ISSN 0012-5008, Doklady Chemistry, 2017, Vol. 472, Part 2, pp. 21–24. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © V.K. Brel, E.I. Goryunov, G.N. Molchanova, I.B. Goryunova, I.Yu. Kudryavtsev, T.V. Baulina, A.A. Khodak, T.V. Strelkova, E.E. Nifant'ev, 2017, published in Doklady Akademii Nauk, 2017, Vol. 472, No. 5, pp. 534–537.

CHEMISTRY

Catalytic Synthesis of *O*-Aryl Methyl(phenyl)phosphonochloridates

V. K. Brel, E. I. Goryunov*, G. N. Molchanova, I. B. Goryunova,
I. Yu. Kudryavtsev, T. V. Baulina, A. A. Khodak, T. V. Strelkova,
and Corresponding Member of the RAS E. E. Nifant'ev

Received September 19, 2016

Abstract—The reaction of methyl- and phenyldichlorophosphonates with phenols in the presence of anhydrous magnesium chloride (catalyst) or magnesium metal (procatalyst) has been used as a simple, efficient, and industrially feasible method for the synthesis of the corresponding *O*-aryl alkyl(aryl)phosphonochloridates.

DOI: 10.1134/S001250081702001X

O-Aryl phenyl- and methylphosphonochloridates are widely used as precursors for the synthesis of various types of organophosphorus compounds of practical interest, in particular, compounds showing biological activity.

However, until now, none of the realized methods for the preparation of these compounds has been free from drawbacks. In particular, the most common method of their synthesis based on the reaction of the corresponding organyldichlorophosphonates $RP(O)Cl_2$ (**Ia**, **Ib**; R = Ph (**a**), R = Me (**b**)) with phenols in the presence of hydrogen chloride scavenger, tertiary amine, requires the use of large amounts of organic solvents and provides no compounds of required purity [1, 2]. A variant of this reaction in the absence of tertiary amine allows preparation of methylphosphonochloridates not contaminated with tertiary amine hydrochlorides but requires long-term heating at high temperature, which has a negative effect on the yield of the final products [3].

One of the possible ways to enhance the efficiency of this reaction can be the use of electrophilic catalysis, which has been previously employed in the Laboratory of Organophosphorus Compounds, Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, to obtain *O*-polyfluoroalkyl phosphonochloridates of different types [4].

Indeed, the phosphorylation of phenol with dichlorophosphonates **Ia** and **Ib** was found to be catalyzed by a number of metal salts [4] showing Lewis acid properties (for example, anhydrous lithium, magnesium, and calcium chlorides), $MgCl_2$ being the most efficient catalyst among them, as well as magnesium metal,[1] which behaves as a procatalyst. Neither hydrogen chloride scavenger nor organic solvent is required in this case. The catalytic reactions proceed in high rate even at moderate heating and with the use of excess of the phosphorylating reagent, twofold is the best, to give target phosphonochloridates RP(O)(Cl)OPh (**IIa** and **IIb**) of high purity in rather high yield (66–71%) (see Scheme 1).

$$\underset{1:2}{PhOH + RP(O)Cl_2} \xrightarrow{120°C,\ [MgCl_2/Mg]} RP(O)(OPh)Cl$$

(**Ia**, **Ib**) (**IIa**, **IIb**)

Yield 66–71%

(**I**), (**II**): R = Ph (**a**); R = Me (**b**)

Scheme 1.

These processes are readily scalable, while excess of the phosphorylating reagent is recovered from the reaction mixture in high yield and of purity that allows its reuse in this reaction without additional purifica-

Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, 119991 Russia
** e-mail: gor.evg@rambler.ru*

---

[1] It dissolves during reaction to form magnesium chloride.

Constants, elemental analysis data, and $^{31}P\{^1H\}$ and $^{19}F\{^1H\}$ spectral data of *O*-aryl methylphosphonochloridates MeP(O)(Cl)OAr **IVa–IVh**

Compound	Ar	Bp, °C/mmHg (mp, °C)	Found, % / calculated, %				Molecular formula	$^{31}P\{^1H\}$NMR (C_6D_6, δ, ppm)
			C	H	Cl	P		
IVa	*p*-EtC_6H_4	99–101/1					$C_9H_{12}ClO_2P$	35.39 s
IVb	*p*-*iso*-PrC_6H_4	101–102/0.5	51.68 51.63	6.16 6.06	15.22 15.24	13.32 13.31	$C_{10}H_{14}ClO_2P$	35.30 s
IVc	*p*-*tert*-BuC_6H_4	130–131/1	53.62 53.56	6.50 6.54	14.24 14.37	12.57 12.56	$C_{11}H_{16}ClO_2P$	35.04 s
IVd	*p*-ClC_6H_4	129–130/1* (36–38)	–	–	–	–	–	35.52 s
IVe	*p*-FC_6H_4	91–92/1** (35–37)	–	–	–	–	–	35.48 (d, $^6J_{P,F}$ = 2.5 Hz)***
IVf	*p*-$MeOC_6H_4$	131–132/1	43.59 43.56	4.70 4.57	16.23 16.07	14.04 14.04	$C_8H_{10}ClO_3P$	33.84 s
IVg	2,6-$Me_2C_6H_3$	126–127/1	49.48 49.45	5.57 5.53	15.98 16.22	14.19 14.17	$C_9H_{12}ClO_2P$	34.35 s
IVh	2-Cl-5-MeC_6H_3	115–116/0.1	40.61 40.20	3.98 3.80	29.95 29.66	13.53 12.96	$C_8H_9Cl_2O_2P$	35.76 s

