



***P*-Dodecylbenzenesulfonic acid (DBSA), a Brønsted acid-Surfactant Catalyst for Synthesis of α , α' -bis(substituted benzylidene)cycloalkanones with Electron-Withdrawing Substituent in Aqueous Media**

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Abstract

An array of aromatic aldehydes with electron withdrawing group underwent crossed-Aldol condensation with cycloalkanone in the presence of catalytic amounts of DBSA under aqueous media to afford the corresponding α , α' -bis(substituted-benzylidene) cycloalkanones in good yields. The electronic effects on aromatic aldehydes could be observed. The present method is operationally simple and use of water as the reaction medium makes the process environmentally benign.

Keywords: Cross-Aldol Condensation, α , α' -Bis(substituted-benzylidene) cycloalkanones, *P*-Dodecylbenzenesulfonic acid (DBSA), Aqueous Media.

Introduction

Cross-Aldol condensation of aromatic aldehydes with cyclic ketones is an important synthetic reaction for preparation of α , α' -bis(substituted-benzylidene)cycloalkanones. These benzylidene derivatives are intermediates of various pharmaceuticals, agrochemicals and perfumes [1]. They are frequently used for synthesis of bioactive pyrimidine compounds [2] and have also

found applications in preparation of liquid-crystalline polymers [3], nonlinear optical materials [4] and in total synthesis of natural products [5].

For synthesis of α , α' -bis (substituted-benzylidene) cycloalkanones, cross-Aldol condensation of cyclic ketones with aldehydes has been classically carried out in the presence of strong acid or base [6]. Various reagents have been introduced as the methodology

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was developed during last few decades which include, TMSCl/NaI [7], molecular I₂ [8], KF-Al₂O₃ [9], Cp₂ZrH₂ [10], SOCl₂ [11], Cu(OTf)₂ [12], BF₃•OEt₂ [13], TiCl₃(CF₃SO₃) [14], TMSCl/Pd-C [15], La⁺³ immobilized organic solid [16], K₂CO₃/PEG-400 [17], Mg (HSO₄)₂ [18], InCl₃ [19], 1-methyl-3-(2-(sulfooxy) ethyl)-1H-imidazol-3-ium chloride [20] and Et₃N in the presence of LiClO₄ [21]. The cross-Aldol condensation for preparation of α, α'-bis(benzylidencycloalkanones) is also catalyzed by animal bone meal (ABM) or Na/ABM [22], ionic liquid [23], sodium-modified-hydroxyapatite (Na-HAP) [24], solid NaOH [25], micellar media [26], ethanolic KOH [27], 2,4,6-trichloro [1,3,5] triazine [28], rare earth (III) perfluorooctanesulfonates [RE(OPf)₃] [29] and potassium hydroxide (KOH) [30].

Such condensation reactions are also carried out by heterogeneous catalyses such as silica chloride [31], silica-supported phosphorus pentoxide (P₂O₅/SiO₂) or silicaphosphin oxide (silphox, [POCl₃-n(SiO₂)_n]) [32], SiO₂-R-SO₃H [33], nanoporous silica-based sulfonic acid [34] and polymer supported sulfonic acid [35]. However, most of these reactions suffer from reverse and/or side reactions resulting in low yields of the desired products.

P-Dodecylbenzenesulfonic acid (DBSA) is a Brønsted acid surfactant-combined catalyst, composed of a polar head and a long non-polar chain that has been studied as a catalyst in organic chemistry [36]. The behavior of DBSA

as a catalyst has been studied in Mannich type reactions [37], Biginelli reaction [38] and also in esterification of various carboxylic acids and alcohols [39]. In this study, the results of synthesis of α, α'-bis(substituted-benzylidene)cycloalkanones using DBSA were reported in environmentally benign conditions.

Experimental

General

Aldehydes were distilled before being used. Reactions were monitored by thin layer chromatography and the products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones. Infrared spectra were recorded on Perkin-Elmer Spectrum 100 FT-IR spectrometer. ¹H NMR spectra were recorded on Bruker Advance 300 MHz spectrometer in CDCl₃, using TMS as an internal standard. Melting points were determined using an Electrothermal 9100 and were uncorrected.

