Tetrahedron Letters 53 (2012) 6940–6942

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthetic utility of Kabachnik-Fields reaction: a convenient one-pot three-component synthesis of *N*-phenyl isoquinolone-1-phosphonates

Amulrao U. Borse [a,*], Nilesh L. Patil [a], Mahesh N. Patil [a], Raghao S. Mali [b]

[a] School of Chemical Sciences, North Maharashtra University, Jalgaon 425001, M.S., India
[b] Former Head, Department of Chemistry, University of Pune, Pune 411007, M.S., India

ARTICLE INFO

Article history:
Received 1 September 2012
Revised 5 October 2012
Accepted 7 October 2012
Available online 13 October 2012

Keywords:
One-pot synthesis
Kabachnik-Fields reaction
N-Phenyl isoquinolone-1-phosphonates
α-Aminophosphonates

ABSTRACT

A convenient, one-pot three-component synthesis of novel *N*-phenyl isoquinolone-1-phosphonates (**4a–4g**) using Kabachnik-Fields reaction, starting from ethyl 2-(2-formyl-4,5-dimethoxyphenyl) acetate (**1**) and anilines (**2a–2g**) is described. The aldehyde (**1**) on reaction with substituted anilines (**2a–2g**) and triethyl phosphite in acetonitrile using trifluroacetic acid as catalyst provides *N*-phenyl isoquinolone-1-phosphonates (**4a–4g**) in good yields.

Recently, α-aminophosphonates have attracted the attention of organic chemists due to their biological activities, such as antibiotic, enzyme inhibitor, HIV protease and as anti-tumor agents.[1] The α-aminophosphonates are considered to be structural analogues of α-amino acids and transition state mimics of peptide hydrolysis.[2] In agrochemistry α-aminophosphonates are used as plant growth regulators, herbicides, insecticides and fungicides.[3] Several α-aminophosphonates have also been used in organic synthesis. For example, phosphorylated allenes are used as versatile building blocks in organic synthesis.[4] Lennoxamine alkaloid and its analogues have been synthesized using phosphorylated isoindolinone.[5a] Couture et al. have used phosphorylated *o*-aroyl and heteroaroyl benzamides for the synthesis of 4-aryl and heteroaryl-1(2*H*)-isoquinolones.[5b] In view of this several methods involving Kabachnik-Fields reaction and Pudovik reactions have been reported for the synthesis of α-aminophosphonates.[6] In Kabachnik-Fields reaction carbonyl compounds, amines are reacted with dialkyl or trialkyl phosphites in presence of catalysts to obtain α-aminophosphonates (Scheme 1).

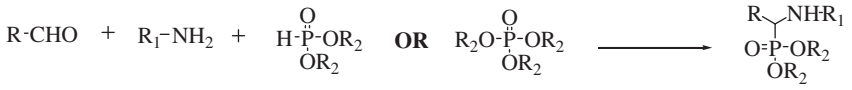
In Pudovik reaction the α-aminophosphonates are obtained from the aldehyde in two steps (Scheme 2).

Although various methods have been reported for the synthesis of simple α-aminophosphonates very few efforts have been made for the synthesis of *N*-aryl or *N*-phenyl tetrahydroisoquinoline-1-phosphonates. Recently, some methods have been developed for α-phosphorylation of *N*-aryl or *N*-phenyl tetrahydroisoquinolines. One of the methods involves molybdenum trioxide catalyzed oxidative cross dehydrogenative coupling (CDC) approach[7] for C–H functionalization of *N*-aryl or *N*-phenyl tetrahydroisoquinolines. The other method makes use of DDQ mediated phosphonation of *N*-aryl or *N*-phenyl tetrahydroisoquinolines. Both these methods make use of pre-formed tetrahydroisoquinolines. Thus, a few methods described above are available for the synthesis of simple α-aminophosphonates and for *N*-aryl or *N*-phenyl tetrahydroisoquinoline-1-phosphonates. However, there is not a single method found in the literature for the synthesis of *N*-phenyl isoquinolone-1-phosphonates. Considering the above aspects, herein we report a convenient, one-pot three-component method for the synthesis of novel *N*-phenyl isoquinolone-1-phosphonates without using pre-formed isoquinolones as starting materials. Recently one-pot multicomponent reactions have been reviewed by Singh and Chowdhury.[8]

