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Solvent Free Synthesis of *α*, *ά*-Bis(Substituted-benzylidene)cycloalkanones Using Covalently Anchored Sulfonic Acid on Silica Gel (SiO_2-R-SO_3H) as an Efficient and Reusable Heterogeneous Catalyst

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Abstract

We wish to report a mild and efficient Crossed-Aldol reaction for the synthesis of α, ά-bis(substituted-benzylidene)cycloalkanones in the presence of catalytic amounts of covalently anchored sulfonic acid onto silica gel under heterogeneous and solvent-free conditions. The present methodology offers several advantages such as excellent yields, simple procedure and work up steps, short reaction times and easy recovery of the catalyst. We have also demonstrated that the catalyst can be reused successfully.

Keywords: Crossed-Aldol Condensation, Heterogeneous Catalysis, *α*, *ά*-Bis(Substituted-benzylidene)cycloalkanones, SiO_2-R-SO_3H, Solvent-Free

1. Introduction

Heterogeneous catalysis has emerged as a process in which catalysts can be recovered and reused to achieve high turn-over numbers [1,2]. Incorporation of an active site onto a large surface solid carrier is one strategy to generate a heterogeneous catalyst. Silica is one such support which displays exceptional chemical and thermal quailties [3,4]. Recently silica functionalized sulfonic acid has been used for a variety of reactions [5-8].

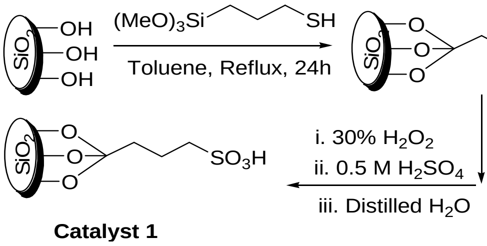
Claisen-Schmidt condensation reaction followed by dehydration affords *α*-alkylidene or *α*-arylidene compounds. Such an introduction of alkylidene or arylidene moieties at the *α*-position of carbonyl compounds has been a useful synthetic tool in natural product chemistry [9]. *α*, *ά*-Bis(substituted-benzylidene)cycloalkanones exhibit numerous biological activities [10-13]. They are also suitable as nonlinear optical materials [14], in preparation of pyridine derivatives [15], 2,7-disubstituted tropones [16] and in the total synthesis of natural products [17].

Such condensation processes are carried out with the aid of strong acids or bases. The yields, however, are generally low and cumbersome separation steps are required [18,19]. It is reported that various complexes of metal ions, such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn (II) may be used as catalysts in condensation reactions [20]. The reported yields, however, are less than 38%. In other cases, amino-functionalized ionic liquid [21] and copper (II) trifluoroacetate [22] have also been used to catalyze the reaction. High yield of products, however, can only be obtained at high temperatures and the purifycation operations are always complicated.

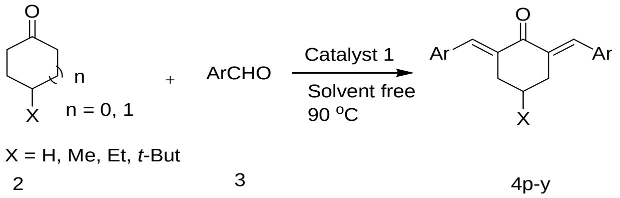
Such condensation reactions are also carried out in solvent-free conditions [23]. Silica sulfonic acid, nanoporous silica-based sulfonic acid and polymer supported sulfonic acid type catalysts are also employed for such condensations. Reaction times are reported to be in 3 - 12 hour range [24-26]. In the present work, we have used covalently anchored sulfonic acid on silica gel (**Catalyst 1**, **Scheme 1**), which its applications have been reported in a few number of organic transformations [6,8,27,28] under solvent-free conditions to prepare *α*, *ά*-bis(substituted-benzylidene) cycloalkanones (**Scheme 2**) in excellent yields, short reaction times and clean work up procedures.

