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Convenient Synthesis of Dialkyl 1-Azidoalkylphosphonates using Tetramethylguanidinium Azide as Azidation Agent

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Abstract: A simple and safe method for the preparation of dialkyl 1-azidoalkylphosphonates from dialkyl 1-(4-nitrobenzenesulfonyloxy)alkylphosphonates (dialkyl 1-(nosyloxy)alkylphosphonates) and tetramethylguanidinium azide (TMGA) has been developed.

Keywords: 1-Azidoalkylphosphonates, azidation, 1-hydroxyalkylphosphonates, nucleophilic substitution, tetramethylguanidinium azide, 1-(sulfonyloxy)alkylphosphonates

INTRODUCTION

1-Azidoalkylphosphonates have been widely used for the synthesis of 1-aminoalkylphosphonates and 1-aminoalkylphosphonic acids,[1–4] polyfunctional aminophosphonates,[5] and phosphonopeptides,[6] as well as for the construction of heterocyclic systems.[7]

1-Azidoalkylphosphonates can be prepared from the hydroxy derivatives via nucleophilic substitution using the Mitsunobu protocol or nucleophilic displacement of the 1-halogeno- or 1-(sulfonyloxy)alkylphosphonates by azides.

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An alternative approach involves the insertion of the azido group into the phosphonate backbone via electrophilic substitution.

The Mitsunobu reaction[8] is widely used for the preparation of 1-azidoalkylphosphonates.[1b,1f,2a,2b,9] However, this general route to 1-azidoalkylphosphonates suffers from the use of highly toxic and explosive hydrazoic acid as the azide source. As an alternative to the Mitsunobu approach, Firouzabadi et al.[10] have reported on the efficient synthesis of diethyl azido(aryl)methylphosphonates from the hydroxy derivatives utilizing the Ph_3P/2,3-dichloro-5,6-dicyanobenzoquinone/NaN_3 system for azidation. However, the method described was limited to benzyl derivatives only.

Only a limited number of dialkyl 1-azidoalkylphosphonates has been obtained via nucleophilic azidation of the 1-(sulfonyloxy)alkylphosphonates with sodium azide in dimethylsulfoxide (DMSO) or dimethylformamide (DMF) because of the low reactivity of 1-(mesyloxy)-[1c] or 1-(tosyloxy)alkyl phosphonates.[11] As a consequence of rather harsh conditions needed for the reaction, it sometimes lead to the formation of mono-dealkylated by-products. In addition, the azidation of the tosyloxyphosphonates was limited to benzyl analogs only.[11] Much better results were obtained for the more reactive, but unstable, 1-(triflyloxy)alkyl-phosphonates.[1e]

Nucleophilic substitution of halogen in 1-halogenoalkylphosphonates with sodium azide was frequently used for the synthesis of the azidophosphonates. The reaction required heating for several hours at high temperatures, often resulting in mono-dealkylation of the substrate and/or product.[12] The formation of by-products could be avoided by application of phosphonamidates as starting materials[13] or by using as substrates the phosphonate esters bearing sterically hindered[5] or electron-withdrawing groups.[1a,14] The electrophilic azidation of the phosphorus-stabilized carbanions using trifluoromethanesulfonyl, tosyl, and trisyl azides as azide function transferring agents was also applied for the synthesis of 1-azidoalkylphosphonates.[15–17]

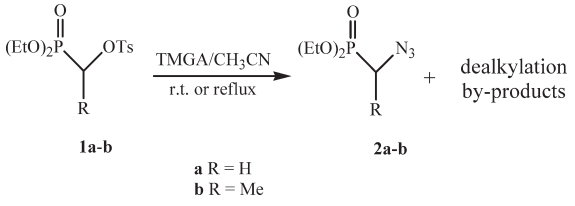
Tetramethylguanidinium azide (TMGA), introduced by Papa,[18] is a stable, safe to use, and commercially available reagent. TMGA is frequently used as a source of the azide in nucleophilic addition, substitution, and heterocyclic ring formation.[19]

To the best of our knowledge, there are no reports of the synthesis of 1-azidoalkylphosphonates using TMGA as the azidating agent.

