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The Participation of Oleic Acid and its Esters in [3+2] Cycloaddition Reactions: A Mini-Review

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Abstract: This mini review presents the state of knowledge on the [3+2] cycloaddition reactions involving fatty acids and their esters with triatomic components (TAC). In general, the literature reports are quite sparse and relatively old. The reaction yield was in the range of 12-85%. The best result of 32CA was obtained from the reaction of butylonitrile N-oxide (**4**) and methyl oleate (**2**). Other tested TAC as components of title reactions were nitrylimines and ozone.

Keywords: [3+2] cycloaddition, TAC, fatty acids, oleic acid esters.

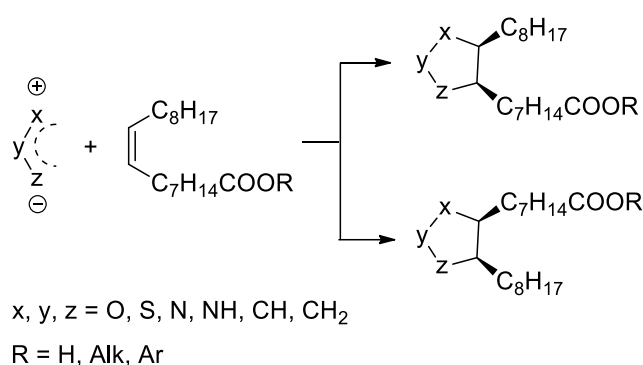
Received: 2024.03.08

Accepted: 2024.03.23

Published: 2024.03.27
DOI: 10.58332/scirad2024v3i1a05

Introduction

Oleic (Z-octadec-9-enoic) acid is a very popular component of many available natural oils and fats [1]. As a renewable raw material is a great component for various types of transformations in modern chemical technology [2,3]. Due to the unsaturated moiety within the molecule, oleic acid and its esters could be potential components for the [3+2] cycloaddition (32CA) (Scheme 1) [4] reactions involving different types of three atom components (TACs) [5]. The target compounds exhibit great potential as the bioactive and potentially surface-active compounds.



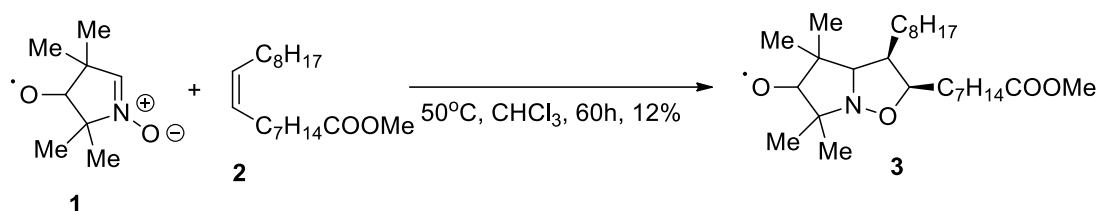
Scheme 1.

Currently, these 32CA reactions are intensively explored. What is important to mention here, this approach enables the preparation of many five-membered compounds which could be characterized by great bioactivity, high regio- and stereoselectivity [6]. Additional advantages of this approach include the absence of catalysts, relatively mild reaction conditions and 100% of atomic economy. In this mini-review, the current state of knowledge regarding the preparative potential of 32CAs involving oleic acid and oleate esters has been critically reviewed and discussed.

Oleic acid and its esters as components of the [3+2] cycloaddition reactions.

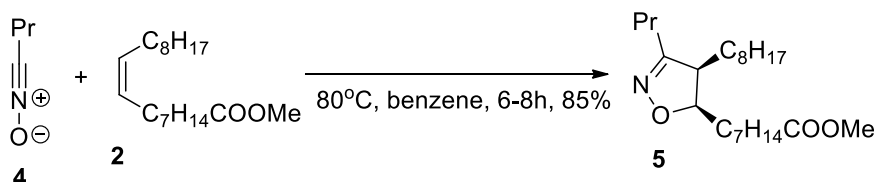
Martin and his team [7] investigated the reaction of the nitroxyl radical, 2,2,5,5-tetramethyl-3-imidazolin-3-oxide-1-oxyl (**1**), with dipolarophiles containing a C=C group, including methyl ester of oleic acid (**2**). The main purpose was to explore the potential use of this paramagnetic heterocyclic nitron in 32CA as a spin label for compounds containing a C=C bond. It was found that prolonged heating of nitron (**1**) with excess methyl oleate (**2**) yields the cycloadduct (**3**), albeit with a low reaction yield, reaching only 12% (Scheme 2). Furthermore, it was investigated that compound (**3**) existed as a mixture of stereoisomers

