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Trimethylsilyl Halide-Promoted Michaelis-Arbuzov Rearrangement

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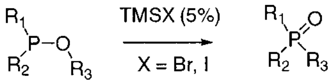
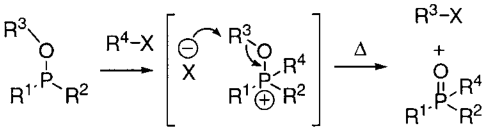
ABSTRACT



We describe a new, straightforward, and easy-to-handle method for achieving an unprecedented trimethylsilyl halide-catalyzed Michaelis–Arbuzov-like rearrangement. This rearrangement occurs at temperatures from room temperature to 80 °C and does not require addition of any alkyl halide. The scope and limitations of this new reaction are explored, as well as its mechanism.

The Michaelis−Arbuzov rearrangement is one of the most extensively investigated reactions in organophosphorus chemistry and is widely used to prepare phosphonates, phosphinates, and phosphine oxides.[1] This rearrangement involves the reaction of an ester of trivalent phosphorus species $R^1R^2P-OR^3$ with alkyl halides R^4X. Although pentacoordinated phosphorane intermediates cannot be completely excluded,[1d] the generally accepted mechanism for this Michaelis−Arbuzov rearrangement, described in Scheme 1, involves formation of a phosphonium intermediate. This first reversible step is followed by thermally induced intramolecular reaction of the conjugate nucleophile (halide X^-) on the α-carbon of the ester $P-OR^3$. The overall process ultimately results in the simultaneous formation of a new alkyl halide R^3X and a pentavalent P═O phosphorus species.

Scheme 1. Mechanism for Arbuzov Rearrangement



Two main flaws have precluded a wider use of this reaction. First, drastic reaction conditions are involved, as high reaction temperatures are required. Second, this reaction yields, together with the pentavalent P═O phosphorus targeted product, another alkyl halide R^3X. Indeed, when this newly formed alkyl halide R^3X is more reactive or less volatile than the departing alkyl halide R^4X, a troublesome competition takes place, and mixtures of phosphorylated products $R^1R^2\mathbf{R^4}P(O)$ and $R^1R^2\mathbf{R^3}P(O)$ are obtained. This side reaction cannot be excluded when benzylic trivalent phosphorus esters are used, unless experimental tricks are used.[2] Interestingly, when desired, this higher reactivity of the second halide R^3X can be used to perform an "autocatalytic" Michaelis-Arbuzov rearrangement, using catalytic amounts of a first alkyl halide R^4X (usually methyl iodide).[3] This latter catalysis is still limited to few reactive phosphites, and consumption of the catalyst results in, among other byproducts, the formation in the same

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

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

[3] Griffiths, J. E.; Burg, A. B. *J. Am. Chem. Soc.* **1962**, *84*, 3442−3450.

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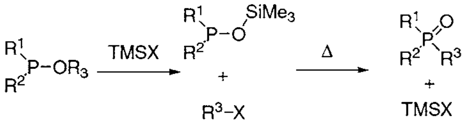
amount of catalyst R^4X, of the corresponding undesired $R^1R^2\mathbf{R^4}P(O)$.

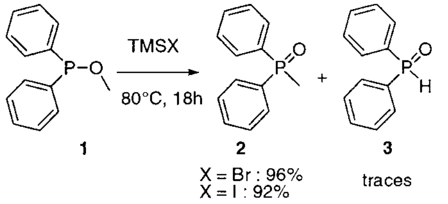
In an effort to take advantage of this "autocatalytic" rearrangement and to prevent use of an auxiliary but troublesome and useless alkyl halide that lowers the final yield, we investigated the use of a catalytic amount of trimethylsilyl halide TMSI or TMSBr on phosphite in a sealed reaction vessel. The aim was to form in situ the required alkyl halide together with a particularly reactive phosphorus(III) silyl ester (Scheme 2).[4]

