Role of Base Catalysts upon the Pudovik Reaction : Unexpected Synthesis of 1,2-Dihydropyridine Phosphonate Derivatives

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Abstract: The role of base catalysts (CsNaX zeolite, hydrotalcite, triethylamine and pyridine derivatives) upon the regioselectivity of the Pudovik reaction is studied. The unexpected synthesis of stable 1,2-dihydropyridine phosphonate derivatives via a one-pot addition reaction under mild conditions is described. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Addition reactions, basic zeolite, hydrotalcite, dihydropyridine phosphonate derivatives, Pudovik reaction.

The Pudovik reaction, one of the most versatile pathways for the formation of carbon-phosphorus bonds, involves the addition of organophosphorus compounds containing a labile P-H bond to unsaturated systems[1] affording addition products with significant applications in a wide range of areas (industrial, biological, and chemical synthetic uses).[2] The reaction may proceed *via* an ionic and/or a radical mechanism, depending upon the structure of the unsaturated substrates, the phosphorus reagents and the experimental conditions,[3] and it can involve some problems of regioselectivity. Thus, the addition reaction of diethylphosphonate with ethyl propiolate in homogeneous basic medium (sodium ethoxide) usually affords a mixture of single and double addition products in low yield.[4] We have recently demonstrated that this reaction is regioselective on Al_2O_3/KOH in dry medium for 5 min at 20 °C, giving rise to the double addition product in quantitative yield, regardless of the stoichiometry of the reagents.[3] Pursuing our investigation into the reactivity of the P-H labile phosphorus derivatives,[5] we now wish to report the influence of base catalysts (hydrotalcites, zeolites or amines) upon the regioselectivity of the Pudovik reaction under anionic activation, in homogeneous and heterogeneous medium. An unexpected synthesis of 1,2-dihydropyridine phosphonate derivatives is described.

Zeolitic and layered materials are most notably used in catalysis for shape-selective reactions.[6] However, whereas solid acid catalysts have been extensively studied and used, the utilization of zeolites as basic heterogeneous catalysts has received much less attention.[7] Thus, we have realized the addition reactions of dialkylphosphonates **1** to ethyl propiolate in either heterogeneous (Methods A, B, D, E) or homogeneous medium (Method C). In order to rigorously compare the efficiency of the various catalysts, the initial yields were obtained by ^{31}P NMR analysis of the crude reaction mixtures prior to purification (Scheme 1, Table 1).

1a-c
a : R = Et; **b** : R = iPr; **c** : R = C16H33
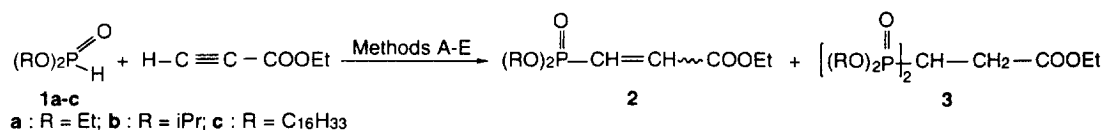
Scheme 1

We have observed that the regioselectivity and the progress of the reaction were dependent on the nature of base catalyst and phosphorus reagent, and the reaction time. So, in the presence of preactivated modified hydrotalcite (Method A) or triethylamine (Method C-D) a mixture of single addition product **2** and double addition product **3** was obtained. When the reaction was occured under the same conditions than above but in the presence of the preactivated basic cesium-exchanged X zeolites (CsNaX) (Method B), the single addition product **2** was the sole detectable product formed in contrast to method E (Al_2O_3/KOH; dry medium process) where the double addition product **3** became the unique adduct whatever the stoichiometry of the reagents and the reaction conditions. This difference of regioselectivity can be explained by the lower basicity and the three dimensional framework of zeolites (shape-selectivity). Actually, the very weak acidic character of the P-H tetracoordinated phosphoryl compounds is well known,[8] and the formation of anions from the phosphonates **1** requires a strong basic catalyst (Michael-like reaction). Consequently, the completion of the reaction was highly improved in the presence of strong supported basic catalyst. Thus, in spite of the high selectivity of zeolites for the single addition product **2**, the progress of the reaction is limited to 10 % (Method B). An order of basicity for the catalysts used can be proposed:

