Formation of New Phosphates from Aldehydes by a DBU-Catalysed Phospha-Brook Rearrangement in a Polar Solvent

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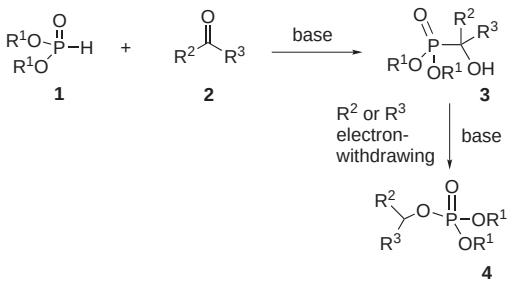
Abstract: Addition of dialkylphosphites to aromatic aldehydes (Pudovik reaction) by treatment with a base results in two different possible reaction pathways depending on the solvent used. Apolar solvents give the normal Pudovik adduct, whereas the use of DBU in a polar solvent allows the formation of a phosphate ester via phospha-Brook rearrangement of the intermediate hydroxyphosphonate.

Key words: Pudovik reaction, dialkylphosphite, phosphate esters, phospha-Brook rearrangement

The addition of phosphorous(III) esters **1** to aldehydes and ketones **2** to form α-hydroxyphosphonates **3** (Pudovik or Abramov reaction, Scheme 1) has attracted much attention due to the biologically interesting properties of their adducts as well as their synthetic utility.[1] More recently the successful coupling of aldehydes with phosphites in an enantioselective manner has increased the potential of these additions.[2] The reaction is usually performed with dialkylphosphites under mild conditions (tertiary amines, alkoxides, KF, r.t.). The outcome of this reaction depends largely on the electronic nature of the carbonyl compounds: for most aldehydes and ketones, hydroxyphosphonates are the only isolated products. In the case of carbonyl compounds possessing anion stabilizing substituents at the α position (α-dicarbonyl compounds,[3] perfluoroalkyl aldehydes and ketones,[4] benzophenones[5] and cyclopentadienones&6;), hydroxyphosphonates **3** formed at low temperatures rearrange to phosphates **4** probably via base-catalysed phospha-Brook mechanism. The conversion of simple aromatic aldehydes to phosphates would represent a synthetically useful reductive procedure for the preparation of phosphates. To the best of our knowledge, this conversion has never been described.

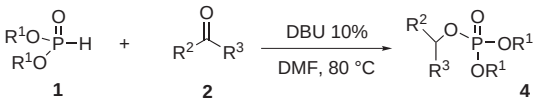


Scheme 1

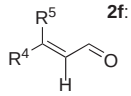
Herein, we wish to report a simple method for the conversion of aromatic aldehydes to their corresponding phosphates using a catalytic amount of DBU in DMF. Thus, when naphthaldehyde **2a** was heated at 80 °C in DMF (0.3 M) with dimethylphosphite (1 equiv) and DBU (0.1 equiv), the phosphate **4a** was obtained in 70% isolated yield after distillation of the solvent and flash column chromatography. Various aldehydes and ketones behaved similarly as shown in Table 1.

Not unexpectedly, electron-poor aldehydes and ketones gave the best yields and the shortest reaction times. Aromatic aldehyde **2d**, substituted by an electron-donating

Table 1 Preparation of Phosphate **4**



1a: R^1 = Me **2a**: R^2 = H, R^3 = 1-naphthyl **2g**: R^2 = Me, R^3 = 2-pyridyl
1b: R^1 = Et **2b**: R^2 = H, R^3 = 2-MePh **2h**: R^2 = CF_3, R^3 = Ph
2c: R^2 = H, R^3 = 2-NO_2Ph **2i**: R^2 = Me, R^3 = Ph
2d: R^2 = H, R^3 = 2-allyloxyPh **2j**: R^2 = H, R^3 = 2-furyl
2e: R^2 = H, R^3 = 4-ClPh **2k**: R^2 = H, R^3 = CH_2CH_2Ph
2f: R^2 = H, R^3 = 2-pyridyl



2l: R^4 = Ph, R^5 = H
2m: R^4 = $(CH_2)_2HC{=}C(Me)_2$, R^5 = Me

1	2	Reaction time (h)	Isolated yield (%)	Product
1a	**2a**	2	70	**4a**
1b	**2a**	10	15	**4b**
1a	**2b**	2.5	68	**4c**
1a	**2c**	1	78	**4d**
1a	**2d**	12	26	**4e**
1a	**2e**	2.5	44[a]	**4f**
1a	**2f**	2	92	**4g**
1a	**2g**	5	57	**4h**
1a	**2h**	2	58	**4i**
1a	**2m**	1	51	**4j**

[a] 4-Chlorobenzyl alcohol (15%) was also isolated after chromatography.

