Tetrahedron Letters 53 (2012) 207–209

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A neighbouring group effect leading to enhanced nucleophilic substitution of amines at the hindered α-carbon atom of an α-hydroxyphosphonate

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ARTICLE INFO

Article history:
Received 30 September 2011
Revised 14 October 2011
Accepted 4 November 2011
Available online 10 November 2011

Keywords:
α-Hydroxyphosphonate
α-Aminophosphonate
Nucleophilic substitution
Microwave
Neighbouring group effect

ABSTRACT

Diethyl α-hydroxy-benzylphosphonate undergoes nucleophilic substitution with primary amines of sufficient reactivity at around 100 °C to afford the corresponding α-aminophosphonates. The substitution can be enhanced by microwave irradiation. The reaction takes place with surprising ease due to the neighbouring group effect of the P=O moiety as was justified by DFT calculations carried out to evaluate the mechanism of the substitution under discussion.

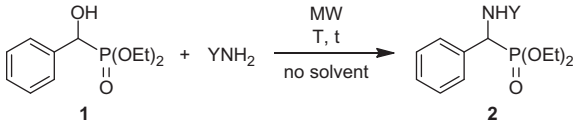
α-Aminophosphonates, structural analogues of α-aminocarboxylates, have attracted significant attention because of their role in the development of inhibitors of GABA-receptors, enzyme inhibitors, antibiotics, antihypertensives and antitumour agents.[1–5]

The Kabachnik–Fields (or phospha-Mannich) reaction involving the condensation of a dialkyl phosphite, an aldehyde or ketone and a primary/secondary amine or ammonia is an important method for the synthesis of α-aminophosphonates.[6–8] Although solvent- and catalyst-free variations[9] and subsequently, a microwave (MW)-assisted method have been elaborated,[10–12] a number of procedures were described that apply a variety of catalysts, such as metal triflates,[13,14] lanthanides,[15] lanthanide triflates,[16,17] other metal halides or salts,[18–23] or other species.[24–27] Our research showed that under MW and solventless conditions, there was no need for a catalyst.[28]

Another possibility for the preparation of α-aminophosphonates involves nucleophilic substitution at the secondary carbon atom of α-hydroxyphosphonates by amines. Due to the hindered hydroxy function, α-hydroxyphosphonates were not expected to undergo substitution by amines[29] and it was not a surprise that this reaction could only be accomplished in the presence of an acidic alumina catalyst on MW irradiation without the use of any solvent. The yields were 50–65%.[30]

However, our earlier experiments showed that this reaction may also take place on simple heating in the absence of any catalyst. It is problematic that the procedure of Kaboudin[30] could not be reproduced, as the syntheses were carried out in a domestic MW oven and no temperatures were provided. Hence, it was a challenge for us to revisit the α-hydroxyphosphonate → α-aminophosphonate transformation.

Diethyl α-hydroxy-benzylphosphonate (**1**) was chosen as the starting material which was reacted with primary amines under MW and solventless conditions (Scheme 1 and Table 1).[31]



Scheme 1. Nucleophilic substitution of diethyl α-hydroxy-benzyl-phosphonate by amines.

Using propylamine at 100 °C, the outcome depended on the molar quantity of the amine. If only one equivalent of *n*-propylamine was used, the conversion of α-hydroxyphosphonate **1** into the corresponding α-aminophosphonate **2a** was 57% after 45 min (Table 1, entry 1). However, by using 3 equiv of the amine, the substitution took place quantitatively after 10 min, and the preparative yield of aminophosphonate **2a** was 78% (Table 1, entry 2). The reaction took place similarly with *n*-butylamine giving product **2b** in a

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doi:10.1016/j.tetlet.2011.11.026

Table 1
The reaction of α-hydroxyphosphonates with primary amines under MW conditions

Entry	Y	Amine (equiv)	T (°C)	t (min)	**1** → **2** Conversion[a]	Yield of **2** (%)
1	Pr	1	100	45	57 (**2a**)	[b]
2	Pr	3	100[c]	10	100 (**2a**)	78 (**2a**)
3	Bu	3	100	15	100 (**2b**)	86 (**2b**)
4	^{i}Pr	3	100	40	100 (**2c**)	63 (**2c**)
5	^{i}Bu	3	100	40	100 (**2d**)	54 (**2d**)
6	Bn	1	110	60[d]	82 (**2e**)	[b]
7	Bn	3	110[e]	15	100 (**2e**)	60 (**2e**)
8	$PhCH_2CH_2$	3	110	30	100 (**2f**)	58 (**2f**)
9	^{c}Hex	1	110	40	100 (**2g**)	72 (**2g**)
10	^{c}Hex	3	110	10	100 (**2g**)	84 (**2g**)
11	Ph	3	130	120	0	[b]
12	Ph	3	160	120	0	[b]

[a] On the basis of relative ^{31}P NMR spectroscopic intensities.
[b] No yields were determined.
[c] In the comparative thermal experiment, complete conversion required 45 min and the yield was 48%.
[d] No change on further irradiation.
[e] In the comparative thermal experiment, complete conversion required 1 h and the yield was 41%.

