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Efficient oxidation of cycloalkanols by sodium nitrite with molecular oxygen in trifluoroacetic acid

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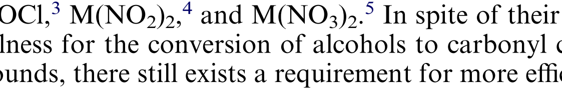
Abstract—Oxidation of aliphatic cycloalkanols by sodium nitrite in trifluoroacetic acid gave α,ω-dicarboxylic acids in good yields. Adipic acid was obtained in a quantitative yield from cyclohexanol using 1 equiv of sodium nitrite under oxygen atmosphere but the oxidation required more than 3 equiv of sodium nitrite under nitrogen atmosphere. The oxidation method was applicable to the conversion of 1-alkanols to the corresponding carboxylic acids.

Nitrosonium ion (NO^+) and nitronium ion ($NO_2{}^+$) salts have been known to be usable for the oxidation of alcohols. The reported salts are $NOBF_4$,[1] NO_2BF_4,[1c,2] $NOCl$,[3] $M(NO_2)_2$,[4] and $M(NO_3)_2$.[5] In spite of their usefulness for the conversion of alcohols to carbonyl compounds, there still exists a requirement for more efficient methods using readily accessible reagents with easy handling. Recently, $NaNO_2$ in acetic anhydride as a solvent has been reported to be effective for the oxidation of primary alcohols to aldehydes.[6] We report herein an efficient oxidation of cycloalkanols **1** to α,ω-dicarboxylic acids **2** using $NaNO_2$ with molecular oxygen in trifluoroacetic acid (Eq. 1).[7] The use of $NaNO_2$ as an oxidizing reagent and trifluoroacetic acid as a solvent is essential since the use of $NOBF_4$ or $NaNO_3$ in place of $NaNO_2$ in trifluoroacetic acid or $NaNO_2$ in other solvents (acetic acid, methanesulfonic acid, or acetic anhydride, etc.) than trifluoroacetic acid did not afford **2**.



(1)

1 **2**

Among the oxidation of **1**, the oxidation of cyclohexanol (**1a**) to adipic acid (**2a**) has been well known to be achieved by nitric acid oxidation.[8] The nitric acid oxidation involves an active species such as nitrosonium ion (NO^+) and nitronium ion ($NO_2{}^+$), the rates of which formation in situ are critical for efficiency of the oxidation. So, nitric acid oxidation requires careful control of the reaction temperature, the concentration of the substrate and nitric acid, and the presence of metal ion (M) additives such as vanadium(V) or copper(II) catalysts to smoothly initiate and promote the oxidation,[9] but it sometimes brings about decrease of the yield as well as formation of overoxidation products.[10] On the other hand, our method is carried out at room temperature under an atmosphere of molecular oxygen or air.[11]

A typical reaction condition is exemplified by the conversion of **1a** to **2a** as follows (Eq. 2). Cyclohexanol (**1a**) (1 mmol) was dissolved in trifluoroacetic acid (5 mL) and then $NaNO_2$ (2.0 mmol) was added to the solution at 0 °C under an atmosphere of oxygen. After the resulting solution was stirred at room temperature for 5 h, the solvent was recovered in vacuo (30 mmHg) at room temperature[12] and the residue was added into an aqueous 5% $NaHCO_3$. After the solution was treated with methylene chloride, the aqueous solution was acidified with a 10% HCl solution followed by an extraction with ethyl acetate to give **2a**. The yield of **2a** was quantitative. Although cyclohexanone (**3a**) was not observed in the oxidation, it might be an intermediate in the

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Keywords: Cyclohexanol; Oxidation; Nitrosonium ion; Adipic acid; Trifluoroacetic acid.