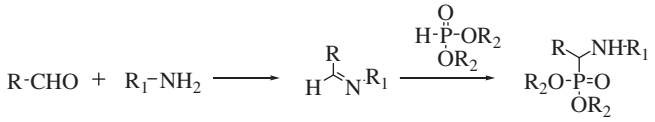
Initially it was decided to synthesize the parent *N*-phenyl isoquinolone-1-phosphonate (**4a**) in two steps starting from ethyl 2-(2-formyl-4,5-dimethoxyphenyl) acetate (**1**) via the intermediacy of α-aminophosphonate (**3a**) as shown in Scheme 3. Thus, a solution of ethyl 2-(2-formyl-4,5-dimethoxyphenyl) acetate (**1**), 4-fluroaniline (**2a**), and triethylphosphite in dry acetonitrile was stirred at room temperature in presence of 4 Å molecular sieves and catalytic amount of TFA (20 mol %) to obtain α-aminophosphonate (**3a**) in 72% yield. In IR (KBr) spectrum it showed peaks at 3292 and 1712 cm^{-1} for –NH and ester carbonyl group. In ^1H NMR ($CDCl_3$) spectrum it showed absence of aldehyde proton, present in **1** and appearance of benzylic proton at 4.97 δ as doublet (J_{H-P} = 22.3 Hz). In ^1H NMR spectrum it also showed a broad singlet

* Corresponding author. Tel.: +91 257 2257427; fax: +91 257 2258403.
E-mail address: amulborse@gmail.com (A.U. Borse).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.030



Scheme 1. Kabachnik-Fields reaction for the synthesis of α-aminophosphonates.



Scheme 2. Pudovik reaction for the synthesis of α-aminophosphonates in two steps.

at 4.60 δ for –NH, a multiplet at 4.04–4.15 δ for four protons of two P-OCH_2-CH_3 and another multiplet at 3.92–3.97 δ for –OCH_2-CH_3. The methyl protons of two P-OCH$_2$-CH_3 groups appeared as multiplet at 1.22–1.30 δ and the methyl protons of –OCH$_2$-CH_3 group appeared as triplet at 1.12 δ. In formation of **3a,** from **1** and **2a** using triethylphosphite, one-pot three-component Kabachnik-Fields reaction, occurs. The starting compound **(1)** was prepared from the commercially available 3,4-dimethoxyphenyl acetic acid, using the reported procedure.[9]

The next step was the cyclization of α-aminophosphonates (**3a**) to obtain the corresponding *N*-phenyl isoquinolone-1-phosphonate (**4a**). TFA was used as a catalyst in acetonitrile for cyclization. Under refluxing condition the desired product *N*-phenyl isoquinolone-1-phosphonate (**4a)** was obtained in 61% yield. The structure of **4a** was determined on the basis of analytical and spectral data. In IR (KBr) spectrum it showed a peak at 1660 cm^{-1} for lactam carbonyl which indicated the cyclization of **3a** to **4a**. In ^{1}H NMR ($CDCl_3$) spectrum it showed a multiplet at 3.91–3.99 δ for two methoxyl, one P-OCH_2-CH_3 and one methylene proton of P-OCH_2-CH_3. The remaining one methylene proton of P-OCH_2-CH_3 appeared as multiplet at 3.67–3.71 δ. Two triplets were seen at 1.16 δ and 1.13 δ for two methyl groups of P-OCH$_2$-CH_3. When the methylene protons were irradiated at 3.91–3.99 δ region the two triplets which appeared at 1.16 δ and 1.13 δ collapsed in to a singlet and triplet, respectively. This showed that one methylene group of P-OCH_2-CH_3 has merged in the multiplet which appeared at 3.91–3.99 δ. The structure **4a** was confirmed by ^{1}H–1H COSY and HSQC NMR techniques. In

Table 1
One-pot synthesis of *N*-phenyl isoquinolone-1-phosphonates (**4a–4g**)

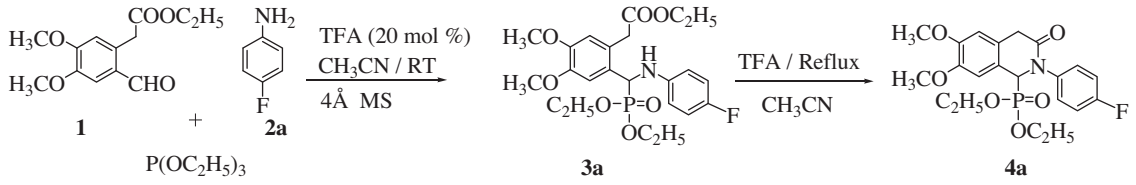
Product	R	Time (h)		Yield[a] (%)	mp (°C)
		RT + Reflux			
4a	4-F	6	17	70	212–214
4b	4-Cl	6	17	69	218–220
4c	H	5	17	74	206–208
4d	4-Br	6	16	68	202–204
4e	3-Cl	7	19	66	220–222
4f	4-CH_3	7	18	71	216–218
4g	4-C_2H_5	8	19	64	148–150

[a] Isolated yield.

