



“On water” cascade synthesis of benzopyranopyrazoles and their macrocycles

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ARTICLE INFO

Article history:

Received 29 January 2018

Revised 3 March 2018

Accepted 5 March 2018

Available online 6 March 2018

This paper is dedicated with best wishes to Professor Goverdhan Mehta on the occasion of his 75th birthday.

Keywords:

Benzopyranopyrazole

Cascade reaction

Diazo compound

Open flask chemistry

Water

ABSTRACT

Reported herein is an intramolecular 1,3-dipolar cycloaddition strategy for rapid entry into benzopyranopyrazoles (BPP) on water medium as “open flask chemistry” approach. The *in situ* generation of diazo functionality in two-step sequence from the appropriate alkylated salicylaldehydes undergoes smooth [3 + 2]-cycloaddition with unactivated alkynes/alkenes furnishing benzopyranopyrazoles in good yield. This methodology was also extended for the synthesis of pyrazole incorporated macrocycles. This cascade protocol involving water medium provides an atom-economical and environment friendly approach.

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Introduction

Synthesis of pyrazoles remains of great interest due to their wide applications in the pharmaceutical and agrochemical industries.^{1,2} Currently, pyrazoles are being constantly employed as potential building blocks in drug discovery endeavours³ and also found as a inevitable key constituents of ligands for transition metals,⁴ receptor in supramolecular chemistry,⁵ liquid crystals^{6a} and polymers.^{6b} The most popular and classic approach for obtaining pyrazoles is the condensation of 1,3-dicarbonyl compounds with hydrazine derivatives.⁷ An alternative approach to the pyrazole framework is 1,3-dipolar cycloaddition of N=N dipoles onto C=C double⁸ or triple⁹ bonds. Benzopyranopyrazoles (Fig. 1) were well-known¹⁰ to have important biological activities and usually synthesized¹¹ via intermolecular fashion involving leaving groups resulting in the emission of waste.

During the last two decades, water has become a very attractive solvent for a number of efficient organic reactions at different temperature.¹² Water promotes or accelerates an excellent supporting medium with numerous advantages including the ease of product isolation, non-toxicity, non-flammability, high heat capacity and

redox stability. Many organic transformations¹³ were known to promote by water. A factor limiting the widespread application of on-water chemistry is the requirement for at least one reagent to be liquid in order to generate the oil-in-water emulsion that is critical for catalysis.^{13d} Aqueous insolubility is an essential requirement for on-water chemistry as it enhanced acidity of interfacial water molecules that catalyses the reaction inside the emulsion droplet.¹⁴ Substituted pyrazoles were obtained in THF-water in the presence of Pd-catalyst¹⁵ and cyclization of diketesters or 1,3-diketones with semicarbazide hydrochloride under “on water” conditions.^{15b} Moreover in aqueous sulfonic^{16a} or phosphoric acid^{16b} catalyzed condensation reactions of hydrazines with diketones effectively yielded highly substituted pyrazoles. A Lewis acid promoted 1,3-dipolar cycloaddition of diazo compounds in water medium has been reported.^{8d} In some cases, elevated temperature,^{17a,b} catalysts^{8b,17c} and the use of transition-metal catalysts^{8d,g,17d,8c} are inevitable for these transformations. Therefore, there remains a need for identifying improved methods for the synthesis of biologically interesting benzopyranopyrazoles employing simple building blocks and minimal synthetic steps. Inspired by our ongoing interest¹⁸ in the synthesis of nitrogen containing fused heterocycles from diazo precursors, we herein report “on water” cascade reactions towards the synthesis of benzopyranopyrazoles (BPP) and pyrazole incorporated macrocycles in an intramolecular manner.

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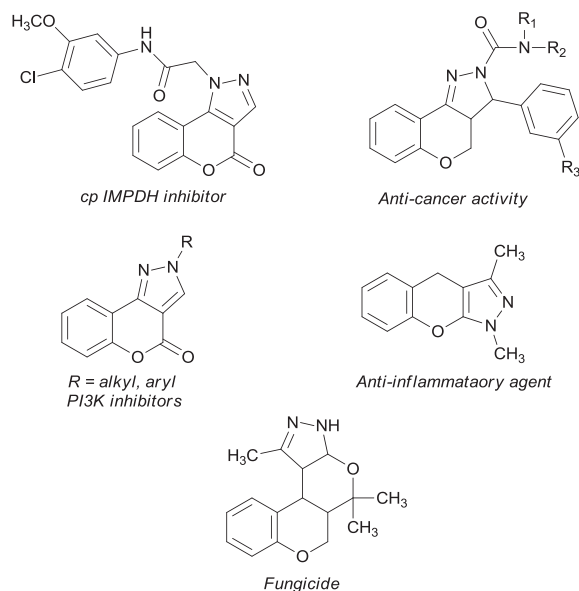
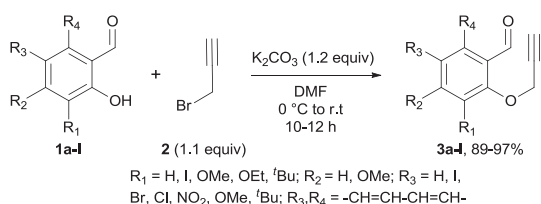


Fig. 1. Examples of bioactive benzopyranopyrazoles.