Herein we report a simple protocol for the synthesis of dialkyl 1-azidoalkylphosphonates **2** from the easily available dialkyl 1-(4-nitrobenzenesulfonyloxy)alkylphosphonates **4** and TMGA.

RESULTS AND DISCUSSION

At first, we focused on the Mitsunobu reaction of diethyl hydroxymethylphosphonate using a triphenylphosphine/diethyl azodicarboxylate system and TMGA as the azide source. An inseparable mixture of the diethyl



Scheme 1.

azidomethylphosphonate, starting hydroxyphosphonate, and unknown organophosphorus compounds was formed, however, independent of the reaction conditions.

Next, diethyl tosyloxymethylphosphonate[20] (**1a**) and diethyl 1-(tosyloxy) ethylphosphonate[20] (**1b**) were chosen as a model phosphonates, and TMGA (1.2 equivalents) was used for the displacement of the tosyloxy group (Scheme 1). The results are presented in Table 1.

As shown in Table 1, the treatment of **1a** with TMGA in acetonitrile at room temperature for 11 days resulted in 90% conversion of **1a**. However, the requisite diethyl azidomethylphosphonate (**2a**) was accompanied by 13% of the dealkylation by-products (^{31}P NMR) formed from **1a** and **2a** (Table 1, entry 1). When the reaction was carried out in boiling acetonitrile for 4 h, the complete conversion of **1a** was observed, but the amount of the side-products increased to 30%, and pure azide **2a** was isolated in 61% yield only (Table 1, entry 2). Only 50% of conversion of more hindered diethyl 1-(tosyloxy)ethylphosphonate (**1b**) was observed under similar conditions, and the amount of the by-products increased to 33% (Table 1, entry 3).

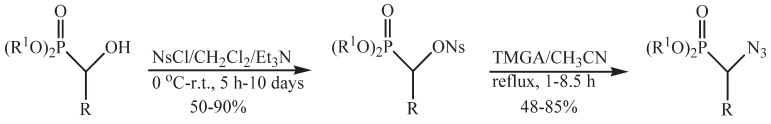
These results prompted us to focus attention on azidation of the much more reactive dialkyl 1-(4-nitrobenzenesulfonyloxy)alkylphosphonates **4a**–**f** instead of tosyl derivatives **1** (Scheme 2). Starting nosyloxyphosphonates **4** were prepared in 50–90% yield from the corresponding 1-hydroxyalkyl-

Table 1. Azidolysis of diethyl 1-(tosyloxy)alkylphosphonates (**1**) with TMGA

Entry	Product 2	R	Reaction conditions	Conversion[a] (%)	Dealkylation by-products[a] (%)
1	**2a**	H	Rt/11 days	90	13
2	**2a**	H	Reflux/4 h	100[b]	30
3	**2b**	Me	Reflux/5 h	50	33

[a]Determined by ^{31}P NMR of the crude reaction mixture. Additional signals of the by-products at 6.7–12.4 ppm were observed.

[b]Isolated in 61% yield.



3a-f **4a-f** **2a-f**

Scheme 2. **a**, $R^1 = Et$, R = H; **b**, $R^1 = Et$, R = Me; **c**, $R^1 = Et$, R = *i*-Pr; **d**, $R^1 = Et$, R = *i*-Bu; **e**, $R^1 = Et$, R = Ph; **f**, R^1 = *i*-Pr, R = H, and Ns = 4-$O_2NC_6H_4SO_2^-$.

phosphonates[21] **3a**–**f** and 4-nitrobenzenesulfonyloxyl chloride, according to the procedure described previously.[22] The azidation of **4** was carried out in acetonitrile using 1.2 equivalents of TMGA as a source of azide. The results are summarized in Table 2.

