C. R. Chimie 21 (2018) 71–79

Contents lists available at ScienceDirect

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Preliminary communication/Communication

Aqueous mortar–pestle grinding: An efficient, attractive, and viable technique for the regioselective synthesis of β-amino alcohols

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ARTICLE INFO

Article history:
Received 21 June 2017
Accepted 13 November 2017

Keywords:
Epoxide
Regioselectivity
Benzotriazole
β-Amino alcohol
Aqueous grinding

ABSTRACT

A green and highly regioselective approach for the synthesis of β-amino alcohols (with yields from 15 to 98%) via the aminolysis of epoxides by varied amines using LiBr under aqueous mortar–pestle grinding conditions has been described. Use of a mild catalyst, ordinary grinding, time economy, cost effectiveness, complete regioselectivity, and a very good to excellent yield of desired products makes this process an attractive route for the synthesis of biologically significant pharmacophores. Furthermore, the developed protocol has been successfully extended to the synthesis of novel series of β-amino alcohols (**3r**–**ad**) bearing benzofused 1,2,3-triazole heterocycle with complete regioselectivity. The structure of the synthesized molecules has been characterized by spectroscopic techniques such as ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and mass spectroscopy/elemental analysis.

1. Introduction

Like aziridines, epoxides are well-known ring-strained heterocyclic systems in organic chemistry. The incredible reactivity of epoxides is accountable for the synthesis of a wide range of interesting molecular entities, and hence, these have been preferred as starting materials to design a variety of novel chemical transformations under controlled reaction pathways [1]. Generally, epoxides are vulnerable to several chemical species such as nucleophiles, electrophiles, acids, bases, and oxidizing and reducing reagents. The aminolysis of epoxides constitutes a well-acknowledged route in the literature [2], as the resulting product β-amino alcohols represent a broad range of β-adrenergic blockers. They have a diverse range of clinical applications in the treatment of cardiovascular diseases such as hypertension, angina pectoris [3,4], cardiac arrhythmias [5], and open angle glaucoma [6] and also reported to have diverse applications in medicinal chemistry [7]. Apart from this, they also find utility in the synthesis of biologically active synthetic and natural products [8], unnatural amino acids [8a,9], ligands in asymmetric synthesis and auxiliaries [9], and more recently as organocatalysts [10]. Literature reveals several routes for the synthesis of β-amino alcohols, but most of these are plagued with one or more drawbacks such as the use of strong acid salts (metal triflates) [2c,d,v], long reaction times [2a,c,d], excess solvents [2f], heavy-metal Lewis acids [2b,f], elevated temperature and pressure [2r–v], supercritical carbon dioxide (sc-CO_2) [2w], poor regioselectivity especially with metal amides [2z], and the use of expensive, toxic, and stoichiometric amounts of reagents. On the other hand, epoxides rearrange and polymerize under acidic and basic conditions, which decreases the overall productivity of the process.

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https://doi.org/10.1016/j.crci.2017.11.004
1631-0748/

Recent reports by Yadav et al. demonstrating the use of active nanocrystalline sulfated titania (catalyst) [11a] and Sakthivel et al. describing MCM-22 as a catalyst [11b] for the regioselective ring opening of epoxides are an indication of renewed interest in the field of ring-opening reactions to generate β-amino alcohols. Therefore, design and development of an environmentally benign route for the regioselective synthesis of β-amino alcohols is still meaningful.

Over the past few decades, mechanochemical synthesis (MCS) has attracted attention of many synthetic chemists as an amazing conventional technology [12]. Friščić and Do have described mechanochemistry as the 'force of synthesis' [12d]. Various types of chemical transformations such as Knoevenagel condensations [13a], aldol condensations [13b], Dieckmann condensations [13c], Grignard reactions [13d], Reformatsky reactions [13e], reductions [13f], click reactions [13g], and others [14] have been performed using the MCS technique. Motivated by the efficacy of MCS technique, efforts have been put forth for the regioselective aminolysis of epoxides using aqueous LiBr under ordinary mortar–pestle grinding to deliver β-amino alcohols in good to excellent yield.

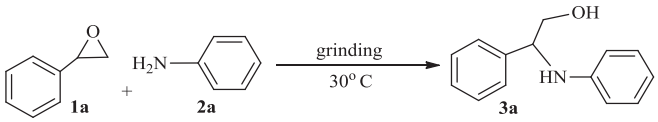
Furthermore, the developed protocol has been successfully applied to generate a novel series of benzotriazole-based β-amino alcohols as potential drug candidates owing to the fact that heterocyclic β-amino alcohols are the core component of many known β-blockers (Fig. 1) [15]. Furthermore, benzotriazole-based organic compounds are also known to embrace a wide range of activities [16], such as antifungal [17,18], antibacterial [18,21], anticancer [19], anti-HIV agents [19,20], anticonvulsant [21], and anti-inflammatory [21]. It is worth mentioning that the present exploration is an expansion of our efforts for the development of new synthetic routes for the synthesis bioactive molecules [22].

2. Results and discussion

At the outset, styrene oxide and aniline were selected as a model substrate for mortar–pestle grinding in the presence of two drops of water. A reasonable progress of reaction was observed (Table 1, entry 1), which gave us a clue that grinding under aqueous condition could be a better combination for the ring opening of epoxides. This observation may be correlated with the earlier findings by Saidi et al. [2a] from aqueous point of view. Subsequently, lithium bromide (10 mol %) was introduced to boost the aminolytic process. Delightfully, the reaction was completed in just 15 min with much improved yield (Table 1, entry 2). Choice of a lithium-based catalyst is simply because of its recyclability and the oxophilicity of lithium cation, which has been extensively discussed in the literature [23].

Next, LiBr charge was optimized. At 5 mol % loading, yield decreased marginally to 92% (Table 1, entry 3); however, with 15 mol % loading, the corresponding product was obtained in 98% (Table 1, entry 4). Additional acid catalysts

Table 1
Optimization of reaction conditions for epoxide ring opening.[a]



Entry	Catalyst (mol %)	Solvent (two drops)	Time (min)	% Yield (**3a**)[b]
1	No catalyst	Water	30	55
2	LiBr (10)	Water	15	98
3	LiBr (5)	Water	15	92
4	LiBr (15)	Water	15	98
5	NaCl (10)	Water	20	70
6	LiI (10)	Water	15	75
7	LiCl (10)	Water	20	70
8	NaBr (10)	Water	20	65
9	$AlCl_3$ (10)	Water	15	75
10	$AlBr_3$ (10)	Water	15	78
11	$FeCl_3$ (10)	Water	15	80
12	LiBr (10)	Toluene	20	65
13	LiBr (10)	1,4–Dioxane	25	65
14	LiBr (10)	THF	25	60
15	LiBr (10)	DMF	25	52
16	LiBr (10)	DMSO	25	67
17	LiBr (10)	PEG-200	20	66
18	LiBr (10)	Water	30	65[c]
19	LiBr (10)	Neat	25	87
20	LiBr (10)	Neat	40	90[d]

[a] Reaction was carried out using **1a** (1 mmol) and **2a** (1.1 mmol).
[b] Isolated yield of purified product **3a**.
[c] Reaction carried out at 30 °C using magnetic stirring.
[d] Reaction perfomed at 75 °C under the magnetic stirring.