-2,4-dione (**2a**), and diethyl phosphite (**3**) in a 1:1:2 mole ratio was attempted in the presence of catalytic amount of ytterbium chloride ($YbCl_3$) at room temperature under solvent-free condition. As we predicted, the product was obtained as a mixture of diethyl (2,4-dimethyl-2,3-dihydro-1H-benzo[*b*][1,4] diazepin-2-yl)phosphonate (monophosphonate **4a)** and tetraethyl (2,4-dimethyl-2,3,4,5-tetrahydro-1H-benzo[*b*][1,4]diazepine-2, 4-diyl)bis(phosphonate) (diphosphonate **5a)** with the yield of 56% and 8%, respectively (Table 1, entry 6). Then, various conditions including solvent, temperature, and the molar ratio of the respective substrates were screened in order to address their influence on the activity and selectivity of the reaction. The results are listed in Table 1. Obviously, the molar ratio of the three substrates was the key factor affecting the ratio between **4a** and **5a**. When **1a, 2a**, and **3** were mixed at an 1:1:1 mole ratio, the monophosphonate **4a** was obtained as the major product in 61% yield and only trace of diphosphonate **5a** was detected, whereas an 1:1:4 mole ratio afforded **5a** as the major product in 57% yield (entries 1 and 9). Bearing in mind that solvent can affect the reactivity, several classical organic solvents were chosen as the medium for comparison to optimize the process and it was found that solvent-free condition was the best choice (entries 1–5). Reaction temperature was also investigated. Raising the temperature from room temperature to 60°C resulted in a decrease in the yield of **4a** accompanied by an increase of **5a** at 1:1:2 mole ratio of the substrates (entries 6–8). However, the reaction carried out at 1:1:4 mole ratio and 40°C provided the highest overall yield and selective formation of product **5a** (entry 10).

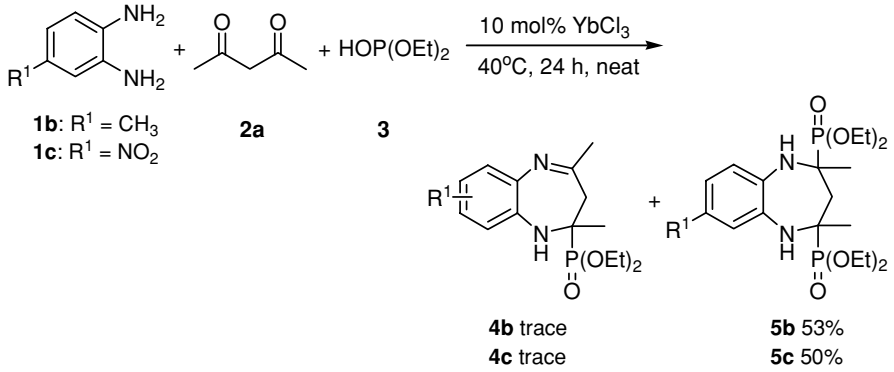
TABLE 1 Conditions Screening for $YbCl_3$-Catalyzed Condensation of *o*-Diaminobenzene, Pentane-2,4-dione, and Diethyl Phosphite[a]



