Tetrahedron Letters 50 (2009) 6627–6630

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Practical and reliable synthesis of dialkyl *N*-arylphosphoramidates with nitroarenes as substrates

Reda Haggam, Jürgen Conrad, Uwe Beifuss *

Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstraße 30, D-70599 Stuttgart, Germany

ARTICLE INFO

Article history:
Received 18 August 2009
Accepted 8 September 2009
Available online 19 September 2009

Keywords:
Nitroarenes
Deoxygenation
Phosphoramidates
Microwaves

ABSTRACT

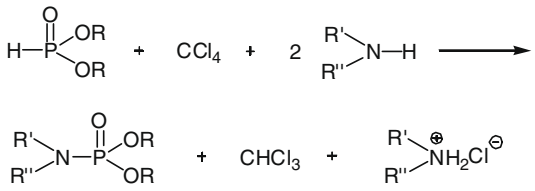
A new single-step transformation of readily available nitroarenes with trialkyl phosphites, which can be performed both under thermal and microwave conditions, delivers dialkyl *N*-arylphosphoramidates in good yields and short reaction times.

Phosporamidate oligonucleotides are among the most prominent synthetic derivatives that have been considered for diagnostic and therapeutic applications within the scope of the antisense concept.[1,2] The development of phosphoramidate-substituted nucleoside analogs has also become an area of intense interest due to the anticancer, antiviral (anti-HIV), and spermicidal activities of the nucleoside analogs.[3]

In addition, phosphoramidates play a significant role in synthesis. One of the most important fields for dialkyl-, dibenzyl-, and diphenyl phosphoramidates is the protection of amino groups.[4] Many synthetic applications of *N*-arylphosphoramidates rely on the properties of their stabilized anions. For example, *N*-arylphosphoramidates have been used for the preparation of imines by aza-Wittig reactions.[5] Another example is the alkylation of diethyl phosphoramidates as a simple method for the synthesis of secondary amines.[6] Other applications come from the field of heterocycles and include the preparation of 2,4-(1*H*,3*H*)-quinazolinediones.[7] Recently *N*-arylphosphoramidates have been used to synthesize functionalized aziridines by means of nucleophile-induced cyclization.[8] Baylis–Hillman adducts have been reacted with *N*-arylphosphoramidates to afford 1,2-disubstituted azetidines in a highly diastereoselective manner.[9] Treatment of aza-Michael adducts with *N*-arylphosphoramidates yielded 1,2,4-trisubstituted azetidines in a one-pot procedure.[10]

Despite this interest in phosphoramidates the number of known synthetic approaches is limited. The standard method dates back to Todd and Atherton who published the reaction of ammonia, primary and secondary amines with a dialkyl or dibenzyl phosphite and a halogen source like CCl_4 (Scheme 1).[11] Weak bases like aniline can be phosphorylated only if an extra equivalent of a strong base like a tertiary amine is added. Valuable modifications of the original method have been introduced that are based on the use of alternative halogen sources[12] and phase transfer catalysts.[13] Other methods for the synthesis of phosphoramidates include the phosphorylation of amines by condensation with phosphate diesters in the presence of PPh_3 and CCl_4,[14] the nucleophilic substitution of phosphate diesters by alkylamines,[15] and the oxidation of phosphite triesters with I_2 in the presence of alkylamines.[16] All methods for the synthesis of phosphoramidates mentioned so far have in common that amines are used as starting materials and that they are subjected to phosphorylation.

Recently we needed to convert nitroarenes into *N*-arylphosphoramidates. Much to our astonishment we found that the number of synthetic methods for this kind of transformation is rather limited and that the reports in the literature are inconsistent. Cadogan et al. reported that they obtained mixtures of the corresponding dialkyl *N*-arylphosphoramidates $(RO)_2P(=O)NHAr$ (5–26%), dialkyl *N*-alkyl-*N*-arylphosphoramidates $(RO)_2P(=O)NRAr$ (8–30%), dialkyl



Scheme 1. Synthesis of phosphoramidates according to Todd and Atherton.