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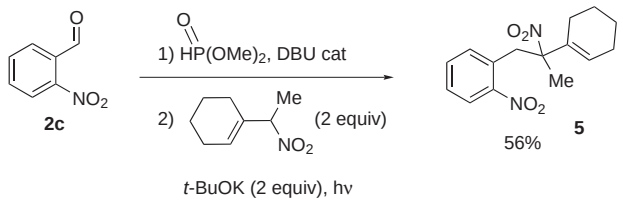
allyloxy group, gave the rearranged phosphate **4e** in a low 26% yield along with its hydroxyphosphonate precursor (21% isolated yield). Furfural **2j** does not rearrange under these conditions whereas electron-poor pyridine-2-aldehyde (**2f**) gives phosphate **4g** in good yield after a short reaction time.

α,β-Unsaturated aldehydes give various products in moderate to poor yields. Although one report of phosphate formation from cinnamaldehyde upon treatment with dialkylphosphite was found in the literature,[7] under our conditions, inseparable mixtures are obtained with cinnamaldehyde **2l**. However, when citral **2m** is used, the phosphate adduct **4j** is isolated in 51% isolated yield. These facts can be best explained by the lower efficiency of competing Michael additions when the substitution pattern on the olefin is increased. Simple aliphatic aldehyde **2k** forms the related hydroxyphosphonate as the only isolable compound (90% isolated yield). In contrast to the results observed with dimethylphosphite; hydroxyphosphonates obtained from diethylphosphite are reluctant to rearrange under these conditions, forming phosphates in low yields with long reaction times (**4b**).

Ketones are less reactive and do not form phosphates (e.g. **2i**) unless substituted by electron withdrawing groups: 2-pyridyl methyl ketone (**2g**) and trifluoroacetophenone (**2h**) gave phosphates **4h** and **4i** in 57% and 58% isolated yields, respectively.

These new conditions afford a straightforward reductive procedure for the formation of allylic and benzylic mixed phosphate esters. Besides their biological interest, these esters can be used as intermediates in further synthetic transformations. In this sense, the presence of a nitro group on the aromatic aldehyde could trigger both phosphite addition and photostimulated $S_{RN}1$ reaction[8] of the resulting phosphate with various nucleophiles. Indeed, the addition of dimethylphosphite to nitrobenzaldehyde (**2c**) followed by further addition of nitroethylcyclohexene, potassium *tert*-butoxide and irradiation of the mixture afforded the new nitro derivatives **5** in 56% isolated yield (Scheme 2).



Scheme 2

Other promising applications such as the use of silylated hydroxyphosphonates to induce pinacol-type couplings are underway and will be reported in due course.

Phosphate 4a; Typical Procedure

To a solution of **2a** in DMF (0.3 M, solvent distilled and stored on molecular sieves) was added dimethylphosphite (1 equiv) in DBU (10%) under argon. The reaction was left at r.t. for 1 h and was then heated for 2 h at 80 °C. The solvent was distilled under reduced pressure and the crude was purified by flash chromatography on silica gel (CH_2Cl_2–EtOAc, 70:30).

IR: 1500, 1460, 1270, 1040 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.91–7.37 (m, 7 H), 5.30 (d, *J* = 12.0 Hz, 2 H), 3.76 (d, *J* = 12.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 135.2, 133.5, 131.6, 127.9, 127.5, 127.4, 127.2, 126.7, 125.7, 124.8, 71.7, 49.5.

MS (ID, IC, NH_3): *m*/*z* = 268 (MH^+).

Anal. Calcd for $C_{13}H_{15}O_4P$: C, 58.65; H, 5.68. Found: C, 58.82; H, 5.86.

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