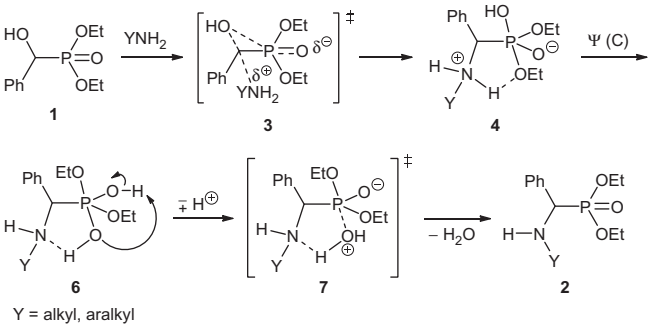
yield of 86% (Table 1, entry 3). Applying *i*-propylamine and *i*-butylamine, the reactions took somewhat longer (40 min) at 100 °C and products **2c** and **2d** were isolated in 63% and 54% yields, respectively (Table 1, entries 4 and 5). A similar tendency was experienced with benzylamine as that with *n*-propylamine. Carrying out the reaction at 110 °C with 1 equiv of the amine, the conversion was 82% after 1 h (and the substitution did not proceed on further irradiation), while using three equivalents of the reagent, the conversion was complete after 15 min affording the α-aminophosphonate **2e** in a yield of 60% (Table 1, entries 6 and 7). The situation was similar with phenylethylamine affording aminophosphonate **2f** in a yield of 58% (Table 1, entry 8). Cyclohexylamine was so reactive such that only one equivalent was sufficient at 110 °C to ensure quantitative conversion; on using three equivalents the substitution was much faster (Table 1, entries 9 and 10). The α-aminophosphonate **2g** was obtained in 72% and 84% yields. Aniline was unreactive and there was no reaction at 130 °C or even at 160 °C (Table 1, entries 11 and 12).

In comparative thermal experiments the substitutions were slower and the yields lower (Table 1, entries 2 and 7). It is noteworthy that the reaction also takes place under thermal conditions. Kaboudin claimed that the substitution of α-hydroxyphosphonate **1** with amines (e.g., with cyclohexylamine) failed on heating, but no exact temperature was provided.[30]

Among the α-aminophosphonates, **2a**,[33] **2e**[33] and **2g**[34] have been described and characterised. Compound **2b** was characterised only partially.[29] Species **2c**[35] and **2f**[36] have been described, but no spectral characterisation was provided. Aminophosphonate **2d** is new. Accordingly, compounds **2b–d** and **2f** have now been fully characterised by ^{31}P, ^{13}C and ^{1}H NMR spectroscopic and HRMS data.

As previously mentioned, α-hydroxyphosphonates are considered as potential intermediates in the Kabachnik–Fields reaction.[8] In this case, a substitution analogous with the cases discussed in this paper is the last step. The energy gain of this substitution is only around 2.4 kJ mol^{-1}.[37] The involvement of another kind of intermediate that is an imine (or Schiff-base), may be of more general importance.[38]

The reaction mechanism was evaluated using B3LYP/6-31G(d,p) calculations.[39] The first and, at the same time, rate determining step of this multistep reaction sequence (Scheme 2 and Fig. 1) starts with the departure of the OH$^-$ group from the α-carbon atom. This step is promoted by the simultaneous interaction of



Scheme 2. Mechanism for the substitution of diethyl α-hydroxy-benzylphosphonate by amines supported by B3LYP/6-31G(d,p) calculations.

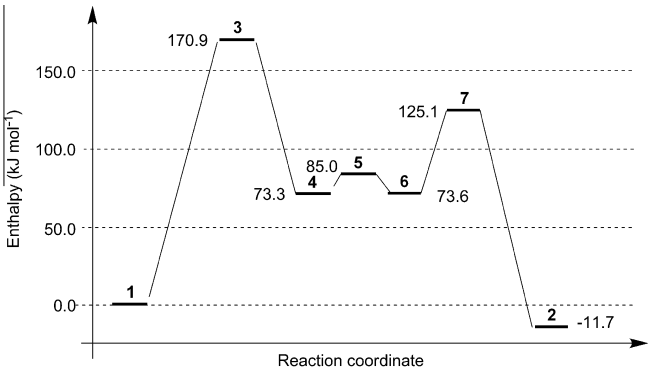


Figure 1. The enthalpy (H) pathway for the transformation **1** → **2**. PR1 = pseudorotation 1.