General experimental procedure for cross-aldol condensation of cyclic ketones and aldehydes

A mixture of cycloalkanone (2 mmol), substituted benzaldehydes (4 mmol) and DBSA (0.4 mmol) was stirred at reflux in 5 ml methanol-water mixture (1:1). The progress of the reaction was monitored by TLC. After

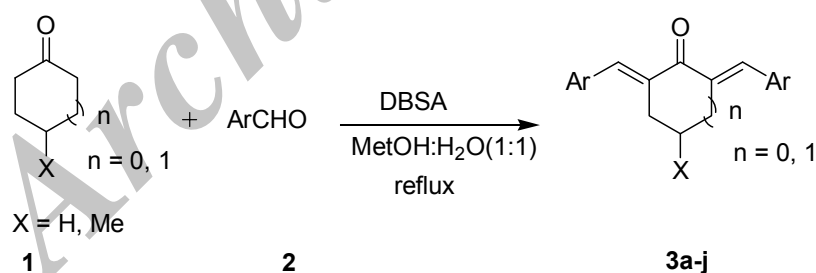
completion of the reaction (6-12 h) and upon cooling, solid material precipitated from the solution (Table 2). The precipitates were filtered off, washed with water and were recrystallized from EtOH to afford pure α, α' -bis (substituted-benzylidene) cycloalkanones as yellow-white solids.

Compound 4a : (2*E*, 6*E*) -2 , 6-bis (4-nitrobenzylidene) cyclohexanone: m.p. 162-163 °C. ¹H NMR (300 MHz, CDCl₃) δ : 1.02 (m, 2H, CH₂), 2.94 (4H, t, *J* = 3.7 Hz, 2CH₂), 7.60 (4H, d, *J* = 8.60 Hz, H-Ar), 7.83 (2H, s, H-olefin). 8.30 (4H, d, *J* = 6.60 Hz, H-Ar). ¹³C NMR (75 MHz, CDCl₃) δ : 22.7, 28.5, 123.6, 130.8, 135.0, 138.7, 142.3, 147.4, 189.2. IR (KBr, cm⁻¹): 1668, 1590, 1513, 1341. Anal. Calcd. for C₂₀H₁₆N₂O: C 65.93, H 4.43, N 7.69;

found C 66.12, H 7.45, N 7.50.

Results and discussion

To the best knowledge of the present authors, a reliable method for Aldol condensation of aromatic aldehyde with cycloalkanones in presence of DBSA as a catalyst in aqueous media has not been reported yet. Attempts were made to report a green, efficient, convenient and facile method for condensation of aldehydes with cycloalkanones, leading to the corresponding α, α' -bis(substituted-benzylidene) cycloalkanones in the presence of DBSA as a homogeneous catalyst (Scheme 1). DBSA was used as a source of H⁺ to catalyze this reaction and it was found to be a good catalyst for preparation of α, α' -bis(substituted-benzylidene) cycloalkanones.



Scheme 1. Synthesis of bis(substituted-benzylidene)cycloalkanones.

Initially, the focus was on systematic evaluation of different solvents for the model reaction of 4-nitrobenzaldehyde and cyclohexanone in the presence of DBSA in water at reflux. The attempts for studying and optimizing the reaction conditions showed that carrying out

the reaction in H₂O failed whereas using the amounts of EtOH to the media had satisfactory results (Table 1, entry 5). The results revealed that the highest yield was obtained by the solvent system water/methanol (1:1) (Table 1, entry 9).

Table 1. Reactions of cyclohexanone with 4-nitrobenzaldehyde in the presence of various amounts of DBSA in different protic solvent.