Scheme 2. Proposed Mechanism for TMSX-Catalyzed Rearrangement



We found, as described in Scheme 3, that when the reaction was performed with methyl diphenyl phosphinite **1**, in sealed tubes and at moderate temperature (80 °C), such an Arbuzov rearrangement did take place with either TMSI or TMSBr (20 mol %). No reaction was observed with TMSCl. After overnight heating at 80 °C, cooling the mixture to room temperature afforded a white (TMSBr) to pale brown (TMSI) solid. ^{31}P NMR analysis showed that the products obtained were mainly phosphine oxide **2**, together with traces of hydrolysis product diphenylphosphine oxide **3**. After a single recrystallization in cyclohexane, white crystals of phosphine oxide **2**[5] were obtained in 96% (TSMBr) and 92% (TMSI) yields. Interestingly, the reaction also occurred when performed at room temperature in dry CH_2Cl_2 (0.5 M phosphonite **1**), with 10 mol % catalyst, albeit much slower. After 5 days, phosphine oxide **2** was isolated in 64% (TMSBr) and 75% (TMSI) yield. NMR analysis of the crude material revealed the presence of both hydrolysis product diphenylphosphine oxide **3** (estimated as 15 and 12%, respectively) and oxidation product *O*-methyl diphenyl phosphonate, related to unreacted starting material (estimated as 11 and 2%, respectively).

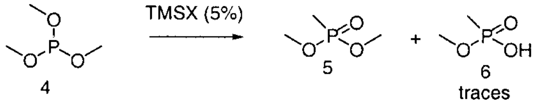
Scheme 3. Treatment of Phosphinite **1** with Trimethylsilyl Halide



The proposed reaction mechanism was further confirmed by the observation that, when treated with methyl iodide, *O*-trimethylsilyloxy diphenylphosphinite (prepared from diphenylphosphine oxide **3** and hexamethyldisilazane)[6] led to phosphine oxide **2** under the same reaction conditions (87% yield when heated overnight at 80 °C and 83% yield when stirred for 5 days at room temperature).[7] ^{31}P NMR analyses of the crude reaction mixture (in $CDCl_3$) did not provide evidence of nucleophilic addition of TMSI on phosphorus ($Ph_2P{-}Si$ phosphonium salts display a ^{31}P NMR shift at ca. 54 ppm;[8] the only detected reaction intermediate displayed a 75.2 ppm ^{31}P NMR shift and could be attributed to the phosphonium salt corresponding to the alkylation of *O*-trimethylsilyloxy diphenylphosphinite by methyl iodide).[9]

Interestingly, such an Arbuzov rearrangement is not limited to heat-sensitive and reactive diphenylphosphinites.[10] Scheme 4 indicates, for instance, yields in *O*,*O*-dimethyl methylphosphonate **5** when trimethyl phosphite **4** is placed in the presence of trimethylsilyl bromide or iodide.

Scheme 4. Yield of Isolated Methylphosphonate **5** from Trimethyl Phosphite **4** Rearrangement Using TMSX as a Catalyst



	RT 24h	50°C 6h	100°C 3h
X = I	52%	95%	89%
X = Br	5%	62%	91%

Catalyst purity and quality proved to be a pivotal issue for higher rearrangement yields. Use of exceedingly sensitive trimethylsilyl iodide was particularly detrimental when it was degraded and gave irreproducible results according to the batch used. Thus, from a practical point of view, although longer reaction times were required, use of trimethylsilyl bromide was favored.

To determine the scope of this catalyzed Arbuzov rearrangement, various *O*-alkyl phosphinites were assayed

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[4] (a) Thottathil, J. K.; Przybyla, C. A.; Moniot, J. L. *Tetrahedron Lett.* **1984**, *25*, 4737−4740. (b) Thottathil, J. K. *Handbook of Organophosphorus Chemistry*; Engeln, R., Ed.; Marcel Dekker, Inc.: New York, 1992. (c) Matqiari, M.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Org. Lett.* **2001**, *3*, 659−662.

[5] Melting point (109−111°C) and spectroscopic data were in perfect agreement with commercially available phosphine oxide and literature data; see, for example: Wittig, G.; Maercker, A. *Chem. Ber*. **1964**, *97*, 747−768. Even, L.; Florentin, D.; Marquet, A. *Bull. Soc. Chem. Fr.* **1990**, *6*, 758−768. Elementary analysis was also in perfect accordance (calcd for $C_{13}H_{13}OP$: C, 72.22; H, 6.06. Found: C, 72.28; H, 6.27).

[6] Hansen, H. I.; Kehler, J. *Synthesis* **1999**, 1925−1930.

