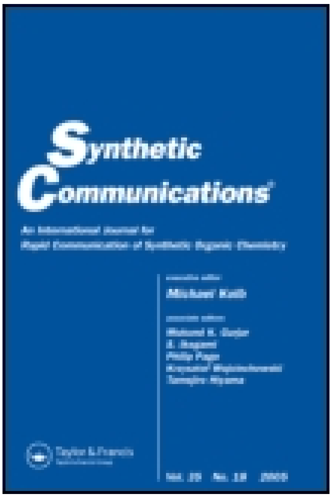

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# SOLVENT-FREE, CROSS-ALDOL CONDENSATION REACTION USING SILICA-SUPPORTED, PHOSPHORUS-CONTAINING REAGENTS LEADING TO $\alpha,\alpha'$-BIS(ARYLIDENE)CYCLOALKANONES

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***This article describes an efficient, simple, and clean method for the synthesis of $\alpha,\alpha'$-bis(arylidene, furylidene and cinnamylidene)cycloalkanones under solvent-free conditions. The cross-aldol condensation of cycloalkanones with aldehydes in the presence of silica-supported phosphorus pentoxide ($P_2O_5/SiO_2$) or silicaphosphinoxide (silphox, $[POCl_{3-n}(SiO_2)_n]$) as heterogeneous reagents produces the title compounds in good to excellent yields.***

***Keywords***: $\alpha,\alpha'$-Bis(arylidene)cycloalkanone; cross-aldol condensation; green chemistry; $P_2O_5/SiO_2$; silphox; solvent-free

The aldol condensation reaction has been widely applied for carbon-carbon bond formation in organic synthesis.[1] Among them, the cross-aldol condensation of arylaldehydes with cycloalkanones leads to $\alpha,\alpha'$-bis(arylidene)cycloalkanones, which have attracted much attention due to their use as precursors for the synthesis of pyrimidine derivatives,[2] and their intriguing biological activities such as antiangiogenic,[3] quinine reductase inducer,[4] cytotoxic,[5] and cholesterol-lowering properties.[6] The aldol condensation reaction has been originally catalyzed by strong acids,[7] and more likely by bases.[8] However, in these conditions, the reactions suffer from reverse and/or side reactions.[9] Moreover, some metal (II) ions such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II), with different ligands have been introduced as catalysts to replace acids or bases, but the yields were not satisfactory in most cases.[10] Continuing efforts to find new catalysts have resulted in the introduction of several reagents such as $RuCl_3$,[11] $SmI_3$,[12] $Cp_2ZrH_2$,[13] $Cp_2TiPh_2$,[14] $TiCl_3$-$(SO_3CF_3)$,[15] Rn(III)-porphyrin,[16] Pd/C-(TMSCl),[17] $KF/Al_2O_3$,[18] and

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bis(*p*-ethoxyphenyl)telluroxide.[19] Nevertheless, most of these methods are associated with the following drawbacks: (i) long reaction times, (ii) low yields, and (iii) Unwanted side reactions. Moreover, in some cases, high temperatures in sealed ampoules or tubes are needed and/or the cost of the catalysts or toxic reagents makes general use impractical. Therefore, it is important to develop more convenient and efficient methods for the preparation of aldol-condensation products, especially $\alpha,\alpha'$-bis(arylidene)cycloalkanones.

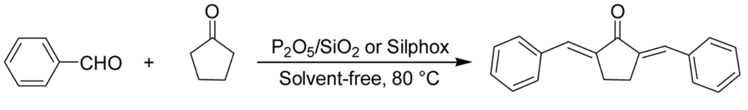
Recently, the use of catalysts and reagents supported on solid supports as well as solvent-free conditions has been extensively developed because such reagents not only simplify the purification processes, but also help to prevent the release of toxic reaction residues into the environment.[20,21] Moreover, due to moisture sensitivity of some reagents, their application of them in organic reactions is difficult. This problem can be solved by their immobilization onto solid supports.[20,21] Handling of solid-supported reagents is also easy. In addition, these reagents can be easily removed from the reaction mixture by filtration. Silica-supported phosphorus-containing reagents are among the most interesting solid-supported reagents, and are inexpensive, commercially available and environmentally benign, allowing them to be used in various organic transformations.[21]