The data given in Table 2 showed that diethyl nosyloxymethylphosphonate (**4a**), contrary to its tosyl derivative **1a**, underwent complete conversion into the azide **2a** within 1 h in boiling acetonitrile, and pure **2a** was isolated in 85% yield after vacuum distillation (Table 2, entry 1). Moreover, dealkylation of the diethylphosphoryl group did not occur either under reflux conditions or at room temperature. However, the displacement reaction was sensitive to the steric hindrance of the phosphoryl group, and therefore diisopropyl azidomethylphosphonate (**2f**) was prepared in 52% yield (Table 2, entry 6). The reaction proceeded well with α-alkyl substituted nosylates **4b**–**d**, and the corresponding azides **2b**–**d** were obtained in 56–72% yields after flash chromatography or vacuum distillation (Table 2, entries 2–4). However, the steric hindrance of the α-alkyl substituent in **4** influenced the elongation of the reaction time as well as a slight decrease of yields. The azidation of diethyl 1-(nosyloxy)benzylphosphonate (**4e**) occurred as fast as that of unsubstituted nosylate **4a** (Table 2, entry 5). In this case, however, a large amount of

Table 2. Dialkyl 1-azidoalkylphosphonates **2a**–**f** prepared

Entry	Product 2	R	R^1	Reaction conditions	Isolated yield[a] (%)
1	**2a**	H	Et	Reflux/1 h[b]	85
2	**2b**	Me	Et	Reflux/3.5 h	65
3	**2c**	*i*-Pr	Et	Reflux/8.5 h	56
4	**2d**	*i*-Bu	Et	Reflux/8 h	72
5	**2e**	Ph	Et	Reflux/1 h	48[c]
6	**2f**	H	*i*-Pr	Reflux/1.5 h	52

[a]Based on dialkyl 1-(nosyloxy)alkylphosphonates **4**.

[b]When the reaction was carried out at room temperature for 24 h, the azide **2a** was isolated in 74% yield.

[c]Complete conversion of **4e** was observed. The mono-dealkylation by-products derived from **2e** and **4e** were formed in 30% yield as determined by ^{31}P NMR.

dealkylation by-products (30% as determined by ^{31}P NMR) was formed under standard conditions, and the pure azide **2e** was isolated in 48% yield only.

All azides obtained are known compounds, and their spectral (IR, ^{1}H, ^{31}P, and ^{13}C NMR) and analytical (elemental analysis) data stay in agreement with those reported earlier.[1c,1d,9]

CONCLUSION

In summary, we have demonstrated that the azidation of the easily available representative dialkyl 1-(nosyloxy)alkylphosphonates with TMGA affords dialkyl 1-azidoalkylphosphonates in moderate to good yields.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance DPX 250 instrument at 250.13 MHz for ^{1}H NMR, 62.90 MHz for ^{13}C NMR, and 101.3 MHz for ^{31}P NMR in $CDCl_3$ solution, using tetramethylsilane as internal and 85% H_3PO_4 as external standard. Positive chemical shifts are downfield from external 85% H_3PO_4 for ^{31}P NMR spectra. Chemical shifts (δ) are indicated in parts per million (ppm) and coupling constants (J) in hertz. Elemental analyses were performed on a Perkin-Elmer PE 2400 Analyzer. IR spectra were measured on a Specord M80 (Zeiss) instrument as thin film and are reported in centimeters^{-1}. Flash chromatography was performed with a glass column packed with Baker silica gel (30–60 μm). Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and were used without further purification. TMGA was prepared as described in the literature.[18] Dialkyl 1-hydroxyalkylphosphonates **3a**,**f**[21a] and **3b**–**e**[21b] were prepared according to the described procedures. Diethyl 1-(tosyloxy)alkylphosphonates **1a** and **1b** were obtained from diethyl 1-hydroxyalkylphosphonates and tosyl chloride in the same way as described previously.[20] Dialkyl 1-(nosyloxy)alkylphosphonates **4a**–**f** were obtained by the modification of the method described previously.[22]

General Procedure for the Synthesis of Dialkyl 1-(4-Nitrobenzenesulfonyloxy)alkylphosphonates 4a–f

The freshly crystallized 4-nitrobenzenesulfonyl chloride (0.665 g, 3 mmol) was added in 10 portions to the solution of triethylamine (0.42 mL, 3 mmol) and diethyl 1-hydroxyalkylphosphonate **3a**,**b**,**d**–**f** (2 mmol) in dichloromethane (10 mL) cooled to 0 °C. [In the case of the diethyl 1-hydroxy-2-methylpropylphosphonate (**3c**), a catalytic amount of DMAP

(0.02 mmol), 5 mmol of nosyl chloride, and 5 mmol of Et_3N were used for the reaction.] The mixture was stirred at 0 °C for 20 min and for the appropriate time (5 h to 10 days) at room temperature. After completion of the reaction (as indicated by ^{31}P NMR), the solvent was evaporated under reduced pressure, and the solid residue was extracted with diethyl ether (4 × 10 mL). The solvent was evaporated under reduced pressure, and the solid residue was purified by crystallization or by flash chromatography.

