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Short communication

Synthesis and initial thermal behavior investigation of 2-alkenyl substituted pyrazine *N*-oxides

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ABSTRACT

The systematic syntheses of 2-alkenylpyrazine N-oxides through palladium-catalyzed C-2 selective C—H olefination reaction was disclosed. Various acrylate esters substituted pyrazine N-oxides were obtained in up to 93% yields. Thermogravimetric analysis indicated that the fracture temperature of particular compound **3 f** was about 267 °C. The pyrolysis of compound **3 f** could generate several aroma compounds such as 2,5-dimethylpyrazine, 2,3,5-trimethylpyrazine and benzyl alcohol. The results of the pyrolysis experiment perfectly proved the flavoring property of the products as potential flavor additives.

1. Introduction

Pyrazine moieties are significant and versatile building blocks which exist widely in a large number of natural products, functionalmaterials, pharmaceuticals as well as odour compounds [1–4]. For this reason, methodologies for the synthesis of these molecular architectures have experienced huge developments in recent years [5–8]. Among them, the 2-alkenylpyrazine represents one of the typical scaffolds possessing special activities, as exemplified in Fig. 1. Compound **a** was found to be a novel potent HCV NS5B polymerase thumb pocket inhibitor [9]. Compound **b** ((*E*)-*tert*-butyl-3-(pyrazin-3-yl)acrylate) is a key intermediate for the synthesis of potent HIV protease inhibitors–γ-hydroxy-2-(fluoroalkylamino-carbonyl)-1-piperazinepentan-amide [10]. Compound **c** (2,5-dimethyl-3-ethenylpyrazine) is a well-known flavor which exists as the aroma volatile in roasted peanuts [11].

Because of the usefulness of 2-alkenylpyrazines, considerable efforts have been devoted to developing new processes to construct them. Traditionally, palladium-catalyzed Heck coupling reactions have been used to prepare such motifs (Scheme 1, **a**) [12, 13]. However, such methodologies rely on the pre-functionalized aryl (pseudo)halides which can cause significant environmental pollution [14, 15]. In recent years, transition-metal catalyzed C—H bond activation has emerged as a powerful method in the field of organic synthesis due to the fact that products always can be obtained in highly concise procedure [16, 17]. Thus, direct activation and functionalization of C—H bond has received continuous attention and witnessed significant progress during the past decades [18–20]. In particular, the direct oxidative olefination of pyridine *N*-oxides [21], quinoline *N*-oxides [22–25], as well as pyridine [26, 27] through cleavage of two C—H bonds represent an environmentally benign and economically more attractive strategy. (Scheme 1, **b** and **c**).

To our surprise, a quick overview of the C—H activation methodologies utilized for the synthesis of alkenyl substituted pyrazine esters shows that only two examples have emerged recently [21, 26]. In addition, our group has synthesized two family of pyrazine esters which were proved to be interesting potential flavor precursors (Scheme 2) [28]. For this reason, we embarked on the development of alkenylation reaction of pyrazine *N*-oxides to form a new family of pyrazine esters. In this paper, the results of the systematic syntheses and thermal behavior investigation of the 2-alkenylpyrazine *N*-oxides were reported.

2. Results and discussion

2.1. Synthesis of the pyrazine N-oxide derivatives

We initiated our studies according to the reported conditions. Firstly, palladium-catalyzed oxidative olefination reaction between 2,5-dimethylpyrazine and ethyl acrylate was examined in DMF under heating conditions [26]. Unfortunately, no desired product was obtained in this reaction (eq. a, Scheme 3). Mindful of the studies on C—H alkenylation of azaheterocycle *N*-oxides under metal-free conditions [23–25], a series of experiments were conducted using 2,5-