In this article, we report a new, green, and highly efficient method for the synthesis of $\alpha,\alpha'$-bis(arylidene, furylidene and cinnamylidene)cycloalkanones via the cross-aldol condensation of aldehydes with cycloalkanones using $P_2O_5/SiO_2$ or silphox as non-toxic, readily producible, and heterogeneous reagents under solvent-free conditions at 80 °C (Scheme 1).

To find the optimized reaction conditions for the synthesis of $\alpha,\alpha'$-bis-(arylidene)cycloalkanones, the condensation of cyclopentanone (2 mmol) with benzaldehyde (4.2 mmol) was chosen as a model reaction (Scheme 1), and its behavior was studied in the presence of different amounts of some phosphorus-containing reagents under solvent-free conditions at 80 °C. The results are shown in Table 1. As it can be seen in Table 1, $P_2O_5/SiO_2$ (1 g) and silphox (1 g) were the best reagents for the reaction. The condensation of cyclopentanone with benzaldehyde was also examined using only $SiO_2$; however, in these conditions, the product was obtained in 48% yield after 5 h (Table 1, Entry 12). Increasing the reaction time did not improve the yield.

In another study, the model reaction was examined at different temperatures in the presence of $P_2O_5/SiO_2$ and silphox under solvent-free conditions (Table 2). As Table 2 indicates, the best results were obtained at 80 °C using both reagents.

To compare the efficiency as well as capacity of the solvent-free conditions with respect to solution conditions, the reaction of cyclopentanone (2 mmol) with benzaldehyde (4.2 mmol) was also tested in the presence of silica-supported $P_2O_5$ and silphox in several solvents (10 mL), such as MeCN, $CH_2Cl_2$, $CHCl_3$, THF, EtOH,



**Scheme 1.** The condensation of cyclopentanone with benzaldehyde.

**Table 1.** The condensation of cyclopentanone (2 mmol) with benzaldehyde (4.2 mmol) using different amounts of some reagents under solvent-free conditions at 80 °C

| Entry | Reagent | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | – | 24 | No reaction |
| 2 | $P_2O_5$ (0.4 g) | 4 | 50 |
| 3 | $P_2O_5/SiO_2$ (1 g) | 2.5 | 90 |
| 4 | $P_2O_5/SiO_2$ (0.8 g) | 3 | 81 |
| 5 | $P_2O_5/SiO_2$ (1.2 g) | 2.5 | 90 |
| 6 | $POCl_3$ (0.2 mL) | 3 | 36 |
| 7 | $PCl_3$ (0.2 mL) | 4 | 29 |
| 8 | $PCl_5$ (0.2 g) | 3.5 | 26 |
| 9 | Silphox (1 g) | 0.5 | 95 |
| 10 | Silphox (0.8 g) | 0.75 | 88 |
| 11 | Silphox (1.2 g) | 0.5 | 94 |
| 12 | Silphoz (1 g) | 3 | 69 |
| 13 | $SiO_2$ (1 g) | 5 | 48 |

[a] Isolated yield.

and toluene under reflux conditions. However, a mixture of products was obtained in poor yields under these conditions.

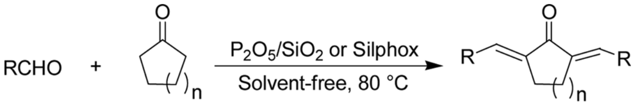
After optimization of the reaction conditions, different types of aromatic aldehydes (including aromatic aldehydes possessing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic rings, furfural and cinnamaldehyde) were condensed with cycloalkanones (cyclopentanone, cyclohexanone, and cycloheptanone) in the presence of the silica-supported phosphorus-containing reagents under solvent-free conditions at 80 °C. The results are summarized in the Table 3. As it is shown in Table 3, the reactions were completed within 2.5–10 and 0.5–2.5 h in the presence of $P_2O_5/SiO_2$ and silphox, respectively; and the desired cross-aldol condensation products were obtained in good to excellent yields. Under the reactions conditions, no self-condensation of the starting materials was observed. Attempts to achieve mono-condensation from one side of the

