

REVIEW PAPER

Review on the Synthesis of Pyrazine and Its Derivatives

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ABSTRACT

Pyrazine is a kind of natural product which can be found in plants, animals, insects, marine organisms and microorganisms. The main function of pyrazine in living organisms is used as flavor of the raw foods. Pyrazine and its derivatives were also produced in industries mainly for fragrance, flavor and pharmaceutical applications. This review describes the historical development of pyrazine including the discovery and synthesis, to the recent synthetic approach of pyrazinium. In general, six synthetic approaches namely condensation reaction, ring closure, metal catalysis, green reaction, Maillard reaction and acid catalyst on *N*-substitution have been reviewed in this paper. The first five approaches are mainly aimed for the substitution at 2, 3, 5 and 6 positions in pyrazine ring, whereas the last approach is specifically for 1 and 4 positions in pyrazine.

Keywords: Diazine, pyrazine, and Maillard reaction

INTRODUCTION

Diazine is described as a compound with monocyclic aromatic ring that contains two nitrogen atoms with a molecular formula of C₄H₄N₂. The three isomers of diazine are pyridazine, pyrimidine and pyrazine (Figure 1).

Pyrazine, or more commonly known as 1,4-diazine, refers to the 6 membered heterocyclic compounds with two nitrogen atoms in *para* position. This heteroaromatic compound is 6 π -electron-deficient and resembles in planar configuration. Pyrazine exhibits inductive resonance properties (Figure 2) and demonstrates the weakest basicity among diazine compounds, even weaker than pyridine. This is due to the electron withdrawing effect

of nitrogen atoms that is positioned at *para* position (Sato, 2014). The specific dissociation constant for pyrazine are $pK_{a1}=0.65$ and $pK_{a2}=-5.78$ (Dolezal & Zitko, 2015).

OCCURRENCES

Pyrazine can be found ubiquitously in nature but only in relatively low quantity (Müller & Rappert, 2010). Naturally occurring pyrazine is regarded as an important component that contributes greatly to the flavor of raw and processed food (Maga, 1992). Synthetic pyrazine derivatives are actively utilized not only in fragrance and flavor industry, but also in pharmaceutical industry (Maga, 1992).

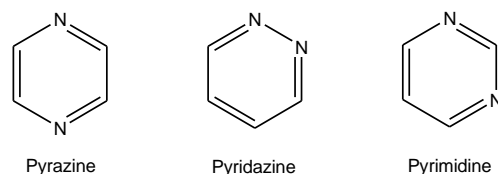


Figure 1. Isomers of diazine.

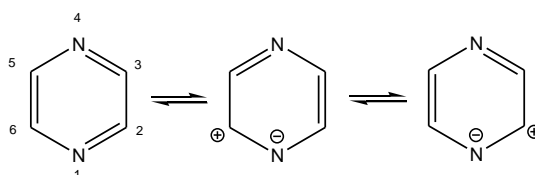


Figure 2. Inductive effects of pyrazine.