Catalysis Communications 83 (2016) 58–61

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short communication

Cationic chiral surfactant based micelle-guided asymmetric Morita-Baylis-Hillman reaction

Bashir Ahmad Shairgojray [a], Aijaz Ahmad Dar [b], Bilal A. Bhat [a,*]

[a] CSIR-Medicinal Chemistry Division, Indian Institute of Integrative Medicine, Sanatnagar, Srinagar 190005, J&K, India
[b] Physical Chemistry Division, Department of Chemistry, University of Kashmir, Srinagar 190006, J&K, India

ARTICLE INFO

Article history:
Received 17 February 2016
Received in revised form 31 March 2016
Accepted 17 May 2016
Available online 18 May 2016

Keywords:
Ephedrinium salts
Morita-Baylis-Hillman reaction
Asymmetric induction
Enantiomeric excess
Micellar micro-environment

ABSTRACT

Cationic chiral surfactant (*1R, 2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB) was utilized for the first time in inducing asymmetry to Morita-Baylis-Hillman reaction in aqueous medium. Proton NMR studies carried out to determine the locus of the reaction in micro-heterogeneous micellar environment, were found useful in proposing a plausible model for asymmetric induction. This work demonstrates that under such mild and non-hazardous reactions conditions, the reaction rates increase, good yields are favored and above all reasonable enantiomeric excesses are obtained.

1. Introduction

Morita-Baylis-Hillman (MBH) reaction is a powerful chemical transformation where simple starting materials are converted into highly functionalized molecular synthons in a catalytic process [1–2]. As a result this reaction has been applied to synthesis of natural products [3,4], biologically relevant heterocycles [5,6] and more importantly in synthesizing versatile chiral building blocks [7–9]. However, the reaction has traditionally suffered from low reaction rates leading to limited substrate scope, but recent developments have focused on improving rates [10–14] and changed its scope considerably. In our own efforts towards synthesizing natural products using MBH-adducts as building blocks, we also suffered with its sluggish reaction rates and lower yields [15–18]. It is important to mention that over the years many chiral catalysts have been employed to develop asymmetric versions of MBH-reaction to produce variety of chiral building blocks. The diversity of chiral catalysts tested include Lewis acids and Lewis bases, Bronsted acids, thioureas, bulky ammonium salts, ionic liquids, phosphines and many more bi-functional organocatalysts including proline [19–22].

During the endeavour to increase efficiency of chemical reactions, micellar catalysis is gaining considerable attention among scientific community owing to their efficient outcome and involvement of green protocols [23]. These micellar environments are considered to be the nano-reactors having unique features that include isolation of the substrates from bulk solvent, enhancement of organic species solubilization in water, increase the local concentration and reactivity of reagents and promote chemo- regio- & stereo-selectivities [23,24]. Keeping in view these features of micellar-guided reactions, we earlier developed an expeditious protocol for MBH-reaction that utilizes the cationic surfactant cetyltrimethylammonium bromide (CTAB) as catalyst enhancing its reaction kinetics substantially. A plausible model was proposed that explains the stabilization of enolate-intermediate in the conjugate addition step of MBH- reaction through the positive charge on the self-organized aggregates of these cationic micellar structures thereby driving the reaction faster. To further capitalize on the utility of the micelles as catalysts in MBH-reaction, we sought to develop a generalized, fast and enantioselective variant of this reaction with the use of an enantiopure cationic surfactant, (*1R,2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB) [25] which is expected to induce enantio-selectivity in addition to increase the reactions kinetics.

2. Experimental

2.1. Representative procedure for MBH reaction of 4-nitrobenzaldehyde with acrylonitrile in presence of chiral DMEB surfactant

The micellar solution was prepared by dissolving DMEB (100 mg, 0.22 mmol) in distilled water (4 mL) and the resulting solution was stirred for 20 min at room temperature. To this solution, 4-nitrobenzaldehyde (30 mg, 0.19 mmol), acrylonitrile (14 μL, 0.19 mmol) and DABCO (4 mg, 0.038 mmol) were added followed by continuous stirring till the reaction was over in 6 h. After the completion of reaction (monitored by TLC), the crude product was extracted with ethylacetate

* Corresponding author.
E-mail address: bilal@iiim.ac.in (B.A. Bhat).

http://dx.doi.org/10.1016/j.catcom.2016.05.010
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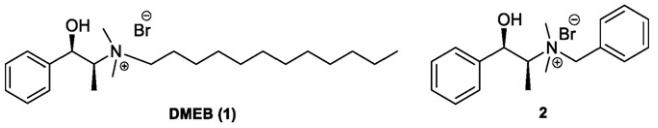
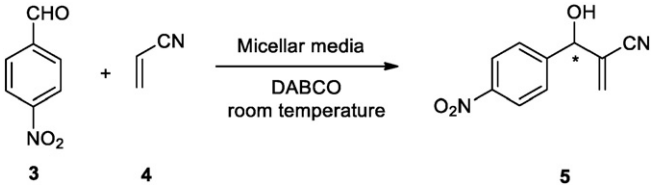


Fig. 1. Structure of ephedrinium slats, (*1R,2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide, DMEB (**1**) and (*1R, 2S*)-(−)-*N*-benzyl-*N*-methylephedrinium bromide (**2**) used in this study.