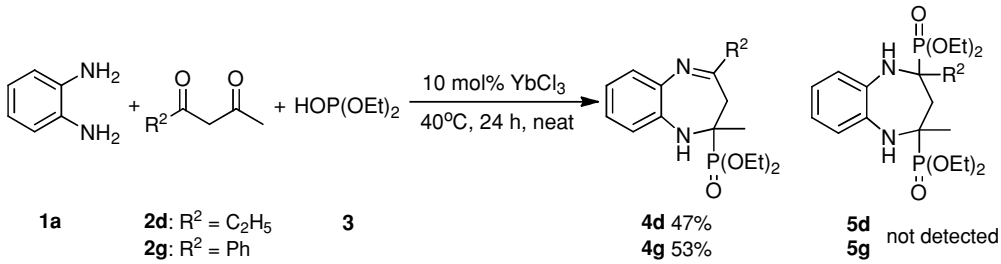
Entry	*Ratio of* ***1a/2a/3***	*Solvent*	*Temperature (°C)*	*Yield of* ***4a*** *(%)*	*Yield of* ***5a*** *(%)*
1	1:1:1	–	22	61	Trace
2	1:1:1	CH_3CN	22	42	Trace
3	1:1:1	THF	22	41	Trace
4	1:1:1	Toluene	22	35	Trace
5	1:1:1	CH_2Cl_2	22	18	Trace
6	1:1:2	–	22	56	8
7	1:1:2	–	40	34	24
8	1:1:2	–	60	14	25
9	1:1:4	–	22	Trace	57
10	1:1:4	–	40	14	65
11	1:1:4	–	50	22	55

[a] Typical reaction conditions: *o*-diaminobenzene, pentane-2,4-dione,and $YbCl_3$ (10 mol% relative to *o*-diaminobenzene) were mixed and stirred for 1 h, and diethyl phosphite was then added, and the mixture was stirred for another 24 h.

The syntheses of diphosphonates **5** using substituted *o*-diaminobenzene were then attempted under the conditions described in Table 1, entry 10 (**1: 2a: 3** = 1:1:4, 40°C), and the corresponding products were obtained as an inseparable mixture of cis- and trans-stereoisomer in moderate yields (Scheme 1).



SCHEME 1 Synthesis of diphosphonates.



SCHEME 2 Synthesis of monophosphonates.

When benzoylacetone (**2g**) was used instead of pentane-2,4-dione to generate the corresponding diphosphonate **5g** under the same conditions mentioned above, no hoped-for product was detected while monophosphonate **4g** was obtained in 53% yield (Scheme 2). Similarly, hexane-2,4-dione (**2d**) afforded monophosphonate **4d** in 47% yield without the formation of the corresponding diphosphonate **5d**. The results indicated that the effect of the steric hindrance plays an important role in the addition of the second portion of diethyl phosphite to imine. Once the exocyclic alkyl adjacent to the carbon–nitrogen double bond of the monophosphonate **4** was larger than methyl, the nucleophilic addition of diethyl phosphite to the imine, that forms the diphosphonate **5**, would not occur. This gives us a chance to develop the methodology to synthesis benzodiazepine-based monophosphonate selectively.

Then the attention was turned to establishing the optimum conditions for the synthesis of 1,5-benzodiazepin-2-yl-phosphonate and the reaction of *o*-diaminobenzene, benzoylacetone, and diethyl phosphite was investigated as the model. First, several lanthanide halides were screened and the results listed in Table 2 showed the influence of central metal on the catalytic activity. The active sequence is Yb > Gd > Sm > La, which is in contrast to the order of their ionic radius. Further investigation on the reaction temperature demonstrated that raising the temperature to a certain extent led to an increase in yield whereas overheating affected the yield in the negative direction (Table 2, entries 4–6), and the best yield was obtained at 40°C. Increasing the catalyst loading did not lead to an increase of yield (entry 7). Samarium diiodide (SmI_2), the representative compound of divalent lanthanide, also showed moderate activity (entry 8).

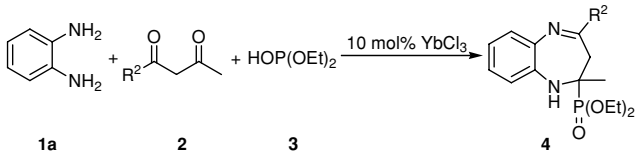
To demonstrate the generality of this method, the process was extended to a serial of acyl acetone with $YbCl_3$ as the representative lanthanide catalyst. The corresponding benzodiazepine-based phosphonates were obtained in moderate yields, and the results are summarized in Table 3. The

