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Silver nanoparticle-catalysed phenolysis of epoxides under neutral conditions: Scope and limitations of metal nanoparticles and applications towards drug synthesis

Kapileswar Seth, Sudipta Raha Roy, Damodara N. Kommi, Bhavin V. Pipaliya, Asit K. Chakraborti *

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar, Punjab 160 062, India

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ABSTRACT

Chemo- and regio-selective epoxide phenolysis is reported for the first time under neutral condition catalysed by silver nanoparticles. Other metal nanoparticles (e.g., Au, Pd, Cu, In, and Ru) are less effective. The choice of solvent is critical with 2-propanol being the best followed by DEF. Amongst various stabilisers used (surfactants, PEGs, tetra-alkylammonium halides) the tetra-alkylammonium halides are found to be the most effective (TBAF > TBAB > TBACl > TBAI). The role of the silver nanoparticles is envisaged as synchronous mode epoxide-phenol dual activation via a cooperative network of coordination, anion–π interaction, and hydrogen bond. The silver nanoparticles are recovered and reused for five consecutive times. The reaction has been used for the synthesis of propranolol and naftopidil as a few representative cardiovascular drugs.

1. Introduction

Epoxide phenolysis is a highly sought for organic reaction in drug discovery and development as it provides direct access to the essential pharmacophoric feature **A** present in wide ranges of drugs such as guaifenesin (**1**) (used for cold and cough), mephenesin (**2**) and chlorphenesin (**3**) (used as muscle relaxants), and the broad ranges of β-adrenergic blocking agents (cardiovascular drugs), e.g., propranolol (**4**), naftopidil (**5**), etc. (Fig. 1).

A few existing methodologies for epoxide phenolysis are performed under basic conditions using a large amount of the base (or the preformed phenolate) and stoichiometric amount or excess quantities of a phase transfer catalyst or surfactant [1]. Catalyst systems containing a basic moiety either covalently attached to a central metal ion [2] or as the counter anion are also reported but require excess of the epoxide [3]. Herein we report for the first time epoxide phenolysis under neutral (base-free) condition using silver nanoparticle (AgNP) as the catalyst.

2. Experimental

2.1. General information

The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CDCl_3$: 7.26/77.0) using Me_4Si as an internal standard. Chemical shifts (δ) are given in ppm and J values are given in Hz. The IR spectra were recorded either on KBr pellets (for solids) or neat (for liquids) on a FTIR spectrometer. The HRMS spectra were recorded on a mass spectrometer. The UV spectra were recorded on a UV-VIS Spectrophotometer. Melting points were measured using melting point apparatus. Open column chromatography was performed on Silica gel [60–120 mesh] and the TLC was performed on Silica gel F254. The solvents were distilled prior to use. Evaporation of solvents was performed at reduced pressure, using a rotary evaporator. All chemicals were purchased and used as received. All the TEM images were taken on carbon coated Cu grids in an instrument equipped with EDX facility.

2.2. The AgNP-catalysed epoxide phenolysis

Method A: Typical procedure for epoxide phenolysis catalysed by the in situ generated AgNPs in ^{i}PrOH (Table 2, entry 2): The mixture of TBAF (0.487 g, 2 mmol, 1 equiv) and $AgNO_3$ (1.7 mg,

* Corresponding author. Tel.: +91 0172 2214683x686; fax: +91 0172 2214692.
E-mail addresses: akchakraborti@niper.ac.in, akchakraborti@rediffmail.com (A.K. Chakraborti).

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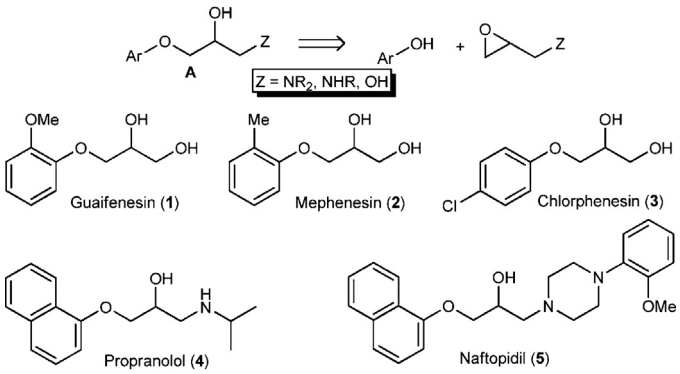

Fig. 1. Representative drugs with the structural motif **A**.

