Angewandte Chemie

Making Carbon-Phosphorus Bonds

Lewis Acid Catalyzed Room-Temperature Michaelis–Arbuzov Rearrangement**

Pierre-Yves Renard, Philippe Vayron, Eric Leclerc, Alain Valleix, and Charles Mioskowski**

The Michaelis–Arbuzov rearrangement is one of the most extensively investigated reactions in organophosphorus chemistry, and is widely used in many fields of chemistry, from organic synthesis to catalyst design, to prepare phosphonates, phosphinates, and phosphane oxides.[1] This rearrangement involves the reaction of an ester of a trivalent phosphorus species $R^1R^2P{-}OR^3$ with alkyl halides R^4X. Although pentacoordinate phosphorane intermediates cannot be completely excluded,[1d] the generally accepted mechanism for this Michaelis–Arbuzov rearrangement (Scheme 1) involves formation of a phosphonium intermediate through nucleophilic addition of the phosphorus lone pair

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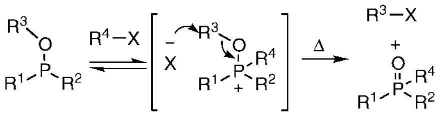
[*] Dr. P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix
Service de Marquage Moléculaire et de Chimie Bioorganique
CEA Saclay, 91191 Gif sur Yvette Cedex (France)
Fax: (+33) 1-69-08-79-91
E-mail: pierre-yves.renard@cea.fr

Dr. C. Mioskowski
Laboratoire de synthèse bioorganique (UMR 7514)
faculté de pharmacie, université Louis Pasteur
74, route du Rhin 67401 Illkirch-Graffenstaden (France)
Fax: (+33) 3-90-24-43-06
E-mail: mioskow@aspirine.u-strasbg.fr

[**] This work was financially supported by the Délégation Générale pour L'Armement.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200250270



Scheme 1. Mechanism of the Michaelis–Arbuzov rearrangement.

to the alkyl halide. This first reversible step is followed by thermally induced intramolecular reaction of the conjugate nucleophile (halide X-) on the α carbon atom of the ester P–OR^3. The overall process gives the simultaneous formation of a new alkyl halide R^{3}X and a tetracoordinate phosphorus species.

Two main flaws have precluded wider use of this reaction. First, the drastic reactions conditions: apart from a with few particularly reactive halides, high reaction temperatures are required. Second, this reaction yields, together with the tetracoordinate P(=O) phosphorus target product, another alkyl halide R^{3}X. However, when this newly formed alkyl halide R^{3}X is more reactive, or less volatile than the initial alkyl halide R^{4}X, a troublesome competition takes place, and mixtures of phosphorylated products are obtained.[2] When desired, the higher reactivity of the second halide R^{3}X can be used to perform an "autocatalytic" Michaelis–Arbuzov rearrangement, by using catalytic amounts of the first alkyl halide R^{4}X (usually methyl iodide).[3] This latter "catalytic" reaction is still limited to a few reactive phosphites, and consumption of the catalyst yields, among other by-products, a corresponding amount of an undesired R^{1}R^{2}R^{4}P(O) phosphorus (v) product.

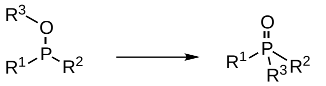
While the Arbuzov rearrangement has long been known, apart from the thermally induced alkyl-halide catalysis[3] already mentioned and the related iodine[4] or alkali-metal–iodide[5] catalysts, the only true thermal Arbuzov-rearrangement catalyst described to date is nickel(II) chloride.[1d,6] A few intramolecular rearrangements, limited to highly reactive phosphinites or requiring very high temperature or pressure, have been described,[7] and no efficient room-temperature catalysts have been described so far. Our idea was to test the use of oxophilic Lewis acids which could bind to the oxygen atom, and thus weaken the O–C bond, enhancing the reaction rate of the second, energy-requiring step of the Arbuzov rearrangement.

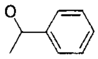
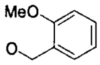
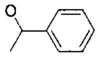
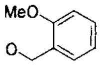
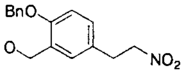
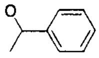
A first screening was conducted on methyl diphenylphosphinite (**1**; see Supporting Information), described as one of the most isomerization-sensitive phosphinites.[9] When the reaction was performed at room temperature, in CDCl$_3$ using 3 M phosphinite **1** and 5% Lewis acid catalyst, most of the Lewis acids described as epoxide ring-opening activators (and thus efficient oxygen-binding Lewis acids) did catalyze an efficient isomerization of **1** into methyldiphenylphosphane oxide (**2**). The best catalysts were found to be BF$_3$·OEt$_2$ and trimethylsilyl trifluoromethane sulfonate (TMSOTf; 87 and 91% yield, respectively). Moderate heating (60°C) resulted in complete transformation within an hour (see Supporting Information).

