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One-pot combination of the Wittig olefination with oxidation, hydrogenation, bromination, and photocyclization reactions

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Abstract—Co-polycondensation of tetramethoxysilane, 2-diphenyl(phosphino)ethyltri(ethoxy)silane, and *N*-2-(aminoethyl)-3-aminopropyltri(methoxy)silane forms a heterogenized tertiary phosphine reagent (HPR) that reacts with benzyl chlorides and aldehydes to give alkenes. This Wittig condensation can be coupled, as a one-pot process, with hydrogenation, oxidation, bromination or photocyclization.

In the framework of our studies on the conversion of multi-step reactions into economically and environmentally favored one-pot processes,[1–3] we found that Wittig reactions with a sol–gel entrapped tertiary phosphine can be combined in the same vessel with several other processes. Since the alkenes are fundamental building blocks for numerous chemicals, several attempts have already been made to develop special technologies for such combinations.[4] Notable are the reactions performed under solid-state synthesis conditions[5] which in a few cases proceed in a highly selective fashion,[6] but more often form a complex mixture of products.[7] In this letter, we report an alternative system for one-pot combination of the Wittig olefination with other processes based on separate entrapment of some of the reacting components *within* silica sol–gel matrices.[8]

The polycondensation of tetramethoxysilane (TMOS), 2-diphenyl(phosphino)ethyltri(ethoxy)silane, $Ph_2P(CH_2)_2Si(OEt)_3$, and *N*-(2-aminoethyl)-3-aminopropyltri(methoxy)silane, $H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$, affords heterogenized phosphorus containing reagents (HPR)[9] that can be applied in the condensation of aldehydes and benzyl halides. Some representative examples for the applications of this reagent to the Wittig olefination reaction are listed in Table 1. The diamine may be

Table 1. Condensation of some aldehydes and benzyl chlorides in the presence of HPR[a]

Entry	Aldehyde	Halide	Reaction time, h	Products (yield in the first run, %)[b]
1	C_6H_5CHO	$C_6H_5CH_2Cl$	12	*E*-$C_6H_5CH{=}CHC_6H_5$ (80)
2	4-$CH_3C_6H_4CHO$	$C_6H_5CH_2Cl$	12	*E*-4-$CH_3C_6H_4CH{=}CHC_6H_5$ (91)
3	4-ClC_6H_4CHO	$C_6H_5CH_2Cl$	12	*E*-4-$ClC_6H_4CH{=}CHC_6H_5$ (84)
4	4-$O_2NC_6H_4CHO$	$C_6H_5CH_2Cl$	16	*E*-4-$O_2NC_6H_4CH{=}CHC_6H_5$ (53)
5	2-ClC_6H_4CHO	$C_6H_5CH_2Cl$	12	*E*-2-$ClC_6H_4CH{=}CHC_6H_5$ (72)
6	C_6H_5CHO	4-$CH_3C_6H_4CH_2Cl$	12	*E*-4-$CH_3C_6H_4CH{=}CHC_6H_5$ (90)
7	4-$CH_3C_6H_4CHO$	4-$CH_3C_6H_4CH_2Cl$	12	*E*-4-$CH_3C_6H_4CH{=}CHC_6H_4$–4-CH_3 (81)
8	4-$O_2NC_6H_4CHO$	4-$O_2NC_6H_4CH_2Cl$	16	*E*-4-$O_2NC_6H_4CH{=}CHC_6H_4$–4-NO_2 (36)

[a] Reaction conditions: HPR [generated from 0.66 mmol $Ph_2(CH_2)_2Si(OEt)_3$ and 0.83 mmol $H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$], chloride (0.5 mmol), aldehyde (0.5 mmol), and dry toluene (7 ml), stirring under N_2 at 110 °C. The filtered solution was concentrated and the product was separated by chromatography and analyzed by GC, GCMS, and ^1H and ^{13}C NMR by comparing with authentic samples.

[b] The yields are the average of at least two reactions that did not differ by more than 5%.

Keywords: Catalysis; One-pot synthesis; Silica sol–gel; Wittig reaction.

