Solvent-free Imino-Aldol Three-component Couplings on a Conveniently-prepared and Reusable Phosphoric Acid-Silica Gel Support

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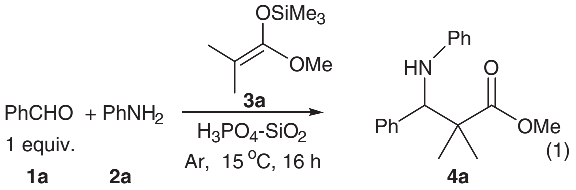
A new solvent-free procedure for the synthesis of β-amino carbonyl compounds in generally moderate to excellent yields has been developed. Three-component Mannich-type couplings between aldehydes (aromatic, aliphatic, alicyclic, and heterocyclic), aromatic amines and silyl enol equivalents proceeded smoothly on a conveniently prepared and reusable phosphoric acid-silica gel solid support.

The Lewis-acid catalyzed imino-aldol coupling of aldehydes with amines and silylated enol equivalents to form β-amino carbonyl compounds is a key facet of organic synthesis.[1] Development of aldol-type reactions, in recent years, has been influenced by an increasing pressure on the fine chemical industry to adopt cleaner, more eco-friendly production methods[2] and this has resulted in the use of more benign solvents[3] as well as new procedures with solid-supported acid catalysts which can offer ease of work up and opportunities for recycling.[4,5]

The combination of phosphoric acid with silica for use as a solid acid catalyst is not a new one. Phosphoric acid immobilized on silica produces a liquid-phase catalyst that has been widely exploited over many years[6] in reactions such as the isomerisation of 1,2-epoxyalkanes,[7] dehydration of alcohols,[8] and the industrial hydration of ethylene.[9] The form of the silica (often a gel or diatomaceous earth), amount of phosphoric acid and preparation method vary to meet the different acid strength requirements of the individual reactions but an extensive period of heat treatment, generally in a calcining oven at temperatures of 120 °C and above, tends to be a common step within each process.

As part of our continuing interest in the development of imino-aldol reactions[10] we chose to try a solvent-free approach, using phosphoric acid supported on silica gel as a solid acid catalyst and wish to disclose the results herewith.[11]



We began the investigation with a test reaction between benzaldehyde (**1a**), aniline (**2a**) and [(1-methoxy-2-methyl-1-propenyl)oxy]trimethylsilane (**3a**) (Eq 1). The support was prepared simply by vigorously stirring chromatography grade silica gel (60 Å, 230–400 mesh)[12] with the required amount of phosphoric acid (supplied by the manufacturer, Wako Pure Chemical Industries, as an 85% aqueous solution) and then subjecting it to a period of intense heating with a hot air gun before adding the organic reagents when the support had cooled. A 1200-mg portion[13] was used in order to preserve a powdery consistency and encourage uniform stirring characteristics as far as possible in the presence of the liquid organic reagents. Thus, silica gel (1200 mg) containing approximately 4 mmol of phosphoric acid was vigorously stirred and then strongly heated in situ for 10 min before adding **1a** (1 mmol), **2a** (1.1 mmol), and **3a** (1.2 mmol) in quick succession, but stirring overnight at 15 °C under argon afforded 2,2-dimethyl-3-phenyl-3-phenylaminopropionic acid methyl ester (**4a**) in low yield (Entry 1, Table 1). In a similar reaction, increasing the amount of **3a** to 2.2 mmol gave little improvement (Entry 2, Table 1) but when we repeated this reaction, having first extended the support heating period to 30 min, **4a** was obtained in 67% yield (Entry 3, Table 1).

Table 1. The influence of varying the pre-heating time, acid content of the support, and the amount of **3a** on the synthesis of **4a** according to Eq 1

Entry	Heating[a] Time/min	H_3PO_4/equiv.	**3a**/equiv.	Yield of **4a**/%[b]
1	10	4	1.2	28
2	〃	〃	2.2	37
3	30	〃	〃	67
4	〃	2	1.9	84
5	〃	〃	〃	86[c]
6	〃	〃	〃	71[d]
7	〃	1	〃	60
8	—	2	〃	40[e]
9	30	—	〃	42[f]

[a]Using a Hakko Heating Gun, No. 880B, AC 100 V – 800 W, 50/60 Hz. [b]Isolated yield. [c]Reaction performed at −5 °C. [d]Reaction performed at 25 °C. [e]Using phosphoric acid alone. [f]Using silica gel alone.

