Catalysis Communications 27 (2012) 179–183

Contents lists available at SciVerse ScienceDirect

Catalysis Communications

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

Short Communication

Bio-compatible eutectic mixture for multi-component synthesis: A valuable acidic catalyst for synthesis of novel 2,3-dihydroquinazolin-4(1H)-one derivatives

Hyacintha Rennet Lobo, Balvant Shyam Singh, Ganapati Subray Shankarling *

Department of Dyestuff Technology, Institute of Chemical Technology, N. P. Marg, Matunga, Mumbai, 400019, India

ARTICLE INFO

Article history:
Received 1 June 2012
Received in revised form 2 July 2012
Accepted 19 July 2012
Available online 27 July 2012

Keywords:
Quinazolinone
Multi-component reaction
Deep eutectic solvent
Choline chloride
Malonic acid

ABSTRACT

Novel derivatives of quinazolin-4(1H)-one derivatives were effectively synthesized via one-pot multi-component reaction of isatoic anhydride, aldehyde and aromatic amines using acidic catalyst in methanol. The catalyst, being a deep eutectic mixture of choline chloride and malonic acid, gave better results than several reported catalysts. Moreover, such eutectic mixtures are cost-effective, recyclable, non-toxic and bio-degradable. The methodology was successfully used for incorporating significant phenyl and heterocyclic substitutions at 2,3-positions of quinazolinone core. In addition, studies related to catalyst screening, substrate variation, recyclability and plausible mechanism of reaction are also described.

1. Introduction

2,3-Dihydroquinazolinones belong to an interesting class of heterocycles that possess a wide range of biological and pharmaceutical activities [1–3]. Some examples of very significant quinazolinone molecules include medicinally approved drugs like metolazone, quinethazone, raltitrexed, fenquizone, as well as bio-active natural products such as febrifugine and isofebrifugine [4,5]. A potential drug, ZD 9331, is also in phase II trial for treatment of solid tumors and other neoplasia including colorectal tumors [6].

Conventionally, 2,3-dihydroquinazolinones have been synthesized by variety of procedures as stated in literature [7–12]. However, one-pot synthesis of such significant heterocycles from components like isatoic anhydride, aldehyde and amines using acidic catalyst or media has been the subject of interest for many researchers owing to the growing interest in multi-component reactions (MCRs). MCRs offer several benefits including low cost, shorter reaction times, high atom economy, lesser requirement of energy and easier access to diverse functional compound libraries.

The catalysts reported for the above stated one-pot procedure include inorganic catalysts like aluminium tris(dihydrogen phosphate) [13], silica sulfuric acid [14], alum [15], gallium(III) triflate [16], magnetic Fe_3O_4 particles [17], reaction media like acidic ionic liquid [18] and acetic acid [19]. However, some of these reported procedures hold limitations like low yields, requirement of high reaction temperature, strong acidic conditions, use of expensive and toxic catalysts etc.

Consequently, there is a need for an acidic catalyst that could overcome the demerits and retain the benefits of the earlier procedures but in a simpler and environmentally benign manner. In addition, use of a non-toxic and bio-degradable catalyst would amplify the aspect of environmental benignness of reaction integrated by use of multi-component route.

In an attempt to achieve this, we have explored the catalytic activity of deep eutectic solvents (DES) in multi-component synthesis of quinazolinone derivatives. Deep eutectic solvents are simple ionic mixtures derived by combining quaternary ammonium salts, like choline chloride, with either hydrogen bond donors like urea and glycerol, or with Lewis acids like zinc chloride. The ability to form a hydrogen bond with the halide ion leads to a eutectic combination since these hydrogen-bonding interactions lead to depression in freezing point. Thus the formation of eutectic is more energetically favored relative to the lattice energies of the pure constituents [20]. The class of DES derived from choline chloride is bio-degradable, non-toxic, insensitive towards moisture, recyclable and cost-effective. This is obvious since the component choline is a naturally occuring bio-compatible compound and choline chloride is also commercially produced on a large scale as a chicken feed additive [21]. To add to this, DES also possesses many positive aspects of ionic liquids like low vapor pressure and low flammability.

In the past few years, our research group has explored applicability of deep eutectic mixtures based on choline chloride in several significant organic transformations [22–25]. We now extend their catalytic use in multi-component reaction wherein acidic deep eutectic solvent (DES), prepared from choline chloride and malonic acid was used in one-pot synthesis of novel 2,3-dihydroquinazolin-4(1H)-one derivatives. Earlier, this deep eutectic mixture has been used in electrochemistry [26] and

* Corresponding author. Tel.: +91 22 33612708; fax: +91 22 33611020.
E-mail address: gsshankarling@gmail.com (G.S. Shankarling).

1566-7367/$ – see front matter
http://dx.doi.org/10.1016/j.catcom.2012.07.020

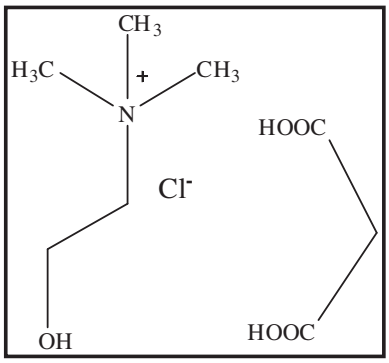


Fig. 1. Deep eutectic mixture of choline chloride and malonic acid.

