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Tetranitromethane as an efficient reagent for the conversion of epoxides into β-hydroxy nitrates

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Abstract

A convenient regioselective method for the preparation of β-hydroxy nitrates based on the ring opening reaction of epoxides by tetranitromethane in the presence of triethylamine is described. A series of substituted β-hydroxy nitrates were obtained in high yields under mild conditions.

Keywords: Tetranitromethane; Epoxides; β-Hydroxy nitrates

Nitrate esters are known to be a potentially useful class of organic compounds, which have found widespread therapeutic applications as drugs for the treatment of heart and vascular diseases due to their NO-donor properties.[1–3] Functionalized alkyl nitrates, especially β-hydroxy nitrates, are utilized medicinally in the capacity of vasodilators.[2] Also, the incorporation of an ONO_2 group on a hydrocarbon skeleton is used in the design of many explosives.[4,5] Moreover, in sugar chemistry the nitrato group is employed as a protecting group, which can be removed easily by catalytic hydrogenation or under basic reaction conditions.[6] Therefore, the search for and development of new efficient approaches to nitrate esters and their derivatives are attracting extensive attention.

There are several methods reported in the literature for the synthesis of β-hydroxy nitrates. For example, β-hydroxy nitrates are usually prepared in poor yields by treating epoxides with concentrated nitric acid[7] or via the nitration of halohydrins with silver nitrate.[8] Recently, a new method for the synthesis of β-hydroxy nitrates based on the reaction of epoxides with cerium ammonium nitrate in the presence of ammonium or tetra-*n*-butylammonium nitrate as a source of nitrate ions was reported.[9] However, some methods are unsuitable for large-scale application owing to their several limitations including the employment of strongly acidic conditions[7] or the need for expensive reagents.[8]

We describe here a novel pathway to β-hydroxy nitrates via epoxide ring opening with tetranitromethane (TNM), which is known to be a smooth nitrating reagent in the synthesis of nitro- and *gem*-dinitro substituted compounds, nitroamines, etc.[10] The trinitromethyl anion should play the role of a nucleophilic agent to ring-open the epoxides. Recently, we reported the first example of epoxide cleavage by trinitromethyl anions generated from nitroform.[11] Due to the high polarity of the C–H bond, nitroform easily produces trinitromethyl anions without additional activation under mild reaction conditions.[12] In contrast, TNM was found to be less active as a nucleophilic agent and does not cleave an epoxide directly without activation with basic reagents. Therefore, we employed triethylamine to increase the nucleophilic properties of TNM.

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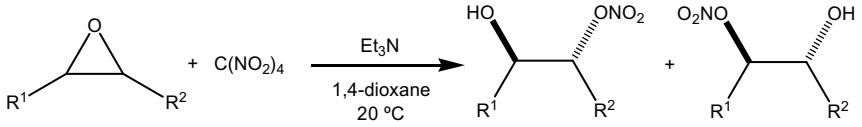
Table 1



1a-l **2a-i,l** **3f,g,j,k**

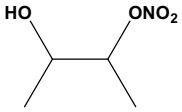
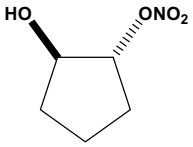
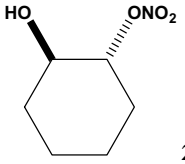
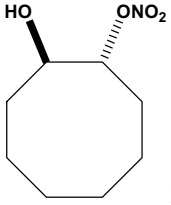
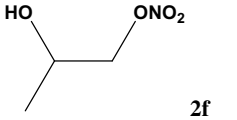
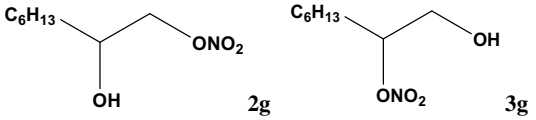
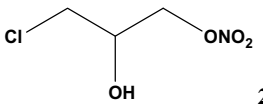
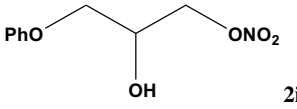
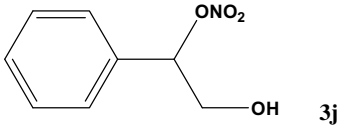
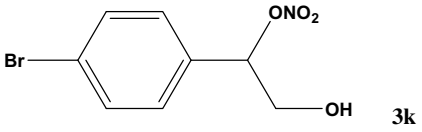
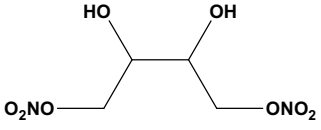
Entry	Epoxide **1**	R^1	R^2	Reaction time, days	β-Hydroxy nitrate **2**, **3**	Yield **2**, **3**[a] (%)
1	**a**	H	H	7	 **2a**	93
2	**b**	Me	Me	7	 **2b**	67
3	**c**	–$(CH_2)_3$–		5	 **2c**	80
4	**d**	–$(CH_2)_4$–		5	 **2d**	85
5	**e**	–$(CH_2)_6$–		7	 **2e**	88
6	**f**	Me	H	7	 **2f** **3f**	87[c]
					65/35[b]	
7	**g**	C_6H_{13}	H	7	 **2g** **3g**	85[c]
					80/20[b]	
8	**h**	$ClCH_2$	H	5	 **2h**	83
9	**i**	$PhOCH_2$	H	6	 **2i**	91