differing in the conformation of the bicyclic segment. This represents the sole known example of [3+2] cycloaddition of nitrones to methyl esters of oleic acid. Cycloadditions of this compound to oleic acid itself have not been reported yet.



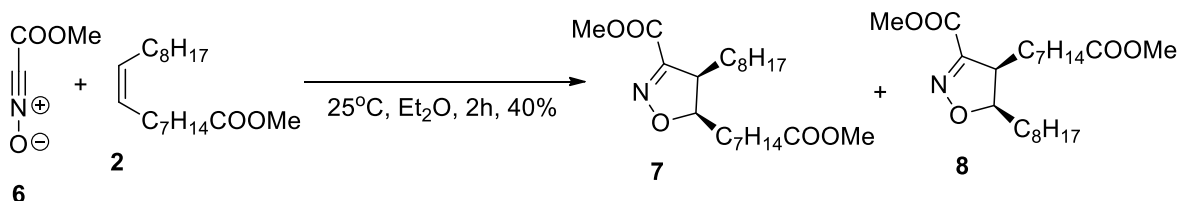
Scheme 2.

Khan and others [8] in their study designed the synthesis of novel heterocyclic analogs of fatty acids with antimicrobial properties. They synthesized a new series of 2-isoxazoline analogs in the course of 32CA reaction of nitril oxide with long-chain acids and their alkenyl/hydroxyalkenyl esters. They employed butylonitrile N-oxide (4) and methyl oleate (2) among others in their investigations. The reaction was conducted *in situ*, in dry, boiling benzene, for 6-8 hours. The desired product, 5-(Carbomethoxyheptyl)-4-octyl-3-propyl-4,5-dihydroisoxazole (5), was obtained with a very good yield of 85% (Scheme 3).



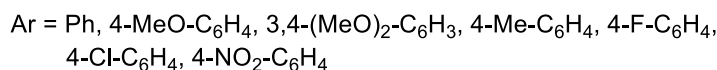
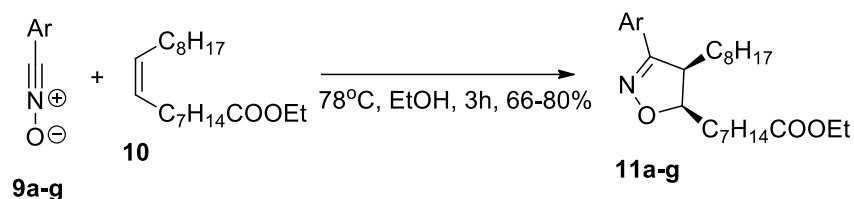
Scheme 3.

Osman and the team [9] conducted studies on the [3+2] cycloaddition of methoxycarbonylformonitrile N-oxide (6), including with methyl oleate (2). The N-oxide was generated *in situ*, and the reaction was carried out in diethyl ether. In this reaction, a mixture of regioisomeric methyl 9,10-isoxazoline-octadecanoates (7) and (8) is formed, with a moderate yield of 40% (Scheme 4).



Scheme 4

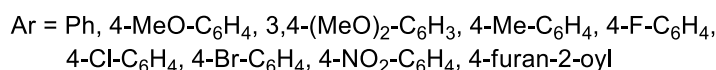
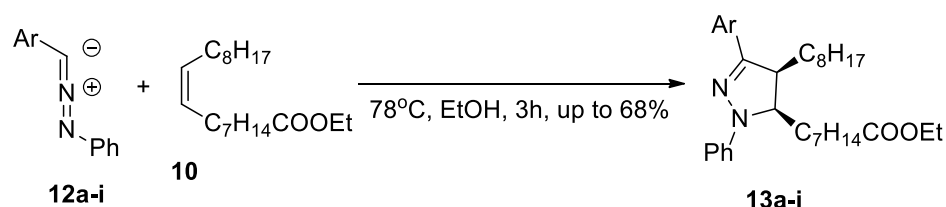
On the other hand, *Kumar* and co-authors [10] investigated similar cycloadditions involving aromatic nitrile N-oxides (9a-g) and ethyl ester of oleic acid (10). The process was conducted in ethanol under a reflux condenser for 3 hours. 2-Aryl-2-isoxazolines (11a-g) were obtained with a good yield ranging from 66% to 80% (Scheme 5).