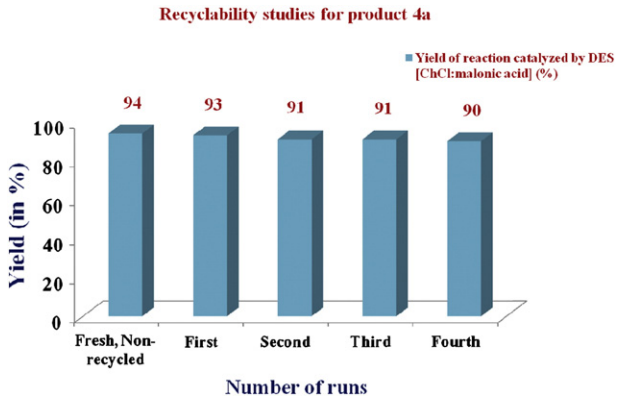


Fig. 2. Studies in recycling of deep eutectic mixture in the multi-component synthesis of quinazolinone derivative 4a.

Table 1
Optimization of catalysts in one-pot synthesis of 2-(4-chlorophenyl)-3-(4-methylphenyl)-2,3-dihydroquinazolin-4(1H)-one.

Sr. no.	Reaction medium[a]	DES[b] Catalyst	Yield (%)[c]
1	Methanol	–	Traces
2	Methanol	5% DES (CHCl: malonic acid)	83
		10% DES (CHCl: malonic acid)	87
		15% DES (CHCl: malonic acid)	88
		20% DES (CHCl: malonic acid)	94
		25% DES (CHCl: malonic acid)	92
3	Methanol	20% DES (CHCl:glycerol)	20
4	Methanol	20% DES (CHCl:urea)	15
5	Methanol	20% DES (CHCl:Zinc chloride)	45

[a] Reaction conditions: isatoic anhydride (1 g, 6.1 mmol), 4-chlorobenzaldehyde (0.87 g, 6.1 mmol), 4-methylaniline (0.67 g, 6.1 mmol), DES catalyst(% v/v), methanol (10 vol), reaction time = 2 h; Reaction temperature = 65 °C.
[b] DES: deep eutectic solvent.
[c] Isolated yields.

inorganic synthesis [27]. However, no report related to the catalytic use of this mixture has been done in multi-component organic synthesis. This catalyst can be easily prepared from inexpensive starting materials in addition to being bio-degradable annd recyclable. We also optimized various parameters of the reaction and studied the recycling of catalyst.

2. Experimental

2.1. Materials and equipments

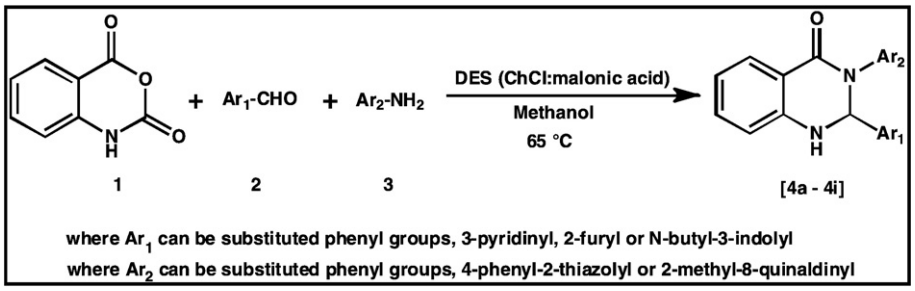
All the solvents and chemicals were procured from S D fine chemicals (India) and were used without further purification. The reactions were monitored by TLC using 0.25 mm E-Merck silica gel 60F254 precoated plates, which were visualized with UV light. ^{1}H NMR and ^{13}C-NMR spectrums were recorded on Varian 300 MHz mercury plus spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Mass spectral data were obtained with micromass-Q-Tof (YA105) spectrometer. Elemental analysis was done on Harieus rapid analyzer.

2.2. Preparation of deep eutectic solvent (DES)

The deep eutectic solvents were prepared by combining choline chloride with various other components like malonic acid, zinc chloride, urea and glycerol according to the procedures reported in the literature [20,28,29]. Choline chloride (100 g, 714 mmol) and malonic acid (75 g, 714 mmol) were heated with stirring at 100 °C until a clear solution began to form. The deep eutectic solvent (Fig. 1) thus formed (175 g, 100%) was cooled and used in reactions without any purification. The reaction was atom efficient since all the atoms present in the starting materials were incorporated in the products.

2.3. General procedure for deep eutectic solvent catalyzed synthesis of 2,3-disubstituted quinazolinones

A mixture of isatoic anhydride (1 g, 6.1 mmol), aldehyde derivative (6.1 mmol) and aniline derivative (6.1 mmol) was stirred in methanol (10 ml) at 65 °C. To this mixture, 20%(v/v) of DES catalyst (2 ml) was added and the stirring was continued at the same temperature till completion of reaction. The progress of reaction was monitored on thin layer chromatography plate. For isolation of product, water was added to the reaction mixture and the product was extracted with ethyl acetate. The ethylacetate was evaporated using rotary evaporator to give crude solid which was purified by column chromatography using hexane: ethyl acetate in 8:2 ratio (v/v). The compounds were characterized using spectroscopic data (FT-IR, Mass, ^{1}H NMR, ^{13}C NMR and elemental analysis). The deep eutectic solvent was recovered by removing the aqueous layer using rotary evaporator. Even though the procedure was described with a 1 g scale, it was easily scalable upto 10 g to obtain yields of about 94%. The recovered catalyst obtained from the scale up batch was re-used upto four runs without any loss in yields (Fig. 2).



Scheme 1. Synthesis of novel quinazolinone derivatives via multi-component reaction by the catalytic activity of acidic deep eutectic mixture.