* Corresponding author. Tel.: +49 711 459 22171; fax: +49 711 459 22951.
E-mail address: ubeifuss@uni-hohenheim.de (U. Beifuss).

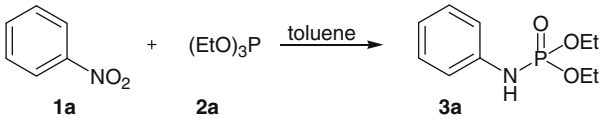
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.09.037

N-alkyl-3*H*-azepin-7-ylphosphonates (0–18%) and dialkyl arylphosphonates $(RO)_2P(=O)Ar$ (0–7%) when substituted nitroarenes were refluxed with an excess of a trialkyl phosphite $(RO)_3P$.[17,18] In contrast to these findings, Sundberg isolated triethyl *N*-arylphosphorimidates $(EtO)_3P{=}NAr$ instead of diethyl *N*-arylphosphoramidates $(EtO)_2P(=O)NHAr$ as the main products when *o*-alkylnitrobenzenes were boiled with excess $(EtO)_3P$.[19,20] A report on the two-step transformation of nitroarenes to anilines with diethyl chlorophosphite as a reagent[21] seemed to be a promising alternative since the corresponding phosphoramidates had been identified as intermediates. Although the scope of this method is quite limited and the reagent is very expensive we repeated some of the reactions reported by Fischer and Sheihet. However, we were unable to reproduce their yields. With *p*-nitrotoluene as the substrate the corresponding aniline was isolated with only 45% instead of >95%. Without the second step, that is, the hydrolysis, it was possible to isolate the corresponding *N*-arylphosphoramidate $(RO)_2P(=O)NHAr$; the yield, however, amounted to only 49%. With these results in mind we were certain that there is no practical and reliable method available yet for the transformation of nitroarenes into *N*-arylphosphoramidates $(RO)_2P(=O)NHAr$.

Here we demonstrate that the reaction of nitroarenes with tervalent phosphorous reagents can be used for the efficient synthesis of dialkyl *N*-arylphosphoramidates in a single step if performed under suitable conditions.

To begin with, nitrobenzene (**1a**) and triethyl phosphite (**2a**) were reacted under different reaction conditions (Scheme 2, Table 1). Under microwave conditions at 200 °C (300 W) in toluene as a solvent the formation of **3a** was observed only if an excess of **2a** was employed. With 2.5 or 3.0 equiv of **2a** the starting material was consumed only partially. Thus mixtures of the substrate **1a** and diethyl *N*-phenylphosphoramidate (**3a**) were isolated after column chromatography. With an excess of 6 equiv **2a** the reaction could be forced into completion and the product **3a** was exclusively formed in 78% yield (Table 1, entries 1–3). Comparable results were observed when the transformations were performed in a sealed tube under thermal conditions (Table 1, entries 4–6). Since the microwave transformation resulted in slightly higher yields than the sealed tube reaction all further transformations were run in a microwave oven.

Then the reaction time of the transformation **1a**→**3a** was optimized (Scheme 2, Table 2). The highest yields were obtained when the microwave-assisted reactions were run for 15–20 min (Table 2, entries 4 and 5). With shorter reaction times (3–10 min) no product was formed (Table 2, entries 1–3); with longer reaction times the yields dropped slightly (Table 2, entries 6 and 7).



Scheme 2. Reaction of **1a** with $(EtO)_3P$ **2a** in toluene.

Table 1
The influence of the amount of $(EtO)_3P$ (**2a**) on the transformation of **1a** into **3a**

Entry	Equiv $(EtO)_3P$	Reaction conditions; temp (°C)/time (min)	Yield **3a** (%)
1	2.5	MW[a]; 200/15	38
2	3.0	MW[a]; 200/15	43
3	6.0	MW[a]; 200/15	78
4	2.0	Sealed tube; 200/15	34
5	4.0	Sealed tube; 200/15	51
6	6.0	Sealed tube; 200/15	71

[a] Microwave irradiations were performed at 300 W/20 bar.