0.01 mmol, 0.5 mol%) in ^{i}PrOH (4 mL) was stirred magnetically under reflux (oil bath temp 80 °C) for 15 min. The oil-bath temperature was reduced to 60 °C followed by addition of **6a** (0.369 g, 2 mmol) and **7a** (0.248 g, 2 mmol) and the mixture was further stirred magnetically at 60 °C until completion of the reaction (6 h, TLC). The reaction mixture was cooled to rt and the ^{i}PrOH was removed under reduced pressure (30 mm Hg). The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 5 mL). The EtOAc layer was separated from the aqueous layer, dried (anh Na_2SO_4); filtered off and evaporated to dryness under vacuum (30 mm Hg). The residue was subjected to column chromatography (60–120 mesh silica-gel; 93:7 hexane–EtOAc as eluent) to afford the **8a** as off white solid (0.463 g, 75%). mp 79–81 °C (lit 79–82 °C) [1c] (0.463 g, 75%). IR (KBr) ν_{max}: 3437, 2927, 1509, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.66 (d, 1H, J = 5.0 Hz, D_2O exchangeable), 3.78 (s, 3H), 4.07–4.16 (m, 4H), 4.34–4.39 (m, 1H), 6.84–6.90 (m, 6H), 7.24–7.28 (m, 2H); MS (ESI) m/z: 308.4 (M^+).

Method B: Typical procedure for epoxide phenolysis catalysed by the in situ generated AgNPs in DEF in the presence of TBAF (Table 2, entry 2): The mixture of TBAF (0.244 g, 1 mmol, 0.5 equiv) and $AgNO_3$ (1.7 mg, 0.01 mmol, 0.5 mol%) was stirred magnetically in DEF (4 mL) at 80 °C for ~5 min. The oil-bath temperature was reduced to 60 °C followed by addition of **6a** (0.369 g, 2 mmol) and **7a** (0.248 g, 2 mmol) and the mixture was further stirred magnetically at 60 °C until completion of the reaction (6 h, TLC). The reaction mixture was cooled to rt; diluted with H_2O (10 mL) and extracted with dichloromethane (2 × 5 mL). The dichloromethane layer was separated from the aqueous layer, dried (anh Na_2SO_4); filtered off and evaporated to dryness under vacuum (30 mm Hg). The residue was passed through chromatography column (silica-gel; 60–120 mesh) and eluted with hexane–EtOAc (93:7) to afford the **8a** as off white solid (0.438 g, 71%).

Method C: Typical procedure for epoxide phenolysis catalysed by the in situ generated AgNPs in DEF in the absence of TBAF (Table 2, entry 2): The solution of $AgNO_3$ (1.7 mg, 0.01 mmol, 0.5 mol%) was stirred magnetically in DEF (4 mL) at 80 °C for ~5 min. The oil-bath temperature was reduced to 60 °C followed by addition of **6a** (0.369 g, 2 mmol) and **7a** (0.248 g, 2 mmol) and the mixture was further stirred magnetically at 60 °C until completion of the reaction (6 h, TLC). The reaction mixture was cooled to rt; diluted with H_2O (10 mL) and extracted with dichloromethane (2 × 5 mL). The dichloromethane layer was separated from the aqueous layer, dried (anh Na_2SO_4); filtered off and evaporated to dryness under vacuum (30 mm Hg). The residue was passed through chromatography column (silica-gel; 60–120 mesh) and eluted with hexane–EtOAc (93:7) to afford the **8a** as off white solid (0.388 g, 63%).