the OH$^-$ group with the phosphorus atom of the adjacent P=O function and is accompanied by attack of the amine on the carbon atom with a partial positive charge to afford intermediate **4** via the transition state (TS) **3**. The amine enters from the opposite side, as in an S_N2 mechanism. The activation enthalpy of 170.9 kJ mol^{-1} belonging to TS **3** can be overcome, especially under MW conditions, due to the beneficial effect of the statistically appearing local overheating. In the next step, pseudorotation [ψ(C)] in species **4** leads to an almost equally stable intermediate **6** via a low energy TS (**5**) that is not shown in Scheme 2. Finally, intramolecular proton transfer from P–OH to the other P–OH brings about elimination of H_2O to provide α-aminophosphonate **2** through TS **7** with an activation enthalpy of 125.1 kJ mol^{-1}. Overall, the process is slightly exothermic.

The reaction enthalpy (ΔH_R), reaction Gibbs free energy (ΔG_R) and reaction entropy (ΔS_R) values obtained by the B3LYP/6-31G(d,p) calculations for the species of the reaction sequence outlined in Scheme 2 are listed in Table 2.

It should be noted that the simple inductive effect from the P=O group may also contribute to the enhanced reactivity of α-hydroxyphosphonate **1** in nucleophilic substitution with amines.

The participation of a P=O group in a nucleophilic substitution on the adjacent carbon atom is a novel example of a beneficial neighbouring group effect. To the best of our knowledge, no similar example has been reported.

In our case, the experimental results on the possibility of a nucleophilic substitution at the hindered carbon atom of α-hydroxyphosphonates are in full agreement with the results of the quantum chemical calculations justifying the substitution due to a beneficial neighbouring group effect.

In conclusion, the sterically hindered substitution reaction of α-hydroxy-benzylphosphonate with primary amines could be performed efficiently under solventless MW conditions applying

Table 2
Summary of the reaction enthalpy (ΔH_R), reaction Gibbs free energy (ΔG_R) in kJ mol^{-1}, and reaction entropy (ΔS_R) in J mol^{-1} K^{-1} of the transformation **1** → **2**. Entropy was calculated at 400 K

Species	ΔH_R	ΔG_R	ΔS_R
1	0.00	0.00	0.00
3	170.9	225.3	136.0
4	73.3	131.5	145.6
5	85.0	145.4	151.0
6	73.6	130.1	122.5
7	125.1	176.3	149.2
2	−11.7	−5.1	16.5

the amine in a twofold excess (that means three equivalents). The substitution was enhanced by the neighbouring effect of the adjacent P═O group. This novel phenomenon was supported by high level DFT calculations.

Acknowledgements

This project was supported by the Hungarian Scientific and Research Fund (OTKA K83118). This work is connected to the scientific programme of the 'Development of quality-oriented and harmonized R+D+I strategy and functional model at BME'. This project is also supported by the New Széchenyi Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002). The authors are indebted to Professor Dr Harry R. Hudson (London Metropolitan University) for his advice.

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	^{31}P NMR ($CDCl_3$)		$(M+H)_{found}$	Formula	$(M+H)_{calcd}$
	Measured	Literature			
2a	23.7	23.8[33]	286.1572	$C_{14}H_{25}NO_3P$	286.1572
2b	23.6	24.0[29]	300.1731	$C_{15}H_{27}NO_3P$	300.1729
2c	24.1		286.1571	$C_{14}H_{25}NO_3P$	286.1572
2d	23.7		300.1725	$C_{15}H_{27}NO_3P$	300.1729
2e	23.7	22.9[33]	334.1572	$C_{18}H_{25}NO_3P$	334.1572
2f	23.4		348.1735	$C_{19}H_{27}NO_3P$	348.1729
2g	24.3	24.2[34]	326.1884	$C_{17}H_{29}NO_3P$	326.1885