2. Result and Discussion

In order to find the optimum reaction conditions, various parameters including solvent, temperature and molar ratio of catalyst to starting material were examined. It was found that the highest yields were obtainable under solvent free conditions with 3.6 mol percent of catalyst to the starting carbonyl compounds. The method is general and encompasses a variety of aromatic aldehyde with electron-donating or electron-withdrawing groups in high yields (**Table 1**). We did expect some degree of selectiveity depending upon the groups attached to the aldehyde moiety, since this could have bearing on the activeity of the aldehyde. It appears that the reaction under these circumstances is rapid enough and thus isn't affected by variations in the activity of carbonyl structure. The structures of compounds 4a-y were deduced from their elemental analysis and their IR, ^{1}H NMR, and ^{13}C NMR spectra. The ^{1}H NMR spectrum of 4t exhibited a doublet signal ($\delta = 0.92$ ppm) for the methyl group, multiple signals ($\delta = 1.86, 2.45, 2.93$ ppm) for the methylene groups and methine protons, a complex signal ($\delta = 7.45 - 8.09$ ppm) for the aromatic protons along with a singlet ($\delta = 8.45$ ppm) due to the two olefin protons. The proton-decoupled ^{13}C NMR spectrum of 4t exhibited 23 distinct resonances in agreement with the bis(substituted-benzylidene) structure.



Scheme 1. Preparation of SiO$_2$-R-SO$_3$H catalyst.



Scheme 2. Synthesis of bis(substituted-benzylidene)cycloalkanones.

Table 1. Preparation of α,ά-bis(substituted benzylidene)cycloalkanones catalyzed by SiO$_2$-R-SO$_3$H at 90˚C under solvent-free conditions.

Entry	Ar	n, x	Time (h)	Product	Yield[a] (%)	Mp (˚C) Found	Mp (˚C) Reported
1	C$_6$H$_5$	n = 0, x = H	1.3	4a	85	189 - 191	188 - 190 [23]
2	p-MeC$_6$H$_4$	n = 0, x = H	1.5	4b	85	241 - 243	243 - 244 [23]
3	p-MeOC6H4	n = 0, x = H	1.4	4c	84	212 - 214	211 - 212 [23]
4	p-ClC$_6$H$_4$	n = 0, x = H	1.0	4d	83	227 - 228	228 - 229 [23]
5	p-NO$_2$C$_6$H$_4$	n = 0, x = H	1.1	4e	80	227 - 230	229 - 231 [23]
6	o-ClC$_6$H$_4$	n = 0, x = H	1.6	4f	75	154 - 157	152 - 153 [22]
7	*α*-Naphttyl	n = 0, x = H	1.3	4g	82	173 - 174	----
8	*β*-Naphttyl	n = 0, x = H	1.5	4h	79	274 - 275	----
9	C$_6$H$_5$	n = 1, x = H	1.2	4i	80	115 - 116	117 - 118 [23]
10	p-MeC$_6$H$_4$	n = 1, x = H	1.6	4j	84	168 - 171	164 - 165 [23]
11	p-MeOC$_6$H$_4$	n = 1, x = H	1.4	4k	85	162 - 163	161 - 163 [23]
12	p-ClC$_6$H$_4$	n = 1, x = H	1.2	4l	81	146 - 148	147 - 148 [23]
13	p-NO$_2$C$_6$H$_4$	n = 1, x = H	1.2	4m	79	162 - 163	161 - 162 [23]
14	o-ClC$_6$H$_4$	n = 1, x = H	1.8	4n	76	102 - 104	102 - 104 [23]
15	α-Naphthyl	n = 1, x = H	1.4	4o	89	199 - 201	----
16	C$_6$H$_5$	n = 1, x = Me	1.5	4p	80	97 - 99	97 - 99 [23]
17	p-MeC$_6$H$_4$	n = 1, x = Me	1.7	4q	80	124 - 126	125 - 127 [23]
18	p-MeOC$_6$H$_4$	n = 1, x = Me	2.0	4r	79	136 - 138	137 - 139 [23]
19	p-ClC$_6$H$_4$	n = 1, x = Me	1.4	4s	83	153 - 157	156 - 160 [23]
20	*α*-Naphthyl	n = 1, x = Me	1.0	4t	75	151 - 153	----
21	*β*-Naphthyl	n = 1, x = Me	1.1	4u	81	160 - 162	----
22	*α*-Naphthyl	n = 1, x = Et	2.0	4v	80	146 - 148	----
23	*β*-Naphttyl	n = 1, x = Et	2.0	4w	84	139 - 140	----
24	*α*-Naphttyl	n = 1, x = *t*-But	1.0	4x	84	189 - 192	----
25	*β*-Naphttyl	n = 1, x = *t*-But	1.0	4y	93	182 - 185	----

[a] Isolated yield.

