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Controllable Brønsted acid-promoted aerobic oxidation via solvation-induced proton transfer: Metal-free construction of quinazolinones and dihydroquinazolinones

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ABSTRACT

A controllable Brønsted acid-driven aerobic oxidation strategy for the efficient and convenient construction of quinazolinone ring system has been developed using bi-SO_3H-functionalized ionic liquids as catalyst under air atmosphere. The tunable syntheses of dihydroquinazolinones and quinazolinones have been achieved using the same catalyst in different reation meduim via solvation-induced proton transfer. The bi-SO_3H-functionalized ionic liquids (ILs) catalyst can be readily recovered and reused for the gram-scale application for at least three runs without any significant impact on the yields of the products. The operational simplicity and environmentally benign procedure are synthetically useful features.

1. Introduction

Aerobic oxidation is an important conversion in the preparation of fine chemicals and a lot of important organic compounds such as aldehydes, ketones and aromatic heterocyclics [1]. Although a number of efficient oxidants have been developed, molecular oxygen can be regarded as the best oxidants compatible with current environmental concerns. However, air is rarely used alone and transition metals were generally required for further activation [2]. In addition, the selective control of oxidation by using molecular oxygen or air as oxidant often become the bottleneck in the regulation of products formation [3].

Quinazolinone ring system represents a very attractive scaffold in a variety of synthetic drugs and natural products [4]. Quinazolinones as well as the 1,2-dihydroquinazolinones are widely used as antibacterial, antiinflammatory, antileishmanial and anti-tumor agents [5–8]. Recently, 2-substituted quinazolin-4(3H)-one and dihydroquinazolinones were used as sensors for detection of amine vapors and Cu^{2+} ions [9,10]. These special utilities of quinazolinone and dihydroquinazolinone derivatives highlight their synthetic necessity [11]. In most cases, the preparation of quinazolinones is achieved through the oxidation of dihydroquinazolinones [12]. Although a number of methodologies to construct quinazolinones via aerobic oxidation have been developed, metal co-catalysts were generally used [13]. Recently, metal-free protocols via aerobic oxidation in wet DMSO and aerobic oxidative amination for syntheses of 2-hetarylquinazolinones have been reported [14,15]. But tunable syntheses of dihydroquinazolinones and quinazolinones via controlled oxidation under such aerobic condition are inadequately addressed.

Herein, we disclosed an example of controllable metal-free Brønsted acid-promoted aerobic oxidation for constructing quinazolinone scaffolds from *o*-anthranilamides with aldehydes under air atmosphere by using bis-sulfonated ILs as catalyst. The tunable syntheses of dihydroquinazolinones and quinazolinones have been expediently achieved via modulation of the proton activity in different reaction medium.

2. Results and Discussion

In ring of quinazolinone, there is an amide-iminol tautomerism in quinazolinones or dihydroquinazolinones [16]. Generally, the amide tautomer of dihydroquinazolinone is more thermodynam-

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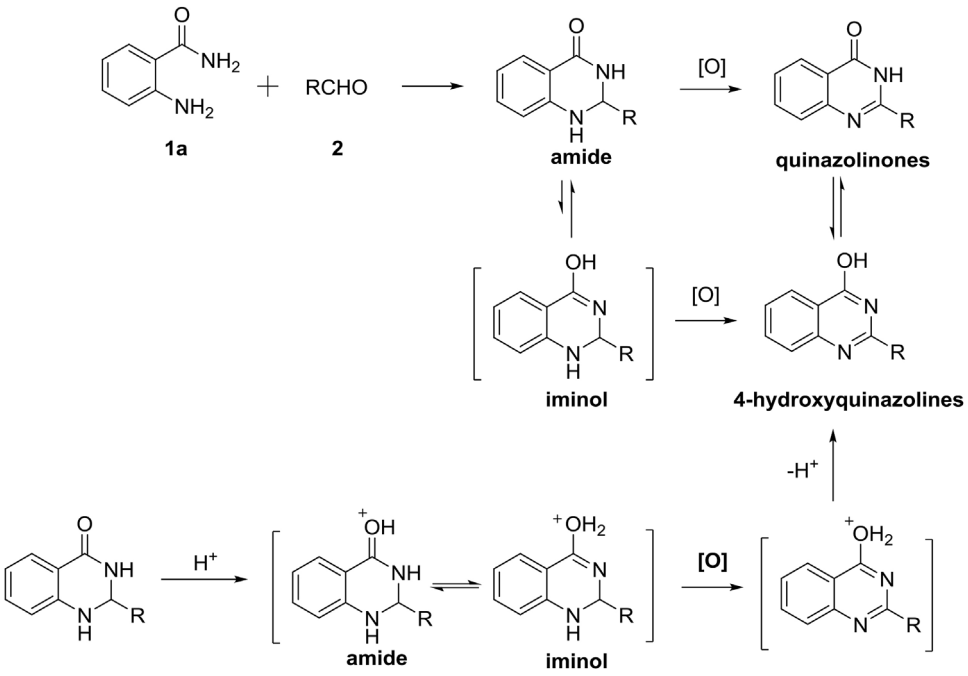

Scheme 1. Working hypothesis.

