RESEARCH LETTER

NH₄H₂PO₄/SiO₂: a recyclable, efficient heterogeneous catalyst for crossed aldol condensation reaction

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Crossed aldol condensation of aromatic aldehydes with cyclic ketones in the presence of catalytic amount of NH₄H₂PO₄/SiO₂ (as a safe, green, and cheap heterogeneous catalyst) under solvent-free condition afforded α,α´-bis(substituted-benzylidene) cycloalkanones in high yields. This method is general with respect to all types of aromatic aldehydes and is an eco-friendly procedure. And the catalyst is easily prepared, stable, reusable, and efficient under the reaction conditions.

Keywords: aromatic aldehydes; α,α´-Bis(substituted-benzylidene) cycloalkanones; crossed aldol condensation; cyclic ketones; NH₄H₂PO₄/SiO₂

Introduction

Cross-aldol condensation of aromatic aldehydes with cyclic ketones is an important protocol for the synthesis of α,α´-bis(substituted-benzylidene)cycloalkanones, which are very important precursors to potentially bioactive pyrimidine derivates (1), intermediates for agrochemical, pharmaceuticals and perfumes (2), new organic material for nonlinear optical applications (3), cytotoxic analogous (4), bis-spiro-pyrrrolidines (5), and the units of liquid crystalline polymers (6). Usually, this condensation process is catalyzed by strong acid or base, however, suffers from side reactions (such as self-condensation of ketones and aldehydes) giving the corresponding products in low yields (7,8). Therefore, numerous studies in the literature to improve the performance of the reaction have existed; the main progress was the following: (1) The aldol reaction was catalyzed by organometallic complexes but the yields were not satisfactory (9) or required long reaction time (10), (2) Lewis acid such as RuCl₃ (11), SmI₃ (12), BF₃Et₂O (13,14), FeCl₃ 6H₂O (15), Mg(HSO₄)₂ (16), KHSO₄ (17), Yb(OTf)₃ (18), Cu(II) trifluoroacetate (19), InCl₃ 4H₂O (20), LiClO₄ (21), NKC-9 (polymer-supported sulfonic acid) (22), SiO₂–Pr–SO₂H (23) were used to promote the aldol reaction, and (3) I₂ (24), TMSCI/NaI (25), LiOH (26), KF/Al₂O₃ (27), [(Me₂Si)₂N]₃Ln(μ-Cl)Li(THF)₃ (28), Silica Chloride (29), BMPTO(bis(p-ethoxyphenyl)telluroxide) (30), TCT(2,4,6-trichloro[1,3,5]triazine) (31) NaOH in micellar medium (32), KOH (33), Na-HAP (34), and animal bone meal (35) were also found to accelerate this type of reaction. However, the use of toxic reagents, long reaction time, low yields, formation of a mixture of products, and tedious separation procedures is among the drawbacks of the reported methods. It is therefore important to find a more convenient method for the preparation of these compounds.

Silica gel and silica-supported reagents has been used as catalyst in organic synthesis because it is easily available, inexpensive, and nontoxic. Use of such a heterogeneous catalyst benefits several potential catalyst reuses and waste production minimizations (36–38).

Among of many silica-supported catalysts employed, NH₄H₂PO₄/SiO₂, one of the solid supported catalysts has already been prepared by our research group (39) and approved to be a potential green catalyst with several advantages such as low toxicity, low cost, ease of handling, and high catalytic activity. In continuation of our work to develop new and eco-friendly synthetic methodologies, herein we report a novel, green, facile, and efficient one-pot method for the synthesis of α,α´-bis(substituted-benzylidene) cycloalkanones catalyzed by NH₄H₂PO₄/SiO₂ under solvent-free condition (Scheme 1).
Results and discussion