Scheme 1. MBH-reaction of 4-nitrobenzaldehyde with acrylonitrile in presence of DABCO and micellar medium.

(3 × 10 mL). The combined organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography (60–120 mesh; eluent, 7:3 petroleum ether and ethylacetate).

3. Results and discussion

In light of the above discussion, we proposed that the chiral micellar environment could be the potential alternative strategy in carrying out the rapid asymmetric version of MBH-reaction. For this purpose, two ephedrinium based enantiopure salts were used to validate our concept. A well known and commercially available chiral surfactant, (*1R, 2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB), **1**, and its non-surfactant variant, (*1R, 2S*)-(−)-*N*-benzyl-*N*-methylephedrinium bromide, **2**, were used in this study (Fig. 1).

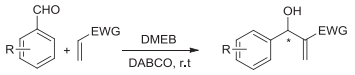
We initially attempted the reaction of 4-nitrobenzaldehyde and acrylonitrile in presence of DABCO in CTAB and proline mixture (Scheme 1). To our surprise, a marginal enantioselectivity was achieved in the MBH-adduct **5** with *ee* = 18% (entry 1, Table 1). We next utilized the chiral surfactant **1** for this reaction. In order to ensure the presence of micelles in the reaction medium we determined the critical micelle concentration (*cmc*) of DMEB in water using the surface tension method. The *cmc* of DMEB was obtained from the plot of surface tension vs logarithm of surfactant concentration and observed to be 4.11 mM. To our delight, it was observed that an aqueous micellar solution of **1** above its *cmc*, the enantiomeric excess (*ee*) of adduct **5** was enhanced upto 52% (Table 1, entry 2). In order to further confirm that the *ee* was achieved due to micellar micro-environment, the *ee* was also carried out in presence of a non-surfactant enantiopure ephedrinium salt **2**. It was interesting to observe that under these conditions, both *ee* and chemical yield of adduct **5** were poor (Table 1, entry 3).

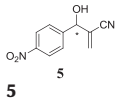
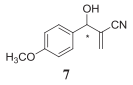
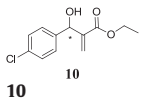
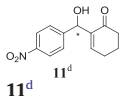
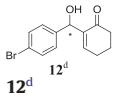
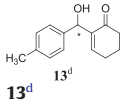
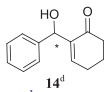
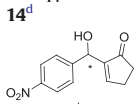
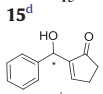
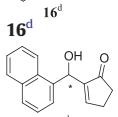
Table 1
Formation of MBH-adduct **5** under various conditions.

Entry	Conditions	Yield of 5	ee (%)
1.	CTAB + L-proline	70	18
2.	(*1R,2S*)-(−)-*N*-dodecyl-*N*-methylephedrinium bromide	72	52
3.	(*1R,2S*)-(−)-*N*-Benzyl-*N*-methylephedrinium bromide[a]	43	03

[a] In order to ensure the solubility of reactants under this reaction condition, THF:H_2O (1:1) were taken as the solvent for the reaction.

Table 2
Range of non-racemic MBH-adducts synthesized using DMEB as a chiral surfactant.



Entry	Product[a]	Reaction time in h	Percentage yield[b]	ee (%)
1	 **5**	6	72	56.0[c] (S)
2	 **6**	5	75	40.0[c] (S)
3	 **7**	37	70	42.0[c] (R)
4	 **8**	18	71	44.0[c] (R)
5	 **9**	15	70	44.0[c] (R)
6	 **10**	16	73	22.0[c] (R)
7	 **11**[d]	13	78	44.3[e] (S)
8	 **12**[d]	21	70	40.6[e] (S)
9	 **13**[d]	19	70	42.8[e] (R)
10	 **14**[d]	23	71	47.6[e] (R)
11	 **15**[d]	15	72	45.7[e] (R)
12	 **16**[d]	17	77	43.9[e] (R)
13	 **17**[d]	22	68	48.4[e] (R)

[a] All reactions were carried out in presence of aqueous solution of DMEB surfactant above its CMC at room temperature using DABCO as a catalyst.
[b] Yields reported are isolated yields.
[c] Enantiomeric excess (*ee*) of MBH- adducts were determined by chiral HPLC using a Chiralcel OD-H column.
[d] For the synthesis of adducts **11–17**, DMAP was used as a tertiary amine catalyst.
[e] Enantiomeric excess of adducts **11–17** were calculated from their specific rotation when compared to enantiopure adducts in literature and absolute configuration of all MBH-adducts were also assigned based on literature reports [9,26–29].

After optimizing the reaction conditions, a wide range of substrates were screened for carrying out the MBH-reaction under DMEB-micellar conditions in presence of DABCO as a catalyst. All the reactions showed a