Additional spectral characterisation:
Compound **2b**: ^{13}C NMR ($CDCl_3$) δ 13.8 ($CH_2CH_2CH_3$), 16.3 (^3J = 13.3, OCH_2CH_3), 16.4 (^2J = 13.2, OCH_2CH_3), 20.2 (CH_2CH_3), 31.9 ($CH_2CH_2CH_3$), 47.7 (J = 16.6, NCH_2), 61.1 (J = 152.6, PCN), 62.7 (^1J = 7.0, OCH_2), 62.9 (^1J = 7.1, OCH_2), 127.7 (J = 3.2, C4′), 128.3 (J = 2.5, C2′),* 128.5 (J = 6.2, C3′),* 136.2 (J = 4.1, C1′), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2, 3H, $CH_2CH_2CH_3$), 1.14 (t, J = 7.1, 3H, OCH_2CH_3), 1.28 (t, J = 7.1, OCH_2CH_3) and 1.23–1.36 (m, CH_2) partially overlapped, total integration = 5, 1.38–1.51 (m, 2H, CH_2), 1.75 (br s, 1H, NH), 2.39–2.57 (m, 2H, NCH_2), 3.77–3.91 (m, 1H, NCHP), 3.91–4.14 (m, 4H, 2 × OCH_2), 7.24–7.47 (m, 5H, Ar). δ_H^{29} ($CDCl_3$) 0.85 (t, J = 7.1, 3H), 1.14 (t, J = 7.2, 3H), 1.27 (t, J = 7.0, 3H), 1.30–1.40 (m, 2H), 1.40–1.50 (m, 2H), 2.05–2.25 (br s, 1H), 2.35–2.60 (m, 2H), 3.70–4.20 (m, 4H), 7.20–7.50 (m, 5H ArH).
Compound **2c**: ^{13}C NMR ($CDCl_3$) δ 16.2 (^3J = 17.2, OCH_2CH_3), 16.3 (^2J = 17.2, OCH_2CH_3), 21.3 ($CH(CH_3)_2$), 23.9 ($CH(CH_3)_2$), 45.7 (J = 16.0, $CHMe_2$), 58.3 (J = 153.6, PCN), 62.6 (^1J = 7.0, OCH_2), 63.0 (^1J = 7.0, OCH_2), 127.6 (J = 3.1, C4′), 128.3 (J = 2.4, C2′),* 128.4 (J = 6.3, C3′),* 136.6 (J = 2.9, C1′), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.3, 3H, $CHCH_3$), 1.01 (d, J = 6.7, 3H, $CHCH_3$), 1.11 (t, J = 7.1, 3H, CH_2CH_3), 1.30 (t, J = 7.1, 3H, CH_2CH_3), 1.88 (br s, 1H, NH), 2.65–2.73 (m, 1H, $CHMe_2$), 3.70–3.83 (m, 1H, NCH), 3.88–4.20 (m, 4H, 2 × OCH_2), 7.24–7.43 (m, 5H, Ar).
Compound **2d**: ^{13}C NMR ($CDCl_3$) δ 16.2 (^3J = 14.4, OCH_2CH_3), 16.3 (^2J = 14.4, OCH_2CH_3), 20.3 ($CH(CH_3)_2$), 20.5 ($CH(CH_3)_2$), 28.2 ($CHMe_2$), 55.9 (J = 16.4, NCH_2), 61.2 (J = 152.5, PCN), 62.6 (^1J = 6.9, OCH_2), 62.9 (^1J = 7.0, OCH_2), 127.6 (J = 3.2, C4′), 128.2 (J = 2.6, C2′),* 128.4 (J = 6.2, C3′),* 136.2 (J = 4.1, C1′), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6.8, 3H, $CHCH_3$), 0.89 (d, J = 6.8, 3H, $CHCH_3$), 1.14 (t, J = 7.1, 3H, CH_2CH_3), 1.28 (t, J = 7.1, 3H, CH_2CH_3), 1.63–1.74 (m, 1H, $CHMe_2$), 1.88 (br s, 1H, NH), 2.25–2.33 (m, 2H, CH_2), 3.79–3.92 (m, 1H, NCH), 3.92–4.18 (m, 4H, 2 × OCH_2), 7.23–7.48 (m, 5H, Ar).
Compound **2f**: ^{13}C NMR ($CDCl_3$) δ 16.2 (^2J = 12.8, OCH_2CH_3), 16.3 (^2J = 12.8, OCH_2CH_3), 36.1 ($PhCH_2$), 49.2 (J = 16.8, NCH_2), 61.0 (J = 152.9, PCN), 62.7 (^1J = 7.0, OCH_2), 62.9 (^1J = 7.1, OCH_2), 126.1 (C4″), 127.8 (J = 3.2, C4′), 128.3 (J = 2.6, C2′),[a] 128.3 (C2″),[b] 128.4 (J = 6.1, C3′),[a] 128.7 (C3″),[b] 135.9 (J = 4.3, C1′), 139.8 (C1″), [a,b]may be reversed; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.1, 3H, CH_2CH_3), 1.23 (t, J = 7.1, 3H, CH_2CH_3), 1.80 (br s, 1H, NH), 2.70–2.84 (m, 4H, 2 × CH_2), 3.75–3.84 (m, 1H, NCH), 3.87–4.10 (m, 4H, 2 × OCH_2), 7.10–7.40 (m, 10H, Ar).

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