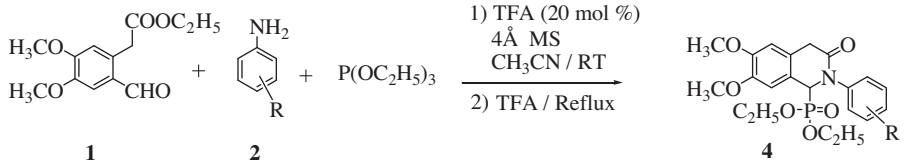
^{1}H–1H COSY NMR spectrum the two benzylic protons were found in different environment and observed at 3.58 δ and 4.13–4.23 δ. Interestingly, the methylene protons of one of the two P-OCH_2-CH_3 groups are found in different environments. Thus, one of the methylene protons is observed at 3.67–3.71 δ and the other is merged in a multiplet at 3.91–3.99 δ along with another methylene protons of P-OCH_2-CH_3. From HSQC spectrum it is confirmed that the methylene carbon of one of the P-OCH_2-CH_3 correlates with two methylene protons observed at different places. Two benzylic protons observed at 3.58 δ and 4.13–4.23 δ on the proton axis correlates with benzylic carbon at 38.11 δ. The carbon at 63.40 δ (J_{C-P} = 153.2 Hz) on the carbon axis correlates with one benzylic proton at 5.03 δ (J_{H-P} = 15.7 Hz).

Though the desired *N*-phenyl isoquinolone-1-phosphonate (**4a**) was obtained in good overall yield in two steps, to improve further, the yield and efficiency of the approach, a one-pot procedure without isolation of α-aminophosphonates (**3a)** was visualized as shown in Scheme 4.

In this approach[10] a mixture of ethyl 2-(2-formyl-4,5-dimethoxyphenyl) acetate (**1**), 4-fluroaniline (**2a)** and triethyl phosphite in dry acetonitrile was stirred at room temperature for 6 h in presence of 4 Å molecular sieves and catalytic amount of TFA (20 mol %) under nitrogen atmosphere. Additional amount of TFA



Scheme 3. Two-step synthesis of *N*-phenyl isoquinolone-1-phosphonate (**4a**).



Scheme 4. One-pot synthesis of *N*-phenyl isoquinolone-1-phosphonates (**4a–4g**).

(6 mmol) was added to it and refluxed to obtain *N*-phenyl isoquinolone-1-phosphonate (**4a)** in 70% yield. Hence it was decided to synthesize *N*-phenyl isoquinolone-1-phosphonates (**4b–4g**) using the one-pot method. Under these conditions the *N*-phenyl isoquinolone-1-phosphonates (**4a–4g**) were obtained in a single step and in good yield (Table 1). It is observed that aniline and 4-methyl anilines provided the desired products in better yields as compared to halogenated anilines.

In conclusion a convenient one-pot three-component method has been developed for the synthesis of novel *N*-phenyl isoquinolone-1-phosphonates (**4a–4g**) from easily available anilines. Our method does not require pre-formed isoquinolones and provide the final products with good yields.

Acknowledgments

This work was supported by the Grant provided to the School of Chemical Sciences, North Maharashtra University (Jalgaon) by University Grant Commission (UGC), New Delhi under SAP programme. One of the authors (NLP) acknowledges UGC, New Delhi for SAP fellowship under the scheme 'Research Fellowship in Sciences for Meritorious Students'. We thank Professor D.D. Dhavale, University of Pune, for useful discussions.

