View Article Online / Journal Homepage / Table of Contents for this issue

A green procedure for the regio- and chemoselective hydrophosphonylation of unsaturated systems using CaO under solventless conditions†

Elisa Martínez-Castro,[a] Óscar López,[a] Inés Maya,[a] José G. Fernández-Bolaños*[a] and Marino Petrini*[b]

Received 21st April 2010, Accepted 2nd June 2010
First published as an Advance Article on the web 11th June 2010
DOI: 10.1039/c0gc00026d

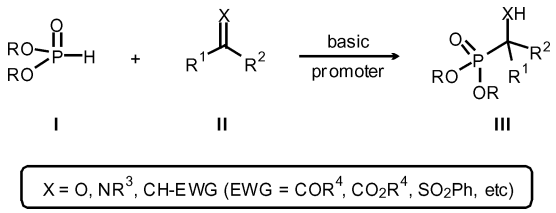
Published on 11 June 2010. Downloaded by State University of New York at Stony Brook on 27/10/2014 04:57:16.

Diethyl phosphite and diphenylphosphine add to a series of unsaturated derivatives using environmentally-friendly calcium oxide as a basic promoter under solventless conditions at room temperature. The corresponding adducts are obtained in a totally regioselective fashion, *via* a 1,4-addition on α,β-unsaturated esters and sulfone, and a 1,2-addition on cyclic and acyclic α,β-unsaturated aldehydes and ketones.

Organophosphorus chemistry has experienced a rapid development, as phosphorous-containing compounds not only exert pivotal biological activities,[1] but have also found a wide range of important industrial and practical applications; thus, they are widely used as pest control agents, as pharmaceutical drugs and as catalysts in numerous processes.[2] Furthermore, the enormous versatility of organophosphorus reagents has allowed the development of an arsenal of phosphorus-based reactions of great importance in current organic chemistry; in this context, optically active organophosphorus compounds have been used as valuable building blocks in natural product syntheses,[3] and have been exploited as ligands in enantioselective reactions.[4]

A very common and powerful way of accessing organophosphorus compounds is the use of reactions involving the formation of C–P bonds with phosphorus-based nucleophiles; thus, the metal-catalyzed addition of dialkyl phosphites to unsaturated derivatives[5] and heteroaryl compounds[6] has been reported. Furthermore, the addition of compounds containing labile P–H bonds such as **I** to activated alkenes or alkynes **II** *via* the phospha-Michael addition (the Pudovik reaction),[7] and the addition of trialkyl or dialkyl phosphites to aldehydes, ketones and imines **II** (the Abramov reaction)[8] to give **III** have received great attention as a way of accessing various organophosphorus derivatives, many of them exhibiting biological activities (Scheme 1).[9]

Such compounds have been prepared by using metal catalysts, including the asymmetric versions,[10] non-metallic heterogeneous[11] and brominated catalysts.[12] Some of these syntheses suffer from the drawbacks of harsh reaction conditions,



Scheme 1 Addition of dialkyl phosphites to unsaturated derivatives.

utilization of toxic and expensive catalysts or low yields (provoked by reversibility of the reaction, and cleavage of the C–P bond).[13]

A very important issue of this process concerns the regioselectivity displayed when α,β-unsaturated carbonyl derivatives are used as substrates in the reaction with dialkyl phosphites. The regioselectivity observed strongly depends on the basic promoter employed, and it can differ considerably between substrates of similar structure. As an example, potassium fluoride on basic alumina, under solventless conditions, is able to provide the 1,2-addition product in the reaction of diethyl phosphite with 3-phenyl-2-propenal, while the 1,4-addition largely predominates when 3-buten-2-one is employed with the same nucleophile.[14]