2.3. Typical procedure for the identification and analysis of the in situ formed AgNP

Method A: The mixture of TBAF (0.487 g, 2 mmol, 1 equiv) and $AgNO_3$ (1.7 mg, 0.01 mmol, 0.5 mol%) in distilled ^{i}PrOH (4 mL) was stirred magnetically under reflux (oil bath temp 80 °C). An aliquot portion (3 μL) of the reaction mixture was withdrawn after 15 min on being subjected to UV measurement exhibited absorption at 350 nm indicating formation of the AgNPs. The sample (3 μL) separately withdrawn from the reaction mixture after 15 min was kept on carbon coated Cu grid after dilution. The grid was air dried and was subjected to TEM and EDX analyses to identify the AgNPs (3–8 nm).

Method B: The mixture of TBAF (0.244 g, 1 mmol, 0.5 equiv) and $AgNO_3$ (1.7 mg, 0.01 mmol, 0.5 mol%) in DEF (4 mL) was stirred magnetically at 80 °C. An aliquot portion (3 μL) of the reaction mixture was withdrawn after ~5 min and was kept on carbon coated Cu grid after dilution. The grid was air dried and was subjected to TEM and EDX analyses to identify the AgNPs (5–8 nm).

2.4. Typical procedure of intermolecular competition study between 4-methoxyphenol **7a** and 4-nitrophenol **7b** (Scheme 3)

The mixture of TBAF (0.487 g, 2 mmol, 1 equiv) and $AgNO_3$ (1.7 mg, 0.01 mmol, 0.5 mol%) was stirred magnetically in ^{i}PrOH (4 mL) at 80 °C for 15 min. Then the temperature of the mixture was reduced to 60 °C into which were added **6b** (0.300 g, 2 mmol), **7a** (0.248 g, 2 mmol, 1 equiv) and **7b** (0.278 g, 2 mmol, 1 equiv). After 6 h, the reaction mixture was cooled to rt and ^{i}PrOH was removed in rotary evaporator under vacuum. The crude mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 5 mL). The EtOAc layer was separated from the aqueous layer, dried (anh Na_2SO_4); filtered off and evaporated to dryness under vacuum (30 mm Hg). The residue was passed through chromatography column (silica-gel; 60–120 mesh) and eluted with hexane–EtOAc solvent system to afford the 1,3-diphenoxy-propan-2-ol **8c** as off white solid (0.115 g, 21%) and 1-(4-nitro-phenoxy)-3-phenoxy-propan-2-ol **8b** as off white solid (0.382 g, 66%).

2.5. The AgNP-catalysed intramolecular competition study

Method A: Typical procedure of intramolecular competition study between phenolic hydroxyl group and alcoholic hydroxyl group of 4-hydroxybenzyl alcohol, **7c** (Scheme 3): A solution of tetrabutylammonium fluoride (TBAF) (0.487 g, 2 mmol, 1 equiv) and $AgNO_3$ (1.7 mg, 0.01 mmol, 0.5 mol%) was stirred magnetically in distilled ^{i}PrOH (4 mL) at 80 °C for 15 min. Then the temperature of the solution was reduced to 60 °C into which were added **6b** (0.300 g, 2 mmol) and 4-hydroxybenzyl alcohol **7c** (0.248 g, 2 mmol, 1 equiv). Upon completion of the reaction (7 h, monitored by TLC), the reaction mixture was cooled to rt and ^{i}PrOH was removed in rotary evaporator under vacuum. The crude mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 5 mL). The EtOAc layer was separated from the aqueous layer, dried (anh Na_2SO_4); filtered off and evaporated to dryness under vacuum (30 mm Hg). The residue was passed through chromatography column (silica-gel; 60–120 mesh) and eluted with hexane–EtOAc solvent system to afford the 1-(4-hydroxymethyl-phenoxy)-3-phenoxy-propan-2-ol **8d** as off white semi-solid (0.362 g, 66%). IR (Neat) ν_{max}: 3437, 2928, 1633, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.10–4.19 (m, 4H), 4.36–4.40 (m, 1H), 4.61 (s, 2H), 6.90–7.01 (m, 6H), 7.28–7.34 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 64.8, 68.7, 68.8, 68.9, 114.6, 114.6, 121.3, 128.7, 129.6, 133.7, 158.0, 158.4; HRMS (ESI) [M+Na]$^+$ = 297.1109; Calculated = 297.1103.

Method B: Typical procedure of intramolecular competition study between phenolic hydroxyl group and alcoholic hydroxyl