* Lit.: bp 119–121°C/0.14 mmHg [10]. ** Lit.: bp 89–91°C/1 mmHg [11]. *** $^{19}F\{^1H\}$ NMR (C_6D_6, δ, ppm): –116.42 (d, $^6J_{F,P}$ = 2.5 Hz).

tion, which as a whole makes these catalytic processes attractive from industrial point of view.

The next stage of our work was to determine the scope of use of catalytic phosphorylation methodology for the synthesis of the corresponding aroxy(organyl)phosphoryl chlorides.

It should be noted that *O*-phenyl phenylphosphonochloridate **IIa** is used for preparing physiologically active organophosphorus compounds [5] (the main field of preparative application for these unsymmetrical monochlorophosphonates), but *O*-phenyl methylphosphonochloridate **IIb** proved to be the most necessary for this purpose (see [1, 6, 7] and references therein).

Taking into account this fact, we determined the scope of applicability for the method of catalytic phosphorylation to prepare unsymmetrical aroxyphosphoryl chlorides by the example of the corresponding *P*-methyl derivatives. For this purpose, we studied the phosphorylation of a number of commercially available mono- and disubstituted phenols (**IIIa–IIIh**, where **a** Ar = *p*-EtC_6H_4, **b** Ar = *p*-*iso*-PrC_6H_4, **c** Ar = *p*-*tert*-BuC_6H_4, **d** Ar = *p*-ClC_6H_4, **e** Ar = *p*-FC_6H_4, **f** Ar = *p*-$MeOC_6H_4$, **g** Ar = 2,6-$Me_2C_6H_3$, **h** Ar = 2-Cl-5-MeC_6H_3) with twofold excess of methyldichlorophosphonate **Ib** on heating in the presence of magnesium metal as a procatalyst[2] (see Scheme 2).

---

[2] It should be emphasized that this technique provides the best combination of a high performance catalyst and handling convenience; therefore, this variant of catalytic synthesis of *O*-aryl phosphonomonochloridates seems to be preferable.

$$\underset{1:2}{ArOH + MeP(O)Cl_2} \xrightarrow{120°C,\ [Mg]} MeP(O)(OAr)Cl$$

(IIIa–IIIh) **(Ib)** **(IVa–IVh)**

Yield 70–75%

III, **IV**: Ar = *p*-EtC_6H_4 (**a**), *p*-*iso*-PrC_6H_4 (**b**), *p*-*tert*-BuC_6H_4 (**c**), *p*-ClC_6H_4 (**d**), *p*-FC_6H_4 (**e**), *p*-$MeOC_6H_4$ (**f**), 2,6-$Me_2C_6H_3$ (**g**), 2-Cl-5-MeC_6H_3 (**h**)

Scheme 2.

Analytically pure *O*-aryl methylphosphonochloridates (**IVa–IVh**)[3] of spectral grade were isolated from reaction mixture by fractional vacuum distillation in rather high yields (70–75%) (table). Like in the catalytic synthesis of methylphosphonochloridate **IIb**, excess phosphorylating agent is recovered in rather pure state for its reuse.

Thus, these data indicate that the method of catalytic phosphorylation is a general simple, efficient, and industrially feasible approach to the synthesis of various *O*-aryl methylphosphonochloridates, which makes these organophosphorus reagents of practical interest readily available.

Moreover, other compounds of this series and akin molecules of *O*-aryl alkyl(aryl)phosphonochloridate series can be undoubtedly prepared by this procedure by the analogy with *O*-aryl phenylphosphonochloridate **IIa**.

EXPERIMENTAL

$^{31}P\{^1H\}$ NMR spectra of the obtained phosphonochloridates and $^{19}F\{^1H\}$ NMR spectra of phosphonochloridate **IVe** were recorded on a Bruker AV-400 spectrometer operating at 161.98 MHz (^{31}P) and 376.49 MHz (^{19}F). External reference for ^{31}P NMR spectra was 85% H_3PO_4, External reference for ^{19}F NMR spectra was $CFCl_3$.