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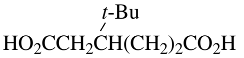
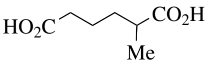
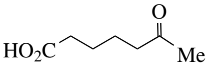
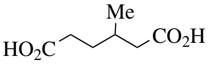
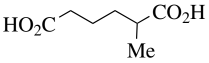
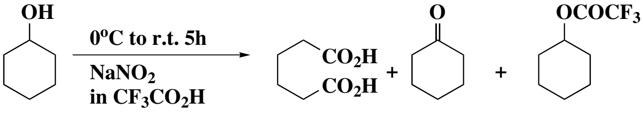
Table 1. Oxidation of cycloalkanols **1** to α,ω-dicarboxylic acids **2** by $NaNO_2$ in CF_3CO_2H[a]

Entry	Cycloalkanols	Reaction time (h)	Dicarboxylic acids	Yield (%)	Ketones	Yield (%)
1	Cyclohexanol **1a**	5	$HO_2C(CH_2)_4CO_2H$ **2a**	100	Cyclohexanone **3a**	0
2	Cyclopentanol **1b**	5	$HO_2C(CH_2)_3CO_2H$ **2b**	47	Cyclopentanone **3b**	51
3	Cycloheptanol **1c**	5	$HO_2C(CH_2)_5CO_2H$ **2c**	58	Cycloheptanone **3c**	30
4	**1c**	12	**2c**	73	**3c**	18
5	Cyclooctanol **1d**	5	$HO_2C(CH_2)_6CO_2H$ **2d**	94	Cyclooctanone **3d**	Trace
6	Cyclododecanol **1e**	5	$HO_2C(CH_2)_{10}CO_2H$ **2e**	80	Cyclododecanone **3e**	10
7	4-*t*-Bu-cyclohexanol **1f**	5	 $HO_2CCH_2\overset{t\text{-Bu}}{C}H(CH_2)_2CO_2H$ **2f**	92	—[b]	
8	2-Me-cyclohexanol **1g**	5	 **2g**	14	—[b]	
			 **2g′**	52		
9	3-Me-cyclohexanol **1h**	5	 **2h**	60	—[b]	
			 **2h′**	30		

[a] Reaction condition: alcohol (1 mmol), $NaNO_2$ (2 equiv), CF_3CO_2H (5 mL), 0 °C to rt.

[b] Isolation not tried.

pathway from **1a** to **2a** since treatment of **3a** with $NaNO_2$ in CF_3CO_2H also afforded **2a** quantitatively.

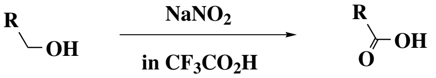


1a **2a** **3a** **4a**

(2)

Under similar reaction conditions, other cycloalkanols **1b–h** were mainly oxidized to the corresponding α,ω-dicarboxylic acids **2b–h**,**h′** and keto acid **2g′**, while cyclic ketones **3** were obtained in some cases depending on the kind of **1** (Table 1).

Furthermore, aliphatic primary alcohols **5a**,**b** were oxidized to the corresponding carboxylic acids **6a**,**b** (Eq. 3), while aliphatic secondary alcohols **7a**,**b** were mainly oxidized to ketones **8a**,**b**. The results are shown in Table 2.



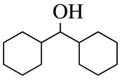
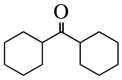
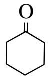
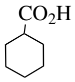
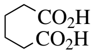
5 **6**

(3)

Table 3. Oxygen effect on the $NaNO_2$ oxidation of **1a**

Entry	Atmosphere	$NaNO_2$ (equiv)	Yield (%)			
			2a	**3a**	**4a**	**1a**
1	N_2	0.5	5	34	7	45
2	N_2	1	12	65	18	0
3	N_2	2	35	59	0	0
4	N_2	3	62	33	0	0
5	N_2	4	97	0	0	0
6	Air	0.5	29	65	0	0
7	Air	1	69	25	0	0
8	Air	2	100	0	0	0
9	O_2	0.5	53	43	0	0
10	O_2	1	99	0	0	0
11	O_2	2	100	0	0	0