**Table 2.** The reaction of cyclopentanone with benzaldehyde using $P_2O_5/SiO_2$ or silphox at different temperatures under solvent-free conditions

| Entry | Reagent | Temperature (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $P_2O_5/SiO_2$ | r.t. | 12 | No reaction |
| 2 | $P_2O_5/SiO_2$ | 50 | 4 | 49 |
| 3 | $P_2O_5/SiO_2$ | 70 | 3.5 | 75 |
| 4 | $P_2O_5/SiO_2$ | 80 | 2.5 | 90 |
| 5 | $P_2O_5/SiO_2$ | 90 | 2.5 | 88 |
| 6 | Silphox | r.t. | 10 | Trace |
| 7 | Silphox | 50 | 3.5 | 65 |
| 8 | Silphox | 70 | 1 | 78 |
| 9 | Silphox | 80 | 0.5 | 95 |
| 10 | Silphox | 90 | 0.5 | 92 |

[a] Isolated yield.

**Table 3.** Synthesis of α,α′-bis(arylidene)cycloalkanones from aldehydes and cycloalkanones in the presence of $P_2O_5/SiO_2$ as well as silphox under solvent-free conditions at 80 °C



| | | | $P_2O_5/SiO_2$ | Silphox | |
|---|---|---|---|---|---|
| Entry | N | R | Time (h)/Yield (%) | Time (h)/Yield (%) | Mp (°) (lit.) |
| 1 | 1 | $C_6H_5$ | 2.5/90 | 0.5/95 | 187–189 (188–189)[19] |
| 2 | 1 | p-$CH_3OC_6H_4$ | 4/92 | 0.5/93 | 207–209 (210–211)[19] |
| 3 | 1 | p-$CH_3C_6H_4$ | 5.5/89 | 1/92 | 243–245 (244–246)[22] |
| 4 | 1 | p-$NO_2C_6H_4$ | 10/74 | 1/85 | 228–230 (229–231)[23] |
| 5 | 1 | m-$NO_2C_6H_4$ | 8/71 | 0.5/83 | 225–227 (226–227)[22] |
| 6 | 1 | p-$ClC_6H_4$ | 4/78 | 0.5/89 | 227–229 (224–226)[18a] |
| 7 | 1 | m-$ClC_6H_4$ | 9/83 | 2/87 | 173–175 (177)[24] |
| 8 | 1 | o-$ClC_6H_4$ | 10/90 | 2.5/92 | 155–157 (152–153)[14] |
| 9 | 1 | 2-Furyl | 4/89 | 1/93 | 162–164 (160–162)[19] |
| 10 | 1 | $C_6H_5CH{=}CH$ | 3/84 | 0.5/92 | 217–219 (215–216)[25] |
| 11 | 2 | $C_6H_5$ | 3/93 | 0.5/95 | 116–118 (117)[10] |
| 12 | 2 | p-$CH_3OC_6H_4$ | 3/87 | 0.5/93 | 161–163 (160–162)[19] |
| 13 | 2 | p-$CH_3C_6H_4$ | 6/86 | 1/95 | 169–171 (170)[14] |
| 14 | 2 | p-$NO_2C_6H_4$ | 4/82 | 1.5/90 | 156–158 (159)[10] |
| 15 | 2 | m-$NO_2C_6H_4$ | 6/76 | 2/86 | 180–182 (181–182)[22] |
| 16 | 2 | p-$ClC_6H_4$ | 3/89 | 2/91 | 147–149 (147–148)[25] |
| 17 | 2 | m-$ClC_6H_4$ | 7/84 | 2.5/94 | 108–110 (105–107)[26] |
| 18 | 2 | o-$ClC_6H_4$ | 6/88 | 1/92 | 103–105 (102–104)[22] |
| 19 | 2 | 2-Furyl | 7/85 | 1/90 | 140–142 (143–145)[26] |
| 20 | 2 | $C_6H_5CH{=}CH$ | 2.5/90 | 2.5/90 | 176–178 (179–180)[19] |
| 21 | 3 | $C_6H_5$ | 3/84 | 1/87 | 105–107 |
| 22 | 3 | 3,4-$(CH_3O)_2C_6H_3$ | 4.5/76 | 1.5/82 | 162–164 |
| 23 | 3 | p-$ClC_6H_4$ | 2.5/88 | 0.5/94 | 131–133 |