Table 2
The influence of the reaction time on the transformation of **1a** into **3a**[a]

Entry	Equiv $(EtO)_3P$	Time (min)	Yield **3a** (%)
1	6.0	3	–
2	6.0	5	–
3	6.0	10	–
4	6.0	15	78
5	6.0	20	78
6	6.0	30	76
7	6.0	40	75

[a]Microwave irradiations were performed at 300 W/200 °C/20 bar.

Further experiments revealed that the power of the microwave irradiation affects the transformation outcome (Scheme 2, Table 3). With microwave irradiation of up to 200 W no product formation was observed after 15 min (Table 3, entries 1–3). With 250 W a mixture of 35% *N*-arylphosphoramidate **3a** and starting material **1a** was isolated (Table 3, entry 4). It was found that it takes 300 W to ensure complete conversion of **1a** within 15 min and a high yield of *N*-arylphosphoramidate **3a** (Table 3, entry 5).

Last but not least the influence of the reaction temperature on the formation of **3a** was studied. It could be established that no reaction between **1a** and **2a** could be observed until 200 °C (Scheme 2, Table 4, entries 1–4).

Optimizing the reaction of **1a** and **2a** resulted in a practical and efficient procedure for the synthesis of **3a** in a high yield. The workup was very easy. First the volatiles were removed by distillation in vacuo and then the dichloromethane soluble residue was washed with water and purified by flash chromatography.[22]

Triethyl phosphite (**2a**) could be replaced by other trialkyl phosphites like trimethyl phosphite (**2b**). Under the optimized reaction conditions described above the transformation of nitrobenzene (**1a**) with trimethyl phosphite (**2b**) delivered the dimethyl *N*-phenylphosphoramidate (**4a**), which was isolated with 58% after column chromatography (Scheme 3).

Table 3
The influence of the microwave power on the transformation of **1a** into **3a**[a]

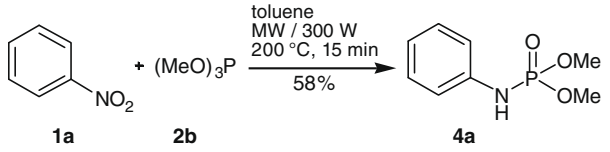
Entry	Equiv $(EtO)_3P$	Time (min)	Power (W)	Yield **3a** (%)
1	6.0	15	50	–
2	6.0	15	150	–
3	6.0	15	200	–
4	6.0	15	250	35
5	6.0	15	300	78

[a]Microwave irradiations were performed at 200 °C/20 bar.

Table 4
The influence of the temperature on the transformation of **1a** into **3a**[a]

Entry	Equiv $(EtO)_3P$	Time (min)	Temp (°C)	Yield **3a** (%)
1	6.0	15	50	–
2	6.0	15	100	–
3	6.0	15	150	–
4	6.0	15	200	78

[a]Microwave irradiations were performed at 300 W/20 bar.



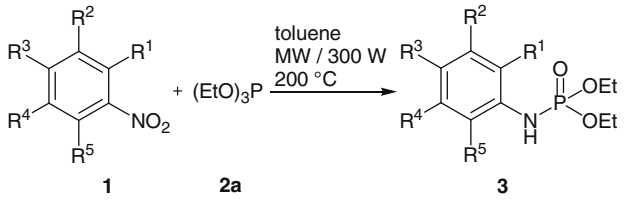
Scheme 3. Reaction of nitrobenzene (**1a**) with $(MeO)_3P$ **2b** in toluene under microwave conditions.

To evaluate the scope of the transformation of nitroarenes into phosphoramidates we examined the effects of substitution on the aromatic ring. A range of substituents at different positions of the aromatic ring was tested. To this end the transformation was performed with a number of mono-, di- and trisubstituted nitroarenes using the optimized protocol (Scheme 4, Table 5). It could be established that a number of nitroarenes carrying one or two methyl groups can be successfully transformed into the corresponding *N*-arylphosphoramidates **3b**–**g**. However, the method is not restricted to methyl-substituted nitroarenes. It is also possible to successfully convert substrates with methoxy-, halide-, methoxycarbonyl-, and cyano-substituents (**1h**–**o**) into the corresponding *N*-arylphosphoramidates **3h**–**o**.[23] Yields were in the range between 52% and 79%; side product formation was negligible.