Table 1 (*continued*)

Entry	Epoxide **1**	R^1	R^2	Reaction time, days	β-Hydroxy nitrate **2**, **3**	Yield **2**, **3**[a] (%)
10	**j**	Ph	H	1	 **3j**	80
11	**k**	*p*-Br–C_6H_4	H	3	 **3k**	75
12	**l**		H	7	 **2l**	47

[a] Isolated yields for **2**, **3**.
[b] The ratio of regioisomers was determined by ^{1}H NMR.
[c] Yield refers to both isomers.

We examined the reactions of epoxides **1a**–**l** with TNM in the presence of triethylamine in 1,4-dioxane at room temperature.[13] The results obtained are summarized in Table 1.

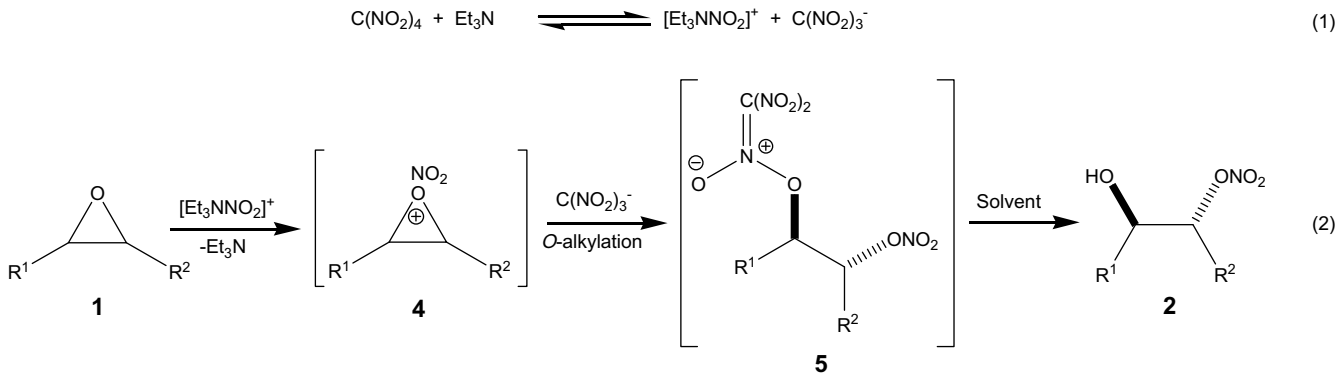
We found that the reaction of epoxides **1a**–**l** with TNM led smoothly to β-hydroxy nitrates **2a**–**l** in high yields. Symmetrical di-substituted epoxides **1b**–**e** (entries 2–5) afforded β-hydroxy nitrates as single diastereomers in accordance with the Furst-Plattner rule under which the cleavage of the epoxide ring by nucleophiles affords the products with trans configurations.[14] The reactions of unsymmetrical epoxides **1f** and **1g** with TNM led to the mixtures of two regioisomers in 65:35 and 80:20 ratios, respectively, in which the primary nitrates prevailed (entries 6 and 7). The reactions of epoxides **1h**–**l** were found to be highly regioselective and only one isomer, either **2** or **3** was obtained (entries 8–12).

The mechanism of the process can be presented as follows (Scheme 1, Eqs. 1 and 2). The key stage of the reaction is the O-alkylation of oxonium cation **4** by the trinitromethyl anion affording unstable nitronate **5**, which gives the final β-hydroxy nitrates **2** after solvolysis (for regioisomer **2**). The same type of nitronate transformation into alcohols has been described earlier.[15]

High regioselectivity was observed in the reactions of epoxides **1h,i** with TNM, as a result, only regioisomers **2h,i** bearing a primary ONO_2 group were obtained. Such a high regioselectivity may be explained in terms of anchimeric assistance by the neighbouring group ($ClCH_2$ or $PhOCH_2$, entries 8 and 9) during the opening of oxonium cation **4**.

