HETEROCYCLES, Vol. 31, No. 8, 1990

DEUTERIOFORMYLATION BY THE OZONOLYSIS OF 2-DEUTERIO-5-PHENYL- OR 5-DEUTERIO-2-PHENYLOXAZOLES

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Abstract —— The ozonolysis of 5-deuterio-2-phenyloxazole (**1b**) gave deuterioformic benzoic anhydride (**3b**) and N-formylbenzamide (**4**). The reaction of the ozonolysate of **1b** with various nucleophiles is not practical due to the formation of 4. Since 2-deuterio-5-phenyloxazole (**2b**) gave **3b** quantitatively under the same conditions, the ozonolysis of **2b** is concluded to be a more practical and convenient preparation of the deuterioformylating agents.

The formylation is one of the most important reactions for the introduction of C1 unit chemically and biologically. Therefore, deuterium and tritium labeled formic acid derivatives should play an important role for the preparation of various labeled compounds and for studying the chemical and biological reaction mechanisms. However, there is no report of an efficient and convenient reaction for the preparation of labeled formic acid derivatives. Previously, we have reported that the ozonolysis of oxazoles formed the acylating reagents in high yields.[1] Actually, the ozonolysis of unsubstituted oxazole was conveniently utilized for the formylation of amines and alcohols.[2] However, some practical problems still remained for the preparation of unsubstituted deuteriooxazole. As an extension of this project, we investigated the ozonolysis of 2-phenyl- (**1a**), 5-phenyloxazoles (**2a**) and the corresponding deuterated derivatives.

When 2-phenyloxazole (**1a**) was treated with excess ozone-oxygen stream in dichloromethane at -78°C, formic benzoic anhydride (**3a**) and N-formylbenzamide (**4**) were obtained in 62 and 31% yields, respectively. Isocyanic acid and carbon dioxide were also formed as by-products. 5-Deuterio-2-phenyloxazole (**1b**) prepared from 5-bromo-2-phenyloxazole by the halogen-metal exchange reaction with n-butyllithium, followed by treating the resulting lithio derivatives with deuterium oxide or deuterio methanol,[3] was treated with ozone under similar conditions to give deuterioformic benzoic anhydride (3b) (71% yield) and 4 (21%). When the ozonolysate of 1b, which consisted of the mixture of 3b and 4, was treated with anilines, deuterioformylated products were obtained with high D-contents. In the case of benzylamine, deuterioformylated product was formed in high yield but in rather low D-content (Table 1). These results were explained by the controlled reaction that 4, treated with benzylamine, afforded N-benzylformamide while 4 was inert to alcohols and anilines.

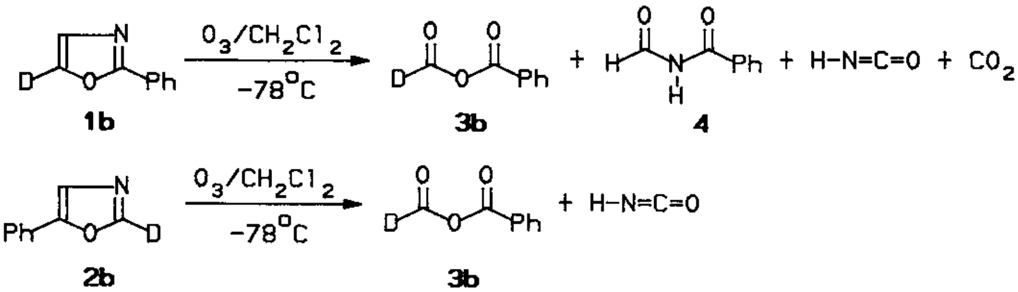

Table 1. Deuterioformylation of Nucleophiles with Ozonolysate of 1b and 2b

		from 1b		from 2b	
nucleophiles	products	Yield(%)	D-content	Yield(%)	D-content
$C_6H_5NHCH_3$	$C_6H_5N(CDO)CH_3$	66	80	85	69
$p\text{-}CH_3C_6H_4NH_2$	$p\text{-}CH_3C_6H_4NHCDO$	66	80	87	70
$C_6H_5CH_2NH_2$	$C_6H_5CH_2NHCDO$	83	70	88	70
$C_6H_5CH_2OH$	$C_6H_5CH_2OCDO$	40	78	55	70

[a] D-Contents of 1b and 2b were 80 and 70%, respectively.