Data

Diethyl (4-Nitrobenzenesulfonyloxy)methylphosphonate (**4a**)[23]

Compound **4a** was crystallized from AcOEt/hexane (2:1) to afford a white solid in 85% yield; mp 56–59 °C. ^1H NMR 1.33 (t, $J = 7.04$, 6H), 4.17 (qu, $J = 7.09$, 4H), 4.32 (d, $J = 9.52$, 2H), 8.12–8.18 (m, 2H), 8.40–8.46 (m, 2H); ^{13}C NMR 16.4 (d, $J = 5.8$), 62.2 (d, $J = 159.7$), 63.4 (d, $J = 5.8$), 124.4, 129.3, 140.5, 150.8; ^{31}P NMR 15.08; IR 792, 1024, 1192, 1248, 1384, 1528, 2984, 3112. Anal. calcd. for $C_{11}H_{16}NO_8PS$ (358.29): C, 37.40; H, 4.56; N, 3.96. Found: C, 37.46; H, 4.52; N, 3.93.

Diethyl 1-(4-Nitrobenzenesulfonyloxy)ethylphosphonate (**4b**)

Compound **4b** was isolated by flash chromatography (AcOEt/hexane 2:1) in 90% yield as a pale yellow solid; mp 49–51 °C. ^1H NMR 1.30, 1.32 (2t, $J = 7.06$, 6H), 1.57 (dd, $J = 7.09$, 16.28, 3H), 4.04–4.22 (m, 4H), 4.81–5.00 (m, 2H), 8.12–8.18 (m, 2H), 8.37–8.44 (m, 2H); ^{13}C NMR 16.1, 16.2 (2d, $J = 3.1$), 63.5 (d, $J = 7.0$), 63.7 (d, $J = 7.0$), 73.2 (d, $J = 173.2$), 124.2, 129.2, 142.0, 150.7; ^{31}P NMR 17.84; IR 784, 924, 1020, 1188, 1352, 1532, 2992, 3112, 3480. Anal. calcd. for $C_{12}H_{18}NO_8PS$ (367.31): C, 39.24; H, 4.94; N, 3.81. Found: C, 39.42; H, 4.71; N, 3.90.

Diethyl 1-(4-Nitrobenzenesulfonyloxy)-2-methylpropylphosphonate (**4c**)

Compound **4c** was isolated by flash chromatography (AcOEt/hexane 1:1) in 68% yield as a pale yellow oil. ^1H NMR 1.05, 1.08 (2d, $J = 6.85$, 6H), 1.28, 1.30 (2t, $J = 7.09$, 6H), 2.20–2.40 (m, 1H), 4.01–4.21 (m, 4H), 4.85 (dd, $J = 4.65$, 9.81, 1H), 8.14–8.22 (m, 2H), 8.37–8.44 (m, 2H); ^{13}C NMR 16.1, 16.2 (2d, $J = 4.0$), 17.5 (d, $J = 4.8$), 19.6 (d, $J = 10.1$), 29.7 (d, $J = 1.72$), 62.9 (d, $J = 3.6$), 63.0 (d, $J = 3.6$), 82.3 (d, $J = 166.3$), 124.0, 129.1, 142.6, 150.5; ^{31}P NMR 17.24; IR 820, 928, 972, 1024, 1188, 1352, 1532, 1608, 2984, 3112. Anal. calcd. for $C_{14}H_{22}NO_8PS$ (395.36): C, 42.53; H, 5.61; N, 3.54. Found: C, 42.64; H, 5.77; N, 3.36.

