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Comments on a novel synthesis of diethyl 1-aminoarylmethylphosphonates on the surface of alumina

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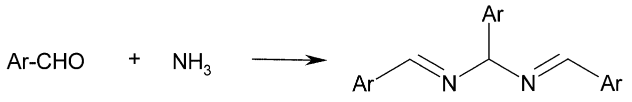
Abstract—Contrary to the literature statement we found that aromatic aldehydes react with diethyl phosphite and hexamethyldisilazane to give 1-(trimethylsilyloxy)-1-arylmethylphosphonates and not 1-amino-1-arylmethylphosphonate derivatives. Therefore, for preparation of diethyl *N*-arylidene-1-amino-1-arylmethylphosphonate, we recommend the direct reaction of hydrobenzamides with diethyl phosphite, instead of aromatic aldehydes, hexamethyldisilazane and alumina as catalyst on solid phase, as has been described previously (Sardarian, A. R.; Kaboudin, B. *Tetrahedron Lett*. **1997**, *38*, 2543–2546). © 2003 Elsevier Science Ltd. All rights reserved.

In 1997 Sardarian and Kaboudin[1] published unexpected results—they claimed a novel synthesis of diethyl 1-amino-1-arylmethylphosphonates[2] in the reaction of aromatic aldehydes, hexamethyldisilazane and diethyl phosphite, via diethyl *N*-arylidene-1-amino-1-arylmethylphosphonate,[3] on the surface of alumina. They suggested that the use of 'the technique of surface-mediated solid phase reaction', alumina in this case, played an essential role in their experiments. Since hexamethyldisilazane does not react with carbonyl compounds[4] and moreover, reacts with aldehydes (or ketones) and dialkyl phosphites to give 1-hydroxyalkylphosphonic acid derivatives—but not 1-aminoalkylphosphonates[5]—there is no reason to believe that addition of 'acidic alumina' would change dramatically the route of this reaction (Scheme 1).

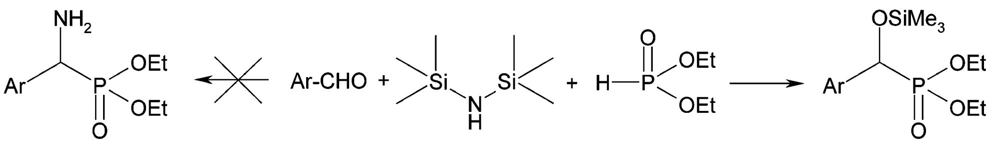
However, the authors described the preparation of nine diethyl 1-amino-1-arylmethylphosphonates with reasonably good yields and for one representative compound they confirmed the structure of the 1-aminophosphonate by NMR and IR. We expect they undoubtedly have also found enough evidence for the rest of their compounds. So, there is no reason to question their results. Nevertheless, the question remains how it is possible to obtain diethyl *N*-arylidene-1-amino-1-arylmethylphosphonates in the reaction of hexamethyldisilazane with aromatic aldehydes and diethyl phosphite?

Therefore, we decided to analyze and reinvestigate this reaction. The results of our investigation can be summarized as follows:

1. We found that the only effect of the application of acidic alumina in this protocol was decomposition of hexamethyldisilazane with evolution of ammonia.[6] The reaction of hexamethyldisilazane with alumina (even



Scheme 2.



Scheme 1.

Keywords: hydrobenzamide; aminoalkylation; aminophosphonate; addition reaction; imine.

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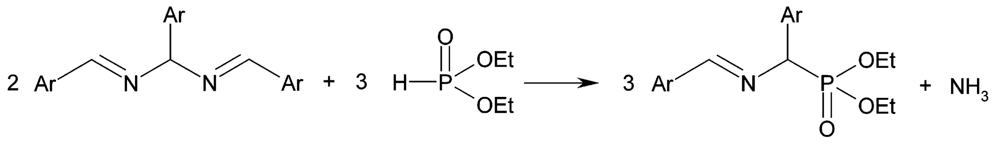

Scheme 3.

dried in an oven) gives ammonia. So, the mixture of hexamethyldisilazane and alumina is just a source of ammonia in this reaction. [7]

2. Ammonia reacts 'in situ' with aromatic aldehydes to give hydrobenzamides (1-aryl-*N*,*N*′-bis(arylidene)-methanediamine) as sole products (Scheme 2).[8]

3. Then, the hydrobenzamide reacts with diethyl phosphite[9] to give a diethyl *N*-arylidene-1-amino-1-arylmethylphosphonate (Scheme 3), which can be easily hydrolyzed to a diethyl 1-amino-1-arylmethylphosphonate and isolated as its sulphonate or hydrochloride.