TABLE 2 Lanthanide Halide Catalyzed Condensation of *o*-Diaminobenzene, Benzoylacetone, and Diethyl Phosphite[a]

Entry	*Catalyst*	*Temperature (°C)*	*Yield (%)*
1	$LaCl_3$	40	29
2	$SmCl_3$	40	31
3	$GdCl_3$	40	36
4	$YbCl_3$	40	58
5	$YbCl_3$	22	43
6	$YbCl_3$	50	50
7[b]	$YbCl_3$	40	53
8	SmI_2	40	45

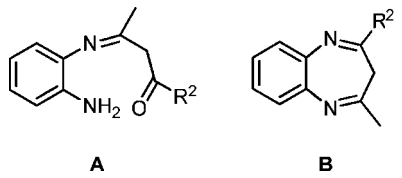
[a] Typical reaction conditions: *o*-diaminobenzene/benzoylacetone/diethyl phosphite = 1:1:1, catalyst loading 10 mol%.
[b] Catalyst loading 20 mol%.

TABLE 3 $YbCl_3$-Catalyzed One-Pot Synthesis of 1,5-Benzodiazepin-2-yl-phosphonates[a]



Entry	*R^2*	*Product*	*Isolated Yield (%)*
1	Me	**4a**	61
2	Et	**4d**	51
3	*i*-Bu	**4e**	60
4	amyl	**4f**	52
5[b]	Ph	**4g**	58[c]
6[d]	4-ClPh	**4h**	55
7[d]	4-BrPh	**4i**	47
8[d]	4-MePh	**4j**	49
9[e]	4-MeOPh	**4k**	44

[a] Typical reaction conditions: *o*-diaminobenzene/1,3-diketone/diethyl phosphite = 1:1:1, 22°C. *o*-Diaminobenzene, 1,3-diketone and 10 mol% $YbCl_3$ were mixed and stirred for 1 h, and diethyl phosphite was then added and the mixture was stirred for another 24 h.
[b] 40°C, 3 h + 12 h.
[c] Along with 30% of 3-(2-aminophenylimino)-1-phenylbutan-1-one.
[d] 50°C, 12 h + 12 h.
[e] 35°C, 12 h + 12 h.



SCHEME 3 Plausible intermediates.

activity of 1-aryl substituted-1,3-butanediones is somewhat lower than that of 1-alkyl substituted ones, and heightened temperature are necessary for the former to get the yields close to those of the latter. For example, pentane-2,4-dione (**2a**) reacted with *o*-diaminobenzene (**1a**) and diethyl phosphite (**3**) at 22°C leading to the corresponding product **4a** in 61% yield (Table 3, entry 1), whereas 1-(4-chlorophenyl)butane-1,3-dione (**2h**) generated a 55% yield of product **4h** despite the reaction was carried out at temperature of 50°C (entry 6).

The moderate yields of the reaction impelled us to infer the plausible mechanism. It was considered that the required benzodiazepine-based phosphonate can be formed via a three-step sequence involving (i) lanthanide-catalyzed condensation of *o*-diaminobenzene with a less hindered carbonyl to produce β-carbonyl imine **A** (Scheme 3), (ii) the second condensation of carbonyl with amino group leading to benzodiazepine **B**, followed by (iii) nucleophilic addition of diethyl phosphite to **B** to generate the target molecule. The analyses of the crude product of the reaction with *o*-diaminobenzene, benzoylacetone, and diethyl phosphite indicated that β-carbonyl imine **6g** was obtained in 30% yield besides the expected product **4g** (Scheme 4). The result suggested that benzodiazepine **B** is relatively difficult to be formed from **A**, probably due to the strong cyclic tension caused by the two imino groups existing in the same seven-membered ring. However, once **B** is generated, it is very reactive and transform to **4g** quickly. The hardness of the formation of **B** presumably resulted in the lower yield of the product.