The structures of diethyl *N*-arylphosphoramidates **3a**–**o** described here have been elucidated unambiguously by NMR-spectroscopic methods including HH-COSY, HMBC, and HSQC experiments.

We assume that in the first step of the reaction cascade the nitroarene **1** is reduced with triethyl phosphite (**2a**) to the corresponding nitrosoarene **5** and triethyl phosphate (**6a**) (Scheme 5).[24] Further reduction with triethyl phosphite (**2a**) gives the arylnitrene **7** which reacts with **2a** to yield the *N*-arylphosphorimidate **8** as an intermediate. The latter undergoes hydrolysis under the conditions of workup/purification by chromatography to afford the *N*-arylphosphoramidate **3**. In accordance with this proposal the *N*-arylphosphoramidates **3** could not be obtained when aniline (**9**) was treated with an excess of either triethyl phosphite (**2a**) or triethyl phosphate (**6a**) under various reaction conditions.

Our results demonstrate that—in contrast to previous reports—the reaction of nitroarenes with trialkyl phosphites is a practical and reliable method for the selective preparation of dialkyl *N*-arylphosphoramidates if performed under suitable reaction conditions.

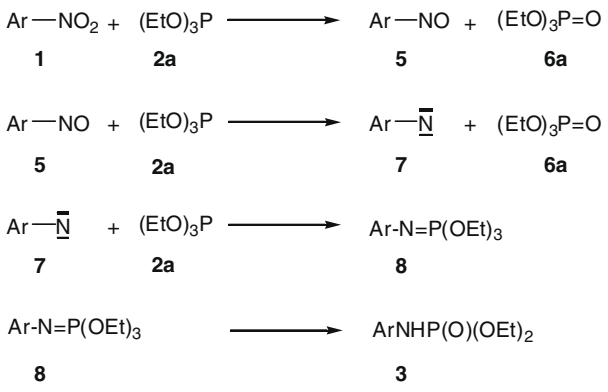


Scheme 4. Reaction of nitroarenes **1** with $(EtO)_3P$ **2a** in toluene under microwave conditions.

Table 5
Synthesis of diethyl *N*-arylphosphoramidates **3a**–**o** in a single step reaction of **1a**–**o** with **2a** under microwave conditions

Entry	1	R^1	R^2	R^3	R^4	R^5	Time (min)	3	Yield 3[a] (%)
1	**a**	H	H	H	H	H	15	**a**	78
2	**b**	Me	H	H	H	H	15	**b**	68
3	**c**	H	Me	H	H	H	15	**c**	73
4	**d**	H	H	Me	H	H	15	**d**	66
5	**e**	Me	H	H	Me	H	15	**e**	75
6	**f**	H	Me	H	Me	H	15	**f**	79
7	**g**	Me	H	Me	H	H	15	**g**	77
8	**h**	H	H	OMe	H	H	15	**h**	71
9	**i**	H	H	Cl	H	H	10	**i**	52
10	**j**	Br	H	H	H	H	10	**j**	68
11	**k**	I	H	H	H	H	10	**k**	56
12	**l**	H	H	CO_2Me	H	H	10	**l**	62
13	**m**	H	H	CN	H	H	10	**m**	63
14	**n**	Br	H	H	OMe	H	10	**n**	73
15	**o**	Cl	Me	Cl	H	H	10	**o**	57

[a] Isolated yields.



Scheme 5. Proposal for the reaction mechanism.

Acknowledgments

R. Haggam is grateful to the Ministry of Higher Education, Egypt, for the award of a Ph.D. fellowship. We thank Ms. S. Mika, Dr. H. Leutbecher, and Dipl.-Chem. F. Mert-Balci for the recording of NMR and mass spectra.

