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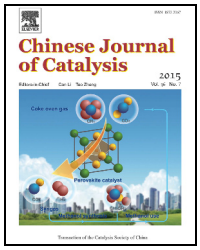

Article

Stereoselective synthesis of *vic*-halohydrins and an unusual Knoevenagel product from an organocatalyzed aldol reaction: A non-enamine mode

P. B. Thorat, S. V. Goswami, V. P. Sondankar, S. R. Bhusare *

Department of Chemistry, Dnyanopasak College, Parbhani-431401, MS, India

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ABSTRACT

Stereoselective synthesis by an aldol reaction between chloroacetone and aldehyde was studied using a synthesized chiral organocatalyst and triethylamine. The reaction gave α-chloro-β-hydroxy ketones in excellent yield with high *anti* selectivity and enantioselectivity. The chiral organocatalyst was also used in the Knoevenagel reaction, which gave α-cyano-β-hydroxy ketones at a low temperature and the usual Knoevenagel product at a high temperature. Both products were obtained in good to moderate yield with good *anti* selectivity in the case of α-cyano-β-hydroxy ketone derivatives.

1. Introduction

Vic-halohydrins are important intermediates for the synthesis of biologically active compounds and natural products such as bagonists [1], substituted pyrrolidines [2], polychlorosulfolipid [3], and insect sex pheromones [4]. These molecules are building blocks for various bioactive products and natural compounds. Thus efforts have been made to develop effective techniques to synthesize these compounds. The ring opening of enantiomerically pure epoxides is one of the most popular process [5] but suffers from the disadvantage of the formation of regioisomers. The asymmetric reduction of prochiral α-halo ketones by chiral catalysts such as oxazaborolidine with borane [1–2,6], Ru [1,7], or Rh [7,8] by asymmetric hydrogenation has shown good enantioselectivity.

The condensation reaction of carbonyl compounds with an active methylene compound in the presence of a base is known as Knoevenagel condensation [8]. The Knoevenagel reaction is an important C–C bond forming reaction because the synthesized alkenes are very useful intermediates in organic synthesis [9]. For example, Knoevenagel condensation has been successfully combined with hetero-Diels-Alder reactions, Michael addition reactions, ene reactions, and sigmatropic rearrangement for the synthesis of highly functionalized molecules [10–13].

Asymmetric organocatalysis has become an important area of research in organic synthesis. The development of organocatalyzed reactions for the stereoselective construction of C–C bonds has been intensively investigated. Since the discovery by List *et al.* [14] that L-proline can mimic enantioselectively catalyzed intermolecular aldol reactions, many organocatalysts have been synthesized with the aim of increasing their activity and stereoselectivity [15–17]. These reactions are typical of

* Corresponding author. Tel: +91-2452-242411; Fax: +91-2452-242493; E-mail: bhusare71@yahoo.com
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enamine based organocatalysis and proceeds *via* the reversible condensation of the catalytic amine with a ketone to provide a nucleophilic enamine intermediate. In these reactions, the carboxylic acid functionality on proline is important, and it is postulated that it activates and orients the aldehyde acceptor *via* a hydrogen bonding interaction.

Alternatively, the utility of a *N*-sulfinyl group [18–22] as both a chiral directing group and acidifying element in hydrogen-bonded organocatalysts has been demonstrated. In these reactions, the sulfinyl N–H bond is postulated to activate the substrate by the formation of a key hydrogen bonding interaction. The inductive electron-withdrawing effect of the sulfinyl group acidifies the N–H bond, which serves to modulate the hydrogen bonding interaction. In addition, the close proximity of the stereogenic sulfur to the active site of the catalyst contributes to high stereoselectivity control in these reactions. On the basis of the success of hydrogen bonding organocatalysis, we studied pyrrolidine based organocatalysis in the absence of a Lewis basic primary or secondary amine functionality, which occurs exclusively *via* hydrogen bonding and van der Waals interactions.

We restricted enamine/imine formation by introducing an acetyl group onto the active nitrogen site in the pyrrolidine ring and replaced the carboxylic group by an amide and sulfinyl group. To perform hydrogen bonding organocatalysis, we synthesized the organocatalysts shown in Fig. 1. Earlier results have been reported in a previous communication [23].

2. Experimental

2.1. General details

All solvents used were commercial anhydrous grade used without further purification. Aluminium sheets 20 cm × 20 cm, silica gel 60 F_{254}, Merck grade was used for thin layer chromatography to determine the progress of the reaction. Column chromatography was carried out over silica gel (80–120 mesh). The optical rotation was measured on a Polax-2L digital polarimeter. The melting point was determined in an open capillary tube and was uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on an Avance 300 MHz spectrometer using $CDCl_3$ solvent. Mass spectra were obtained on a Polaris-Q Thermoscientific GC-MS. Elemental analyses were obtained using a flash EA 1112. Enantiomeric purity was determined on a PerkinElmer Series 200 HPLC System.