The reaction velocity proved to be moderately sensitive to substrate concentration and required a polar and aprotic solvent ($CHCl_3 > CH_2Cl_2 \approx CH_3CN \gg$ benzene, or toluene). Moreover, while an increase from 5 to 20 molar% of catalyst did somewhat speed up the reaction, use of over 50 molar% of catalyst diminished the reaction rate, and use of excess catalyst completely stopped the reaction. This observation, together with the substrate-concentration sensitivity, is a first indication of a bimolecular process involving both a catalyst-activated species and a phosphinite that is not coordinated to a Lewis acid (see below).

Optimized reaction conditions were then sought for a wide array of substrates. As illustrated in Table 1, addition of 5 molar% TMSOTf to phosphinite bearing primary *O*-alkyl

Table 1: Lewis acid promoted Arbuzov rearrangement of phosphinites.[a]



Entry	R^1	R^2	OR^3	Reaction conditions[b]	Reaction time [h]	Yield[c] [%]
1	Ph	Ph	OMe	A	72	87
2	Ph	Ph	OMe	B	72	91
3	Ph	Ph	OMe	C	1	98
4	Ph	Ph	OMe	D	1	95
5	Ph	Ph	OEt	C	18	85
6	Ph	Ph	OBn	A	72	87
7	Ph	Ph	OBn	C	3	90
8	Ph	Ph		C	18	86
9	Ph	Ph	 MeO O	C	2	91
10	Et	Et	OBn	A	72	92
11	Ph	Me	OMe	C	3	75
12	Ph	Me	OEt	C	18	63
13	Ph	Me		C	3	78[d]
14	Ph	Me	 MeO O	A	72	68
15	Ph	Me	 BnO O NO$_2$	C	18	44
16	Ph	*t*Bu	OBn	C	72	52
17	Ph	*t*Bu	OMe	C	72	47
18	Ph	*t*Bu		C	72	20[d]
19	*t*Bu	*t*Bu	OMe	E	72	degradation
20	cy[e]	cy	OMe	E	72	traces

[a] Unless stated, the reaction was performed at a phosphinite concentration of 1.0 M in chloroform with 5 mol% catalyst. [b] Reaction conditions: A: TMSOTf, 25°C, B: BF$_3$.OEt$_2$, 20°C, C: TMSOTf, 60°C, D: BF$_3$OEt$_2$, 60°C, E: no solvent, TMSOTf, 80°C. [c] Yield of purified phosphane oxide. [d] 2 isomers 1:1. [e] Cyclohexyl.

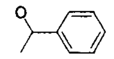
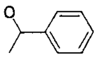
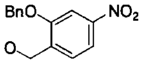
groups initiated an Arbuzov rearrangement to phosphane oxide with fairly high yields in a few days at room temperature when the phosphorus(III) ester was reactive (methyl or benzyl, entries 1, 6, 10, and 14). Use of $BF_3.OEt_2$ also gave satisfactory results (entries 2, 4).

Interestingly, *O*-ethyl phosphinites, which are far less reactive in Arbuzov rearrangements, also isomerize when moderately (60 °C) heated (entries 5 and 12), as do activated phosphinites bearing secondary *O*-alkyl groups (*sec*-phenethyl esters, entries 8, 13, and 18).

Reaction is as yet limited to the migration of primary alkyl groups or activated secondary alkyl groups, as is the Arbuzov rearrangement involving alkyl halides. Sterically hindered alkyl substituents at the phosphorus center also dramatically hamper the rearrangement process (entries 18–20, and to a lesser extent, entries 16 and 17).

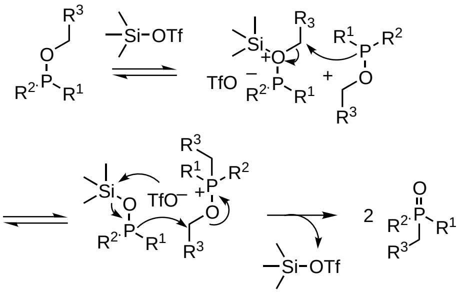
The reaction was then extended to less reactive phosphonites and phosphites. As illustrated in Table 2, Arbuzov rearrangement to the corresponding tetracoordinate phosphorus esters also readily occurred. As observed for the bimolecular Michaelis–Arbuzov rearrangement using alkyl halides, and as described for phosphinites (see Table 1), deactivation of the α carbon atom of the rearranging ester drastically lowers the rates of the reaction. A particularly high selectivity with respect to the migrating ester group was observed (benzyl > methyl ≫ ethyl, in the reactions given in entries 6 and 7, only traces of ethyl-migration products were detected).