As an attempt to improve the Pudovik- and Abramov-type reactions on electrophilic substrates, we searched for *green conditions*, avoiding the use of solvents and expensive or hazardous catalysts; so, simple heterogeneous catalysts under solventless conditions appeared as a promising synthetic route. We have also investigated the regioselectivity of the reaction in the presence of several electrophilic moieties. In this context, the addition of diethyl phosphite on methyl acrylate **1** using solid Na_2CO_3 (1.0 equiv.), or polymer-supported Na_2CO_3 (0.5 equiv.) led to either no reaction or low yield, respectively. Although the use of MgO has been reported[15] for the Abramov reaction on simple aromatic aldehydes, in our hands it did not work when methyl acrylate was used as substrate. The utilization of eco-friendly and inexpensive CaO as a promoter for nucleophilic additions has been rather neglected, and only a sparing number of examples in which it promotes nitroaldol reaction and conjugate addition of methanol to 3-buten-2-one have been reported.[16] Satisfactory results for these processes are recorded only upon activation of the oxide at 873 K. We were delighted to observe that *unactivated* CaO (1.0 equiv.) under solventless conditions and at rt was able to promote the conjugate addition of diethyl phosphite to methyl acrylate **1** leading to phosphonate **9** in excellent yield (80%) (Table 1, Entry 1). The same behavior was observed using diphenyl phosphine as nucleophile to give derivative **10** in a 49% yield (Table 1, Entry 2).

[a]*Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 1203, E-41071, Seville, Spain. E-mail: bolanos@us.es; Fax: +34 954 624960; Tel: +34 954 550996*
[b]*School of Science and Technology, Chemistry Division, Università di Camerino, via S.Agostino, 1, I-62032, Camerino, Italy. E-mail: marino.petrini@unicam.it; Fax: +39 0737 402297; Tel: +39 0737 402253*

† Electronic supplementary information (ESI) available: General experimental and characterization data for compounds **9–17**, **20**. See DOI: 10.1039/c0gc00026d

View Article Online

Published on 11 June 2010. Downloaded by State University of New York at Stony Brook on 27/10/2014 04:57:16.

Table 1 Addition of diethyl phosphite and diphenylphosphine to various unsaturated compounds

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1	**1**	**9**	18	80
2	**1**	**10**	18	49[b]
3	**2**	**11**	18	91
4	**3**	**12**	18	82
5	**4**	**13**	3	87[c]
6	**5**	**14**	48	78
7	**6**	**15**	72	67
8	**7**	**16**	48	86
9	**8**	**17**	18	90

[a] Yield of pure isolated product with $(EtO)_2PH(O)$ as the nucleophile. [b] Ph_2PH was used as the nucleophile. [c] Reaction carried out on a larger scale (10.0 mmol of **4**) gave adduct **13** in 74% isolated yield with a reaction time of 5 h.

The antiperiplanar arrangement of the carbonyl and the phosphonyl groups in the major conformation of compound **9** is supported by the high value of the vicinal $^3J_{P,CO}$ coupling constant (18.2 Hz).[17] CaO also proved to be a good catalyst for the conjugated addition to unsaturated sulfones, such as phenylvinyl sulfone **2** to afford phosphonate **11** in excellent yield (91%, Table 1, Entry 3). Nevertheless, when acyclic α,β-unsaturated aldehydes and ketones are used as substrates (acrolein **3** and methyl vinyl ketone **4**, Table 1, Entries 4,5) the conjugate addition process is largely suppressed and the 1,2-addition products **12** and **13** are the only final products recovered in substantial amount from the reaction mixture (82 and 87% yields, respectively). A scale-up procedure for the synthesis of compound **13** was also carried out, but this gave only a limited yield decrease (74%, Table 1, footnote *c*). This unusual regioselectivity is seldom observed with dialkyl phosphites, since 1,4-addition using different conditions (*e.g.* DBU, superbases, KOH and alumina-supported KOH)[18] or Zn-based catalysts[19] has been generally reported. The particular activity of CaO in promoting 1,2-addition is further corroborated by the results obtained in the reaction of less reactive enones, such as 2-cyclohexenone **5** and 2-cyclopentenone **6** with diethyl phosphite, which also proceed smoothly at room temperature to give hydroxy derivatives **14** and **15** (78% and 67% yield respectively, Table 1, Entries 6,7), although longer reaction times were needed.[20] In contrast, 1,4-adduct was obtained by heating 2-cyclopentenone with triethyl phosphite in phenol at 100 °C.[21] The 1,2-addition was proved by NMR, as compounds **12–15** showed peaks in ^{1}H- and ^{13}C-NMR spectra in the alkene region (roughly 6.1–5.2 ppm, 138–115 ppm). A possible explanation for the regioselectivity displayed by unsaturated carbonyl derivatives **3–6** with CaO may be found in the enhancement of the electrophilic character of the carbonyl group provided by the coordination of the oxygen atom with the metal cation on the solid surface. This interaction has been evidenced by Hattori *et al.* evaluating the IR spectra of aldehydes adsorbed on MgO, assuming that similar behavior is predictable for related metal oxides.[16] An attempt to speed up the reaction by heating the solid mixture containing methyl vinyl ketone **4** and diethyl phosphite to 60 °C was effective in reducing the reaction time to 1.5 h. However, a reversal in regioselectivity was observed at that temperature since a 1 : 4 ratio of 1,2- to 1,4-adduct was obtained in 82% yield (see ESI for details†). This result confirms that 1,2-addition is a kinetically controlled process (and thus favored at low temperatures), while upon heating, formation of the thermodinamically more stable conjugated adduct predominates.