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Table 2. Combined multi-step one-pot reactions with HPR

Entry	Non-entrapped reaction components	Sol–gel entrapped components[a]	Temp (°C)	Time (h)	Products (yield, %)
1	$PhCH_2Cl$, PhCHO, H_2	HPR, $RhCl(PPh_3)_3$	110	20	$(PhCH_2)_2$ (77)
2	$PhCH_2Cl$, $PhCH_2OH$	HPR, PyCr[b]	98	12	*E*-PhCH═CHPh (68)
3	$PhCH_2Cl$, $PhCH_2OH$, H_2	HPR, PyCr,[b] $RhCl(PPh_3)_3$	110	20	$(PhCH_2)_2$ (52)
4	$PhCH_2Cl$, PhCHO	HPR, $Py^+HBr_3^-$	80	20[c]	PhCHBrCHBrPh (54), *E*-PhCH═CHPh (18)
5	$PhCH_2Cl$, PhCHO	HPR, $Py^+HBr_3^-$	80	12	PhCHBrCHBrPh (40), *E*-PhCH═CHPh (28)
6	$PhCH_2Cl$, PhCHO, O_2, I_2 (*hν*)	HPR	78	20[d]	$C_{14}H_{10}$[e] (55), *E*- and *Z*-PhCH═CHPh (20)[f]

[a] In separated sol–gel matrices.

[b] A 1:1.05 molar mixture of 2-(trimethoxysilylethyl)pyridine and chromium trioxide was used.

[c] The Wittig condensation was conducted for 12 h followed by treatment with the entrapped bromination reagent for 8 h.

[d] The Wittig condensation was conducted for 12 h followed by UV irradiation for 8 h.

[e] Phenanthrene.

[f] Minute changes in the irradiation conditions caused significant differences in the ratio of the *Z*:*E* isomers, but the total yield remained the same.

omitted from the HPR and added, instead, to the solution of the aldehyde and the halide. Reactions conducted with entrapped or free diamine give essentially the same results. Surprisingly, unlike the Wittig reaction under conventional conditions,[10] the experiments listed in Table 1 afford solely products with an *E* configuration (see Table 2).

Solid-state ^{31}P NMR studies[11] suggest that in the absence of entrapped diamine, the heterogenized tertiary phosphine, and benzyl chloride form, after heating in toluene for 6.5 h at 50 °C, a sol–gel entrapped phosphonium salt. The resulting ceramic material has a broad ^{31}P NMR peak centered at 30.25 ppm,[11] which resembles that of soluble $[Ph_2P(CH_2Ph)(CH_2)_2Si(OEt)_3]^+Cl^-$ at 29.44 obtained by interaction of $Ph_2P(CH_2)_2Si(OEt)_3$ and $PhCH_2Cl$ under homogeneous conditions. The solid-state ^{31}P NMR signal of the product of benzyl chloride and HPR (that contains immobilized diamine) appears at −9.62 ppm. This suggests the formation of a heterogenized ylide. It resembles the ^{31}P signal of the ylide generated from $[Ph_2P(CH_2Ph)(CH_2)_2Si(OEt)_3]^+Cl^-$ and $H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$ in toluene, which appears at −9.44 ppm.[11]

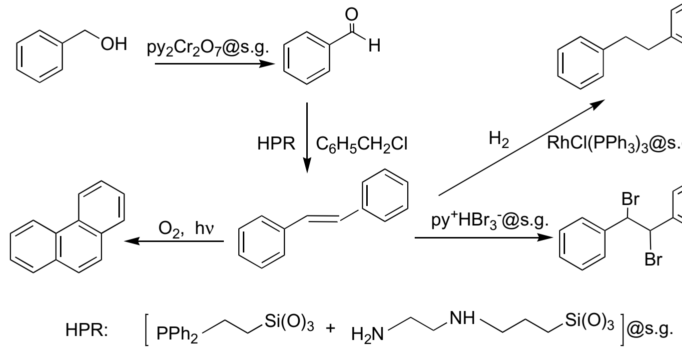
The electronic nature of the reagents affects the heterogenic Wittig reaction in a rather unexpected way. Unlike the effect in the conventional process,[10] electron donating methyl substituents (Table 1, entries 2 and 7) enhance the rate, while electron attracting groups (entries 4 and 8) cause it to slow down. The effect of the steric constraints can be deduced from comparison of the reactions of the isomeric 2- and 4-chlorobenzaldehydes listed as entries 3 and 5.