In conclusion, for the preparation of diethyl 1-amino-1-arylmethylphosphonates via diethyl *N*-arylidene-1-amino-1-arylmethylphosphonates we recommend the direct reaction of hydrobenzamide with diethyl phosphite,[10] instead of aromatic aldehydes with hexamethyldisilazane and alumina as the catalyst and solid phase, as has been described previously.[1]

References

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2. The 1-amino-1-arylmethylphosphonates are very well known compounds. For examples of their previous preparation, see: (a) Chalmers, M. E.; Kosolapoff, G. M. *J. Am. Chem. Soc.* **1953**, *75*, 5278; (b) Gross, H.; Beisert, S.; Costisella, B. *J. Prakt. Chem.* **1981**, *323*, 877; (c) Issleib, K.; Doepfer, K.-P.; Balszuweit, A. *Z. Naturforsch. B Anorg. Chem. Org. Chem.* **1981**, *36*, 1392; (d) Kabachnik, M. I.; Medwed', T. Ya. *Izv. Akad. Nauk SSSR Ser. Khim.* **1953**, 868; Kabachnik, M. I.; Medwed', T. Ya. *Dokl. AN SSSR* **1952**, *83*, 689; (e) Kreutzkamp, N.; Cordes, G. *Justus Liebigs Ann. Chem.* **1959**, *623*, 103; (f) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1978**, 521; (g) Kudzin, Z. H.; Kotynski, A. *Synthesis* **1980**, 1028; (h) Kudzin, Z. H.; Majchrzak, M. W. *J. Organomet. Chem.* **1989**, *376*, 245; (i) Lukszo, J.; Tyka, R. *Pol. J. Chem.* **1978**, *52*, 959; (j) Lukszo, J.; Tyka, R. *Synthesis* **1977**, 239; (k) Rachon, J.; Wasielewski, C. *Rocz. Chem.* **1975**, *49*, 397; (l) Takahashi, H.; Yoshioka, M.; Imai, N.; Onimura, K.; Kobayashi, S. *Synthesis* **1994**, 763; (m) Topolski, M.; Rachon, J. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *55*, 97; (n) Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2528; (o) Yuan, C.; Wang, G.; Chen, S. *Synthesis* **1990**, 522.
3. The *N*-arylidene-1-amino-1-arylmethylphosphonates were also described previously. See for examples: (a) Dehnel, A.; Kanabus-Kaminska, J. M.; Lavielle, G. *Can. J. Chem.* **1988**, *66*, 310; (b) Dehnel, A.; Finet, J. P.; Lavielle, G. *Synthesis* **1977**, 474; (c) Heymes, A.; Chekroun, I. *Synthesis* **1987**, 245; (d) Malenko, D. M.; Nesterova, L. I.; Luk'yanenko, S. N.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1990**, *60*, 1186; (e) Onis'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1996**, *66*, 1283; (f) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Prokopenko, V. P.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1990**, *60*, 523; (g) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1987**, *57*, 1233; (h) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1993**, *63*, 1906; (i) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1997**, *67*, 1642; (j) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Turov, A. V. *Zh. Obshch. Khim.* **1990**, *60*, 1425; (k) Russell, G. A.; Yao, C.-F. *J. Org. Chem.* **1992**, *57*, 6508; (l) Tupchienko, S. K.; Dudchenko, T. N.; Sinitsa, A. D. *Zh. Obshch. Khim.* **1985**, *55*, 776.
4. Since the hexamethyldisilazane does not react with a freshly distilled dry aldehyde, a simple preparation of trimethylsilylimines in the reaction of an aldehyde with hexamethyldisilazane is possible only under harsh conditions for nonenolizable aldehydes. For a recent review see: (a) Panunzio, M.; Zarantonello, P. *Org. Process Res. Develop.* **1998**, *2*, 49–59. For examples of the preparation and use of *N*-trimethylsilylimines see: (b) Cainelli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron Lett.* **1987**, *28*, 5369; (c) Cainelli, G.; Panunzio, M.; Giacomini, D. *Tetrahedron Lett.* **1991**, *32*, 121; (d) Chan, L.-H.; Rochow, E. G. *J. Organomet. Chem.* **1967**, *9*, 231; (e) Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Clowers, J. S.; Vandervelde, D. G.; Himes, R. H. *J. Org. Chem.* **1996**, *61*, 2664–2676; (f) Georg, G. I.; Harriman, G. C. B.; Peterson, S. A. *J. Org. Chem.* **1995**, *60*, 7366; (g) Guillemin, J.-C.; Ammi, L.; Denis, J.-M. *Tetrahedron Lett.* **1988**, *29*, 1287; (h) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819; (i) Hart, D. J.; Kanai, K.-I.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289; (j) Kruger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132.
5. 1-Amino-1-arylmethylphosphonates were prepared for the first time by Kabachnik and Medved[2d] in a reaction of ammonia, diethyl phosphite and an aldehyde (or ketones), the so called Kabachnik–Medved reaction—for a recent review see: (a) Cherkasov, R. A.; Galkin, V. I. *Uspekhi Khim.* **1998**, *67*, 940–968. However, the use of ammonia in this, Mannich type, reaction gave a rather low yield of the desired product. Imines are not the primary products of the reactions of ammonia with aldehydes or ketones. Ammonia reacts with formaldehyde to give hexamethylenetetramine, with aliphatic aldehydes to give 2,4,6-trialkyl-1,3,5-hexahydrotriazines and with aromatic aldehydes to give hydrobenzamides. For a disscussion see: (b) Nielsen, A. T.; Atkins, R. L.; Moore, D. W.; Scott, R.; Mallory, D.; LaBerge, J. M. *J. Org. Chem.* **1973**, *38*, 3288. Moreover, an equilibrium between hex-