Chemoselectivity of two competing reactions involving diethyl phosphite was also assessed on phenacyl bromide **7**; of the two competing reactions, namely the carbonyl addition, and the S_N2 reaction on the α-carbon, only the former took place to give **16** (86%, Table 1, Entry 8), indicating the addition to be a faster process than the nucleophilic substitution.

Methyl (2-bromomethyl)acrylate **8** represents an interesting substrate, since in reactions with nucleophiles it often undergoes a S_N2' reaction involving conjugate addition to the C=C bond with subsequent bromide elimination which restores the unsaturation in the final product. This trend was also observed in the reaction of **8** with diethyl phosphite that produced **17** in 90% yield (Table 1, Entry 9). Unexpectedly, fast transesterification of the methyl ester moiety, probably promoted by CaO during the work-up step with ethanol, finally afforded the ethyl ester of the phosphonylated product **17**. The reaction outcome was evidenced by the alkene signals in the ^{1}H-NMR (6.25 and 5.75 ppm) and ^{13}C-NMR (131.5, 128.5 ppm) spectra, as well as the absence of the bromine atom from the mass spectrum. Remarkably, compounds **9**, **11–17** exhibited anisochronism of diastereotopic methylene/methyl groups on the phosphonate moiety, observed either by ^{1}H-NMR or ^{13}C-NMR spectra; the same observation was reported in some phosphonates and hydroxyphosphonates in the literature.[22]

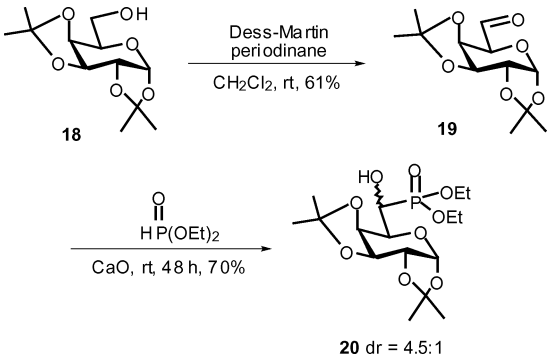
We have also assessed our procedure for the addition of diethyl phosphite on sugar-derived aldehydes; carbohydrate containing

 This journal is © The Royal Society of Chemistry 2010

View Article Online

Published on 11 June 2010. Downloaded by State University of New York at Stony Brook on 27/10/2014 04:57:16.

phosphonate and α-hydroxyphosphonate moieties have been described as phosphate mimics with stable C–P linkages, some of them exhibiting important biological properties.[23] Aldehyde **19** was easily obtained from commercially available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **18** by oxidation mediated by Dess–Martin periodinane (Scheme 2).[24]



Scheme 2 Addition of diethyl phosphite to carbohydrate-derived aldehyde **19**.

Treatment of **19** with diethyl phosphite in the presence of CaO (1.0 equiv.) led to the formation of 6-*C*-phosphonate **20**, obtained as a non-resolved mixture of diastereoisomers in a 4.5 : 1 ratio, as deduced from ^{1}H-NMR spectrum. The pyranose ring of both isomers adopts the $^{\circ}S_2$ conformation,[25] as deduced from the vicinal coupling constants. Assignment of the configuration at C-6 was carried out by studying the conformational preference around the C5–C6 bond (Fig. 1).

