Direct Synthesis of Amino-substituted Aromatic Phosphonates via Palladium-catalyzed Coupling of Aromatic Mono- and Dibromides with Diethyl Phosphite

Alla Bessmertnykh,* Christiane Morkos Douaihy, and Roger Guilard*
Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB)-UMR CNRS 5260, 9, av. Alain Savary, 21078 Dijon, France

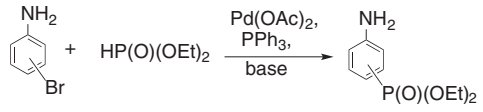
(Received April 23, 2009; CL-090404; E-mail: Roger.Guilard@u-bourgogne.fr)

An efficient Pd-catalyzed carbon–phosphorus bond-forming route is described for the direct synthesis of diethyl arylphosphonates bearing amino and alkylamino groups on the aromatic ring.

The formation of carbon–heteroatom bonds (C–N, C–O, C–S, and C–P) by transition-metal-catalyzed cross-coupling methodology has been topic of intensive studies during recent years. Palladium-catalyzed reaction of aryl halides with dialkyl phosphite disclosed by Hirao et al. is one very attractive route to dialkyl arylphosphonates.[1] However, so far the optimal conditions for the phosphorylation of substituted aromatics are often unknown and practically key compounds should be prepared by other ways. For example, dialkyl aminoarylphosphonates cannot be obtained by the Pd-catalyzed reaction of bromoanilines with diethyl phosphite under classical Hirao conditions.[1b,2] These derivatives, key intermediates for the synthesis of biologically active compounds, versatile ligands for metal ions and usual building blocks in material chemistry, are generally synthesized either by photoactivated substitution of aryl iodides[2] or by multistep procedures.[3] When this manuscript was in preparation, the catalytic phosphorylation of *o*-bromoaniline was described,[4] and convenient conditions for expensive iodoanilines were disclosed.[5] Inspired by our success in the phosphorylation of aminopyridines,[6] we report here a general synthesis of diethyl arylphosphonates bearing amino and alkylamino groups on the benzene, naphthalene, or anthracene ring through Pd-catalyzed phosphorylation of mono- and dibromides by diethyl phosphite in ethanol (Scheme 1).

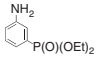
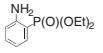
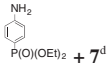
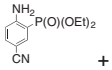
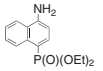
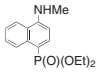
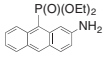
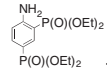
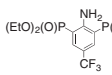
On the basis of our preliminary outcomes,[6] the reaction of bromoanilines with diethyl phosphite (1.2 equiv) was conducted in the presence of triethylamine (NEt_3) (1.5 equiv), 5 mol % of $Pd(OAc)_2$ and 15 mol % of triphenylphosphine in ethanol at reflux under nitrogen atmosphere. The obtained results are summarized in the Table 1.[7]

The reaction of *m*-bromoaniline (**1**) and *o*-bromoaniline (**3**) proceeded smoothly and gave phosphonates **2** and **4** in 90 and 93% yield, respectively (Entries 1 and 2). Unfortunately, the yield of the product decreased significantly for *p*-bromoaniline (**5**) (Entry 3). GC-MS analysis of the reaction mixture has shown that diethyl phenylphosphonate (**7**) was formed as a major by-product. ^{1}H NMR monitoring of the reaction progress showed



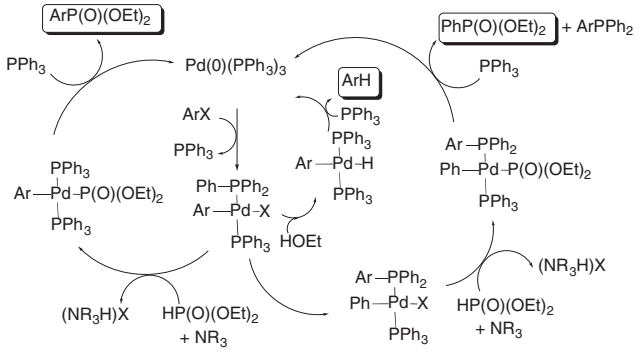
Scheme 1. General synthesis of amino-substituted diethyl arylphosphonates.