Shortening of reaction times and the use of an eco-friendly catalyst are two major merits of this work. Reusability of the catalyst is also an added advantage in its own right.

The reuse of the catalyst is a major factor in a new synthetic procedure. To test this, a series of ten consecutive runs of the reaction of benzaldehyde and cyclohexnone with catalyst 1 were carried out. The results, however, demonstrated no significant change in the activity of the catalyst. The results in **Table 2** show a 12.5% loss of activity over ten recycles.

3. Experimental

3.1. Instruments and Characterization

Melting points were measured on an Electrothermal 9200 apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-300 AVANCE spectrometer at 300.13 MHz. IR spectra were recorded on a Bomem MB-Series FTIR. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

3.2. General Procedure for the Preparation of Catalyst 1

For the preparation of sulfonic acid covalently anchored onto the surface of silica gel (SiO_2-R-SO_3H), activated silica was refluxed with trimethoxy (3-sulfanylpropyl) silane in toluene for 24 h. This gave 3-sulfanylpropyl-substituted silica, which was then oxidized with 30% hydrogen peroxide in the presence of concentrated sulfuric acid, to give SiO_2-R-SO_3H (**Scheme 1**). The detailed experimental procedure for the preparation and characterization of this silica gel/sulfonic acid catalyst is reported elsewhere [8].

3.3. General Procedure for the Synthesis of *α*, *ά*-Bis(Substituted-benzylidene)cycloalkanones

A mixture of a substituted benzaldehyde (8 mmol), cycloalkanone (4 mmol) and catalyst (0.3 g, 3.6 mol% of SO_3H) was stirred at 90˚C for an appropriate time. The reaction mixture was diluted with $CHCl_3$ (15 ml), catalyst was filtered off, washed with acetonitrile and distilled water, dried at 110˚C for 3 h and was used for the next run directly. The filtrate was evaporated and the resulting solid product was recrystallized from ethanol. The results are shown in **Table 1**.

Table 2. Reusability of catalyst 1 at 90˚C.

Run	1	2	3	4	5	6	7	8	9	10
Yield (%)	80	80	79	77	77	75	75	72	70	70

3.4. The Spectral Data of Unreported Compounds Is Given Below

(2*E*,5*E*)-2,5-*Bis*((*naphthalen*-1-*yl*)*methylene*)*cyclopentanone* (4*g*): Mp = 173˚C - 174˚C. IR (KBr, cm^{-1}): 1703, 1629. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01 (s, 4H, 2CH_2), 7.51 - 7.64 (m, 6H, H-Ar), 7.67 (d, 2H, J = 7.0 Hz, H-Ar), 7.90 (dd, 4H, J = 9.0, 2.2 Hz, H-Ar), 8.27 (d, 2H, J = 8.0 Hz, H-Ar), 8.44 (s, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.0, 124.0, 125.1, 126.2, 126.7, 127.1, 127.5, 128.7, 129.8, 130.4, 130.5, 132.3, 132.4, 133.6, 139.8, 195.7. Anal. Calc. for $C_{27}H_{20}O$ (360.15): C, 89.97; H, 5.59. Found: C, 89.96; H, 5.57.

(2*E*,5*E*)-2,5-*Bis*((*naphthalen*-6-*yl*)*methylene*)*cyclopentanone* (4*h*): Mp = 274˚C - 275˚C. IR (KBr, cm^{-1}): 1695, 1683, 1615. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.30 (s, 4H, 2CH_2), 7.53 - 7.56 (m, 4H, H-Ar), 7.73 - 7.80 (m, 4H, H-Ar), 7.85 - 7.93 (m, 6H, H-Ar), 8.11 (s, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.9, 124.1, 125.1, 126.4, 126.8, 127.3, 127.6, 127.9, 128.4, 128.8, 129.9, 130.2, 130.6, 133.0, 133.1, 133.5, 136.4, 136.6, 137.0, 137.4, 195.4. Anal. Calc. for $C_{27}H_{20}O$ (360.15): C, 89.97; H, 5.59. Found: C, 89.93; H, 5.55.

