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FORMYLATION REACTION USING THE OZONOLYSATE OF OXAZOLE

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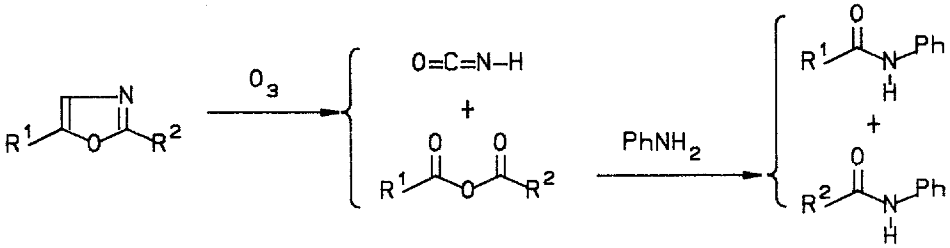
The ozonolysis of oxazole (1) did not give formic anhydride (3), but gave N-formylformamide (5), which reacted with various nucleophiles to afford the corresponding formylated products in high yield. This formylating reaction should be useful in the organic syntheses.

Recently a number of formylating reagents were reviewed.[1] However, almost all of them involved some inconveniences in the practical use for the organic synthesis. Since the development of a convenient formylating reagent has been awaited, we will describe such a reagent, which is prepared from oxazole (1) by ozonolysis.

Some of formylating reagents were too unstable to be stored, and others required the drastic conditions due to their lower reactivities. Formic anhydride and formyl chloride have scarcely been used for the formylation because of their unstable properties, while general acid anhydrides and acid chlorides were widely used as acylating reagents. In the previous paper,[2] 2,5-disubstituted oxazoles ($R^1 \neq H$, $R^2 \neq H$) have been reported to afford acid anhydrides in high yield by ozonolysis. Since oxazole ($R^1 = R^2 = H$) is a commercially available stable substance, the ozonolysis of 1 could be expected to generate conveniently formic anhydride as a formylating reagent.



Indeed, when aniline was treated in dichloromethane at room temperature for 1 hour with the ozonolysate mixture prepared from 1 at -78°C, formanilide was obtained in 87 % yield as well as formamide (2), which was easily washed out with water. Here, an equimolar amount of ozone was required to the ozonolysis of 1, and the resulting ozonolysate reacted with an equimolar amount of aniline. Similarly, aliphatic amines and amino acid esters were formylated as summarized in the Table. In the case of alcohols, the formylation proceeded slowly during over 20 hr. Although formic anhydride (3) was reported to be unstable above -40°C,[1] this slow formylation reaction of alcohols suggested that this ozonolysate of 1 should maintain the reactivity towards the nucleophiles at room temperature for long period of times, and be less reactive compared with the ordinary acid anhydrides such as formyl acetate (4). Indeed, the formylation of 2-phenylethanol with this ozonolysate was 2.4 time slower than that by 4 without catalyst. From these facts, the formation of formic anhydride (3) was doubtful by the ozonolysis of 1.

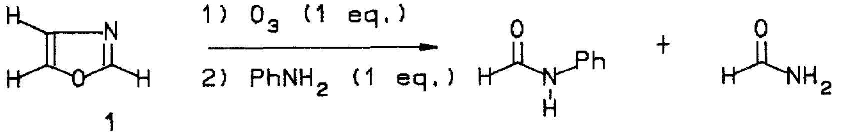
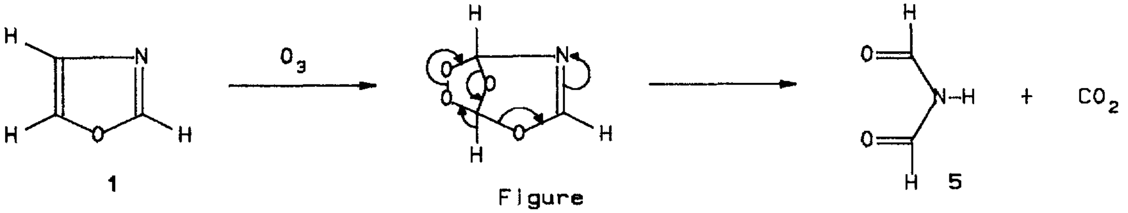


Table: Formylation of amines and alcohols with Ozonolysate of 1

Aniline	Yield (%)	Amine	Yield (%)	Alcohol	Yield (%)
$C_6H_5NH_2$	87	$C_6H_5CH_2NH_2$	80	$C_6H_5CH_2OH$	55
4-$CH_3OC_6H_4NH_2$	88	$C_6H_5CH_2CH_2NH_2$	99	$C_6H_5CH_2CH_2OH$	71
4-$CH_3C_6H_4NH_2$	87	$C_6H_5CH_2CH(CO_2CH_3)NH_2$	99	$CH_3CH_2CH_2CH_2OH$	76
4-$ClC_6H_4NH_2$	73	$(CH_3CH_2)_2NH$	78	l-Menthol	60
$C_6H_5NHCH_3$	74	Pyrrolidine	79	Cholesterol	59



Figure

By means of mass and ir measurement without isolation, carbon dioxide was detected in the ozonolysate. Moreover, the ir and the ^1H-nmr spectra of the ozonolysate was obviously different from the reported spectra of 3.[3] After the distillation of the ozonolysate at 90°C/5 mmHg, the distillate was identified as N-formylformamide (5) by the ir and the nmr spectra.[4,5] Further, the reaction of 5 with amines was reported to give the corresponding N-substituted formamide as well as the formation of 2.[4] From these facts, the reaction mechanism of the formation of 5 from 1 was speculated as illustrated in the Figure.

After all, the ozonolysis of oxazole (1) did not give formic anhydride (3), but gave N-formylformamide (5). The resulting intermediate 5 reacted with various nucleophiles to afford the corresponding formylated products at room temperature in high yield without the requirement of any catalyst. Through this formylation reaction, the only by-product formed was formamide (2), which was non-acidic, non-basic and washable with water. Moreover, oxazole (1) as the starting substance is the commercially available stable compound, and the ozonolysis is widely utilized convenient reaction. From these reasons, the ozonolysate of 1 is concluded to be of practical use as one of the most convenient formylating reagents.

References

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