Reactions of propargylic alcohols with nitric oxide

Ying-Lin Shen, Wen-Tao Wu, Qiang Liu, Guai-Li Wu and Long-Min Wu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Propargylic alcohols are selectively oxidised by nitric oxide and trace oxygen to the corresponding carbonyl compounds (ynones) at ambient temperature in acetonitrile.

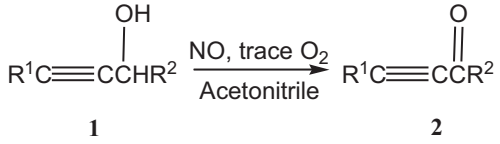
Keywords: propargylic alcohol, nitric oxide, oxidation

In continuation of our investigations of reactions of nitric oxide (NO) with various organic molecules,[1] we have performed the oxidation of propargylic alcohols with NO in the presence of trace oxygen. Grossi reported that NO reacted with alkyl alcohols to give alkyl nitrites.[2] In the present work, we have found that NO selectively oxidised the hydroxyl group of 1,3-diphenyl substituted propargylic alcohols to a carbonyl group at ambient temperature in acetonitrile (Fig. 1). Typical results are listed in Table 1.

It has been found that the selective oxidations occurred in high yield when substituents at the propargylic chains were aryl groups, whereas yields went down if one of the two substituents was alkyl, such as **1f**. No reaction occurred when both the substituents were alkyl groups, such as **1h** and **1i**. Electron-donating substituents on the phenyl ring shortened the reaction time, whereas electron-withdrawing ones prolonged it. Nevertheless, the latter provided a good selectivity.

The influence of solvent on product yields was investigated using **1a** as a substrate (Table 2). The results suggest that ethereal solvents and acetonitrile appear to be very favourable for the oxidation, whereas chloroform, dichloromethane, and carbon tetrachloride disfavour the oxidation reaction.

No reaction occurred when the system was completely protected from air. Yet, under an air atmosphere the reaction afforded the propargylic-type nitrate ester as the main product. When the system contained traces of oxygen, **1** afforded only **2**. As it is well-known, NO is a highly stable free radical and does not react directly with substrates.[3] In this system, an active species is most likely to be N_2O_3. A possible mechanism is postulated to account for the results (Fig. 2).[2-5] In the presence of oxygen NO is readily oxidised to NO_2 and then converted into N_2O_3 by reaction with the excess of NO.[6] N_2O_3 reacts with **1** most likely to give a ketyl-like radical **3**, which couples to NO to form the C-nitroso intermediate **4**. **4** eliminates an HNO to afford the end product **2**.[4] In principle, the C–H bond at the propargylic site is more susceptible for scission by radical species based upon the average bond dissociation energy (BDE) for O–H and C–H bonds, which are estimated at *ca* 410 and *ca* 330 kJ mol^{-1}, respectively. Yet, in the case of 1,3-diarylated propargylic alcohols the BDE for the propargylic C–H should be decreased in the presence of the alkyne triple bond, the hydroxyl group and the additional radical-stabilising aryl groups. Therefore, the formation of **3** is most likely to be possible. It is noteworthy that **3** is highly resonance-stabilised by the alkyne triple bond, the hydroxyl group and the additional aryl groups. Thus, the stability of **3** seems to be the key step of the reaction. This is the real reason why no reaction occurs in the cases of **1h** and **1i**. The reaction of **1** with N_2O_3 will release NO_2, which regenerates another N_2O_3. An alternative pathway is suggested as follows: the anionic species of **1**, **5**, undergoes an electron transfer reaction with NO to give **6** which couples with NO to generate **7**. However, our studies obviate the alternative given in Fig. 2. The oxidation potentials of **1** are measured to be above 1.0 V. Their anionic species have lower oxidation potentials of 0 to – 0.2 V. This implies that they could be oxidised by NO, whose reduction potential is 0.3–0.7 V.[7] Indeed, the reactions under consideration were not observed when NO was carried into the anhydrous and anaerobic acetonitrile solution of anions at room temperature under the protection of argon.



1 **2**

Fig. 1 Outline of the oxidation of propargylic alcohols with NO.