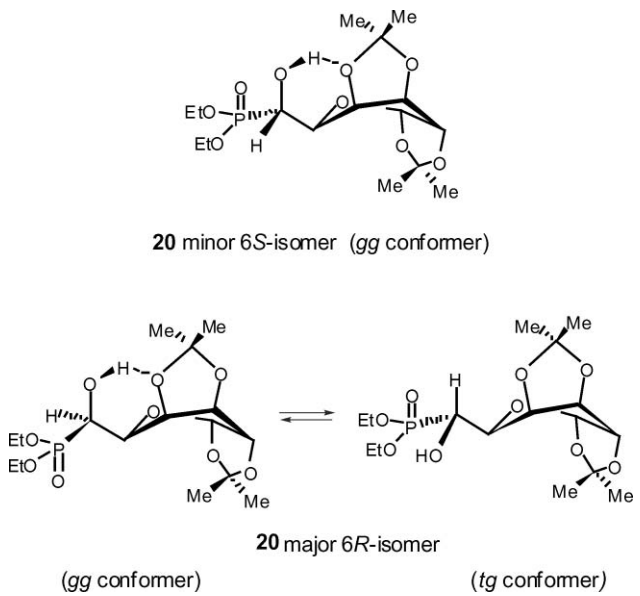


Fig. 1 Conformational preference for hydroxyphosphonate **20**.

The high values of the coupling constants $^3J_{C4,P}$ (8.8 Hz) and $^3J_{P,OH}$ (24 Hz) for the minor diastereoisomer, together with the low value for $^3J_{5,6}$ (4.8 Hz) is in agreement with the 6*S* configuration and a preferred *gg* conformation[26] around the C5–C6 bond, stabilized by an O6–H···O4 hydrogen bond. For the major 5*R* configuration, equilibrium between the *gg* and *tg* staggered conformations can be deduced.

In conclusion, we have developed an environmentally friendly and high-yielding procedure for the nucleophilic addition of phosphines and dialkyl phosphites on a series of electrophiles, using inexpensive CaO under mild and solventless conditions. The reactions proceed following a general trend by which simple and α,β-unsaturated carbonyls give exclusively the 1,2-addition reaction. Conversely, methyl acrylate and vinyl sulfone regioselectively lead to the 1,4-addition process. This green procedure was also successfully applied to sugar aldehydes to afford carbohydrate-derived α-hydroxyphosphonates.

Experimental

General method for the addition of diphenylphosphine and diethyl phosphite to unsaturated derivatives

Calcium oxide (1.0 mmol) was added to a mixture of **1–8**,**19** (1.0 mmol) and diphenyl phosphine or diethyl phosphite (1.0 mmol). The corresponding mixture was stirred at rt for 3–72 h, EtOAc (or EtOH for **8**) was added, and the suspension was filtered through a Celite pad. The filtrate was concentrated to dryness and purified by column chromatography to give compounds **9–17**,**20** in 49–91% yields.

Acknowledgements

Financial support from the University of Camerino, MIUR, the Integrated Action HI-2006-0131, the Dirección General de Investigación of Spain, and the Junta de Andalucía (Grants CTQ2008-02813 and FQM 134) is gratefully acknowledged. E.M.-C. thanks MICINN for a grant.