Initially, the reaction was performed by reacting cyclohexanone (1 equiv) and benzaldehyde (2 equiv) in the presence of 0.05 g of NH₄H₂PO₄/SiO₂ as a catalyst under solvent-free condition at 80°C. Under these conditions, only a trace amount of product was obtained after 150 min. The conditions for this transformation were optimized and the results are shown in Table 1. No product was obtained in the absence of the catalyst (Table 1, entry 1) even when the reaction time was extended to 180 min., thus demonstrating the importance of NH₄H₂PO₄/SiO₂. The amount of the catalyst required for the transformation was investigated by the use of 0.05–0.15 g of catalyst. Under these conditions, the yields were in a range of 10–90% (Table 1). The use of 0.15 g of NH₄H₂PO₄/SiO₂ gave the best result (Table 1, entry 9). The reaction worked well with electron-withdrawing (NO₂, Cl) as well as electron-donating (Me, MeO, N(CH₃)₂) groups, giving various α,α’-bis(substituted-benzylidene) cycloalkanones in 85–94% yields. As it

Table 1. Reaction of benzaldehyde and cyclohexanone under solvent-free conditions.

| Entry | NH₄H₂PO₄/SiO₂ (g) | Temperature (°C) | Time (min) | Yield (%) |
|-------|-------------------|------------------|------------|-----------|
| 1     | 0.00              | 80–110           | 180        | Trace     |
| 2     | 0.05              | 80               | 150        | Trace     |
| 3     | 0.05              | 80               | 120        | Trace     |
| 4     | 0.05              | 110              | 60         | 10        |
| 5     | 0.1               | 80               | 30         | 10        |
| 6     | 0.1               | 110              | 30         | 20        |
| 7     | 0.15              | 80               | 30         | 85        |
| 8     | 0.15              | 110              | 20         | 90        |
| 9     | 0.15              | 110              | 15         | 90        |

Table 2. Preparation of α,α’-bis(substituted benzylidene)cycloalkanones catalyzed by NH₄H₂PO₄/SiO₂ at 110°C under solvent-free conditions.

| Entry | Ar     | Z               | Time (min) | Product | Yield (%) | Mp (°C) | Lit. Mp (°C) |
|-------|--------|-----------------|------------|---------|-----------|---------|--------------|
| 1     | C₆H₅   | CH₂             | 15         | 3a      | 90        | 188–189 | 188–190 (I8) |
| 2     | p-MeC₆H₄ | CH₂            | 10         | 3b      | 85        | 242–243 | 243–244 (I8) |
| 3     | p-MeOC₆H₄ | CH₂        | 8          | 3c      | 90        | 211–212 | 211–212 (I8) |
| 4     | p-NO₂C₆H₄ | CH₂        | 10         | 3d      | 92        | 228–229 | 228–229 (I8) |
| 5     | p-NO₂C₆H₄ | CH₂        | 15         | 3e      | 90        | 229–230 | 229–231 (I8) |
| 6     | p-Me₂NC₆H₄ | CH₂     | 15         | 3f      | 85        | 271–273 | 270–273 (I8) |
| 7     | C₆H₅CH = CH | CH₂ | 20         | 3g      | 85        | 222–223 | 215–216 (I8) |
| 8     | o-CIC₆H₄ | CH₂            | 12         | 3h      | 85        | 154–156 | 152–153 (I0) |
| 9     | C₆H₅   | CH₂CH₂         | 10         | 3i      | 90        | 116–117 | 117–118 (I8) |
| 10    | p-MeC₆H₄ | CH₂CH₂       | 10         | 3j      | 92        | 170–171 | 164–165 (I8) |
| 11    | p-MeOCC₆H₄ | CH₂CH₂   | 10         | 3k      | 90        | 162–164 | 161–163 (I8) |
| 12    | p-ClC₆H₄ | CH₂CH₂       | 12         | 3l      | 90        | 146–148 | 147–148 (I1) |
| 13    | p-ClC₆H₄ | CH₂CH₂       | 10         | 3m      | 94        | 160–162 | 161–162 (I8) |
| 14    | p-Me₂NC₆H₄ | CH₂CH₂ | 20         | 3n      | 92        | 250–252 | 250–252 (I8) |
| 15    | C₆H₅CH = CH | CH₂CH₂ | 20         | 3o      | 90        | 179–180 | 177–178 (I8) |
| 16    | o-CIC₆H₄ | CH₂CH₂       | 20         | 3p      | 85        | 103–104 | 102–104 (S1) |
| 17    | C₆H₅   | CH(Me)CH₂     | 15         | 3q      | 90        | 99–100  | 97–99  (S1)  |
| 18    | p-MeC₆H₄ | CH(Me)CH₂    | 15         | 3r      | 90        | 125–127 | 125–127 (S1) |
| 19    | p-MeOCC₆H₄ | CH(Me)CH₂ | 15         | 3s      | 92        | 137–139 | 137–139 (S1) |
| 20    | p-CIC₆H₄ | CH(Me)CH₂    | 15         | 3t      | 94        | 158–160 | 156–160 (S1) |
Figure 1. (A) Infrared spectra of SiO$_2$ (Silica gel only). (B) Infrared spectra of catalyst (NH$_4$H$_2$PO$_4$/SiO$_2$) before using it. (C) Infrared spectra of catalyst (NH$_4$H$_2$PO$_4$/SiO$_2$) after using it.
is shown in Table 2, the method is general and encompasses a variety of aromatic aldehydes with excellent yields. The reaction worked with aliphatic aldehydes but did not react well.