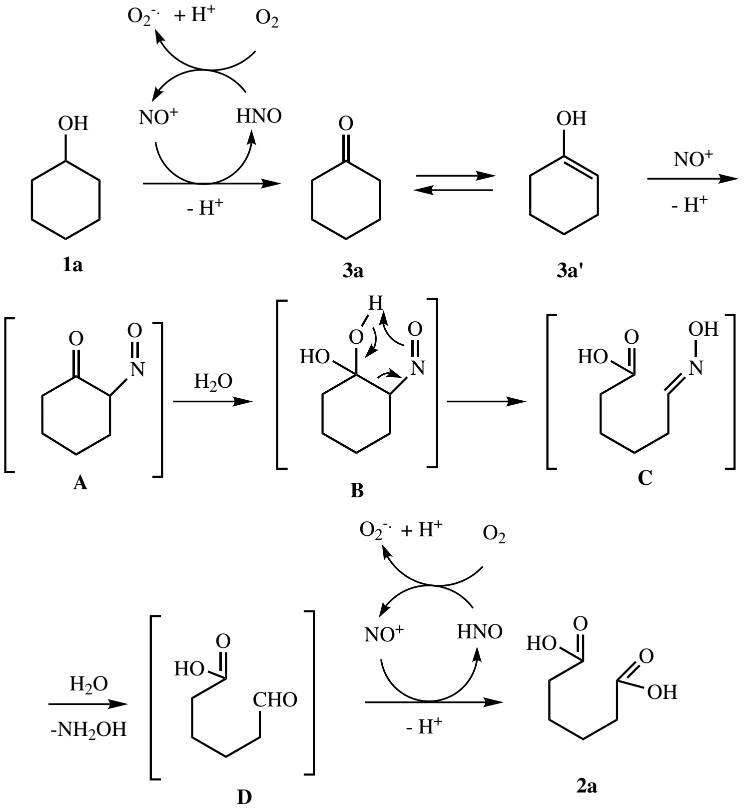
Table 2. Oxidation of aliphatic primary alcohols **5a–d** and secondary alcohols **7a**,**b**[a]

Entry	Alcohols		Yield (%) of products			
1	1-Dodecanol	**5a**	$CH_3(CH_2)_{10}CO_2H$		**6a** (100)	
2	1-Octanol	**5b**	$CH_3(CH_2)_6CO_2H$		**6b** (96)	
3	$PhCH_2OH$	**5c**	$PhCO_2H$		**6c** (99)	
4[b]	$HO(CH_2)_{12}OH$	**5d**	$HO_2C(CH_2)_{10}CO_2H$		**6d** (100)	
5	2-Octanol	**7a**	2-Octanone		**8a** (77)	
6		**7b**	 **8b** (79)	 **3a** (7)	 **9** (trace)	 **2a** (trace)

[a] Reaction condition; alcohol (1 mmol), $NaNO_2$ (2 equiv), CF_3CO_2H (5 mL), 0 °C to rt 5 h under air.

[b] $NaNO_2$ (4 equiv).

$$NaNO_2 + 2CF_3CO_2H \longrightarrow NO^+CF_3CO_2^- + CF_3CO_2Na + H_2O$$



Scheme 1. Plausible mechanism for oxidation of cyclohexanol (**1a**) by $NANO_2$ in CF_3CO_2H.

In order to clarify the reaction mechanism, oxidation of **1a** to **2a** was carried out under an atmosphere of oxygen, air, and nitrogen, respectively. The results are shown in Table 3.

Under an atmosphere of nitrogen, 4 equiv of $NaNO_2$ were necessary to complete the conversion of **1a** to **2a** (entry 5), while the use of 2 or 3 equiv of $NaNO_2$ gave a mixture of **2a** and **3a** (entries 3 and 4), and the use of less than 1 equiv of $NaNO_2$ resulted in formation of cyclohexyl trifluoroacetate (**4a**) and/or recovery of some amount of **2a** (entries 1 and 2). Aerobic atmosphere condition improved the efficiency of $NaNO_2$ as an oxidant (entries 6–8), and under an oxygen atmosphere more than 1 equiv of $NaNO_2$ completed the conversion of **1a** to **2a** (entries 10 and 11), suggesting a regeneration of NO^+ by oxidation of HNO with the oxygen atom, while a mixture of **2a** and **3a** was formed by a half equivalent of $NaNO_2$ under an oxygen atmosphere (entry 9).

On the basis of these results and the reported mechanism[8a,10b,d,e] for the nitric acid oxidation of **1a**, we propose a plausible mechanism for the oxidation of **1a** to **2a** by $NaNO_2$ in CF_3CO_2H as shown in Scheme 1, where intermediates **A**–**D** may be involved.[11] The fact that more than 1 equiv of $NaNO_2$ was necessary for the completion of the oxidation of **1a** to **2a** suggests a consumption of 1 equiv of $NaNO_2$ as hydroxylamine, though hydroxylamine was not detected.

The method presented herein is very promising from a practical viewpoint for oxidation of alcohols since the reaction conditions are mild, yields are high, sodium nitrite is a very cheap oxidizing reagent, and most of trifluoroacetic acid can be recovered. Further application of this method to other organic compounds than alcohols is now under investigation.

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