[a] Isolated yield.

cycloalkanones, in the presence of lower amounts of the aldehydes, was not successful, and only bis-aldol products were produced.

In conclusion, the presented method is a highly efficient, green, inexpensive, clean, and selective protocol for the cross-aldol condensation of cycloalkanones with aldehydes to provide α,α′-bis(arylidene)cycloalkanones in high yields and with relatively short reaction times.

## EXPERIMENTAL

All chemicals were purchased from Merck or Fluka Chemical Companies. The $^1$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

## Preparation of $P_2O_5/SiO_2$ (30% w/w)

A mixture of $SiO_2$ [silica gel 60, 0.063–0.200 mm (70–230 mesh ASTM), 3.5 g] and $P_2O_5$ (1.5 g) was ground vigorously to give the reagent, $P_2O_5/SiO_2$, as a white powder (5.0 g). This reagent can be stored for months in a capped bottle without deterioration.

## Preparation of Silphox

Under a nitrogen atmosphere, we added $POCl_3$ (64.0 g, 0.5 mol) at room temperature to a flask containing dry plate silica gel (6.0 g) and stirred slowly with a mechanical stirrer for 30 min. The mixture was then heated to 60 °C while it was stirring under pressure of nitrogen for 3 h to remove all produced HCl. Afterward, the reaction mixture was cooled to room temperature, filtered, and the resulting precipitate washed with dry $CH_2Cl_2$ (50 mL) to give silphox as a white solid (9.1–9.3 g), which was stored in a capped bottle.[21j] The reagent can be stored for month without any change.

## General Procedure for the Preparation of α,α′-Bis(arylidene)cycloalkanones Using $P_2O_5/SiO_2$ or Silphox

A mixture of cycloalkanone (2 mmol), aldehyde (4.2 mmol), and the silica-supported phosphorus containing reagent (1.0 g) was added in a 25 mL round-bottomed flask connected to a reflux condenser. The mixture was stirred at 80 °C for the appropriate time (Table 3). Afterward, the reaction mixture was cooled to room temperature, EtOAc (60 mL) was added and heated for 5 minutes. The reagent was removed by filtration, and the filtrate was concentrated. The solid residue was recrystallized from ethanol to afford pure product.

## Selected Spectral Data of the Products

**2,5-Bis(3-chlorobenzylidene)cyclopentanone (Table 3, Entry 7).** Yellow needles; mp 173–175 °C (lit.[24] 177 °C); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 3.01$ (s, 4H), 7.29–7.33 (m, 4H), 7.39–7.42 (m, 2H), 7.43 (s, 2H), 7.51 (t, $J = 1.2$ Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 27.0$, 128.6, 129.6, 130.5, 130.7, 132.5, 135.3, 137.1, 138.6, 196.0; Anal. calcd. for $C_{19}H_{14}Cl_2O$: C, 69.32; H, 4.29. Found: C, 69.58; H, 4.48.