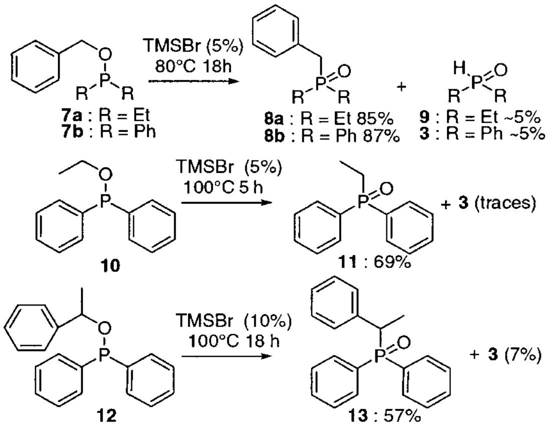
[7] See also: Bondarenko, N. A.; Tsvetkov, E. N. *J. Gen. Chem. USSR (Engl. Trans.)* **1989**, *59*, 1361−1364.

[8] Gomeyla, N. D.; Feschenko, N. G. *J. Gen. Chem. USSR (Engl. Trans.)* **1991**, *61*, 2338−2341.

[9] (a) Romanenko, V. D.; Tovstenko, V. I.; Markovskii, L. N. *Synthesis* **1980**, 823−825. Walther, B.; Schöps; Kolbe, W. *Z. Chem.* **1980**, *20*, 189−190. (c) Laurenço, C.; Villien, L.; Kaufmann, G. *J. Chem. Res., Miniprints* **1982**, 0232−0252. (d) Colle, K. S.; Lewis, E. S. *J. Org. Chem.* **1978**, *43*, 571−574.

[10] Arbuzov, A. E.; Nikonorov, K. V. *Zh. Obschch. Khim.* **1948**, *18*, 2008.

Scheme 5. Rearrangement of Phosphinites

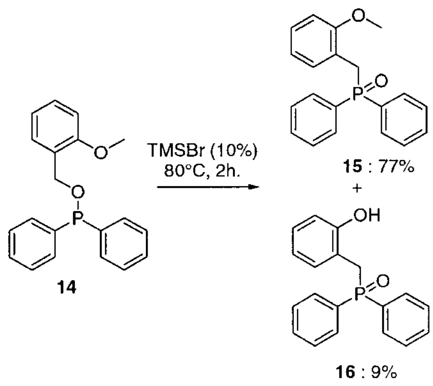


(Scheme 5). Activated *O*-benzyl phosphinites such as **7a** or **7b** were readily transformed into the corresponding phosphine oxide through heating at 80 °C with 5% TMSBr as a catalyst. After heating for 1 h, the yield was 70% for **8a** and 78% for **8b**. Overnight heating resulted in complete disappearance of the starting material and in 85% (**8a**) and 87% (**8b**) isolated yields. In both cases, only traces of hydrolysis dialkylphosphine oxides **3** and **9** were detected.

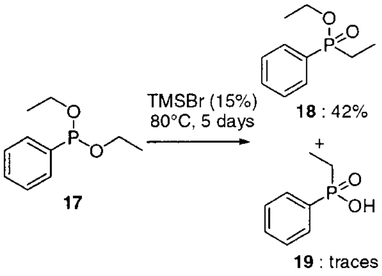
Transfer of an ethyl group (**10**) or of a secondary benzylic (2-phenethyl) group (**12**) required higher temperatures (100 °C) and, after overnight heating, gave somewhat lower yields. Altogether, heating the reaction mixture for 5 days at 100 °C gave an acceptable 69% yield of ethyldiphenyl phosphine oxide **11** and 57% yield of 2-phenethyl diphenyl phosphine oxide **13**. On the other hand, O to P transfer of unactivated secondary alkyl phosphorus(III) esters was not observed. When *O*-isopropyl or *O*-menthyl diphenylphosphinite was heated with trimethylsilyl bromide or iodide, no rearrangement took place. Among many byproducts, only hydrolysis and elimination products were identified.