ahydrotriazines and imines has never been proved. Since the hexahydrotriazines react with diethyl phosphites to give complex mixtures of products with low yields of aminophosphonates, several groups have tried to improve the yield of aminoalkylation of tervalent phosphorus compound, essentially by introducing ammonia equivalents such as benzylamine: (c) Tyka R. *Tetrahedron Lett.* **1970**, *9*, 677; 1-phenylcyclopentylamine (see Refs 2i,j); benzhydrylamine (see Ref. 2c); and tritylamine: (d) Soroka, M.; Zygmunt, J. *Synthesis* **1988**, 370. We have also tried hexamethyldisilazane as an ammonia equivalent. However, in the reaction of dry acetaldehyde with hexamethyldisilazane and diethyl phosphite we isolated only diethyl 1-trimethylsilyloxyethylphosphonate in almost quantitative yield without any trace of aminophosphonate. Similar results were obtained with benzaldehyde—also the trimethylsilylated 1-hydroxyphosphonate was the sole product of this reaction. In the cases of acetone or cyclohexanone the corresponding diethyl 1-hydroxyalkylphosphonates were isolated in crystalline states. According to our observation hexamethyldisilazane is an excellent base in the Abramov reaction: (d) Abramov, V. S. *Zh. Obshch. Khim.* **1952**, *22*, 647; and when 1-hydroxyalkylphosphonates are not sterically hindered, it is also a silylating agent which converts hydroxyphosphonic acids into their *O*-trimethylsilyl derivatives. *O*-trimethylsilyl-1-hydroxyalkylphosphonates are well known compounds. For examples see: (e) Nesterov, L. V.; Krepysheva, N. J.; Sabirova, R. A.; Romanova, G. N. *Zh. Obshch. Khim.* **1971**, *41*, 2449; (f) Novikova, Z. S.; Mashoshina, S. N.; Sapozhnikova, T. A.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1970**, *41*, 2622; (g) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467 and references cited therein.