**2,6-Bis(3-chlorobenzylidene)cyclohexanone (Table 3, Entry 17).** Yellow needles; mp 108–110 °C (lit.[26]105–107 °C); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 1.69$ (quintet, $J = 5.7$ Hz, 2H), 2.78 (t, $J = 5.7$ Hz, 4H), 7.30–7.37 (m, 6H), 7.41 (s, 2H), 7.62 (t, $J = 1.2$ Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 23.7$, 27.9, 126.3, 127.9, 129.3, 130.4, 130.9, 133.2, 135.8, 137.8, 188.9; Anal. calcd. for $C_{20}H_{16}Cl_2O$: C, 69.98; H, 4.70. Found: C, 69.76; H, 4.87.

**2,6-Bis(2-chlorobenzylidene)cyclohexanone (Table 3, Entry 18).** Yellow needles; mp 103–105 °C (lit.[22]102–104 °C); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 1.75$ (quintet, $J = 5.8$ Hz, 2H), 2.78 (t, $J = 5.8$ Hz, 4H), 7.28 (m, 4H), 7.34 (d, $J = 3.4$, 2H), 7.45 (d, $J = 3.3$ Hz, 2H), 7.89 (t, $J = 1.2$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 23.2$, 28.7, 126.8, 130.8, 130.9, 131.0, 134.5, 135.0, 135.5, 138.3, 189.2; Anal. calcd. for $C_{20}H_{16}Cl_2O$: C, 69.98; H, 4.70. Found: C, 69.80; H, 4.56.

**(2*E*,6*E*)-2,6-Bis((*E*)-3-phenylallylidene)cyclohexanone (Table 3, Entry 20).** Yellow solid; mp 176–178 °C (lit.[19]179–180 °C); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.85$ (quintet, $J = 5.8$ Hz, 2H), 2.81 (t, $J = 5.8$ Hz, 4H), 6.97 (d, $J = 15.4$ Hz, 2H), 7.10 (dd, 2H, J = 15.4, 1.2 Hz), 7.28 (m, 2H), 7.36 (m, 4H), 7.48–7.54 (m, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 22.5$, 27.8, 124.7, 124.8, 127.5, 129.3, 135.9, 136.8, 137.3, 141.4, 188.3; Anal. calcd. for $C_{24}H_{22}O$: C, 88.31; H, 6.79. Found: C, 88.52; H, 6.63.

**(2*E*,7*E*)-2,7-Dibenzylidenecycloheptanone (Table 3, Entry 21).** Pale yellow solid; mp 105–107 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 2.03$ (br, s, 4H), 2.75 (br, s, 4H), 7.37 (t, $J = 7.2$ Hz, 2H), 7.43 (s, 2H), 7.45 (m, 4H), 7.51 (d, $J = 7.5$ Hz, 4H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 28.5$, 29.3, 128.7, 128.9, 129.9, 136.1, 136.4, 142.2, 199.9; MS: m/z = 288 ($M^+$); Anal. calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.69; H, 6.84.

**(2*E*,7*E*)-2,7-Bis(3,4-dimethoxybenzylidene)cycloheptanone (Table 3, Entry 22).** Pale yellow solid; mp 162–164 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 2.05$ (br, s, 4H), 2.77 (br, s, 4H), 3.91 (s, 6H), 3.96 (s, 6H), 6.94 (d, $J = 8.5$ Hz, 2H), 7.05 (s, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 7.39 (s, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 28.7$, 29.1, 56.3, 56.4, 111.5, 113.3, 123.1, 129.2, 135.9, 140.5, 149.2, 149.7, 199.9; MS: m/z = 408 ($M^+$); Anal. calcd. for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.32; H, 6.80.

**(2*E*,7*E*)-2,7-Bis(4-chlorobenzylidene)cycloheptanone (Table 3, Entry 23).** Pale yellow solid; mp 131–133 °C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 2.00$ (br, s, 4H), 2.71 (br, s, 4H), 7.38 (s, 2H), 7.41–7.45 (m, 8H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 28.4$, 29.1, 129.2, 131.1, 134.6, 134.7, 135.0, 142.4, 199.3; MS: m/z = 357 ($M^+$); Anal. calcd. for $C_{21}H_{18}Cl_2O$: C, 70.60; H, 5.08. Found: C, 70.87; H, 4.93.

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