(2*E*,6*E*)-2,6-*Bis*((*naphthalen*-1-*yl*)*methylene*)*cyclohexanone* (4*o*): Mp = 200˚C. IR (KBr, cm^{-1}): 1663, 1606, 1578. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (m, 2H, CH_2), 2.81 (m, 4H, 2CH_2), 7.46 - 7.60 (m, 8H, H-Ar), 7.86 - 7.92 (m, 4H, H-Ar), 8.07 - 8.09 (m, 4H, H-Ar), 8.45 (s, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 28.7, 124.1, 124.8, 125.0, 126.1, 126.4, 126.9, 128.1, 128.5, 128.9, 129.3, 132.0, 133.2, 133.5, 134.9, 135.2, 135.3, 138.3, 190.1. Anal. Calc. for $C_{28}H_{22}O$ (374.17): C, 89.81; H, 5.92. Found: C, 89.79; H, 5.90.

(2*E*,6*E*)-4-*Methyl*-2,6-*bis*((*naphthalen*-1-*yl*)*methylene*) *cyclohexanone* (4*t*): Mp = 151˚C - 153˚C. IR (KBr, cm^{-1}): 1700, 1671, 1614, 1588. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, 3H, J = 6.5 Hz, Me), 1.86 (m, 1H, CH), 2.45 (m, 2H, CH_2), 2.93 (dd, 2H, J = 15.5, 3.4, CH_2), 7.45 - 7.60 (m, 6H, H-Ar), 7.87 - 7.93 (m, 4H, H-Ar), 8.06 - 8.09 (m, 2H, H-Ar), 8.45 (s, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.3, 29.9, 37.0, 123.9, 124.8, 125.1, 125.4, 125.5, 126.2, 126.4, 127.0, 127.6, 128.5, 128.9, 129.3, 129.5, 132.0, 133.2, 133.5, 135.5, 135.6, 137.4, 189.9. Anal. Calc. for $C_{29}H_{24}O$ (388.18): C, 89.66; H, 6.23. Found: C, 89.61; H, 6.20.

(2*E*,6*E*)-4-*Methyl*-2-((*naphthalen*-2-*yl*)*methylene*)-6-((*naphthalen*-3-*yl*)*methylene*)*cyclohexanone* (4*u*): Mp = 160˚C. IR (KBr, cm^{-1}): 1667, 1657, 1601, 1590. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, 3H, J = 6.8 Hz, Me), 1.95 (m, 1H, CH), 2.67 (m, 2H, CH_2), 3.02 (dd, 2H, J = 15.5, 3.5, CH_2), 7.51 - 7.61 (m, 6H, H-Ar), 7.84 - 7.95 (m, 6H, H-Ar), 8.00 (s, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 29.5, 36.6, 126.4, 126.8, 127.6, 127.9, 128.4, 130.2, 133.0, 133.1, 133.5, 135.6, 137.3, 190.1. Anal. Calc. for $C_{29}H_{24}O$ (388.18): C, 89.66; H, 6.23. Found: C, 89.61; H, 6.20.

(2*E*,6*E*)-4-*Ethyl*-2,6-*bis*((*naphthalen*-1-*yl*)*methylene*) *cyclohexanone* (4*v*): Mp = 146˚C - 148˚C. IR (KBr, cm^{-1}): 1669, 1607, 1589. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.70 (t, 3H, *J* = 7.4 Hz, CH_3), 1.29 (m, 2H, CH_2-Me), 1.62 (m, 1H, CH), 2.46 (m, 2H, CH_2), 2.98 (dd, 2H, J = 15.6, 3.3 Hz, CH_2), 7.46 - 7.60 (m, 8H, H-Ar), 7.87 - 7.93 (m, 4H, H-Ar), 8.07 - 8.11 (m, 2H, H-Ar), 8.47 (s, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3, 28.1, 34.2, 36.1, 124.8, 125.0, 126.1, 126.4, 126.9, 127.6, 127.9, 128.1, 128.5, 128.9, 132.0, 133.1, 133.5, 135.2, 135.6, 137.3, 190.2. Anal. Calc. for $C_{30}H_{26}O$ (402.2): C, 89.51; H, 6.51. Found: C, 89.46; H, 6.47.