Experimental

**Preparation of NH₄H₂PO₄/SiO₂**

The catalyst was prepared by mixing silica gel (1.5 g, Merck grade 60, 230–400 mesh) with a solution of NH₄H₂PO₄ (0.6 g, 5 mmol) in distilled water (10 mL). The resulting mixture was stirred for 30 min to absorb NH₄H₂PO₄ on the surface of silica gel (Scheme 2). After removal of water in a rotary evaporator, the solid powder was dried at 120°C for 2–3 h under reduced pressure. The drying temperature was maintained below the decomposition temperature of the salt.

Infrared spectra of silica gel and catalyst, before and after using it, were shown in Figure 1. Frequency comparison of IR spectra show the appearance of absorption in region 1400 cm⁻¹. This absorption is due to the P–O stretching vibrations of –OPO₃H₂ groups present that was shown in Scheme 2.

**Synthesis of α,α´-bis(substituted-benzylidene) cycloalkanones: general procedure**

A mixture of aromatic aldehyde (2 mmol), cyclic ketones (1 mmol), and NH₄H₂PO₄/SiO₂ (0.15 g) was stirred for 2 min at room temperature and then the temperature was raised to 110°C and maintained for the appropriate time (Table 2). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with hot ethanol and the catalyst was separated by simple filtration and recovered NH₄H₂PO₄/SiO₂ was reused in subsequent reactions without significant decrease in activity even after five runs (Table 3).

**Conclusions**

We described herein an ammonium dihydrogen phosphate adsorbed on silica gel (NH₄H₂PO₄/SiO₂) catalyzed highly efficient, one-pot, green protocol for the synthesis of α,α´-bis(substituted-benzylidene) cycloalkanones by the condensation of aromatic aldehydes and cyclic ketones under solvent-free condition in very good to excellent yields. The present methodology offers several advantages such as simple procedure, low cost, easy work-up, short reaction time, and milder condition.

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**References**

1. Deli, J.; Lorand, T.; Szabo, D.; Foldesi, A. Pharmazie. 1984, 39, 539–540.

2. Ogawa, M.; Ishii, Y.; Nakano, T.; Irifune, S. Jpn. Kokai Tokkyo. 1988, JP 63192446 A2; Ogawa, M.; Ishii, Y.; Nakano, T.; Irifune, S. Chem. Abstr. 1988, 63, 238034.
Appendix A: Supporting information for

![Chemical Structure 1](image1)

![IR Spectrum 1](image2)

![Chemical Structure 2](image3)

![IR Spectrum 2](image4)
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