Phenyldichlorophosphonate **Ia** (Acros, 97%) and methyldichlorophosphonate **Ib** (Aldrich, 98%) were distilled in vacuum prior to use. Phenol and its mono- and disubstituted derivatives **IIIa–IIIh** (Acros, 97–99%), as well as anhydrous magnesium chloride (Acros, 99.9%) and magnesium metal (granules, 20–230 mesh, Aldrich, 98%) were used as received.

Synthesis of *O*-phenyl phenylphosphonochloridate IIa. Phenyldichlorophosphonate **Ia** (40 g, 0.205 mol) and next 0.243 g (0.00256 mol) of finely divided anhydrous magnesium chloride was added to 9.7 g (0.102 mol) of phenol under an argon atmosphere, the mixture was heated for 1.5 h at 120°C until hydrogen chloride evolution ceased, the mixture was kept for 0.5 h in vacuum (~15 mmHg) at ambient temperature and fractionally distilled in vacuum to give 17.2 g of *O*-phenyl phenylphosphonochloridate **IIa**. Yield 66%. Bp 154–155°C/0.5 mmHg. Lit.: bp 152–155°C/0.3 mmHg [8].

$^{31}P\{^1H\}$ NMR (neat, δ, ppm): 24.13 s.

Synthesis of *O*-phenyl methylphosphonochloridate IIb. Molten methyldichlorophosphonate **Ib** (133 g, 1 mol) and next 300 mg (0.0125 mol) of magnesium metal was added to 47 g (0.5 mol) of phenol under an argon atmosphere, the mixture was heated for 2.5 h at 120°C until hydrogen chloride evolution ceased, the mixture was kept for 0.5 h in vacuum (~15 mmHg) at ambient temperature and fractionally distilled in vacuum to give 68 g of *O*-phenyl methylphosphonochloridate **IIa**. Yield 71%. Bp 107°C/1 mmHg. Lit data: bp 80°C/0.5 mmHg [9].

$^{31}P\{^1H\}$ NMR (neat, δ, ppm): 36.31 s.

Synthesis of *O*-aryl methylphosphonochloridates IVa–IVh (general procedure). Molten methyldichlorophosphonate **Ib** (67 g, 0.5 mol) and next 150 mg (6.25 mmol) of magnesium metal was added to 0.25 mol) of mono- or disubstituted phenol **IIIa–IIIh** under an argon atmosphere, the mixture was heated for several hours at 120°C until hydrogen chloride evolution ceased, the mixture was kept for 0.5 h in vacuum (~15 mmHg) at ambient temperature and fractionally distilled in vacuum. The constants, elemental analysis data, and $^{31}P\{^1H\}$ spectral data of the prepared *O*-aryl methylphosphonochloridates are presented in the table.

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research, project no. 14–03–00525-a.

REFERENCES

1. Reddy, P.M., Viragh, C., and Kovach, I.M., *Phosphorus, Sulfur Silicon*, 2002, vol. 177, nos. 6/7, pp. 1597–1600.
2. Kluger, R., Thatcher, G.R.J., and Stallings, W.C., *Can. J. Chem.*, 1987, vol. 65, no. 8, pp. 1838–1844.
3. Gefter, E.L., *Zh. Obshch. Khim.*, 1961. vol. 31, no. 10, pp. 3316–3319.

---

[3] It should be noted that phosphoryl chlorides **IVd** and **IVe** previously obtained by classical methods were high-boiling liquids, whereas both these compounds prepared by catalytic phosphorylation are crystalline solids.

4. Kabachnik, M.I., Zakharov, L.S., Goryunov, E.I., et al., *Zh. Obshch. Khim.*, 1994, vol. 64, no. 6, pp. 902–912.

5. El Mastri, M. and Berlin, K.D., *Org. Prep. Proc. Int.*, 1995, vol. 27, no. 2, pp. 161–169.

6. Makarov, M.V., Leonova, E.S., Rybalkina, E.Yu., et al., *Eur. J. Med. Chem.*, 2010, vol. 45, no. 3, pp. 992–1000.

7. Leonova, E.S., Makarov, M.V., Rybalkina, E.Yu., et al., Eur. J. Med. Chem., 2010, vol. 45, no. 12, pp. 5926–5934.

8. Marsi, K.L., VanderWerf, C.A., and McEwen, W.E., *J. Am. Chem. Soc.*, 1956, vol. 78, no. 13, pp. 3063–3066.

9. Hudson, R.F. and Keay, L., *J. Chem. Soc.*, 1960, no. 4, pp. 1859–1864.

10. Mel'nikov, N.N., Grapov, A.F., and Lebedeva, N.V., *Zh. Obshch. Khim.*, 1966, vol. 36, no. 3, pp. 457–461.

11. Sharova, E.V., Genkina, G.K., Matveeva, E.V., et al., *Izv. Akad. Nauk, Ser. Khim.*, 2014, no. 11, pp. 2546–2550.

Translated by I. Kudryavtsev