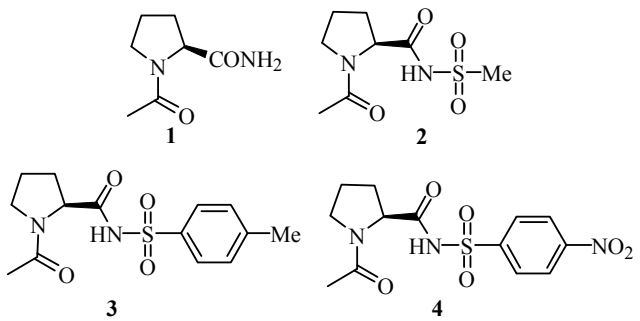

Fig. 1. Pyrrolidine based organocatalysts.

2.2. Preparation of organocatalysts ***1*–*4***

The synthesis and characterization of the organocatalyst was described in our previous communication [23].

2.3. General procedure for the aldol reaction for the synthesis of ***7a*–*7f***

To a solution of chloroacetone **6** (1.5 eq.) dissolved in ethanol, a few drops of triethylamine (3–4 drops) was added and the reaction mixture was stirred for 15–20 min. To this stirred solution, an aromatic aldehyde **5(a–f)** (1.0 eq.) and a catalytic amount of the organocatalyst (*S*)-1-acetyl-*N*-tosylpyrrolidine-2-carboxamide **3** was added and reacted and stirred for an appropriate time (Table 2). The progress of reaction was monitored by thin layer chromatography. After completion of the reaction, the solvent was evaporated under vacuum. The crude product was partitioned between ethyl acetate and water. The organic layer was collected, and the aqueous phase was extracted with ethyl acetate. The collected organic layer was washed with saturated brine solution, and the product was purified using column chromatography using silica gel (80–120 mesh).

3-Chloro-4-hydroxy-4-(4-nitrophenyl)butan-2-one (**7a**). Light yellow solid (182 mg, 90%), M.P. 142–144 °C [19]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.52 (m, 2H), 7.12–7.28 (m, 2H), 6.01 and 5.76 (bs, 1H, OH for *syn* and *anti*), 5.21 (s, 1H) *syn*, 4.96 (d, 1H, J = 8.7 Hz) *anti*, 4.29 (s, 1H) *anti*, 3.95 (s, 1H) *syn*, 2.08 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 209.9, 154.5, 149.8, 129.7, 123.2, 68.9, 59.1, 28.1; GC-MS m/z 243 (M+); Elemental analysis: Anal. Calcd for $C_{10}H_{10}ClNO_4$: C, 49.30; H, 4.14; Cl, 14.55; N, 5.75; O, 26.27; Found C, 49.31; H, 4.17; Cl, 14.57; N, 5.76; O, 26.29. Enantiomeric purity was determined by chiral HPLC using Whelk-O1 (25 cm × 4.6 mm), 20:80:0.5 IPA/hexane/HOAc, flow rate 1.0 mL/min, λ = 254 nm; t_R(major) = 17.2 min, t_R(minor) = 25.5 min, *ee* = 92%.

3-Chloro-4-(4-fluorophenyl)-4-hydroxybutan-2-one (**7b**). Colorless solid, (158 mg, 92%), M.P. 77–79 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.66 (m, 2H), 7.23–7.34 (m, 2H), 5.79 and 5.46 (bs, 1H, OH for *syn* and *anti*), 5.21 (s, 1H) *syn*, 4.88 (d, 1H, J = 8.2 Hz) *anti*, 4.33 (s, 1H) *anti*, 3.89 (s, 1H) *syn*, 1.98 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 208.4, 151.8, 147.6, 128.9, 124.5, 70.4, 57.9, 29.1; GC-MS m/z 246 (M+); Elemental analysis: Anal. Calcd for $C_{11}H_{12}ClFO_3$: C, 53.56; H, 4.90; Cl, 14.37; F, 7.70; O, 19.46; Found C, 53.54; H, 4.91; Cl, 14.40; F, 7.73; O, 19.44. Enantiomeric purity was determined by chiral HPLC using Whelk-O1 (25 cm × 4.6 mm), 20:80:0.5 IPA/hexane/HOAc, flow rate 1.0 mL/min, λ = 254 nm; t_R(major) = 23.2 min, t_R(minor) = 27.1 min, *ee* = 92%.

4-(2-Chloro-1-hydroxy-3-oxobutyl)benzonitrile (**7c**). Viscous oil (171 mg, 88%) [19]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.94 (m, 4H), 6.14 and 5.82 (bs, 1H, OH for *syn* and *anti*), 5.61 (s, 1H) *syn*, 4.37 (d, 1H, J = 9.3 Hz) *anti*, 4.45 (s, 1H) *anti*, 3.95 (s, 1H) *syn*, 2.17 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 205.1, 149.1, 132.7, 128.3, 112.2, 106.6, 81.1, 64.4, 23.4; GC-MS m/z 223 (M+); Elemental analysis: Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; Cl, 15.85; N, 6.26; O, 14.31; Found C, 59.10; H,