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Nickel- and Palladium-Catalyzed Cross-Coupling as a Route to 1- and 2-Alkoxy- or Dialkylaminovinylphosphonates.

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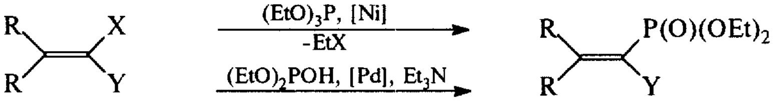
Abstract: 1- and 2-alkoxy- or dialkylaminovinylphosphonates were synthesized using reactions of the corresponding vinylhalides with di- and triethylphosphites in the presence of catalytic amounts of Ni salts and Pd complexes. The best way for synthesis of 1-alkoxy or dialkylaminoderivatives is the Pd-catalyzed cross-coupling reaction with $(EtO)_2POH$ and the best way for 2-alkoxy- or dialkylaminovinylphosphonates is the Arbuzov reaction with $(EtO)_3P$ catalyzed by Ni salts.

1- And 2-alkoxy- as well as 1- and 2-dialkylaminoalkenylphosphonates are very interesting compounds as precursors of keto- and aldophosphonates.[1,2] They are also useful as models for the investigation of mechanisms of some biochemical processes.[3,4] Up to now all known methods of synthesis of these types of compound gave moderate or even poor yields.[5-8]

It was shown earlier that vinylphosphonates without functional groups can be obtained by Ni-[9] or Pd-catalyzed[10] reactions from the corresponding vinyl bromides and triflates.

Here we describe the cross-coupling reactions of 1-bromo-, 2-bromo-, 2,2-dibromoalkenyl-alkylethers and 1-chloro- and 2-bromoenamines with triethylphosphite catalyzed by nickel complexes or with diethylphosphite catalyzed by palladium complexes in the presence of base as general methods for the synthesis of 1- and 2-alkoxy- and 1- and 2-dialkylaminoalkenylphosphonates.



1a-c

2a-c

a R = H, Y = OEt, X = Br
b R = H, Y = OBu, X = Br
c R = Me, Y = NEt_2, X = Cl

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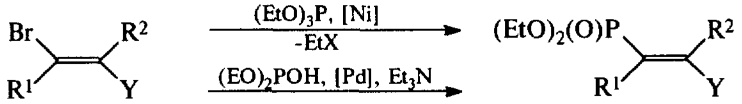
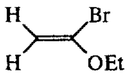
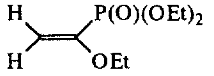
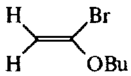
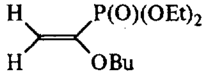
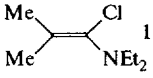
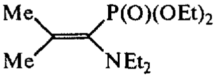
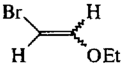
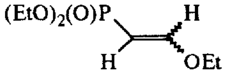
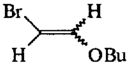
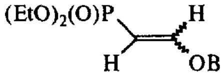
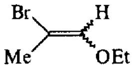
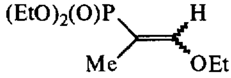
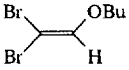
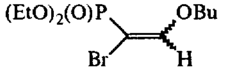
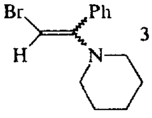
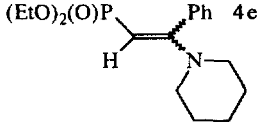


3a-e → 4a-e

a $R^1 = H$, $Y = OEt$, $R^2 = H$
b $R^1 = H$, $Y = OBu$, $R^2 = H$
c $R^1 = Me$, $Y = OEt$, $R^2 = H$
d $R^1 = Br$, $Y = OBu$, $R^2 = H$
e $R^1 = H$, $Y = N(CH_2)_5$, $R^2 = Ph$

TABLE Cross-coupling reactions of 1- and 2-alkoxy- or dialkylaminoalkenes with triethyl[a]- and diethylphosphite[b].