Although it has been reported that strong guanidine bases smoothly transform phosphonium salts to ylides,[12] it seems that the weaker diamine $H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$ requires the activation by the silica in the matrix.[4] While the reaction described in entry 1 gives 80% of *E*-stilbene, the analogous homogeneous process gives (in two steps) only 37% of the product.

During the Wittig condensation the entrapped $Ph_2P(CH_2)_2Si(O)_3$ is converted into the corresponding phosphine oxide, which in the absence of the diamine could be reduced to the active P(III) reagent by $HSiCl_3$ and Me_2NPh[13] and recycled in a second run. Thus when benzyl chloride was reacted with benzaldehydes and $H_2N(CH_2)_3NH(CH_2)_3Si(OMe)_3$ in the presence of the entrapped phosphine, and the latter was recovered by $HSiCl_3$ reduction, we obtained in the first four runs, under the conditions of Table 1, 80%, 68%, 68%, and 65% of *E*-stilbene, respectively.

The main advantage of performing the Wittig reaction with sol–gel entrapped components is the ability to combine this process with other reactions in one pot. For example, it is possible to perform the condensation described in entry 1 together with a hydrogenation process in the presence of the heterogenized Wilkinson catalyst[14] to give 77% of bibenzyl after 20 h. This combined one-pot process has been further extended by the addition of an oxidation step. Instead of starting the condensation with benzaldehyde, this reagent was generated by in situ oxidation of benzyl alcohol with sol–gel entrapped pyridinium dichromate.[15,16] Thus, all three stages, the oxidation of the carbinol, the olefination of the aldehyde, and the hydrogenation of the Wittig product have been performed as a one-pot process (see Scheme 1). The overall yield of bibenzyl from benzyl alcohol was after 20 h in boiling *n*-heptane 52%. In the absence of the immobilized hydrogenation catalyst, only *E*-stilbene was formed in 68% yield.

Two further one-pot multi-step reactions with HPR have been performed. One is the combination of the Wittig condensation with a bromination process, and the second one combines the Wittig reaction with photocyclization (Scheme 1). Stilbene dibromide was obtained by two methods. The first one consisted of a one-pot consecutive process where benzyl chloride, benzaldehyde, and HPR were first heated in *n*-heptane at 80 °C for 12 h followed by the addition of sol–gel-bound pyridinium hydrobromide perbromide[3] and further heating of the mixture at the same temperature for 8 h. *meso*-Dibromobibenzyl was obtained in 54% yield along with 18% of *E*-stilbene and 25% of each of the unreacted starting compounds. Alternatively, the various reaction components were heated together in *n*-heptane at



Scheme 1. Some one-pot reactions combined with the Wittig olefination.

80 °C and afforded after 12 h a mixture of 40% of the dibromide, 16% of *E*-stilbene and 30–32% of unreacted starting reagents. In analogy to the combination of the Heck coupling with photocyclization,[2] we combined a photochemical process with the heterogeneous Wittig condensation. Irradiation of a mixture of HPR, benzyl chloride, benzaldehydes, and benzene at 78 °C in a quartz well with a 150 W medium pressure mercury lamp afforded under an ambient atmosphere after 20 h, 41% of phenanthrene and 10% of isomeric stilbenes. The yield of the cyclization product could be increased to 55% by performing the processes stepwise, that is, by initial interaction of the HPR with benzyl chloride and benzaldehydes for 12 h under an N_2 atmosphere followed by the UV irradiation in the presence of air for 8 h.

In summary, we have shown that the application of the sol–gel technology to the Wittig reaction enables to combine it with other processes as a one-pot process and save the need of isolation and purification of the reaction intermediates.

Acknowledgements

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