Table 2: TMSOTf-promoted Arbuzov rearrangement of phosphonites and phosphites.

Entry	R^1	R^2	OR^3	Reaction conditions[a]	Yield[b] [%]
1	Ph	OMe	OMe	20 °C, 96 h	82
2	Ph	OEt	OEt	60 °C, 72 h	68
3	Ph			60 °C, 18 h	72
4	Ph	O*i*Pr	O*i*Pr	60 °C, 72 h	traces
5	OEt	OEt	OMe	20 °C, 96 h	80
6	OEt	OEt	OMe	60 °C, 18 h	96
7	OEt	OEt	OBn	60 °C, 18 h	87
8	OMe	OMe	OMe	60 °C, 18 h	98
9	OEt	OEt		60 °C, 3 h	93

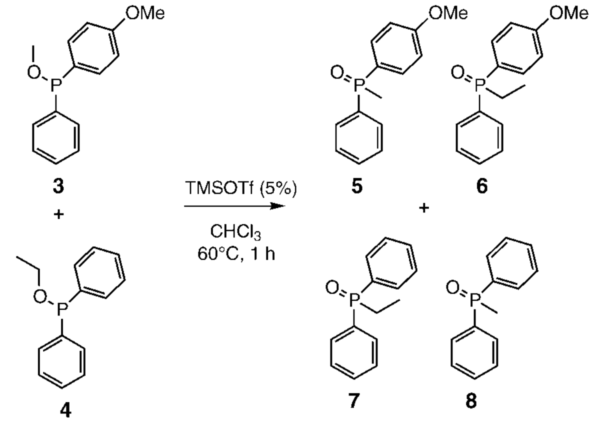
[a] The reaction was performed at a concentration of 1.0 M in chloroform with 5 mol% catalyst. [b] Yield of phosphi(o)nates.

As previously observed, with inhibition of the reaction by excess catalyst, and contrary to the intramolecular mechanism we originally proposed, much of the experimental evidence is strongly in favor of the bimolecular process outlined in Scheme 2.



Scheme 2. Proposed mechanism for Lewis acid catalyzed Arbuzov rearrangement.

- Whatever the oxophilic Lewis acid used (TMSOTf, TBSOTf (TBS = *tert*-butyldimethylsilyl, $Cl_2C{=}N(Me)_2^+$ TfO^-, $Sn(OTf)_2$, and BF_3OEt_2), the reaction occurred in the same way, and the detected reaction intermediates give similar ^{31}P NMR spectroscopy data (major peak at $\delta = 75.2$ to 75.4 ppm for the reaction with methyl diphenylphosphite (**1**), corresponding to the oxonium intermediate).
- No alkyl trifluoromethane sulfonate has been observed in the crude reaction mixtures.
- No room-temperature TMSOTf-catalyzed rearrangement was observed with *S*-methyl diphenylphosphinithioite. This observation is in favor of an oxonium intermediate, since sulfur atoms are less susceptible towards silylation.
- An equimolar mixture of phosphinite **3** and **4** gave an approximately 1:1:1:1 mixture of all possible phosphane oxides **5**–**8** (Scheme 3), as indicated by both ^{31}P NMR spectroscopy and GC/MS experiments. Obtaining an approximately 1:1:1:1 mixture, although the kinetic rates for the migration of individual OMe and OEt groups are different (compare Table 1, entries 3 and 5), not only supports the bimolecular aspect of the mechanism, but also indicates that, if this mechanism is correct, the rate-limiting step is the second one (silyloxyphosphinite addition to the phosphonium intermediate).
- Addition of a catalytic (20%) amount of methyl trifluorome-



Scheme 3. Lewis acid catalyzed Arbuzov rearrangement of an equimolar amount of phosphinites **3** and **4**.

thane sulfonate to **1** gave no rearrangement product **2** at room temperature. Only formation of the corresponding amounts of the quasi-phosphonium salt $[MeO(Ph)_2PMe]^+[OTf]^-$ was detected (^{31}P NMR: $\delta =$ 77.8 ppm in $CDCl_3$). Only heating the reaction mixture to 100 °C, without solvent, gave the formation of **2**, about 15 %, together with a mixture of starting phosphinite, and the oxidation product *O*-methyl diphenylphosphinate.