Scheme 1. 2-(Prop-2-yn-1-yloxy)benzaldehydes.

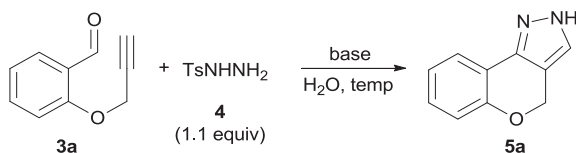
Results and discussion

We herein hypothesized an *in situ* generated aryl diazomethane from propargylated salicylaldehydes and their intramolecular [3+2]-cycloaddition reaction between a suitably placed terminal alkyne/alkene should form benzopyranopyrazoles. Aryl diazomethanes can be generated by the base-mediated decomposi-

tion of the corresponding aryl sulfonyl hydrazones. Hydrazones, in turn, are readily accessed from the corresponding aldehydes. To test this intramolecular dipolar cycloaddition strategy, reaction of the appropriate salicylaldehydes with propargyl bromide in DMF using potassium carbonate as a base at 0 °C to room temperature furnished¹⁹ the desired propargylated salicylaldehydes **3a–I** in good yield (Scheme 1). We then examined the reaction of **3a** with *p*-toluenesulfonyl hydrazide and K_2CO_3 in double distilled water (DD water) at room temperature but in vein even after 48 h and the unreacted starting material was recovered. Repeating the reaction at 60 °C furnished benzopyranopyrazole **5a** in 56% yield (Table 1, entry 1). Other bases, such as NaOH, NaOMe, were less effective in promoting the reaction (Table 1, entries 2, 3). Elevating the reaction temperature to 70 °C could promote the conversion and the reaction furnished the expected product in 89% yield (Table 1, entry 4). Further increasing the reaction temperature to 90 °C, yield of the product turned lower (Table 1, entry 5). Inferior results were obtained with LiOH or *t*BuOK (Table 1, entries 6, 7). Lower yield obtained when the reaction was carried out in un-distilled water (Table 1, entry 8). However, combination of water with organic solvent (THF or MeOH) furnished good yield of product (Table 1, entries 9, 10). Thus, the optimized reaction conditions were found to be K_2CO_3 in DD water at 70 °C. Aldehydes **3** and hydrazide **4** as reactants were initially insoluble and formed a solid heap suspension “on water.” The reactants existing in a solid form began to transform into oily suspension that became homogeneous as the reactions progressed by heating and products started appearing “on water” at optimized conditions (entry 4). Although product **5a** could be isolated in simple filtration, the reaction mixture was extracted with ethyl acetate and evaporating the solvent under vacuum and recrystallization from diethyl ether without column purification.

Next, we examined the substrate scope of the reaction and the results are outlined in Table 2. Benzopyranopyrazoles **5b–d** having methoxy substituent obtained in good yield from the appropriate precursors. The nitro-, chloro- or bromo-substituted propargylated salicylaldehydes furnished the corresponding products **5e–g**. Interestingly, naphthopyranopyrazole and di-*tert*-butylbenzopyranopyrazole **5h,i** were also synthesized in good yield. Reaction of ethoxy- or diiodo-substituted substituted salicylaldehydes afforded the expected products **5j,k** in good yield, respectively. Reaction of aldehyde having both electron-withdrawing and -donating

Table 1
Optimization of reaction conditions.^a



Entry	Solvent	Base	Temp (°C)	Time (h)	Yield (%) ^b
1	H ₂ O	K ₂ CO ₃	60	12	56
2	H ₂ O	NaOH	60	24	31
3	H ₂ O	NaOMe	60	24	54
4	H ₂ O	K ₂ CO ₃	70	12	89
5	H ₂ O	K ₂ CO ₃	90	12	78
6	H ₂ O	LiOH	70	24	39
7	H ₂ O	<i>t</i> BuOK	70	12	56
8	H ₂ O	K ₂ CO ₃	70	24	60 ^c
9	H ₂ O-THF	K ₂ CO ₃	70	12	86 ^d
10	H ₂ O-MeOH	K ₂ CO ₃	70	12	88 ^e

^a Reaction conditions: **3a** (0.62 mmol), **4** (1.1 equiv), base (1.5 equiv), 2.0 mL DD water.

^b Yield refers to the isolated and pure compound of **5a**.

^c Reaction was performed in tap water.

^d H₂O-THF (3:1 ratio).

^e H₂O-MeOH (1:1 ratio).

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