In conclusion, we described here a novel and facile route for the synthesis of benzodiazepine-based phosphonates via three-component condensation of *o*-diaminobenzene, 1,3-diketone and diethyl phosphite with $YbCl_3$ as an efficient catalyst under mild conditions. The reaction is one-pot, atom-economic, and can be handled easily. Further studies on the application of the present method to the synthesis of azaheterocyclic phosphonates are under investigation.

EXPERIMENTAL

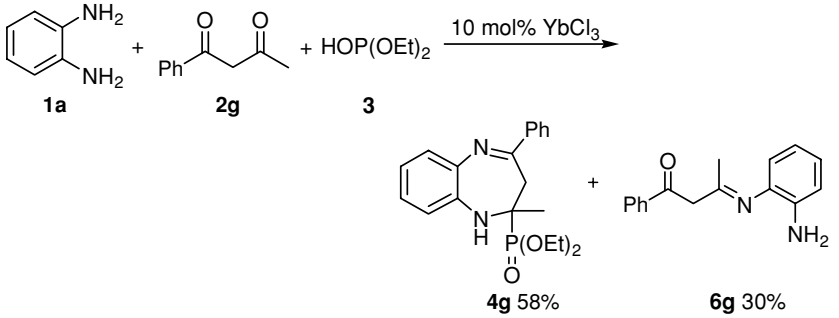
General Remarks

All the manipulations were conducted under dry Ar atmosphere with flame-dried glassware. Lanthanide chlorides were synthesized according to the method described by Taylor and Carter [27]. *o*-Phenylenediamine was recrystallized from hot water containing sodium hydrosulfite and treated with decolorizing charcoal. Diethyl phosphite was prepared by the reported procedure [28].

IR spectra were obtained on a Nicolet FT-IR 1000 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on Varian INOVA-400 and System-300 spectrometers using tetramethylsilane (TMS) as an internal reference. HRMS data were recorded on a Micromass GCT instrument. Elemental analyses were determined on a Carlo Erba EA1110-CHNS-O analyzer.

General Procedure

A mixture of *o*-diaminobenzene (1 mmol), 1,3-diketone (1 mmol), and ytterbium chloride (0.1 mmol) was stirred at room temperature for the given time. Then, diethyl phosphite (1 mmol) was added and the stirring was continued at an appropriate temperature. After completion of the reaction (TLC),



SCHEME 4 $YbCl_3$-catalyzed reaction of *o*-diaminobenzene, benzoylacetone with diethyl phosphite.

saturated $NaHCO_3$ solution was added and the mixture was extracted with ethyl acetate (10 mL × 3). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using acetone–petroleum ether (1:3) as eluent to afford the product. All the products were new compounds and were identified by IR, ^{1}H NMR, ^{13}C NMR, HRMS, and elemental analyses.

*Diethyl (2,4-Dimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phosphonate (**4a**).* mp 103-105°C; IR (KBr) ν : 771, 972, 1026, 1234, 1643, 2978, 3279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13-6.79 (m, 4H), 4.26–4.07 (m, 4H), 3.51 (s, br, 1H), 2.75–2.69 (m, 1H), 2.40 (s, 3H), 2.32 (dd, J = 18.0, 13.6 Hz, 1H), 1.55 (d, J = 14.4 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 140.4, 136.4, 126.9, 125.5, 122.5, 122.2, 70.0 (J_{CP} = 153.4 Hz), 63.7, 62.2, 38.2, 29.6, 24.5, 16.3; HRMS Calcd for $C_{15}H_{23}N_2O_3P$ 310.1446, found 310.1446; Anal. Calcd for $C_{15}H_{23}N_2O_3P$: C, 58.05; H, 7.47; N, 9.03. Found: C, 57.82; H, 7.33; N, 8.95.