Table 1. Cross-coupling of amino-substituted aromatic bromides and dibromides with diethyl phosphite

No	ArBr	Pd:L	RC[a]	*T* /h	Conv /%[b]	Products	Yield /%[c]
1	 **1**	5:15	A	30	98	 **2**	90
2	 **3**	5:15	A	30	98	 **4**	93
3	 **5**	5:15 5:15 2:6	A B A	30 30 48	100 100 60	 + **7**[d] **6**	49 55 51
4	 **8**	5:15 10:30 13:33 5:15	A A A C	30 48 48 24	55 55 45 100[e]	 + **10** **9**	- - - 71
5	 **11**	2:6 2:6	A B	48 48	100 100	 **12**	91 88
6	 **13**	2:6 5:15	A A	60 48	60 100	 **14**	58 85
7	 **15**	10:30 10:30 10:30	B D E	48 48 48	70 100[f] 100[g]	 + **17** **16**	37 49 40
8	 **18**	10:30 10:30	C E	48 48	100 100	 + **20** + **21** + **7** **19**	- 53
9	 **22**	15:45	C	36	100	 **23**	40

[a]Reaction conditions: A: $HP(O)(OEt)_2$ (1.2 equiv), NEt_3 (1.5 equiv); B: $HP(O)(OEt)_2$ (1.2 equiv), NCy_2Me (1.5 equiv); C: $HP(O)(OEt)_2$ (2.4 equiv), NEt_3 (3 equiv); D: $HP(O)(OEt)_2$ (2.4 equiv), NCy_2Me (3 equiv); E: $HP(O)(OEt)_2$ (4.8 equiv), NCy_2Me (3 equiv). [b]Ratio of phosphonate/(bromide + phosphonate) determined by ^{1}H NMR. [c]Yield of the desired product. [d]Ratio of **6**:**7** was 3:1 (^{1}H NMR). [e]Ratio of **9**:**10** was 4:1 (^{1}H NMR). 4-Aminobenzonitrile (**10**) was isolated in 20% yield. [f]Ratio of **16**:**17** was 4:1 (determined by ^{1}H NMR). **17** was isolated and characterized by spectral data. [g]Ratio of **16**:**17** was 7:3 (^{1}H NMR).

that the formation of this by-product was observed at the initial period of the reaction and its amounts reached about 30% of the amount of the phosphonate **6** at the end of the reaction. This led



Scheme 2. Simplified mechanism for the Pd-catalyzed phosphorylation, the aryl–aryl interchange and the hydrodebromination reactions.

us to suggest that compound **7** results from the aryl–aryl interchange reaction[8] in the intermediate $Pd(PPh_3)_2ArX$ complex formed during the phosphorylation catalytic cycle (Scheme 2).[9]

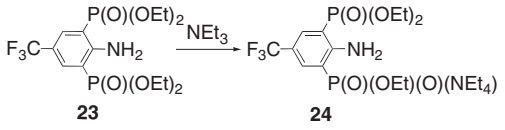
In fact, even this side-reaction has never been described in the palladium-catalyzed phosphorylation reaction, it was suggested as a possible pathway of the formation of phosphine-derived by-products in the palladium-catalyzed cross-coupling reactions.[10] Our additional experiments aiming to optimize the yield of compound **6** were unsuccessful. When dicyclohexylmethylamine (NCy_2Me) was employed as a base a similar product distribution was observed. The reaction in the presence of 2 mol % $Pd(OAc)_2$/6 mol % PPh_3 resulted in lower yields of by-product **7** without observing better yields of the product **6** due to the incomplete conversion of the starting bromide.

When bromide **8** bearing an electron-withdrawing group was allowed to react under standard conditions incomplete reaction was observed (Entry 4). Interestingly, increasing of catalyst loading or ratio of [Pd]/PPh_3 did not afford a satisfactory conversion of the starting bromide. However, the reaction was completed with twice the amount of diethyl phosphite and the desirable product was obtained in 71% yield.

Naphthalene derivatives **11** and **13** were more reactive as compared to anilines (Entries 5 and 6). Compound **11** reacted with diethyl phosphite even in the presence of 2 mol % of the palladium precursor. Both NEt_3 or NCy_2Me can be used as a base, leading to comparable yield (88–91%) of the phosphonate **12** (Entry 5). The *N*-methyl derivative **13** was less reactive but the reaction was still selective. A good yield (85%) for the synthesis of phosphonate **14** was obtained in the presence of 5 mol % of the catalyst precursor (Entry 6). Further increase of the steric bulk on the aromatic bromide results in a significant decrease of the product yield.

With bromoanthracene **15** the reaction was incomplete even when 10 mol % of the catalytic system was employed and the product **16** was isolated in 37% yield (Entry 7). Under optimal conditions, i.e. using 2 equiv of diethyl phosphite, 10 mol % of the catalyst system and NCy_2Me, the starting bromide was fully consumed but the phosphonate **16** was only obtained in 49% yield among 2-aminoanthracene (**17**).