Entry	Catalyst	Solvent	Temperature	Time (h)	Yield (%) ^a
1	DBSA (10%)	H ₂ O	reflux	12	No reaction
2	DBSA (10%)	EtOH	r.t.	12	trace
3	DBSA (10%)	EtOH	reflux	12	40
4	DBSA (10%)	MeOH	reflux	12	45
5	DBSA (10%)	EtOH:H ₂ O (1:1)	reflux	12	40
6	DBSA (10%)	MeOH:H ₂ O (1:1)	reflux	12	45
7	DBSA (15%)	MeOH:H ₂ O (1:1)	reflux	12	60
8	DBSA (20%)	MeOH:H ₂ O (1:1)	reflux	12	70
9	DBSA (25%)	MeOH:H ₂ O (1:1)	reflux	12	80
10	DBSA (30%)	MeOH:H ₂ O (1:1)	reflux	12	80

a) Isolated yield.

As DBSA was emerged as a suitable catalyst for the reaction in 1:1 methanol/water media, then, the attempt was to optimize the catalyst load for the cyclocondensation reaction, leading to the rapid formation of α, α' -bis(substituted-benzylidene)cycloalkanones. The optimization studies indicated that the yield increased smoothly with catalyst load up to 25 mol % and use of larger amounts of the catalyst did not improve the yields while decreasing the amount of catalyst decreased the yields. A negligible amount of the product was formed in the absence of catalyst. Afterward, scope of this reaction was concentrated by a variety of aldehydes and cycloalkanones (Scheme 1) to check viability of this protocol in obtaining a library of substituted α, α' -bis(substituted-benzylidene)cycloalkanones (Table 2).

Table 2. Preparation of α, α' -bis(substituted benzylidene)cycloalkanones catalyzed by DBSA at reflux in Water/Methanol.

Entry	Ar	n, x	Time (h)	Product	Yield (%) ^a	Mp (°C)	
						Found	reported
1	4-NO ₂ C ₆ H ₄	n = 1, x = H	12	3a	80	207-209	208-210
2	3-NO ₂ C ₆ H ₄	n = 1, x = H	9	3b	78	194-197	193-196
3	2-NO ₂ C ₆ H ₄	n = 1, x = H	12	3c	70	150-153	151-154
4	4-BrC ₆ H ₅	n = 1, x = H	12	3d	75	170-173	165-167
5	C ₆ H ₅	n = 1, x = H	16	trace	----		
7	4-MeOC ₆ H ₄	n = 1, x = H	16	not formed	----		
8	4-NO ₂ C ₆ H ₄	n = 1, x = Me	9	3e	80	209-211	----
9	3-NO ₂ C ₆ H ₄	n = 1, x = Me	8	3f	85	161-164	164-167
10	4-MeOC ₆ H ₄	n = 1, x = Me	16	not formed	----		
11	4-NO ₂ C ₆ H ₄	n = 0, x = H	10	3g	85	240-242	229-230
12	3-NO ₂ C ₆ H ₄	n = 0, x = H	6	3h	90	224-226	226-228
13	2-NO ₂ C ₆ H ₄	n = 0, x = H	16	3i	75	160-165	158-159
14	4-BrC ₆ H ₅	n = 0, x = H	12	3j	70	210-213	211-213
15	4-MeOC ₆ H ₄	n = 0, x = H	16	not formed	----		

^a) Isolated yield.

The presence of electron-withdrawing groups at aldehyde moiety led to α , α' -bis(substituted-benzylidene)cycloalkanones (Scheme 2). When these reactions were carried out with benzaldehyde and aldehydes having electron-donating groups (such as Me or OMe), no product was obtained. It can be concluded from the above characteristic that carbonyl group of the substrates (aldehyde moiety), including its electron-withdrawing property, is an important substituent to this reaction in the presence DBSA catalyst.

In conclusion, DBSA was found to be an efficient catalyst for synthesis of α , α' -bis(substituted-benzylidene)cycloalkanones by condensation of cycloalkanone with electron-withdrawing aldehyde in aqueous media. General applicability, operational simplicity, mild reaction conditions and aqueous reaction media are notable advantages of the proposed procedure.

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