*Diethyl (4-Ethyl-2-methyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phosphonate (**4d**).* mp 141−142°C; IR (KBr) ν : 772, 972, 1049, 1227, 1651, 2978, 3279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15–6.79 (m, 4H), 4.27–4.09 (m, 4H), 3.54 (s, br, 1H), 2.74–2.59 (m, 3H), 2.31 (dd, J = 16.8, 9.2 Hz, 1H), 1.54 (d, J = 14.8 Hz, 3H), 1.32–1.24 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:174.5, 140.6, 136.3, 126.9, 125.4, 122.4, 122.1, 69.8 (J_{CP} = 151.8 Hz), 63.5, 62.2, 37.1, 35.3, 24.5, 16.3, 10.3; HRMS Calcd for $C_{16}H_{25}N_2O_3P$ 324.1603, found 324.1602; Anal. Calcd for $C_{16}H_{25}N_2O_3P$: C, 59.25; H, 7.77; N, 8.64. Found: C, 59.18; H, 7.75; N, 8.49.

*Diethyl (4-Isobutyl-2-methyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phosphonate (**4e**).* mp 101−102°C; IR (KBr) ν : 756, 964, 1049, 1227, 1643, 2978, 3287 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.13–6.79 (m, 4H), 4.25–4.06 (m, 4H), 3.55 (s, br, 1H), 2.69 (t, J = 11.6 Hz, 1H), 2.58−2.45 (m, 2H), 2.86 (t, J = 14.8 Hz, 1H), 2.15–2.08 (m, 1H), 1.55 (d, J = 15.2 Hz, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 173.3, 140.5, 136.5, 126.9, 125.4, 122.3, 122.0, 70.0 (J_{CP} = 150.7 Hz), 63.5, 62.2, 51.4, 37.2, 26.4, 24.5, 22.5, 16.3; HRMS Calcd for $C_{18}H_{29}N_2O_3P$ 352.1916, found 352.1904; Anal. Calcd for $C_{18}H_{29}N_2O_3P$: C, 61.35; H, 8.29; N, 7.95. Found: C, 61.17; H, 8.22; N, 7.89.

*Diethyl (2-Methyl-4-pentyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phosphonate (**4f**).* mp 85−86°C; IR (KBr) ν : 764, 964, 1049, 1234, 1643, 2931, 2962, 3279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.12–6.78 (m, 4H), 4.26–4.06 (m, 4H), 3.53 (s, br, 1H), 2.69 (dd, J = 13.2, 10.0 Hz, 1H), 2.63–2.59 (m, 2H), 2.29 (dd, J = 16.4, 13.2 Hz, 1H), 1.71–1.68 (m, 2H), 1.54 (d, J = 14.8 Hz, 3H), 1.38–1.35 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 174.1, 140.7, 136.4, 127.0, 125.5, 122.5, 122.2, 70.1 (J_{CP} = 151.4 Hz), 63.6, 62.3, 42.5, 37.2, 31.6, 26.1, 24.6, 22.5, 16.4, 14.0; HRMS Calcd for $C_{19}H_{31}N_2O_3P$ 366.2072, found 366.2081; Anal. Calcd for $C_{19}H_{31}N_2O_3P$: C, 62.28; H, 8.53; N, 7.64. Found: C, 62.53; H, 8.50; N, 7.69.

*Diethyl (2-Methyl-4-phenyl-2,3-dihydro-1H-benzo[b][1,4]diazepin-2-yl)phosphonate (**4g**).* mp 137−138°C; IR (KBr) ν : 694, 748, 964, 1227, 1605, 3263 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06–6.85 (m, 9H), 4.19–4.02 (m, 4H), 3.68 (s, br, 1H), 3.18 (dd, J = 13.2, 9.6 Hz, 1H), 2.93 (t, J = 13.2 Hz, 1H), 1.52 (d, J = 14.8 Hz, 3H), 1.25 (t, J = 6.8 Hz, 3H), 1.16 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 141.0, 139.3, 136.5, 130.2, 128.2, 127.8, 127.1, 126.0, 122.6, 122.1, 70.7 (J_{CP} = 147.6 Hz), 63.1, 62.3, 33.5, 24.6, 16.3; HRMS Calcd for $C_{20}H_{25}N_2O_3P$ 372.1603, found 372.1589; Anal. Calcd for $C_{20}H_{25}N_2O_3P$: C, 64.50; H, 6.77; N, 7.52. Found: C, 64.57; H, 6.84; N, 7.38.