Scheme 5.

It should be noted that the cycloadditions of nitrile N-oxides to free oleic acid has not been described yet.

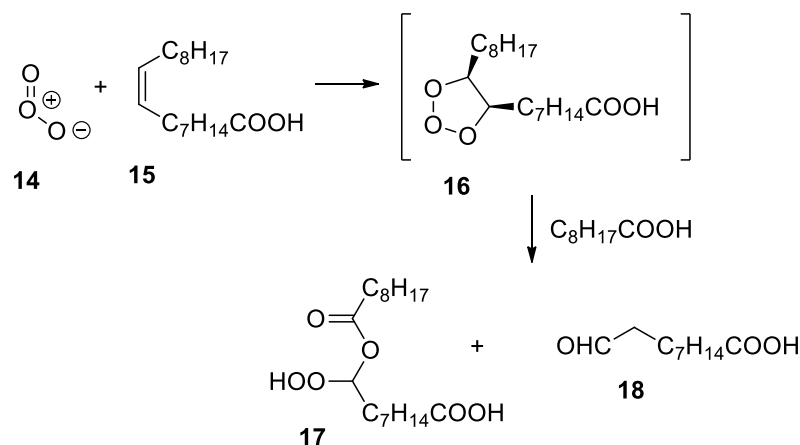
Previously, *Kumar* and co-authors [11] investigated the course of the reaction of [3+2] cycloaddition of ethyl oleate (**10**) with diaryl nitylimines (**12a-i**), generated *in situ* in the reaction of catalytic dehydrogenation of hydrazones using chloramine-T as an oxidizing agent. As a result of the conducted experiments, they obtained 8-(5-Aryl-4-octyl-2-phenyl-3,4-dihydro-2H-pyrazol-3-yl)-octanoic acid ethyl esters (**13a-i**) with good yields, reaching up to 68% (Scheme 6).



Scheme 6.

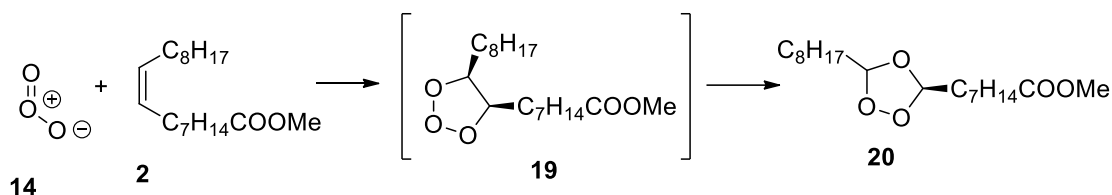
Moreover, the great interest among [3+2] cycloaddition reactions gain processes including ozone addition to alkenes. Many studies on the ozonolysis of organic compounds have been conducted involving low-molecular-weight olefins [12-15]. The products of ozonolysis contain the molecular segment of 1,2,4-trioxolane, which readily degrades into acyclic carbonyl compounds [15-18] Few studies focused on the ozonolysis of long-chain fatty acids and their alkenyl esters.

Rebrovic [19] investigated the ozonolysis reaction of oleic acid (**15**) in the presence of nonanoic acid. Under these conditions, the initially formed 1,2,3-trioxolane (**16**) undergoes decomposition to oxy-functionalized acyclic carboxylic acids (**17**, **18**) (Scheme 7).