6. When we mixed hexamethyldisilazane with any of the alumina samples we had in our stock, we have always observed ammonia evolution (by smell and by pH indicator paper). Mixing alumina with benzaldehyde and hexamethyldisilazane gave hydrobenzamide as the sole product after extraction and evaporation of the solvent. Addition of a few drops of a saturated ethereal solution of water into the mixture of acetaldehyde and hexamethyldisilazane in ether, resulted in precipitation of white crystals identified as 2,4,6-trimethyl-1,3,5-hexahydrotriazine-'acetaldehyde-ammonia trimer' (see Aldrich Catalogue, nr. 10.820-0). The same procedure in the case of benzaldehyde resulted in practically quantitative isolation of hydrobenzamide.
7. Hexamethyldisilazane is a very well known mild 'silanizing' agent. See Fluka's *Silylating Agents*; Fluka Chemie AG 1995 (ISBN 3-905617-13-7), p. 21 and 120.
8. Hydrobenzamide was described for the first time in 1836 by Laurent in the reaction of benzaldehyde ('Bittermandel öl') with gaseous ammonia: (a) Laurent, M. A. *Ann. Pharm.* **1837**, *21*, 130–134; 'Ueber das Hydrobenzamid'; *Ann. Chim. Phys.* **1836**, *62*, 23. It is noteworthy that as early as in 1865 Reinecke and Beilstein reported the preparation of benzylidenaminophenylacetonitrile (sic!) in the reaction of hydrobenzamide with hydrogen cyanide: (b) Reinecke, A.; Beilstein, F. *Ann. Chem.* **1865**, *136*, 173. In the Beilstein data base (Beilstein Informationssysteme GmbH; BS9804PR) 88 substances related to hydrobenzamide and 318 of their reactions were recorded. For recent examples see: (c) Karupaiyan, K.; Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron Lett.* **1997**, *38*, 4281–4284; (d) Larter, M. L.; Phillips, M.; Ortega, F.; Aguirre, G.; Somanathan, R.; Walsh, P. J. *Tetrahedron Lett.* **1998**, *39*, 4785–4788; (e) Kupfer, R.; Brinker, U. H. *J. Org. Chem.* **1996**, *61*, 4185–4186; (f) Kayukov, Ya. S.; Nasakin, O. E.; Urman, Ya. G.; Khrustalev, N. V.; Nesterov, V. N.; Antipin, M. Y.; Lyshchikov, A. N.; Lukin, P. M. *Khim. Geterotsikl. Soedin.* **1996**, *32*, 1395; (g) Nasakin, O. E.; Lyshchikov, A. N.; Lukin, P. M.; Bulaj, A. Kh. *Khim. Geterotsikl. Soedin.* **1994**, *30*, 353; (h) Rey, A. W.; Droghini, R.; Douglas, J. L.; Vemishetti, P.; Boettger, S. D.; Racha, S.; Dillon, J. L. *Can. J. Chem.* **1994**, *72*, 2131; (i) Levai, L.; Bozsing, D.; Benko, P.; Lax, G.; Mikite, G. *Synth. Commun.* **1992**, *22*, 47; (j) Goerlitzer, K.; Schmidt, E. *Arch. Pharm. (Weinheim)* **1991**, *324*, 785. The preparation of hydrobenzamide is also described in (k) Vogel, A. I. *A Text-book of Practical Organic Chemistry*, 3rd ed.; Longmans, Green & Co. Ltd: London, 1961; pp. 735 (Polish Edition **1964**, WNT Warszawa).
9. In fact, the reaction of hydrobenzamides and diethyl phosphite was also reported in the literature: (a) Kreutzkamp, N.; Cordes, G. *Liebigs Ann. Chem.* **1959**, *623*, 103; (b) Rogozhin, S. V.; Davankov, V. A.; Belov, Yu. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, 955; (c) Belov, Yu. P.; Rakhnovich, G. B.; Davankov, V. A.; Godovikov, N. N.; Aleksandrov, G. G.; Struchkov, Ju. T. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 1125; (d) Pudovik, A. N.; Shagidullin, R. R.; Khairullin, V. K.; Vandyukova, I. I.; Chernova, A. V.; Gainullin, R. M.; Pudovik, M. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1996**, 1303; (e) Gross, H.; Beisert, S.; Costisella, B. *J. Prakt. Chem.* **1981**, 323, 877.
10. The following synthesis of diethyl *N*-arylidene-1-amino-1-arylmethylphosphonate is representative: diethyl phosphite (0.30 mole, Aldrich D9,923-4) was added to hydrobenzamide[8k] (0.20 mole, Aldrich 16,764-9). The mixture was heated (80-90°C for about 2 h, until evolution of ammonia ceased). The yield of diethyl *N*-benzylidene-1-amino-1-phenylmethylphosphonate was ascertained by ^{31}P NMR and isolation was accomplished by evaporation to give the crude product in nearly quantitative yield (^{31}P{^{1}H} NMR (CDCl$_3$): 21.2; ^{1}H NMR (CDCl$_3$): 1.2 (dt, 6H, CH$_3$, J=7.4), 4.0 (dq, 4H, CH$_2$, J=7.4), 4.9 (d, 1H, CH-P, J=18.5), 7.4–7.8 (m, 10H, ArH), 8.4 (d, 1H, CH=N, J=4.8) which could be used directly in the next reaction (for the preparation of diethyl 1-amino-1-phenylmethylphosphonate hydrochloride, for example) or purified by vacuum distillation (bp$_{0.1}$ 160–162°C[3b]).