*Diethyl (4-(4-Chlorophenyl)-2-methyl-2,3-dihydro-1H-benzo[b] [1,4]diazepin-2-yl) phosphonate (**4h**).* mp 141–142°C; IR (KBr) ν : 748, 802, 949, 1057, 1088, 1227, 1605, 3271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03–6.85 (m, 8H), 4.19–4.02 (m, 4H), 3.65 (s, br, 1H), 3.17 (dd, J = 13.6, 9.6 Hz, 1H), 2.85 (t, J = 14.8 Hz, 1H), 1.52 (d, J = 14.8 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.9, 140.8, 137.8, 136.5, 136.4, 128.5, 128.4, 127.9, 126.3, 122.7, 122.2, 70.9 (J_{CP} = 149.7 Hz), 63.3, 62.3, 33.6, 24.7, 16.3; HRMS Calcd. for $C_{20}H_{24}ClN_2O_3P$ 406.1213, found 406.1204; Anal. Calcd for $C_{20}H_{24}ClN_2O_3P$: C, 59.04; H, 5.95; N, 6.89. Found: C, 59.18; H, 5.98; N, 6.74.

*Diethyl (4-(4-Bromophenyl)-2-methyl-2,3-dihydro-1H-benzo[b] [1,4]diazepin-2-yl) phosphonate (**4i**).* mp 135–136°C IR (KBr) ν : 772, 833, 949, 1018, 1064, 1227, 1605, 3271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95–6.84 (m, 8H), 4.20–4.02 (m, 4H), 3.65 (s, br, 1H), 3.16 (dd, J = 13.6, 9.2 Hz, 1H), 2.85 (t, J = 14.4 Hz, 1H), 1.52 (d, J = 14.8 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz,

3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 166.1, 140.8, 138.2, 136.5, 131.4, 128.8, 127.9, 126.3, 125.0, 122.8, 122.3, 70.9 (J_{CP} = 149.8 Hz), 63.3, 62.4, 33.6, 24.7, 16.4; HRMS Calcd for $C_{20}H_{24}BrN_2O_3P$ 450.0708, found 450.0703; Anal. Calcd for $C_{20}H_{24}ClN_2O_3P$: C, 53.23; H, 5.36; N, 6.21. Found: C, 53.43; H, 5.40; N, 6.21.

*Diethyl (2-Methyl-4-(p-tolyl)-2,3-dihydro-1H-benzo[b] [1,4]diazepin-2-yl)phosphonate (**4j**).* mp 144–146°C; IR (KBr) ν : 748, 802, 964, 1034, 1234, 1605, 2978, 3287 cm^{-1}; ^{1}H NMR (400M Hz, $CDCl_3$) δ: 7.96–6.83 (m, 8H), 4.19–4.03 (m, 4H), 3.66 (s, br, 1H), 3.14 (dd, J = 13.6, 9.6 Hz, 1H), 2.93 (t, J = 12.8 Hz, 1H), 2.41 (s, 3H), 1.52 (d, J = 15.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.1, 141.2, 140.5, 136.6, 128.9, 127.7, 127.1, 125.7, 122.6, 122.1, 70.6 (J_{CP} = 146.3 Hz), 63.0, 62.3, 33.3, 24.6, 21.2, 16.3; HRMS Calcd for $C_{21}H_{27}N_2O_3P$ 386.1759, found 386.1761; Anal. Calcd for $C_{21}H_{27}N_2O_3P$: C, 65.27; H, 7.04; N, 7.25. Found: C, 65.36; H, 7.03; N, 7.52.

