Extended Abstract

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Biologically active cyclic organic peroxides

Alexander

Institute of Organic Chemistry, Russia

Abstract

In the last decades, organic peroxides have received considerable attention from chemists and drug design experts, which is associated with a need in the search for drugs for the treatment of parasitic diseases, such as malaria and helminth infections. Considerable progress has been made in the design of effective peroxide antimalarial drugs. Some synthetic peroxides exhibit activity equal to or higher than that of artemisinin. Peroxides having antitumor or growth-regulatory activity were also documented. In our work we developed new and green methods for synthesis of various types of peroxides using hydrogen peroxide and carbonyl compounds.

Cyclic peroxides: ozonides, tetraoxanes, and tricyclic monoperoxides demonstrate prospective anticancer and antiparasitic properties. The total synthesis of two stereoisomers of a bioactive cyclic peroxide isolated from the marine sponge Plakortis angulospiculatus has been achieved in 18 steps with an overall yield of 2.8%. Diels–Alder addition of singlet oxygen to an acyclic triene carboxylic acid precursor was used to construct the 3,6-dihydro-1,2-dioxin ring. By comparing spectral data of the synthesized compounds and the natural material, we tentatively assign the absolute stereochemistry for the natural product as 3S,6R,8S,10R.

Synthetic ozonides and tetraoxanes were shown to have high cytotoxicity in vitro when tested on androgen-independent prostate cancer cell lines DU145 and PC3, which is in some cases was higher than that of doxorubicin, cisplatin, etoposide, artemisinin, and artesunate. Activity of ozonide stereoisomers differs from each other. This difference in activity and absence of correlation between activity of stereoisomers and their oxidative properties allow us to suggest existence of a quite specific mechanism of cytotoxicity of these endoperoxides different from a traditional mechanism based mainly on oxidative properties of peroxides.

The direct functionalization of heterocycles has become an increasingly valuable tool in modern drug discovery. However, the introduction of small alkyl groups, such as methyl, by this method has not been realized in the context of complex molecule synthesis since existing methods rely on the use of strong oxidants and elevated temperatures to generate the requisite radical species. Herein, we report the use of stable organic peroxides activated by visible-light photoredox catalysis to achieve the direct methyl-, ethyl-, and cyclopropylation of a variety of biologically active heterocycles. The simple protocol, mild reaction conditions, and unique tolerability of this method make it an important tool for drug discovery.

It is known that organic peroxides have reached a great importance through the years because of unusual reactivity of the O-O bond linkage whose decomposition in free radicals make them applicable in polymerization. In previous works, the effect of the nature of cyclic organic peroxides has been evaluated as initiators in polymerization of styrene (Cerna, et al., 2002; Cañizo, et al., 2004 a). On the other hand, Sanderson and coworkers (1974) while examining peroxides and ozonides in atmospheric pollution studies found that the thermal and photochemical decomposition of cyclic ketone peroxides produce macrocyclic hydrocarbons and lactones. Later, the oxidant power of these peroxides has been evaluated in the presence of aliphatic alcohols (Nesprias et al., 2004; Angelis et al. 2001) have reported a mechanism for the oxidation of benzyl alcohol by dimethyldioxirane as an oxidizing agent. As a consequence of population growth and industrial development an increasing number of biologically resistant organic pollutants are produced and discharged into the environment (like 4-chlorobenzaldehyde). This fact is causing varied problems in drinking and wastewater treatment systems as well as in respect to human health (Balcioğlu, 1998). Considering that cyclic peroxides (Sanderson et al., 1974) and 4- ClBA (Balcioğlu, 1998) have been found as pollutants, it is interesting to evaluate the existence of possible interactions between them. In the present communication, substituted 1,2,4,5-tetraoxacyclohexanes (Figure 1) have been added to a solution of 4-chlorobenzaldehyde (4-ClBA) in hexane or cyclcohexane to evaluate their effect to activate the degradation of the aldheyde.

Various cyclic organic peroxides have been added to a solution of 4-chlorobenzaldehyde in hexane or cyclohexane, in the 120 – 170ºC temperature range, to activate de degradation of the aldehyde. Experimental results demonstrate that 4-chlorobenzaldehyde resists thermal decomposition at 170ºC (38h) in absence of peroxides but its decomposition can be initiated by the presence of peroxides even at lower temperatures (130ºC). The analysis of the reaction products is insufficient to demonstrate if peroxide action is oxidant as it has

been demonstrated when they were decomposed in alcohols as reaction solvents. Only organic products derived from thermal decomposition of cyclic diperoxides have been identified. Under these experimental conditions, the decomposition study of peroxides shows a behavior according with a pseudo first order kinetic law even in the presence of 4-chlorobenzaldehyde. The corresponding kinetic data has been obtained by GC analysis.