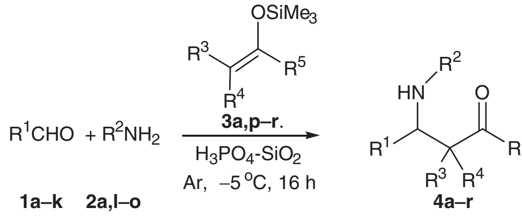
A further improvement in yield (to 84%, Entry 4, Table 1) was obtained when the content of phosphoric acid in the support was halved, while maintaining the same period of pre-reaction heat treatment using the hot air gun, and a similar amount of silyl reagent. It is noteworthy that reducing the amount of phosphoric acid would also have reduced the initial water content that naturally accompanies the reagent. Thus it is possible that the lower water content at the outset may have contributed to the fairly substantial increase in yield.[14] Reducing the reaction temperature had a beneficial effect (Entry 5, Table 1) but an increase in the reaction temperature was disadvantageous (Entry 6, Table 1). A further decrease in the amount of phosphoric acid in the support also had a detrimental effect (Entry 7, Table 1) and poor yields of the required product were obtained when each of the components of the support was used alone (Entries 8 and 9, Table 1).[15]

Encouraged by the higher yields obtained by using 2 mmol of phosphoric acid in the support and by extending the pre-reaction heating period, we examined the efficacy of recycling (Table 2). The phosphoric acid-silica gel recovered from the experiment that gave the product in 84% yield (Entry 4, Table 1) was successfully recycled in three further identical experiments with only a 10% loss of activity on the third occasion (Entry 3, Table 2) compared to its initial use. For each repetition a period of preliminary in situ heating of the support (20 min) was used to drive off organic reagents remaining from the previous experiment.

Table 2. The efficacy of recycling the support used in the synthesis of **4a** according to Eq 1, in the conditions shown in Entry 4, Table 1[a]

Entry	Use of Support	Yield of **4a**/%[b]
1	1st recycling	79
2	2nd recycling	80
3	3rd recycling	76

[a]Recovered phosphoric acid-silica gel (used initially in the experiment that gave 84% of 4a (Entry 4, Table 1)) was strongly heated in situ with a hot air gun for 20 min and stirred with **1a** (1 mmol), **2a** (1.1 mmol), and **3a** (1.9 mmol) under argon for 16 h at 15 °C. [b]Isolated yield.



(2)

The scope of the reaction using phosphoric acid-silica gel was investigated with a range of aromatic and aliphatic aldehydes **1b**–**1k** [*p*-methoxybenzaldehyde (**1b**), *o*-methoxybenzaldehyde (**1c**), *p*-tolualdehyde (**1d**), *o*-chlorobenzaldehyde (**1e**), 2-furaldehyde (**1f**), 2-thiophenecarboxaldehyde (**1g**), cyclohexanecarboxaldehyde (**1h**), isovaleraldehyde (**1i**), *trans*-cinnamaldehyde (**1j**), *n*-butyraldehyde (**1k**)], amines **2l**–**2o** [*o*-anisidine (**2l**), *p*-anisidine (**2m**), *o*-chloroaniline (**2n**), benzylamine (**2o**)] and silyl reagents **3p**–**3r** [1-phenyl-1-(trimethylsiloxy)ethylene (**3p**), 1-methoxy-1-trimethylsilyloxypropene (**3q**), 1-trimethylsilyloxycyclohexene (**3r**)] according to Eq 2.[16]

The corresponding β-amino carbonyl compounds **4**, were obtained in good to excellent yields from coupling aromatic aldehydes, **1a**–**1g** with **2a** and **3a** (Entries 1–7, Table 3) while, with the exception of **1i** which coupled with **2a** and **3a** to give **4i** in 82% yield (Entry 9, Table 3), more modest amounts resulted from the reactions between **2a**, **3a**, and aliphatic aldehydes **1h**–**1k** (Entries 8–11, Table 3). The use of aromatic amines **2l**–**2n** with **1a** and **3a** proved moderately successful under the reaction conditions (Entries 12–14, Table 3) but a reaction between **1a**, **3a**, and **2o**, the more strongly basic aliphatic amine, gave none of the desired product.