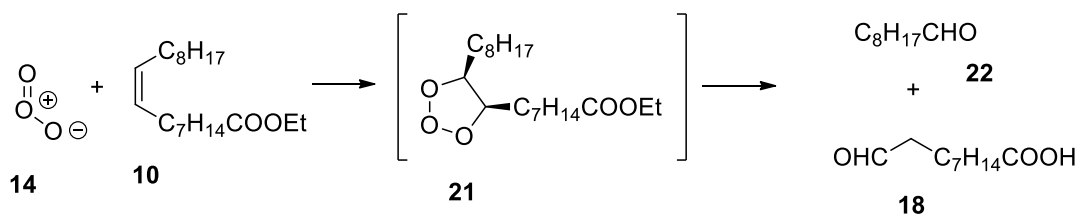
Scheme 7.

Nishikawa and others [20] investigated the course of ozonolysis of methyl oleate (**2**). The authors determined that the primary cycloaddition product (**19**) undergoes rearrangement to 3,5-dialkyl-1,2,4-trioxolane (**20**), which they successfully identified (Scheme 8).



Scheme 8.

On the other hand, *Cataldo* [21] conducted research on the chemical and thermochemical aspects of the ozonolysis of ethyl oleate (**10**). In his studies, he demonstrated that the primary product of ethyl oleate ozonolysis is the 1,2,3-trioxolane (**21**) as it was expected. However, under reaction conditions, it undergoes decomposition into simple carbonyl compounds (Scheme 9).



Scheme 9.

Diaz [22] and co-authors investigated the progress of the ozonolysis process of oleic acid and its methyl ester depending on the polarity of the used solvent. They applied ethanol, water, hexane, and carbon tetrachloride for the tests. As a result, it was observed that in the case of oleic acid, the polarity of the solvent does not significantly affect on the course of ozonolysis. However, in the case of methyl oleate ozonolysis, the reaction products largely depend on the used solvent. In hexane, identified trioxolanes were formed during the course

of reaction. On the other hand, in the presence of ethanol, the main products were ethoxyhydroperoxides. Similar reactions in water lead to complex mixtures of trioxolanes, carbonyl compounds, and oligomeric substances.

Gallimore [23] and others conducted experimental and computational studies on the ozonolysis of oleic acid particles in aerosol. These reactions produce complex mixtures of acyclic compounds, among which nonanoic acid and 9-oxononanoic acid were identified.

Meanwhile, the *Pfrang* research team [24] presented a study on the kinetics of oxidation and fate of monolayers of methyl oleate (**2**) at the air-water interface exposed to ozone.

It is worth mentioning that the reaction rates of almost all 32CAs cycloaddition processes with triatomic components (TAC) are very slow and have low efficiency [25-28]. The most practical 32CAs are conducted using catalytic converters to achieve higher efficiency and lower pollutant profiles. In comparison, recent studies on the 32CA of fullerene C₂₀ (compared to regular unsaturated bonds) have shown that these reactions are very fast. For example, the rate constant for the reaction of C₂₀ fullerene with nitrile-2-furan oxide is $1.4(10^7)\text{M}^{-1}\text{s}^{-1}$. However, the rate constant of the 32CA process between norbornadiene and 3,4-dihydroisoquinoline N-oxide is approximately $2.56(10^{-5})\text{M}^{-1}\text{s}^{-1}$ [29].

Conclusions

The state of art regarding [3+2] cycloaddition (32CA) involving oleic acid and its esters is rather limited and the available literature on cycloaddition involving them is negligible. There is a major gap of current literature in this area, which may be caused due to the difficulty with conducting such reactions. Oleic acid and its esters do not possess activated double bonds in any way – neither towards electrophilic nor nucleophilic agents. Additionally, two large alkyl substituents effectively shield the C=C bond. It is significant in this context that, unlike most inactivated alkenes, oleic acid and its esters react with three-atom components almost always in a completely regioselective manner. Only the cycloaddition involving methoxycarbonylformonitrile oxide leads to a mixture of regioisomeric cycloadducts. Nevertheless, the 32CA reactions of higher fatty acids and their esters seem to be an interesting and highly relevant topic, considering that they are natural products, inexpensive, and widely used in many industries. Potential products should exhibit both biological activity, as well as, surfactant properties.

Acknowledgements

The work was created as a result of the implementation of a scientific activity under the MINIATURA 7 program no. DEC-2023/07/X/ST5/00836 financed by the National Science Center.

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