References and notes

1. (a) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29; (b) Paige, L. A.; Zheng, G. Q.; DeFrees, S. A.; Cassady, J. M.; Geahlen, R. L. *J. Med. Chem.* **1989**, *32*, 1665; (c) Peyman, A.; Stahl, W.; Wagner, K.; Ruppert, D.; Budt, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2601; (d) Jin, L.; Song, B.; Zhang, G.; Xu, R.; Zhang, S.; Gao, X.; Hu, D.; Yang, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1537.
2. (a) *Aminophosphonic and Aminophosphinic Acids Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Wiley: New York, Chichester, 2000; (b) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177; (c) Laureyn, I.; Stevens, C. V.; Soroka, M.; Malyse, P. *Arkivoc* **2003**, 102; (d) Redmore, D. *J. Org. Chem.* **1978**, *43*, 992; (e) Boutin, J. A.; Cudennec, C. A.; Hautefaye, P.; Lavielle, G.; Pierre, A.; Schaeffer, C. *J. Med. Chem.* **1998**, *1991*, 34.
3. (a) Miliszkiewicz, D.; Wieczorek, P.; Lejczak, B.; Kowalik, E.; Kafarski, P. *Pestic. Sci.* **1992**, *34*, 349; (b) Maier, L.; Spoerri, H. *Phosphorous, Sulfur Silicon Relat. Elem.* **1991**, *61*, 69.
4. (a) *Allenes in Organic Synthesis*; Schuster, H. F., Coppola, G. M., Eds.; Wiley: New York, NY, 1984. pp. 247–252; (b) Patois, C.; Ricard, L.; Savignac, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1577.
5. (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491; (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Woisel, P. *Tetrahedron* **1996**, *52*, 4433.
6. (a) Zefirov, S. N.; Matveeva, E. D. *Arkivoc* **2008**, 1–17; (b) Kabachnik, M. I.; Medved, T. Y. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 689; (c) Pudovik, A. N. *Dokl. Akad. Nauk SSSR* **1952**, *83*, 865. *Chem. Abstr.* **1953**, *47*, 4300; (d) Pudovik, A. N.; Konovaloa, I. V. *Synthesis* **1979**, 81.
7. (a) Wang, H.; Li, X.; Wu, F.; Wan, B. *Tetrahedron Lett.* **2012**, *53*, 681; (b) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Tetrahedron Lett.* **2012**, *53*, 1456; (c) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 8679; (d) Hari, D. P.; Konig, B. *Org. Lett.* **2011**, *13*, 3852; (e) Basle, O.; Li, C.-J. *Chem. Commun.* **2009**, 4124; (f) Han, W.; Mayer, P.; Ofial, A. R. *Adv. Synth. Catal.* **2010**, *352*, 1667.
8. Singh, M. S.; Chowdhury, S. *RSC Adv.* **2012**, *2*, 4547.
9. (a) Stearman, C. J.; Wilson, M.; Padwa, A. *J. Org. Chem.* **2009**, *74*, 3491; (b) Kraus, G. A.; Krolski, M. E. *J. Org. Chem.* **1986**, *51*, 3347.
10. *General procedure for one-pot synthesis of N-phenyl isoquinolone-1-phosphonates* (**4a–4g**): To a solution of aldehyde **1** (1.0 mmol), substituted aniline **2a–2g** (1.1 mmol) and triethylphosphite (1.2 mmol) in dry acetonitrile (15 mL) was added 4Å molecular sieves (1 g) and catalytic amount of TFA (20 mol %) using a syringe under N_2 atmosphere. The yellow reaction mixture was stirred at room temperature for 5–8 h. TFA (6.0 mmol) was added using a syringe under N_2 atmosphere and the reaction was refluxed for the time given against each compound. Acetonitrile removed at reduced pressure and the reaction mixture was poured into ice cold water (20 mL). It was extracted using DCM (3×20 mL).The combined organic layer washed with 20 mL aqueous sodium bicarbonate solution (10%), water (25 mL) and dried using sodium sulphate. Evaporation of the solvent gave yellow residue which was chromatographed over silica gel using hexane/ethyl acetate (7:3) as solvent for elution to obtain *N*-phenyl isoquinolone-1-phosphonates (**4a–4g**) as white amorphous powder. Data for a representative compound **4a** is given below. **4a**. Yield 70%; mp. 212–214 °C; R_f (96% $CHCl_3$:MeOH) 0.25; IR (KBr, cm^{-1}): 2983, 2935, 1660, 1517, 1460, 1396, 1307, 1259, 1236, 1213, 1111, 1054, 1022, 962; 1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.36 (dd, 2H, Ar*H*, J_{H-F} = 5 Hz, J = 8.8 Hz), 7.10 (t, 2H, Ar*H*, J_{H-F} = 8.6 Hz, J = 8.5 Hz), 6.84 (s, 1H, Ar*H*), 6.71 (s, 1H, Ar*H*), 5.03 (d, 1H, J_{H-P} = 15.7 Hz, PC*H*N), 4.13–4.23 (m, 1H, ArC*H*), 3.91–3.99 (m, 9H, $2 \times OCH_3$, OCH_2CH_3, $OCHCH_3$), 3.67–3.71 (m, 1H, $OCHCH_3$), 3.58 (d, 1H, ArC*H*, J = 18.6 Hz), 1.16 &1.13 (t, 3H each, J = 7.0 Hz, $2 \times OCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.26, 161.20 (d, J_{C-F} = 246.4 Hz), 149.40 (d, J = 3.5 Hz), 147.56 (d, J = 2.3 Hz), 137.73, 129.31 (d, J = 8.0 Hz), 125.85 (d, J = 4.6 Hz), 119.84, 115.86, 115.5, 110.11 (d, J = 6.3 Hz), 63.40 (d, J_{C-P} = 153.2 Hz), 63.18 (d, J = 6.9 Hz), 62.53 (d, J = 6.9 Hz), 56 (d, J = 6.9 Hz), 38.11, 16.23, 16.17; ^{31}P NMR: δ 18.28; LCMS (m/z), 438 (M+H); Anal. calcd for $C_{21}H_{25}FNO_6P$: C, 57.66; H, 5.76%; found: C, 57.26; H, 6.03%.