Table 1
Hammett acidity Function (H_0) values of different Brønsted acidic ionic liquids and H_2SO_4.

entry	acid	A_{max}	[I] %	$[HI]^+$ %	H_0
1	–	0.565	100	0	–
2	C1	0.523	92.50	7.50	2.08
3	C2	0.492	87.07	12.93	1.81
4	C3	0.359	63.53	36.47	1.231
5	H_2SO_4	0.510	90.26	9.73	1.95

ically stable than the iminol tautomer. Anticipating that the iminol tautomer of dihydroquinazolinones could convert to iminol tautomer of quinazolinones (4-hydroxyquinazolines) more easily through oxidation-dehydroaromatization in air (Scheme 1), we realized that the controlled syntheses of dihydroquinazolinones and quinazolinones under aerobic condition might be able to be achieved through the control of amide-iminol tautomerism. To a certain extent, acid can promote the formation of iminol tautomer [16]. Therefore, we resorted to acid-driven aerobic oxidation strategy.

Due to the remarkable properties of ILs such as designable structure and good compatibility in water and organic solvent, tuning the acidity of ILs can be achieved by the structure design and modification. In order to test our working hypothesis, three SO_3H-functionalized acidic ILs (Fig. 1) with different acidity were designed and synthesized. Hammett function (H_0) [17], which can be calculated by the formula ($H_0 = 0.99 + \lg[I]/[HI]^+$), was used to assess the acidity of ILs catalysts in organic solvents (Table 1). C3 showed strongest acidity in selected acids (Table 1, entry 4). We began our efforts on examining the model reaction between 2-aminobenzamide (1a) and benzaldehyde (2a) in the presence of acid using air as oxidant. The results are summarized in Table 2. The addition of acid could promote the aerobic oxidation using EtOH as solvent. And strong acid did better results on the formation of quinazolinone (4a). The C3 which was the strongest acidity in EtOH showed the best catalytic activity in this aerobic oxidation (Table 2, entry 7 and 8). In addition, the yield of quinazolinone (4a) could be reached 85% in the presence of C2 when the reaction time increased to 12 h (Table 2, entry 6). In consideration of the efficiency of catalysts, we choose C3 for further investigation. The following examination on the catalyst loading of C3 and reaction temperature was performed. The results showed that the reaction time needed to be prolonged to get a better yield when the catalyst loading of C3 or reaction temperature was decreased (Table 2, entries 9–13). The effect of organic solvents on this aerobic oxidation was also investigated (Table 2, entries 14–18). Polar solvents were favourable for the formation of quinazolinone 4a. For instance, the yield of quinazolinone 4a was 98% in ethanol (Table 2, entry 8), 80% in DMF (Table 2, entry 18). The green solvent such as PEG-400 also afforded a good yield (89%) of 4a (Table 2, entry 17). It is probably because the iminol tautomer can be stabilized through hydrogen bonding formation in the polarity condition.

With these expected results in hand, we subsequently investigated the possibility of blocking oxidation process via proton salvation effect to reduced proton activity under such aerobic oxidation using the same catalyst. To pursue this goal, water was added to reaction mixture. It was observed that the yield of 4a decreased from 82% to 17% with increasing water fractions from 10 to 90 vol% (Table 2, entries 19–21). Pure water gave 90% yield of 3a instead of 4a (Table 2, entry 22). Dihydroquinazolinone 3a could also be obtained at a yield of 88% even at room temperature (Table 2, entry 23). The yields of the 4a decreased in the presence of water probably due to the formation of the hydrated proton (H_3O^+) from Brønsted acid catalyst and water which reduces catalytic activity of C3 [20]. Thus, we have successfully achieved the regulation of aerobic oxidation.

Next, the scope and generality of this controlled Brønsted acid-promoted aerobic oxidation was explored under such operational condition. In consideration of the solubility of the catalyst and substrates, shorten reaction time, high yield and environmental acceptance, the operational condition we chose for syntheses of quinazolinones was the treatment of anthranilamides and aldehydes in the presence of C3 at 80 °C in EtOH. It was observed that the reactions of substituted 2-aminobenzamide with aldehydes proceeded smoothly and most of pure products were obtained by simple washing and recrystallization without using silica gel column chromatography. Aromatic aldehydes with electron withdrawing or electron donating groups can be successfully converted