Table 3. The synthesis of **4** according to Eq 2 in the presence of a phosphoric acid-silica gel solid support

Entry	R^1	R^2	R^3	R^4	R^5	**4**/%[a]
1	C_6H_5	Ph	Me	Me	OMe	**4a**/86
2	*p*-$MeOC_6H_4$	〃	〃	〃	〃	**4b**/84
3	*o*-$MeOC_6H_4$	〃	〃	〃	〃	**4c**/94
4	*p*-MeC_6H_4	〃	〃	〃	〃	**4d**/90
5	*o*-ClC_6H_4	〃	〃	〃	〃	**4e**/71
6	2-furyl	〃	〃	〃	〃	**4f**/88
7	2-thiophene	〃	〃	〃	〃	**4g**/82
8	cyclohexyl	〃	〃	〃	〃	**4h**/59
9	$(CH_3)_2CHCH_2$	〃	〃	〃	〃	**4i**/82
10	$C_6H_5CH{=}CH$	〃	〃	〃	〃	**4j**/60
11	$CH_3CH_2CH_2$	〃	〃	〃	〃	**4k**/49
12	Ph	*o*-$MeOC_6H_4$	〃	〃	〃	**4l**/69
13	〃	*p*-$MeOC_6H_4$	〃	〃	〃	**4m**/60
14	〃	*o*-ClC_6H_4	〃	〃	〃	**4n**/53
15	〃	benzyl	〃	〃	〃	**4o**/—
16	〃	Ph	H	H	Ph	**4p**/7
17	〃	〃	Me	〃	OMe	**4q**/64[b]
18	〃	〃	H	–(C_4H_8)–		**4r**/69[b]

[a]Isolated yield. [b]*syn*:*anti* ratio, 50:50.

The silyl enol ether **3p** also behaved very poorly (Entry 16, Table 3) giving acetophenone as the major product when it was reacted with **1a** and **2a**. However, greater success was achieved in reactions between **1a**, **2a**, and silyl reagents **3q** and **3r**, giving 64 and 69% respectively, of the desired coupling products (Entries 17 and 18, Table 3).

In conclusion, a convenient solvent-free procedure for performing imino-aldol couplings, using a phosphoric acid-silica gel solid acid support, has been developed which affords the respective β-amino carbonyl compounds in generally moderate to excellent yields. The reaction has demonstrated that a functional and reusable solid acid can be readily produced from combining phosphoric acid and silica gel without the need for extensive preparation steps and we continue to investigate its synthetic capabilities.

References and Notes

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11 Presented at the 84th Annual Meeting of the Chemical Society of Japan, Kobe, March 2004, Abstr., No. 3K2-11.
12 Reactions using silica gels of various pore and mesh sizes revealed that reducing the mesh size reduced the product yield, whereas changing the pore size had comparatively little effect.
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14 In a reaction performed at −5 °C, deliberate addition of water (1 mmol) to the prepared support, before adding the organic reagents, afforded only 40% of **4a**. When no water was added, but the pre-formed imine, *N*-benzylidineaniline was used, coupling with **3a** gave **4a** in 84% yield.
15 Presented at the 81st Annual Meeting of the Chemical Society of Japan, Tokyo, March 2002, Abstr., No. 2G9-09. Silica gel is an established dehydrating reagent but its effect, in the present study, is unknown.
16 A typical reaction procedure: To a mixture (1200 mg) of H_3PO_4 (2 mmol) and silica gel, vigorously stirred, then strongly heated in situ with a hot air gun for 30 min under vacuum and cooled to −5 °C in argon, were added aniline (110.8 mg, 1.19 mmol), *p*-tolualdehyde (114.5 mg, 0.95 mmol) and [(1-methoxy-2-methyl-1-propenyl)oxy]trimethylsilane (345.8 mg, 1.98 mmol) in quick succession. After stirring for 16 h at −5 °C the mixture was washed with diethyl ether (20 cm^3), filtered through a plug of cotton wool and, after evaporation of solvent, the organic residue was purified by TLC (*n*-hexane:ethyl acetate = 7:1 as an eluent) to give 2,2-dimethyl-3-phenylamino-3-*p*-tolylpropionic acid methyl ester (255 mg, 90%) as a yellow solid.

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