(2*E*,6*E*)-4-*Ethyl*-2-((*naphthalen*-2-*yl*)*methylene*)-6-((*naphthalen*-3-*yl*)*methylene*)*cyclohexanone* (4*w*): Mp = 139˚C - 140˚C. IR (KBr, cm^{-1}): 1696, 1663, 1601, 1565. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, J = 7.4 Hz, CH_3), 1.45 (m, 2H, CH_2-Me), 1.71 (m, 1H, CH), 2.67 (m, 2H, CH_2), 3.23 (dd, 2H, J = 15.6, 3.3 Hz, CH_2), 7.51 - 7.55 (m, 4H, H-Ar and H-olefine), 7.60 (dd, 2H, J = 8.5, 1.3 Hz, H-Ar), 7.84 - 7.90 (m, 6H, H-Ar), 7.95 - 8.0 (m, 4H, H-Ar and H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.5, 28.5, 34.2, 35.7, 126.4, 126.8, 127.7, 127.9, 128.4, 128.8, 130.2, 133.1, 133.1, 133.6, 135.6, 137.4, 190.4. Anal. Calc. for $C_{30}H_{26}O$ (402.2): C, 89.51; H, 6.51. Found: C, 89.48; H, 6.49.

(2*E*,6*E*)-4-*Tert-butyl*-2,6-*bis*((*naphthalen*-1-*yl*)*methylene*)*cyclohexanone* (4*x*): Mp = 189˚C - 192˚C IR (KBr, cm^{-1}): 1659, 1595, 1575, 1566. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 (s, 9H, 3Me), 1.52 (m, 1H, CH), 2.38 (t, 2H, J = 15 Hz, CH_2), 3.07 (d, 2H, J = 15.1 Hz, CH_2), 7.47 - 7.60 (m, 8H, H-Ar), 7.86 - 7.93 (m, 4H, H-Ar), 8.08 - 8.12 (m, 2H, H-Ar), 8.44 (s br, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.0, 27.1, 29.7, 30.0, 32.5, 44.7, 44.9, 124.8, 125.0, 126.1, 126.4, 126.7, 127.5, 127.6, 128.0, 128.5, 128.9, 130.4,132.1, 133.1, 133.5, 135.2, 137.5, 138.1, 190.3. Anal. Calc. for $C_{32}H_{30}O$ (430.23): C, 89.26; H, 7.02. Found: C, 89.21; H, 6.97.

(2*E*,6*E*)-4-*Tert-butyl*-2-((*naphthalen*-2-*yl*)*methylene*)-6-((*naphthalen*-3-*yl*)*methylene*)*cyclohexanone* (4*y*): Mp = 182˚C - 185˚C. IR (KBr, cm^{-1}): 1695, 1662, 1600, 1563. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.67 (s, 9H, 3Me), 1.51 (m, 1H, CH), 2.57 (t, 2H, J = 15 Hz, CH_2), 3.27 (d, 2H, J = 15.1 Hz, CH_2), 7.46 - 7.57 (m, 6H, H-Ar), 7.60 - 8.05 (m, 8H, H-Ar), 8.10 (s br, 2H, H-olefin). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.3, 29.6, 32.5, 44.5, 126.4, 126.8, 127.5, 127.6, 128.0, 128.4, 130.3, 130.6, 133.0, 133.1, 133.6, 136.4, 136.6, 137.0, 137.4, 190.5. Anal. Calc. for $C_{32}H_{30}O$ (430.23): C, 89.26; H, 7.02. Found: C, 89.23; H, 7.01.

4. Conclusions

We are reporting a new method for preparation of α, ά-bis(substituted-benzylidene)cycloalkanones using SiO_2-R-SO_3H. The catalyst is reusable with only small loss of activity over ten trials. Simple experimental procedure, use of small quantities of catalyst, no toxicity, no corrosiveness, short reaction times, inexpensive solid catalyst, high yields, mild reaction conditions and clean work up steps are significant merits of this work.

5. References

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