References and notes

1. For selected reviews on antisense oligonucleotides, see for example: (a) De Mesmaeker, A.; Häner, R.; Martin, P.; Moser, H. E. *Acc. Chem. Res.* **1995**, *28*, 366; (b) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543.
2. (a) Awad, A. M.; Sobkowski, M.; Seliger, H. *Nucleosides, Nucleotides, Nucleic Acids* **2004**, *23*, 777; (b) Faria, M.; Spiller, D. G.; Dubertret, C.; Nelson, J. S.; White, M. R. H.; Scherman, D.; Hélène, C.; Giovannangeli, C. *Nat. Biotechnol.* **2001**, *19*, 40; (c) Skorski, T.; Perrotti, D.; Nieborowska-Skorska, M.; Gryaznov, S.; Calabretta, B. *Proc. Natl. Acad. U.S.A.* **1997**, *94*, 3966; (d) Heidenreich, O.; Gryaznov, S.; Nerenberg, M. *Nucleic Acids Res.* **1997**, *25*, 776; (e) Gryaznov, S.; Skorski, T.; Cucco, C.; Nieborowska-Skorska, M.; Chiu, C. Y.; Lloyd, D.; Chen, J. K.; Koziolkiewicz, M.; Calabretta, B. *Nucleic Acids Res.* **1996**, *24*, 1508; (f) Gryaznov, S. M.; Chen, J. K. *J. Am. Chem. Soc.* **1994**, *116*, 3143.
3. For a review, see: (a) Venkatachalam, T. K.; Goodman, P. A.; Qazi, S.; ÓCruz, O.; Uckun, F. M. *Curr. Pharm. Design* **2004**, *10*, 1713; (b) Venkatachalam, T. K.; Samuel, P.; Qazi, S.; Uckun, F. M. *Bioorg. Med. Chem.* **2005**, *13*, 5408; (c) Uckun, F. M.; Samuel, P.; Qazi, S.; Chen, C.; Pendergrass, S.; Venkatachalam, T. K. *Antiviral Chem. Chemother.* **2002**, *13*, 197; (d) Freel Meyers, C. L.; Borch, R. F. *J. Med. Chem.* **2000**, *43*, 4319.
4. Wuts, P. G. M.; Greene, T. W. *Greenés Protective Groups in Organic Synthesis*, 4th ed.; Wiley: New Jersey, 2006. pp 844–847.
5. Ciufolini, M. A.; Spencer, G. O. *J. Org. Chem.* **1989**, *54*, 4739.
6. Zwierzak, A.; Brylikowska-Piotrowicz, J. *Angew. Chem., Int. Ed.* **1977**, *16*, 107.
7. Minami, T.; Ogata, M.; Hirao, I.; Tanaka, M.; Agawa, T. *Synthesis* **1982**, 231.
8. Yadav, L. D. S.; Rai, A.; Rai, V. K.; Awasthi, C. *Tetrahedron Lett.* **2008**, *49*, 687.
9. Yadav, L. D. S.; Srivastava, V. P.; Patel, R. *Tetrahedron Lett.* **2008**, *49*, 5652.
10. Yadav, L. D. S.; Awasthi, C.; Rai, V. K.; Rai, A. *Tetrahedron Lett.* **2007**, *48*, 8037.
11. Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, 660.
12. (a) Mielniczak, G.; Łopusiński, A. *J. Synth. Commun.* **2003**, *33*, 3851. and references cited therein; (b) Atherton, F. R.; Todd, A. R. *J. Chem. Soc.* **1947**, 674.
13. (a) Zwierzak, A.; Osowska, K. *Synthesis* **1984**, 223; (b) Zwierzak, A. *Synthesis* **1975**, 507.
14. (a) Appel, R.; Einig, H. *Z. Anorg. Allg. Chem.* **1975**, *414*, 241; (b) Appel, R. *Angew. Chem., Int. Ed.* **1977**, *14*, 801.
15. Meyer, R. B.; Shuman, D. A.; Robins, R. K. *Tetrahedron Lett.* **1973**, 269.
16. (a) Jäger, A.; Levy, M. J.; Hecht, S. M. *Biochemistry* **1988**, *27*, 7237; (b) Nemer, M. J.; Ogilvie, K. K. *Tetrahedron Lett.* **1980**, *21*, 4149.
17. Cadogan, J. I. G.; Marshall, R.; Smith, D. M.; Todd, M. J. *J. Chem. Soc. (C)* **1970**, 2441.
18. Cadogan, J. I. G.; Sears, D. J.; Smith, D. M.; Todd, M. J. *J. Chem. Soc. (C)* **1969**, 2813.
19. Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604.
20. Sundberg, R. J. *J. Am. Chem. Soc.* **1966**, *88*, 3781.
21. Fischer, B.; Sheihet, L. *J. Org. Chem.* **1998**, *63*, 393.
22. General procedure for the synthesis of diethyl *N*-arylphosphoramidates **3** under microwave conditions: A mixture of **1** (1 mmol), triethyl phosphite (**2a**) (6 mmol) and toluene (3 mL) was sealed in a 10 mL septum reaction vial and irradiated with microwaves (Discover™ by CEM, 2450 MHz, 300 W, 200 °C). After removal of triethyl phosphite (**2a**) and triethyl phosphate (**6a**) at reduced pressure (10^{-1} mbar) and temperatures between 40 and 70 °C the residue was diluted with CH_2Cl_2 (30 mL), and washed with water (2 × 50 mL) and brine (3 × 20 mL). After drying over anhydrous $MgSO_4$ and concentration in vacuo the resulting residue was purified by flash chromatography over silica gel.