In this competitive reaction, the acceleration of 3b formation was expected to depress the formation of 4. Previous paper reported that the formation of baezoic anhydride was accelerated by the introduction of electron-donating substituent on the para position of 2-phenyl group of 2,5-diphenyloxazole.[1] Therefore, 5-deuterio-2-(p-t-butylphenyl)oxazole was synthesized and treated with excess ozone in oder to get deuterioformic p-t-butylbenzoic anhydride without N-formyl-(p-t-butyl)benzamide (5). However, any remarkable substituent effect on 2-phenyl group could not be observed, and 5 was unfortunately included in the product mixture. From these results, it was suggested that the formation of 3b and their analogues from 2-substituted 5-deuteriooxazoles always proceeded accompanied with the formation of N-acylamide, which caused the lower yields and

D-contents in formylation.

As another preparation of 3b, the ozonolysis of 2-deuterio-5-phenyloxazole (2b) seemed to be applicable. When 5-phenyloxazole (**2a**) was treated with excess ozone-oxygen stream at -78°C in dichloromethane, formic benzoic anhydride (3a) was obtained in 90% *yield as well as isocyanic acid as a by-product.* Furthermore, the ozonolysis of 2-deuterio-5-phenyloxazole (2b), which was prepared from 2a by the method of Schollkopf,[4] gave deuterioformic benzoic anhydride (3b). The reaction of the ozonolysate mixture of 2b with p-toluidine afforded N-deuterioformyl-p-toluidine in 87% yield retaining the D-content from that of 2b. p-Tolylurea and benzoic acid were also produced in 78 and 85% yields, respectively. Similarly, various nucleophiles such as anilines, benzylamine, and benzyl alcohol were deuterioformylated as summarized in the Table 1. After all, by the treatment of nucleophiles with the ozonolysate mixture of 2-deuterio-5-phenyloxazole (2b), the corresponding deuterioformylated products were obtained in good yields. In addition, there were appreciable retention of D-contents of formylated products. Furthermore, by the introduction of tritium at C-2 position on oxazole ring of **2a**, this deuterioformylation reaction should be applicable for the preparation of tritium labeled formic acid derivatives.

EXPERIMENTAL

^{1}H-Nmr spectra were recorded using a Hitachi R-24 (60 MHz) and a JEOL FX-100 (100 MHz) Spectrometers with tetramethylsilane as an internal standard. Ir *spectra were measured* on a Jasco A-3 Infrared Spectrophotometer. Hplc was performed on a Jasco BIP-1 High Pressure Liquid Chromatograph on Megapak SIL-C_{18} column with aqueous methanol with diphenyl as an internal standard.

Materials.

5-Bromo-2-phenyloxazole, 2-phenyloxazole (1a), 5-deuterio-2-phenyloxazole (2a), and 5-deuterio-2-(p-t-butylphenyl)oxazole were prepared as previously reported.[1,3] 5-Phenyloxazole (**2a**) was obtained by Leusen's method.[5] 2-Deuterio-5-phenyloxazole (2b) was prepared from **2a** according to the Schollkopf's method.[4]

General procedure for ozonolysis of oxazoles.

To the solution of oxazoles (1 mmol) in dry dichloromethane (10 ml), ozone-oxygen stream was bubbled at -78°C. When the reaction mixture became blue, the bubbling was stopped, and the excess ozone was released out by bubbling of argon. The resulting chilled solution was treated with various nucleophiles (2 *mmol) and stirred another 1 h at room temperature.* The formation of the products was monitored by hplc. The D-content was evaluated by the ^{1}H-nmr of the isolated products and the results were summarized in the Table 1.

The analysis of ozonolysate of 2-phenyloxazole (1a) and 5-phenyloxazole (2a).

The ozonolysate of **1a** and **2a** was directly measured the ir spectra, where the characteristic bands of isocyanic acid and carbon dioxide appeared at 2250 and 2350 cm^{-1}, respectively. Also the formation of p-tolylurea by the treatment with p-toluidine supported the presence of isocyanic acid. The formation of N-formylbenzamide (4) was monitored on hplc by the comparison with an authentic sample, which was prepared by Finkbeiner's method.[6] The presence of formic benzoic anhydride (**3a**) in ozonolysate of **1a** and **2a** was detected by the characteristic ir bands at 1785, 1755, 1045, and 1020 cm^{-1}.[7] On the reaction with p-toluidine, the presence of **3a** in ozonolysate was also supported by the formation of N-formyl-p-toluidine and benzoic acid with the comparable yields.

Reaction of N-formylbenzamide (4) with nucleophiles.

To a solution of 4 (1 mmol) in dry dichloromethane (10 ml), p-toluidine (2 mmol) was added at room temperature. The formation of N-formyl-p-toluidine was not detected by hplc after 24 h, and 4 was recovered quantitatively. Similarly, formylation reaction did not occur by the use of benzyl alcohol. On the other hand, 4 reacted quantitatively with benzylamine to yield N-benzylformamide under the same conditions.

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Received, 15th May, 1990