Unexpected results were obtained in the reactions of styrene oxides **1j,k** with TNM:β-hydroxy nitrates **3j**,**k** bearing a secondary ONO_2 group were the products. It may be assumed that in these cases the cleavage of the oxonium cation **4** is accompanied by phenonium ion formation as described previously.[14] Attack of the trinitromethyl anion at the less substituted methylene group of the phenonium ion takes place leading to **3j**,**k** exclusively.

High regioselectivity was also observed in the reaction of the butadiene diepoxide **1l** with TNM in the presence of triethylamine (in a 1:4:2 molar ratio). Erythritol 1,4-



Scheme 1.

dinitrate **2l** was the only product of this reaction (Table 1, entry 12).

The structures of all the synthesized nitrates were established unequivocally by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

The method suggested for the nitration of epoxides with TNM has a remarkable advantage: even simple epoxides such as **1a**,**f** did not polymerize under the action of TNM, although this problem arises when other nitrating agents are employed for epoxide opening.

In conclusion, the good regioselectivity, high yields of products and the mildness of the reaction conditions, simplicity of the work-up and availability of the reagents make this method an efficient and useful alternative to other methods for the preparation of β-hydroxy nitrates.

Caution: Although we have not met any problems in handling these compounds, full safety precautions should be taken due to their potentially explosive nature.

Acknowledgements

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13. *General procedure*: Triethylamine (0.14 ml, 1 mmol) after cooling in an ice bath was added gradually to a solution of TNM (0.22 ml, 2 mmol) in 1,4-dioxane (2 ml). The mixture was stirred for 5 min with cooling, and then the corresponding epoxide (1 mmol) was added. The resulting mixture was stirred at room temperature for the specified time according to Table 1. TLC and NMR spectra were used to monitor the progress of the reactions. The solvent was evaporated and the product was isolated by column chromatography (hexane–ethyl acetate, 5:1).
2-Hydroxyoctyl nitrate (**2g**), *major isomer*. Yellow oil, R_f 0.1 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, $^{3}J = 7.1$ Hz, 3H, CH_3), 1.30–1.52 (m, 10H), 2.22 (br s, 1H, IH), 3.91–3.96 (m, 1H, CH), 4.35 (dd, $^{2}J = 11.1$, $^{3}J = 7.6$ Hz, 1 H, CH_2), 4.50 (dd, $^{2}J = 11.1$, $^{3}J = 3.0$ Hz, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6, 25.2, 29.1, 31.7, 33.2 (CH_2), 68.3 (CH), 76.8 (CH_2).
1-Hydroxyoctan-2-yl nitrate (**2g**), *minor isomer*. Yellow oil, R_f 0.1 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, $^{3}J = 7.1$ Hz, 3H, CH_3), 1.30–1.68 (m, 10H), 2.25 (br s, 1H, IH), 3.74 (dd, $^{2}J = 12.7$, $^{3}J = 6.3$ Hz, 1 H, CH_2), 3.83 (dd, $^{2}J = 12.7$, $^{3}J = 3.2$ Hz, 1H, CH_2), 5.09–5.15 (m, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.5, 25.2, 29.0, 31.6, 33.2, 62.5 (CH_2), 84.9 (CH).
2-(4-Bromophenyl)-2-hydroxyethyl nitrate (**3k**). White crystals, R_f 0.19 ($CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD): δ 3.44 (br s, 1H, IH), 3.81 (dd, $^{2}J = 12.6$, $^{3}J = 4.0$ Hz, 1H, CH_2), 3.90 (dd, $^{2}J = 12.6$, $^{3}J = 7.8$ Hz, 1H, CH_2), 5.88 (dd, $^{3}J = 4.0$, 7.8 Hz, 1H, CH), 7.25 (d, $^{2}J = 8.6$ Hz, 2H, Dh), 7.53 (d, $^{2}J = 8.6$ Hz, 2H, Dh). ^{13}C NMR (100 MHz, CD_3OD): δ 63.5 (CH_2), 85.2 (CH), 123.6(C), 128.4(2 × CH, Ph), 132.2 (2 × CH, Ph), 134.9 (C). Anal. Calcd for $C_8H_8BrNO_4$: C, 36.67; H, 3.08; N, 5.34. Found: C, 36.82; H, 3.20; N, 5.55.
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