Al_2O_3/KOH >> Al_2O_3/Et_3N > Et_3N > Et_3N/DMSO > modified Hydrotalcite > Cs-exchanged X zeolites

**Table 1** - Comparative studies of the reactivity of **1a** towards ethylpropiolate in basic media.

Method	Catalyst (base/1a w/w)	T (°C)	Time	Solvent	2a (%)	3a (%)
A	modified hydrotalcite[a] (0.7)	100	7 h 30[b]	DMSO	10	20
B	CsNaX zeolite[a] (0.7)	"	7 h 30[b]	DMSO	10	-
C	Et_3N (0.7)	20	20 min	DMSO	5	15
C	" (0.7)	"	"	-	12	20
C	" (10)	"	"	-	6	51
D	Et_3N/Al_2O_3 (10)	"	"	-	16	56
E	KOH/Al_2O_3 (10)	"	5 min	-	-	>95[3]

[a] Freshly preactivated catalyst (calcination in air for 6 h at 400 °C at a heating rate of 1 °C.min^{-1} prior to use).[7a,b]
[b] Yields cannot be improved under prolonged heating (24 h) due to the decomposition of **1a**. Identification of **2a** and **3a** was occured by comparison with authentic samples by ^{31}P NMR and GC/MS.[3,4,9]

The addition rate was enhanced in the absence of solvent (Method C) and by impregnation of the catalyst on a solid support (alumina) (Methods D, E). On the other hand, the selectivity of the reaction in favor of **2** was promoted by the presence of bulky substituents at the phosphorus atom (**2a/3a** = 20/80 whereas **2b/3b** = 40/60) except for Al_2O_3/KOH where the double addition product **3a-c** is the sole reaction product. In contrast to the other methods, the stereoselectivity of **2** is in favor of the *cis* isomer for zeolites (Z/E = 70/30, Method B).

When the addition reaction of stoichiometric amounts of **1a-c** with ethyl propiolate occured in the presence of pyridine (10 equiv.) at 20 °C for 15 min, we observed the formation of an unexpected dialkyl-1,2-dihydropyridine phosphonate **4a-c** in moderate to good yields (Scheme 2). Under our conditions, the phosphonate **1** does not react with ethyl propiolate without a basic catalyst and no adduct was detected between pyridine and ethyl propiolate in the absence of **1**. Thus, we propose a mechanism involving the preliminary
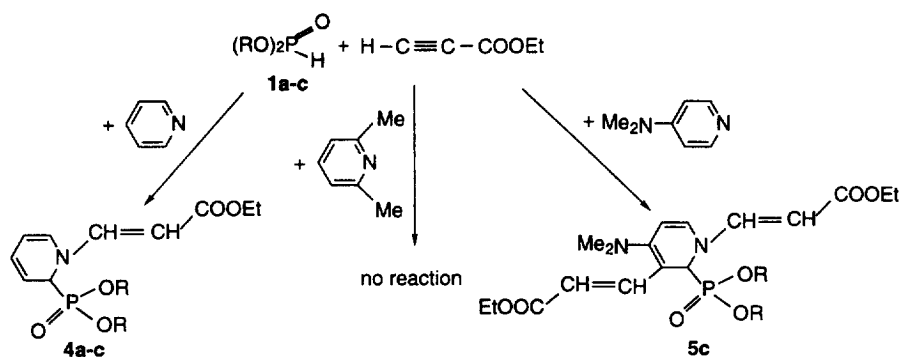
Scheme 2