- Equimolar mixtures of phosphane oxide diastereoisomers (Table 1, entries 13 and 18) and racemic mixtures (Table 1, entry 8) were obtained, even when enantiomerically pure *sec*-phenethyl alcohols were used.
- For the Arbuzov rearrangement, a bimolecular process involving nucleophilic addition of phosphite to phosphonium has already been described,[8] and confirmed by kinetic experiments.[3b] This is actually the only possible mechanism when methyl triflate is used as a halide equivalent, since the nucleophilicity of the corresponding trifluoromethane sulfonate anion TfO^- is particularly low.[9]

In conclusion, we have demonstrated that use of an oxophilic Lewis acid, such as $BF_3.OEt_2$ or TMSOTf, could induce an Arbuzov-like rearrangement. The reaction conditions are particularly mild, since in most cases, room temperature or moderate heating are sufficient, which has not been described before for Arbuzov rearrangements. The scope of the reaction has been extended to phosphites, phosphinites, and phosphonites. As in the corresponding Arbuzov rearrangement using alkyl halides, the migrating groups are limited to both primary and activated secondary alkyl groups. The reaction mechanism has also been clarified, and a bimolecular process is proposed.

This room-temperature, catalyzed Arbuzov rearrangement, offers new reaction pathways for the synthesis of compounds containing carbon–phosphorus bonds, for example, key intermediates for the synthesis of both physiologically active drugs and basic chemical building blocks (via further Wittig or Horner–Wadsworth–Emmons reactions, for instance).

Received: October 1, 2002
Revised: December 18, 2002 [Z50270]

Keywords: Lewis acids · michaelis–arbuzov rearrangement · phosphorus · rearrangement

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[1] a) A. Michaelis, R. Kaehne, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1408; b) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 687; c) The *Chemistry of Organophosphorus Compounds* (Ed.: F. H. Hartley), Wiley, New York, **1996**; d) A. K. Bhattacharya, G. Thyagarajan, *Chem. Rev.* **1981**, *81*, 415–430.

[2] M. Saady, L. Lebeau, C. Mioskowski, *Tetrahedron Lett.* **1995**, *36*, 5183–5186; M. Saady, L. Lebeau, C. Mioskowski, *Helv. Chim. Acta* **1995**, *78*, 670–678.

[3] a) J. E. Griffiths, A. B. Burg, *J. Am. Chem. Soc.* **1962**, *84*, 3442–3450; b) E. S. Lewis, D. Hamp, *J. Org. Chem.* **1983**, *48*, 2025–2029; c) H. J. Woerz, E. Quien, H. P. Latscha, *Z. Naturforsch. B* **1984**, *39*, 1706–1710.

[4] a) V.K. Yadav, *Synth. Commun.* **1990**, *20*, 239–246; b) H. Brunner, W. Zettlmeier, *Bull. Soc. Chim. Belg.* **1991**, *100*, 247–257.

[5] a) V. P. Kukhar', E. I. Sagina, *Zh. Obshch. Khim.* **1976**, *46*, 2686–2689; b) U. Rose, *J. Heterocycl. Chem.* **1991**, *28*, 2005–2012; c) K. Toshima, H. Yamagushi, T. Jyojima, Y. Nogushi, M. Nakata, S. Matsumura, *Tetrahedron Lett.* **1996**, *37*, 1073–1076.

[6] W. Flisch, P. Rußkamp, W. Langer, *Liebigs Ann. Chem.* **1985**, 1413–1421.

[7] a) T. Janecki, R. Bodalski, *Synthesis* **1990**, 799–801; b) R. S. Macomber, D. E. Rardon, D. M. Ho, *J. Org. Chem.* **1992**, *57*, 3874–3881; c) S. Demay, K. Harms, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 4981–4984; d) W. G. Bentrude, S. G. Lee, K. Akutagawa, W. Ye, Y. Charbonnel, *J. Am. Chem. Soc.* **1987**, *109*, 1577; e) D. Shukla, C. Lu, N. P. Schepp, W. G. Bentrude, L.J. Johnston, *J. Org. Chem.* **2000**, *65*, 6167–6172; f) T. Wada, Y. Sato, F. Honda, S.-I. Kawahara, M. Sekine, *J. Am. Chem. Soc.* **1997** *119*, 12710–12721; g) M. R. Banks, R. F. Hudson, *J. Chem. Soc. Perkin Trans. 2* **1989**, 463–467; h) A. E. Arbuzov, K. V. Nikonorov, *Zh. Obshch. Khim.* **1948**, *18*, 2008; h) V. Mark, *Mech. Mol. Migr.* **1969**, *2*, 319–437. Noteworthy is the spontaneous rearrangement of particularly activated triarylmethyl phosphorus-3-esters, for instance D. V. D. Hardy, H. H. Hatt, *J. Chem. Soc.* **1952**, 3778–3783, and references therein.

[8] a) P. Rumpf, *Bull. Soc. Chim. Fr.* **1951**, *18*, 128; b) T. B. Brill, S. J. Landon, *Chem. Rev.* **1984**, *84*, 577–585.

[9] a) K. S. Colle, E. S. Lewis, *J. Org. Chem.* **1978**, *43*, 571–574; b) E. S. Lewis, K. S. Colle, *J. Org. Chem.* **1981**, *46*, 4369–4372.