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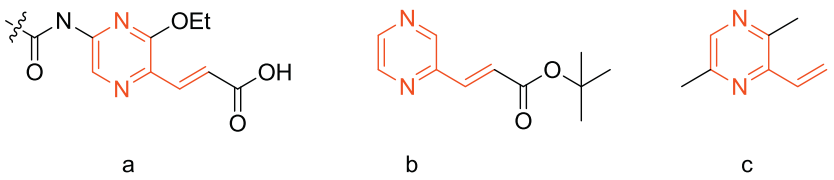
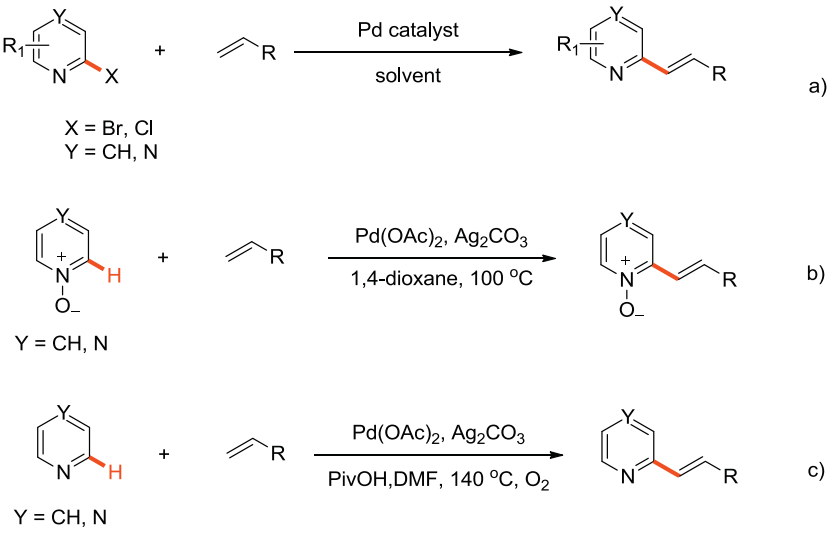
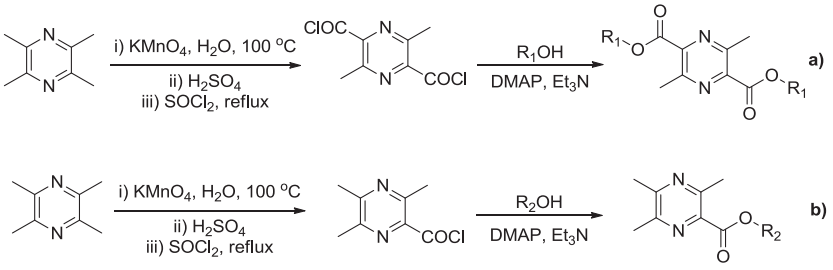


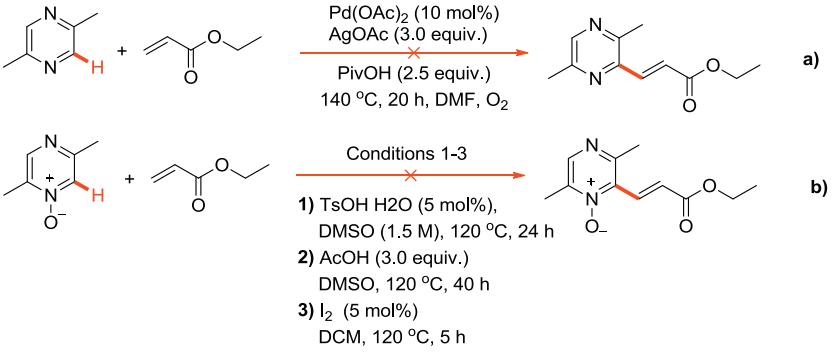
Fig. 1. Examples illustrating the importance of 2-alkenylpyrazines.



Scheme 1. Distinct olefination of pyridines and pyrazines.



Scheme 2. Pyrazine esters prepared by our group.



Scheme 3. Initial experiments on the olefination reaction of pyrazine or pyrazine *N*-oxide.

dimethylpyrazine *N*-oxide and ethyl acrylate or styrene as model substrates catalyzed by *p*-toluenesulfonic acid, acetic acid or iodine, respectively (eq. b, Scheme 3). To our disappointment, no target product was observed under these conditions. These results indicate a considerable difference on the reactivity between pyridine, quinoline and 2,5-dimethylpyrazine.

Subsequently, the reaction was carried out in 1,4-dioxane using 2,5-dimethylpyrazine *N*-oxide (**1a**) and ethyl acrylate (**2a**) as the starting materials catalyzed by $Pd(OAc)_2$, to our delight, the C-2-alkenylated product **3a** was obtained in 26% yield under this condition (entry, 1, Table 1). Compound **3a** was identified by 1D and 2D NMR spectra. Based on this result, a range of palladium and copper catalysts were evaluated in place of $Pd(OAc)_2$ (entries 2–7). All these catalysts proved to be less efficient than $Pd(OAc)_2$. It was found that the oxidant always play a crucial role in this kind of transformations. Among the oxidants examined (Ag_2CO_3, Ag_2O, Ag_2SO_4, $AgNO_3$, AgOAc, $Cu(OAc)_2$, TBHP