addition of pyridine upon the ethyl propiolate with formation of the N-(2-ethyl acrylate) pyridinium cation intermediate (**I**) and the phosphonate anion (Scheme 3). Actually, the synthesis of ammonium salts by addition of tertiary amines to ethylenic electrophiles in the presence of weak acids has been described.[10] Of the charged structures, those involving in (**I**), the least charge separation should be favoured. This is in agreement with the preferential attack of nucleophilic phosphonate anion at the 2-position of the pyridinium ring affording the 1,2-dihydropyridine phosphonate adduct **4**.[11] We did not observe any attack at the 4-position of the pyridinium ring in our case. The 2D-homonuclear (^{1}H-^{1}H) and 2D-heteronuclear (^{13}C-^{1}H) correlations for **4** confirm the proposed structures. Moreover, all proton and all carbon atoms of the pyridine ring are unequivalent, and this excludes the formation of the 1,4-adduct.

Scheme 3
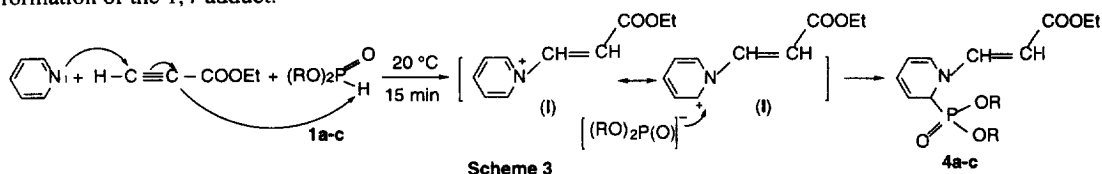
This reaction is dependent on *i)* the ring substitution since no reaction occurs with 2,6-lutidine whereas in the presence of 4-dimethylamino-pyridine (DMAP), the 1,2-dihydropyridine phosphonate bis-adduct **5c** resulting from the addition of two ethyl propiolate moieties upon the pyridinium ring was obtained (Table 2), and *ii)* the electrophilic character of the unsaturated substrate since we have never observed any reaction with acrylonitrile or ethyl acrylate. The dry medium process enhanced the addition rate and improved the yield with respect to the homogeneous medium.

Table 2 - One-pot synthesis of 1,2-dihydropyridine phosphonates **4-5** from dialkylphosphonates **1a-c**, ethyl propiolate and substituted pyridines for 20 min.

$(RO)_2P(O)H$	Nitrogen heterocycle	T (°C)	Adduct [12] (Yield %)
1a	Pyridine[a]	20	**4a** (31)
1a	Pyridine/Al$_2$O$_3$	"	**4a** (62)
1a	"	80	**4a** (77)
1b	"	20	**4b** (25)
1c	"	"	**4c** (82)
1c	DMAP/Al$_2$O$_3$	"	**5c** (70)
1c	2,6-lutidine/Al$_2$O$_3$	"	no reaction

[a] Homogeneous medium.

Synthetic applications of N-alcoxy or N-N linked pyridinium salts in the preparation of a variety of pyridin-2 or 4-yl phosphonates have been described.[12] However, the dihydropyridine intermediates were unstable and they have either postulated or spectroscopically characterized due to their smooth decomposition.[12]

In conclusion, the phosphonates **4** and **5** bearing a dihydropyridine unit - the principal structural unit of several compounds with important pharmacological properties[13] - are original in the pyridine-phosphorus chemistry and they are selectively and easily synthetized *via* a one-pot reaction under mild conditions.

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11. *Typical procedure* - Dialkylphosphonate **1a-c** (1 mmol), ethylpropiolate (1 equiv.) and pyridine (10 equiv.) were added to alumina (1.2 g). The resulting heterogeneous mixture (dry media process) was stirred at 20 °C for 20 min. Adduct **4-5** was extracted with appropriate solvent (Methanol for **4a-b**, chloroforme for **4c-5c**) and purified by column chromatography silica gel for **4a-c** with ethyl acetate (**4a-b**) and hexane/ethyl acetate : 6/4 (**4c**) as eluent, or basic alumina for **5c** with chloroforme as eluent.