Notes and references

1 R. Engel and I. I. Cohen, *Synthesis of Carbon–Phosphorous Bonds* (2nd edn), CRC Press, Boca Raton, 2003; L. D. Quin, *A Guide to Organophosphorus Chemistry*, John Wiley & Sons, New York, 2000.
2 Ó. López, J. G. Fernández-Bolaños and M. V. Gil, *Green Chem.*, 2005, **7**, 431–442; S. J. Hecker and M. D. Erion, *J. Med. Chem.*, 2008, **51**, 2328–2345; J. M. Brunel and G. Buono, *Top. Curr. Chem.*, 2002, **220**, 79–105.
3 B. B. Touré and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439–4486.
4 L. Albrecht, A. Albrecht, H. Krawczyk and K. A. Jørgensen, *Chem. Eur. J.*, 2010, **16**, 28–48.
5 Y. Gao, G. Wang, L. Chen, P. Xu, Y. Zhao, Y. Zhou and L.-B. Han, *J. Am. Chem. Soc.*, 2009, **131**, 7956–7957; V. P. Ananikov, L. L. Khemchyan and I. P. Beletskaya, *Synlett*, 2009, 2375–2381.
6 X.-J. Mu, J.-P. Zou, Q.-F. Quian and W. Zhang, *Org. Lett.*, 2006, **8**, 5291–5293.
7 Q. Yao, *Tetrahedron Lett.*, 2007, **48**, 2749–2753; D. Enders, A. Saint-Dizier, M.-I. Lannou and A. Lenzen, *Eur. J. Org. Chem.*, 2006, 29–49.
8 K. Nakanishi, S. Kotani, M. Sugiura and M. Nakajima, *Tetrahedron*, 2008, **64**, 6415–6419.
9 R. P. McGeary, P. Vella, J. Y. W. Mak, L. W. Guddat and G. Schenk, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 163–166; I. Kraicheva, A. Bogomilova, I. Tsacheva, G. Momekov and K. Troev, *Eur. J. Med. Chem.*, 2009, **44**, 3363–3367.
10 R. G. de Noronha, P. J. Costa, C. C. Romão, M. J. Calhorda and A. C. Fernandes, *Organometallics*, 2009, **28**, 6206–6212; J. P. Abell and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 10521–10523; X. Zhou, X. Liu, X. Yang, D. Shang, J. Xin and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 392–394.
11 A. K. Bhattacharya and K. C. Rana, *Tetrahedron Lett.*, 2008, **49**, 2598–2601.
12 J. Wu, W. Sum and H.-G. Xia, *Green Chem.*, 2006, **8**, 365–367.

View Article Online

13 A. Smahi, A. Solhy, R. Tahir, S. Sebti, J. A. Mayoral, J. I. García, J. M. Fraile and M. Zahouily, *Catal. Commun.*, 2008, **9**, 2503–2508.
14 D. Villemin and R. Racha, *Tetrahedron Lett.*, 1986, **27**, 1789–1790.
15 A. R. Katritzky, B. V. Rogovoy and A. Y. Mitrokhin, *Arkivoc*, 2002, 17–27.
16 K. Akutu, H. Kabashima, T. Seki and H. Hattori, *Appl. Catal., A*, 2003, **247**, 65–74; H. Kabashima, T. Katou and H. Hattori, *Appl. Catal., A*, 2001, **214**, 121–124.
17 S. Králíková, M. Buděšínky, M. Masojídková and I. Rosenberg, *Tetrahedron*, 2006, **62**, 4917–4932.
18 L. A. Wozniak, M. Bukowiecka-Matusiak, I. Burzynska-Pedziwatr and W. J. Stec, *Tetrahedron Lett.*, 2009, **50**, 2620–2623.
19 D. Zhao, Y. Yuan, A. S. C. Chan and R. Wang, *Chem. Eur. J.*, 2009, **15**, 2738–2741.
20 For reaction of compounds **3–6**, products arising from competitive 1,4-addition were observed only in negligible amounts.
21 T. Haemers, J. Wiesner, R. Busson, H. Jomaa and S. van Calenbergh, *Eur. J. Org. Chem.*, 2006, 3856–3867.
22 H. R. Hudson, R. O. Yusuf and R. W. Matthews, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2008, **183**, 1527–1540; H.-P. Guan, Y.-L. Qiu, M. B. Ksebati, E. R. Kern and J. Zemlicka, *Tetrahedron*, 2002, **58**, 6047–6059.
23 J. Foret, B. Courcy, N. Gresh, J.-P. Piquemal and L. Salmon, *Bioorg. Med. Chem.*, 2009, **17**, 7100–7107; Ŝ. Králíková, M. Budêšínsky, I. Tomečková and I. Rosenberg, *Tetrahedron*, 2006, **62**, 9742–9750.
24 S. Meinke and J. Thiem, *Carbohydr. Res.*, 2008, **343**, 1824–1829.
25 M. U. Roslund, K. D. Klika, R. L. Lehtilä, P. Tähtinem, R. Sillanpää and R. Leino, *J. Org. Chem.*, 2004, **69**, 18–25.
26 V. S. R. Rao, P. K. Qasba, P. V. Balaji and R. Chandrasekaran, *Conformation of Carbohydrates*, Harwood Academic Publishers, Amsterdam, 1998.

Published on 11 June 2010. Downloaded by State University of New York at Stony Brook on 27/10/2014 04:57:16.

 This journal is © The Royal Society of Chemistry 2010