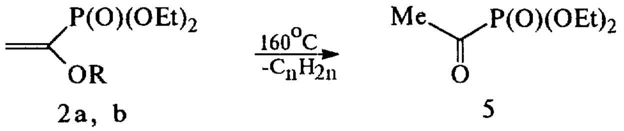
Entry	Vinyl halogenide	Phosphite	Temp (°C)	Time (h)	Product	Yield[c] (%)
1	 1a	$(EtO)_3P$ $(EtO)_2POH$	120 20	1.5 0.25	 2a	80 92
2	 1b	$(EtO)_3P$[d]	120	1.5	 2b	80
3	 1c	$(EtO)_3P$[e] $(EtO)_2POH$[f]	75 20	0.25 2	 2c	98 83
4	 3a	$(EtO)_3P$ $(EtO)_2POH$	160 80	3 12	 4a	90 55
5	 3b	$(EtO)_3P$ $(EtO)_2POH$	160 110	1.5 24	 4b	87 54
6	 3c	$(EtO)_3P$[d] $(EtO)_2POH$	160 110	3 45	 4c	75 41
7	 3d	$(EtO)_3P$	150	0.33	 4d	74
8	 3e	$(EtO)_3P$	130	0.75	 4e	55

[a] Reactions were carried out using 5 mol% $NiBr_2$ under Ar without solvent; [b] Reactions were carried out in benzene using 2 mol% $Pd(PPh_3)_4$ and 1.1 equiv. Et_3N under Ar; [c] Yields of isolated products; all compounds gave satisfactory ^1H, ^{31}P, ^{13}C NMR, IR and microanalysis for new compounds **2c** and **4e**; [d] $NiCl_2$ was used as catalyst; [e] Without catalyst[11]; [f] $PdCl_2(Ph_3P)_2$ was used as catalyst.

Both reactions of 1-bromo and even 1-chloro derivatives proceed very smoothly and require 75-120°C for Ni-catalyzed reactions and room temperature for Pd-catalyzed giving the products in high yields (see Table, entries 1-3). $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ are both efficient in this reaction. Monitoring the Ni-catalyzed Arbusov reaction by ^{31}P NMR shows that the complex $Ni[P(OEt)_3]_4$ is formed[12] from Ni salts ($NiBr_2$ or $NiCl_2$) after the addition of $P(OEt)_3$.

The best way for the synthesis of 1-alkoxyvinylphosphonates **2a, b** is the Pd-catalyzed cross-coupling reaction because of the very mild conditions.

We have shown that 1-alkoxyvinylphosphonates eliminate alkenes on heating above 160°C giving 1-ketophosphonate 5.



2-Bromovinyl ethers **3a-d** and enamine **3e** are much less reactive than 1-bromo isomers and need 130-160°C for Ni-catalyzed reactions with $(EtO)_3P$ and 80-110°C for Pd-catalyzed reactions with $(EtO)_2POH$. The time required for reactions to run to completion is also increased (Table). The yields of products (entries 4-8) in the Pd-catalyzed reactions are lower than in the Ni-catalyzed process. A possible reason according to our NMR data is the formation of a complex of $(EtO)_2POH$ with Et_3N (δp 0.1, J=590 Hz) at high temperature. The reactivity of the complex is much lower in comparison with the free diethylphosphite. The lower isolated yield of **4e** is due to decomposition of the product during the distillation (according to ^{31}P NMR data the yield of **4e** after the reaction is quantitative).

The Pd-catalyzed reaction of 2,2-dibromoderivative **3d** with $(EtO)_2POH$ in the presence of Et_3N gives the reduction product **3b** and traces of 2-butoxyvinyldiethylphosphonate **4b**.[10a]

2-Bromoalkenes **3a-c** were introduced as isomer mixtures. It was shown by a separate study that these isomers do not undergo interconversion under the conditions employed for catalytic reactions. Though phosphonates **4a-d** are initially formed as isomer mixtures, the distillation at 120-150°C leads to isomerisation and after heating at 150°C for 1.5 h, only *E*-isomers (*Z* for **4d**) were isolated.

In conclusion, we have developed a facile general method for the synthesis of a number vinylphosphonates by transition metal catalyzed reactions.

ACKNOWLEDGEMENTS.

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