23. Diethyl *N*-2-bromo-5-methoxyphenylphosphoramidate (**3n**) According to the general procedure 4-bromo-3-nitroanisole (**1n**) (232 mg, 1 mmol) was reacted with triethyl phosphite (**2a**) (995 mg, 6 mmol). After column chromatography (SiO_2; cyclohexane/ethyl acetate = 1:2) the title compound was isolated (247 mg, 73% yield). R_f = 0.41(ethyl acetate–cyclohexane, 2:1). Mp = 58 °C. IR (ATR): 3221, 2986, 1600, 1577, 1493, 1398, 1301, 1254, 1060, 1014, 973, 777 cm^{-1}. UV–vis (MeCN): λ_{max} (log ε) = 275 nm (3.15), 209 nm (3.36). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.34 (t, ^3J = 7.03 Hz, 6H, 2 × CH_3), 3.77 (s, 3H, OCH_3), 4.02–4.24 (m, 4H, 2 × OCH_2), 5.60 (d, $^2J_{P\text{-}H}$ = 8.50 Hz, 1H, NH), 6.43 (dd, ^3J = 8.87 Hz, ^4J = 2.79 Hz, 1H, 4-H), 6.94 (d, ^4J = 2.79 Hz, 1H, 6-H), 7.36 (dd, ^3J = 8.80 Hz, ^5J = 1.17 Hz, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 16.37 ($^3J_{P-C}$ = 6.88 Hz, 2 × CH_3), 55.72 (OCH_3), 63.46 ($^2J_{P-C}$ = 5.09 Hz, 2 × OCH_2), 103.39 ($^3J_{P-C}$ = 12.56 Hz, C-2), 104.03 ($^3J_{P-C}$ = 1.50 Hz, C-6), 108.89 (C-4), 132.99 (C-3), 138.55 ($^2J_{P-C}$ = 2.99 Hz, C-1), 160.11 (C-5). MS (EI, 70 eV): *m*/*z* (%) = 339 (30) [M^+], 337 (32) [M^+], 258 (80) [M^+−Br], 230 (61), 202 (100), 184 (17), 138 (19). HRMS (EI) *m*/*z* calcd for $C_{11}H_{17}NPBrO_4$: 337.0080; found: 337.0080 [M^+]. Elem. Anal. Calcd for $C_{11}H_{17}NPBrO_4$: C, 39.17; H, 5.08; N, 4.16. Found: C, 39.13; H, 4.94; N, 3.91.

24. Cadogan, J. I. G. *J. Chem. Soc., Quart. Rev.* **1968**, 222. and references cited therein.