We then studied the possibility of diphosphorylation of arylene dibromides in a one-step procedure. When 2,4-dibromoaniline (**18**) reacted with 2.4 equiv of diethyl phosphite in the presence of 10 mol % of the catalyst system several products were formed in the reaction mixture. With an excess of diethyl phosphite the reaction selectivity increases and the diphosphonate **19** was isolated in 53% yield among reduced products i.e diethyl 2-aminophosphonate (**20**) (4%), diethyl 4-aminophosphonate (**21**) (10%), and diethyl phenylphosphonate (**7**) (12%) (Entry 8). Dibromide **22** gave the desirable diphosphonate **23** in 40% yield (Entry 9). Surprisingly, the yield of the reaction leading to phosphonate **23** decreased when the reaction time was prolonged up to 3 days. Applying a more polar eluting solvent mixture during a chromatographic purification (10% of MeOH in CH_2Cl_2), the mono ammonium salt **24** has been separated (Scheme 3). Precedent observations of a phosphonate dealkylation in the presence of tertiary amines[11] or hydrazine[12] have been described. Scale-up experiments using 5–10 g bromides **5**, **11**, **13**, and **15** gave the desired phosphonates according to the yields given in Table 1.



23 **24**

Scheme 3. Dealkylation of arylenediphosphonate **23**.

In conclusion, we have developed an efficient catalytic route to diethyl arylphosphonates bearing amino and alkylamino groups on a benzene, naphthalene, or anthracene ring. These conditions can be applied for the synthesis of amino-substituted arylenediphosphonates if corresponding arylene dibromides are used as starting compounds.

References and Notes

1 a) T. Hirao, T. Masunaga, Y. Ohshiro, T. Agawa, *Synthesis* **1981**, 56. b) T. Hirao, T. Masunaga, N. Yamada, Y. Ohshiro, T. Agawa, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909.
2 a) R. Obrycki, C. E. Griffin, *J. Org. Chem.* **1968**, *33*, 632. b) J. J. Bulot, E. E. Aboujaoude, N. Collignon, P. Savignac, *Phosphorus Sulfur Silicon Relat. Elem.* **1984**, *21*, 197. c) R. Beugelmans, M. Chbani, *Bull. Soc. Chim. Fr.* **1995**, *132*, 290. d) N. Defacqz, B. de Bueger, R. Touillaux, A. Cordi, J. Marchand-Brynaert, *Synthesis* **1999**, 1368.
3 a) G. M. Kosolapoff, G. G. Priest, *J. Am. Chem. Soc.* **1953**, *75*, 4847. b) G. P. Basmadjian, S. Singh, B. Sastrodjojo, B. T. Smith, K. Avor, F. Chang, S. L. Mills, T. W. Seale, *Chem. Pharm. Bull.* **1995**, *43*, 1902. c) V. Pénicaud, C. Maillet, P. Janvier, M. Pipelier, B. Bujoli, *Eur. J. Org. Chem.* **1999**, 1745.
4 B. R. Aluri, M. K. Kindermann, P. G. Jones, I. Dix, J. Heinicke, *Inorg. Chem.* **2008**, *47*, 6900.
5 Y. Belabassi, S. Alzghari, J.-L. Montchamp, *J. Organomet. Chem.* **2008**, *693*, 3171.
6 A. Bessmertnykh, C. Morkos Douaihy, S. Muniappan, R. Guilard, *Synthesis* **2008**, 1575.
7 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
8 F. E. Goodson, T. I. Wallow, B. M. Novak, *J. Am. Chem. Soc.* **1997**, *119*, 12441.
9 M. C. Kohler, T. V. Grimes, X. Wang, T. R. Cundari, R. A. Stockland, Jr., *Organometallics* **2009**, *28*, 1193.
10 a) D. F. O'Keefe, M. C. Dannock, S. M. Marcuccio, *Tetrahedron Lett.* **1992**, *33*, 6679. b) D. Barañano, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 2937.
11 K. Gorog, L. Bodnar, E. Dudar, M. Kocsis, S. Gaal, M. Tasnadi, E. Egyhazi, V. M. Varga, I. Kajati, G. Kis, J. Molnar, B. Toth, I. Cserhati, T. Kaptas, S. Csete, U.S. Patent 4 675 431, **1987**.
12 E. N. Dolzhnikova, E. N. Tzvetkov, G. S. Petrova, *Zh. Obshch. Khim.* **1976**, *46*, 1903.

Published on the web (Advance View) June 27, 2009; doi:10.1246/cl.2009.738