*Diethyl (4-(4-Methoxyphenyl)-2-methyl-2,3-dihydro-1H-benzo[b] [1,4]diazepin-2-yl) phosphonate (**4k**).* mp 171–172°C; IR (KBr) ν: 748, 810, 949, 1018, 1227, 1605, 2986, 3279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03–6.83 (m, 8H), 4.19–4.03 (m, 4H), 3.87 (s, 3H), 3.65 (s, br, 1H), 3.13 (dd, J = 13.2, 10.0 Hz, 1H), 2.90 (t, J = 13.2 Hz, 1H), 1.52 (d, J = 14.8 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6, 161.5, 141.4, 136.6, 132.1, 128.9, 127.6, 125.6, 122.7, 122.2, 113.6, 70.6 (J_{CP} = 146.3 Hz), 63.1, 62.4, 55.3, 33.3, 24.6, 16.3; HRMS Calcd for $C_{21}H_{27}N_2O_4P$ 402.1708, found 402.1709; Anal. Calcd for $C_{21}H_{27}N_2O_4P$: C, 62.68; H, 6.76; N, 6.96. Found: C, 62.41; H, 6.73; N, 6.97.

*Tetraethyl (2,4-Dimethyl-2,3,4,5-tetrahydro-1H-benzo[b] [1,4]diazepine-2,4-diyl)bis (phosphonate) (**5a**).* mp 112–113°C; IR (KBr) ν: 748, 949, 1042, 1226, 1597, 2978, 3279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82–6.76 (m, 4H), 4.19–4.08 (m, 8H), 3.96 (s, br, 2H), 2.69–2.60 (m, 1H), 2.31–2.00 (m, 1H), 1.68–1.64 (m, 6H), 1.35–1.22 (m, 12H); HRMS Calcd for $C_{19}H_{34}N_2O_6P_2$ 448.1892, found 448.1888; Anal. Calcd for $C_{19}H_{34}N_2O_6P_2$: C, 50.89; H, 7.64; N, 6.25. Found: C, 51.00; H, 7.53; N, 6.26.

*Tetraethyl (2,4,7-Trimethyl-2,3,4,5-tetrahydro-1H-benzo[b] [1,4]diazepine-2,4-diyl)bis (phosphonate) (**5b**).* mp 130-131°C; IR (KBr) ν: 802, 949, 1049, 1227, 1605, 2986, 3287 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.67–6.59 (m, 3H), 4.18–4.08 (m, 8H), 3.91 (s, br, 1H), 3.87 (s, br, 1H), 2.67–2.57 (m, 1H), 2.20 (s, 3H), 2.03–1.98 (m, 1H), 1.66–1.60 (m, 6H), 1.30–1.23 (m, 12H); HRMS Calcd for $C_{20}H_{36}N_2O_6P_2$ 462.2049, found 462.2060; Anal. Calcd for $C_{20}H_{36}N_2O_6P_2$: C, 51.94; H, 7.85; N, 6.06. Found: C, 52.05; H, 7.82; N, 5.92.

*Tetraethyl (2,4-Dimethyl-7-nitro-2,3,4,5-tetrahydro-1H-benzo[b] [1,4]diazepine-2,4-diyl)bis (phosphonate) (**5c**).* mp 176–177°C; IR (KBr) ν: 833, 964, 1026, 1227, 2986, 3279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69–7.58 (m, 2H), 6.62–6.60 (m, 1H), 4.56 (s, br, 1H), 4.24–4.16 (m, 8H), 4.01 (s, br, 1H), 2.45–2.23 (m, 2H), 1.74–1.60 (m, 6H), 1.37–1.33 (m, 12H); HRMS Calcd for $C_{19}H_{33}N_3O_8P_2$ 493.1743, found 493.1758; Anal. Calcd. for $C_{19}H_{33}N_3O_8P_2$: C, 46.25; H, 6.74; N, 8.52. Found: C, 45.94; H, 6.64; N, 8.19.

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