Another limitation of the method is found with trimethylsilyl halide-sensitive groups. For instance, TMSBr-catalyzed rearrangement of phosphinite **14** (Scheme 6) yielded 77% phosphine oxide **15** but was accompanied by 9% ether cleavage product **16**. On the other hand, when ethyl ester groups were used such as phosphonite **17** (Scheme 7), ethyl group transfer proved to be more difficult (after 5 days of heating at 80 °C, a modest 42% yield of phosphinate **18** was isolated, together with 38% oxidized starting material). Yet, since *O*-ethyl phosphi(o)nates are moderately sensitive to dealkylation by TMSBr, only traces of phosphinic acid **19** were detected.

Scheme 6. Rearrangement of 2-Methoxybenzyl Diphenylphosphinite **14**

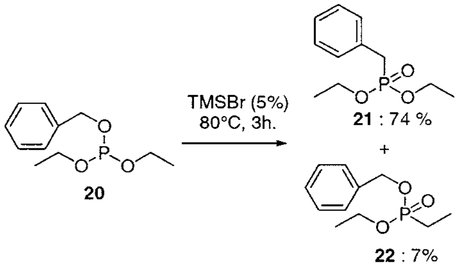


Scheme 7. Phosphonite **17** Arbuzov Rearrangement



Taking advantage of the great difference in reactivity between ethyl and activated benzyl phosphorus(III) ester groups afforded a relatively high selectivity according to the transferred alkyl group. For instance, when diethylbenzyl phosphite **20** (Scheme 8) was heated at 80 °C in the presence of 5% TMSBr, *O*,*O*-diethyl benzylphosphonate **21** was recovered as the major product (74% isolated yield), together with 7% ethyl group transfer product **22**, and traces of diethyl phosphite.

Scheme 8. O to P Alkyl Group Transfer Selectivity



Interestingly, the reaction also occurred, albeit in low yields, with cyclic phosphonites such as **25** or **26**,[11] affording ring contraction phosphinate **27** in 48% isolated yield and phosphinate **28** in 42% isolated yield (Scheme 9),[12] together with ring-opening and tarry polymeric byproducts. The proposed mechanism is formation of an intermediate acyclic silyloxy phosphonite, which could either further react through Arbuzov rearrangement with another phosphite, ending up

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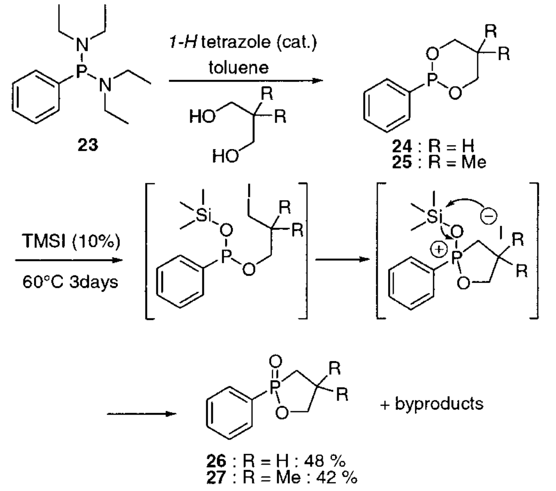
[11] Contrary to results obtained with other phosphorus(III) esters, the best final yields were obtained when the cyclic phosphonite was prepared as described in Scheme 9 from the corresponding phosphoramidite **23**, not from the chlorophosphonite.

Scheme 9. Cyclic Phosphonites



in oligomerization, or intramolecularly rearrange through addition at its phosphorus atom, yielding ring restriction products as shown in Scheme 9.

In conclusion, by directly forming an alkyl halide through trimethylsilyl halide addition to phosphorus(III) esters, we propose a new and catalytic version of the Arbuzov rearrangement. The reaction process does not require the use of any alkyl halide, which could, in some cases, prove to be troublesome. The starting material for the overall O to P alkyl group transfer is a phosphorus(III) ester, which could be very easily obtained from the corresponding alcohol. Yields are very high and amounts of byproducts limited.

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Supporting Information Available: Experimental procedures and data for compounds **2**, **5**, **8a**, **8b**, **11**, **13**, **15**, **16**, **18**, **21**, **26**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Both cyclic phosphinates conformed to the literature description: (a) Chaudhry, A.; Harger, M. J.; Shuff, P.; Thompson A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1347−1352. (b) Singh, G.; Reddy, G. S.; Calabrese, J. C. *J. Org. Chem.* **1984**, *49*, 5132−5136.