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Imino [4+4] cycloaddition products as exclusive and biologically relevant acrolein-amine conjugates are intermediates of 3-formyl-3,4-dehydropiperidine (FDP), an acrolein biomarker

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ABSTRACT

We demonstrated synthetically that the eight-membered heterocycles 2,6,9-triazabicyclo[3.3.1]nonanes and 1,5-diazacyclooctanes are the initial and exclusive products of the reaction, through an imino [4+4] cycloaddition, of biologically relevant amines with acrolein. The stabilities of the aminoacetals within the eight-membered heterocycles determined whether the product was subsequently transformed gradually into the 3-formyl-3,4-dehydropiperidine (FDP), which is widely used as an oxidative stress marker. The reactivity profiles discovered in this study suggested that some of the imino [4+4] cycloaddition products are reactive intermediates of FDP and contribute to the mechanisms underlying the oxidative stress response to acrolein.

1. Introduction

Acrolein is a highly toxic unsaturated aldehyde[1] that can be produced during the burning of oils, charcoal, wood, or plastic. It can also be generated by cells under oxidative stress conditions (through the enzymatic oxidation of threonine or polyamines[2–4]) or during reactive oxygen species (ROS)-mediated oxidation of highly unsaturated lipids.[5] The unsubstituted and most reactive 2-alkenal produced through the latter pathway can react with nearby thiol, hydroxyl, or amino functional groups on DNA,[6] proteins,[7] or phosphatidyl ethanolamines to accelerate the oxidative stress processes associated with various disease states.[8,9] Studies of acrolein conjugates could, therefore, contribute to an understanding of the relationship between acrolein and oxidative stress and, hence, disease at a molecular level.

Acrolein conjugates are currently used as biomarkers of oxidative stress[7] in the contexts of a variety of diseases. Acrolein-amino conjugates involving, for example, lysine δ-amino groups, 3-formyl-3,4-dehydropiperidine (FDP),[7] or 3-methylpyridinium (MP) derivatives[10] have been described (see the structure of FDP illustrated in Scheme 4). Antibodies[11] to these conjugates are widely used for the immunochemical detection of a variety of disease states, such as arteriosclerosis,[11–14] Alzheimer's disease,[15,16] tumors,[17–21] diabetes,[22–26] autoimmune disease,[27,28] high blood pressure,[29] among other diseases.[30–34] Alternatively, acrolein can react with polyamines to produce FDP conjugates that modulate the cytotoxicity of acrolein.[9]

Our research program, which explores the novel reactivities of *N*-alkyl unsaturated imines,[35–37] recently determined, by chance, that the imines derived from *N*-alkyl amines and acrolein participated in the previously unknown 'head-to-tail' [4+4] dimerization (Scheme 1).[38–40] Thus, the reaction of acrolein with general aliphatic amines, for example, alkyl, benzyl, or allyl amines, which are abundant among biomolecules, smoothly provided the 2,6,9-triazabicyclo[3.3.1]nonane derivatives **1** in quantitative yields (Scheme 1a).[38,39] The reaction proceeded through a formal [4+4] reaction of the intermediary imines, followed by the addition of an extra amine at the aminoacetal carbons.

The reaction of acrolein with polyamines (Scheme 1b) that contain consecutive 1,3- or 1,4-diamino moieties, on the other hand, readily provided the eight-membered heterocycles, 1,5-diazacyclooctanes **2**.[40] The nucleophilic amino group substitutions on the imino nitrogen (highlighted by the blue atom in Scheme 1b) accelerated and stabilized the resulting 1,5-diazacyclooctane. The

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