Compound **4c** : ^{31}P NMR (32.44 MHz, CDCl$_3$) δ 17.2; ^{1}H NMR (250.13 MHz, CDCl$_3$) δ 7.32 (d, $^3J_{HH}$ = 14 Hz, 1H, CH-CO$_2$), 6.23 (d,$^3J_{HH}$ = 7 Hz, 1H, H$_6$ ring), 6.00 (ddd, $^3J_{HH}$ = 7 Hz, $^3J_{HH}$ = 10 Hz, $^4J_{HP}$ = 7 Hz, 1H, H$_4$ ring), 5.50 (ddd, $^3J_{HH}$ = 10 Hz, $^3J_{HH}$ = 7 Hz, $^3J_{HP}$ = 7 Hz, 1H, H$_3$ ring), 5.25 (dd, $^3J_{HH}$ = 7 Hz, 1H, H$_5$ ring), 5.11 (dd, $^3J_{HH}$ = 14 Hz,$^2J_{HP}$ = 2 Hz, 1H, H$_7$ ring), 4.75 (dd, $^3J_{HH}$ = 7 Hz,$^2J_{HP}$ = 14 Hz, 1H, H$_2$ ring); ^{13}C NMR (62.90 MHz, CDCl$_3$) δ 168.3 (s, C=O), 147.7 (s, $\underline{C}$H-CO$_2$), 132.0 (s, C$_6$ ring), 124.7 (d, $^3J_{CP}$ = 9.4 Hz, C$_4$ ring), 114.2 (d, $^2J_{CP}$ = 8Hz, C$_3$ ring), 105.5 (s, C$_5$ ring), 92.1 (s, =$\underline{C}$H-N), 56.0 (d, $^1J_{CP}$ = 180 Hz, C$_2$ ring); IR (CHCl$_3$, cm^{-1}) ν 3383-2918 (CH=), 1715.5 (C=O), 1627 (C=C), 1242 (P=O); MS (DCI/NH$_3$) m/z 708 (M+1)$^+$, 725 (M+NH$_4$)$^+$.

Compound **5c** : ^{31}P NMR (32.44 MHz, CDCl$_3$) δ 17.9; ^{1}H NMR (250.13 MHz, CDCl$_3$) δ 7.69 (d, $^3J_{HH}$ = 15 Hz, 1H, CH-CO$_2$), 7.30 (d, $^3J_{HH}$ = 13.5 Hz, 1H, CH-CO$_2$), 6.54 (d, $^3J_{HH}$ = 7.5 Hz, 1H, H$_6$ ring), 5.48 (d, $^3J_{HH}$ = 15 Hz, 1H, =CH-C$_3$), 5.42 (d, $^3J_{HH}$ = 7.5 Hz, 1H, H$_5$ ring), 5.27 (d, $^3J_{HH}$ = 13.5 Hz, 1H, =CH-N), 4.85 (d, $^2J_{HP}$ = 10 Hz, 1H, H$_2$ ring); ^{13}C NMR (62.90 MHz, CDCl$_3$) δ 168.7 (s, C=O), 167.8 (C=O), 153.2 (s, C$_4$ ring), 146.1 (s, $\underline{C}$H-CO$_2$), 142.0 (s, $\underline{C}$H-CO$_2$),135.1 (s, C$_6$ ring), 105.9 (s, =$\underline{C}$H-N), 101.6 (s, =$\underline{C}$H-C$_3$), 95.4 (s, C$_5$ ring), 90.2 (s, C$_3$ ring), 55.6 (d, $^1J_{CP}$ = 164 Hz, C$_2$ ring); IR (CHCl$_3$, cm^{-1}) ν 2921-2852 (CH=), 1696 (C=O), 1610 (C=C),1248 (P=O); HRMS (FAB>0) m/z calcd. 849.6485, found 849.6412 (M)$^+$.
NMR parameters of the hexadecyl substituents are omitted. Compounds **4-5** gave satisfactory analytical data consistent with a hemihydrate structure.

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