Diethyl 1-(4-Nitrobenzenesulfonyloxy)-3-methylbutylphosphonate (**4d**)

Isolated by flash chromatography (AcOEt/hexane 1:1) in 58% yield as a pale yellow solid; mp 62–64 °C. ^{1}H NMR 0.94, 0.96 (2d, $J = 6.18$, 6.03, 6H), 1.22–1.35 (m, 6H), 1.56–1.95 (m, 3H), 4.0–4.22 (m, 4H), 5.05 (ddd, $J = 10.32$, 8.76, 3.37, 1H), 8.13–8.20 (m, 2H), 8.35–8.43 (m, 2H); ^{13}C NMR 16.1, 16.2 (2d, $J = 5.0$), 20.8, 22.9, 23.9 (d, $J = 11.4$), 38.8, 63.0 (d, $J = 1.5$), 63.1 (d, $J = 2.4$), 75.9 (d, $J = 169.1$), 124.0, 129.1, 142.5, 150.5; ^{31}P NMR 18.33; IR 784, 1024, 1184, 1264, 1352, 1360, 1536, 2968. Anal. calcd. for $C_{15}H_{24}NO_8PS$ (409.39): C, 44.01; H, 5.91; N, 3.42. Found: C, 44.14; H, 5.79; N, 3.35.

Diethyl 1-(4-Nitrobenzenesulfonyloxy)benzylphosphonate (**4e**)

Crystallized from diethyl ether to afford a pale yellow solid in 50% yield; mp 100–102 °C. ^{1}H NMR 1.16 (t, $J = 7.07$, 3H), 1.32 (t, $J = 7.07$, 3H), 3.78–4.19 (m, 2H), 4.00–4.25 (m, 2H), 5.74 (d, $J = 15.01$, 2H), 7.15–7.32 (m, 5H) 7.78–7.85 (m, 2H), 8.09–8.17 (m, 2H); ^{13}C NMR 16.0, 16.2 (2d, $J = 5.7$), 16.2, 63.7 (d, $J = 6.7$), 64.1 (d, $J = 6.7$), 78.6 (d, $J = 171.6$), 123.7, 128.34, 128.36, 128.39, 128.43, 129.5 (d, $J = 2.5$), 130.7; ^{31}P NMR 14.12; IR 788, 1024, 1192, 1352, 1532. Anal. calcd. for $C_{17}H_{20}NO_8PS$ (429.38): C, 47.55; H, 4.69; N, 3.26. Found: C, 47.64; H, 4.36; N, 3.23.

Diisopropyl (4-Nitrobenzenesulfonyloxy)methylphosphonate (**4f**)

Crystallized from AcOEt/hexane (2:1) to afford a pale yellow solid in 79% yield; mp 63–65 °C; ^{1}H NMR 1.32 (t, $J = 6.27$, 12H), 4.24 (d, $J = 9.82$, 2H), 4.66–4.84 (m, 2H), 8.12–8.18 (m, 2H), 8.40–8.46 (m, 2H); ^{13}C NMR 23.6, 23.7, 23.8, 62.8 (d, $J = 170.8$), 72.4 (d, $J = 6.5$), 124.4, 129.4, 140.6, 150.8; ^{31}P NMR 12.51; IR 788, 988, 1192, 1256, 1352, 1376, 1532, 2936, 2984. Anal. calcd. for $C_{13}H_{20}NO_8PS$ (381.34): C, 40.95; H, 5.29; N, 3.67. Found: C, 40.86; H, 5.40; N 3.81.

General Procedure for Synthesis of Dialkyl 1-Azidoalkylphosphonates 2a–f

The solution of TMGA (0.190 g, 1.2 mmol) and 1-(nosyloxy)alkylphosphonate **4** (1 mmol) in acetonitrile (4 mL) was refluxed for the appropriate time (see Table 2). The solvent was evaporated under reduced pressure; the residue was dissolved in dichloromethane (20 mL), washed with H_2O (3×2 mL), and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by vacuum distillation (**2a**,**e**) or by flash chromatography (**2b**–**d**,**f**) using dichloromethane–acetone (9:1) as eluent to

give pure **2a–f** as oils. The azides **2a–f** are known compounds, and their spectral (IR, ^{1}H, ^{31}P and ^{13}C NMR) and analytical (elemental analysis) data are in agreement with those reported earlier.[1c,1d,9]

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