* Correspondent. E-mail: nlaoc@lzu.edu.cn

Table 1 Reaction of propargylic alcohols with NO in acetonitrile at ambient temperature[a]

Entry	R^1	R^2	Time /h	Conversion /%	Yield of **2**[b]/%	Yield of **2**[c]/%
1a	Phenyl	4'-Methoxy	20	>99	95	82
1b	Phenyl	Phenyl	38	>99	>99	87
1c	Phenyl	4'-Chloro	64	>99	>99	92
1d	Phenyl	3'-Nitro	64	>99	>99	90
1e	Phenyl	Benzoyl	64	>99	87	69
1f	Phenyl	*iso*-Butyl	64	87	76	54
1g	C_6H_{13}	H	64	37	32	21
1h	H	*iso*-Butyl	64	0	0	0
1i	H	Neopentyl	64	0	0	0

[a]About 15 °C; [b]Determined characterised by GC–MS; [c]Isolated yields after column chromatography.

Experimental

In a typical procedure, **1a** (180 mg) was dissolved in 80 ml of dry acetonitrile. The solution formed was then degassed for 50 min. NO was carried by argon and purified by passing it through a series of scrubbing flasks containing 4 M NaOH, distilled water, and $CaCl_2$ in this order. Purified NO was bubbled through the stirred solution. After completion of the reaction, as observed by TLC, the mixture was concentrated under vacuum, then purified by column chromatography on silica gel (200–300 mesh, ethyl acetate–petroleum ether), and recrystallised from ethyl acetate, giving the end product **2a**.

The product was identified by ^{1}H and ^{13}C NMR, IR and MS. ^{1}H and ^{13}C NMR spectra were recorded on a Varian MercuryPlus 300 NMR spectrometer in chloroform-d_1 with TMS as the internal standard. IR spectra were taken on a Nicolet 170SX IR spectrometer. MS spectra

Table 2 Solvent effect on the reaction of NO with **1a**[a]

Solvent	Conversion /%	Yield[b] of **2a** /%
CH_3CN	>99	85
THF[c]	>99	84
$CHCl_3$	95.7	1.1
1,4-Dioxane	90.3	87
CCl_4	49.0	68
CH_2Cl_2	3.4	24

[a]All the reaction were carried out using 20 mg compounds in 20 ml solvent for 6 h at 35 °C:
[b]Detected by GC–MS:
[c]Tetrahydrofuran.

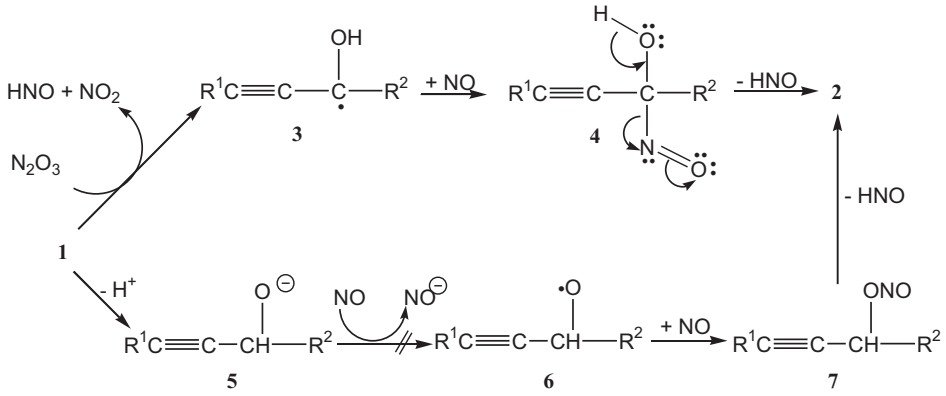


Fig. 2 Reaction mechanisms for the oxidation of propargylic alcohols with NO.

were determined on an HP 5988 GC-MS spectrometer with an EI source. HRMS was conducted on a Bruker Daltonics APEX II FT-ICR instrument using an ESI source. Melting points were measured on a Kofler apparatus and are uncorrected.

General procedure for preparing anions: a propargylic alcohol (0.12 mmol) was dissolved in 30 ml of dry acetonitrile and then a slight excess of NaH was added. The mixture was stirred at room temperature for about 2 h under the protection of argon and then filtered.

Redox potentials were measured in anhydrous acetonitrile at ambient temperature using cyclic voltammetry performed on an electrochemical analyser (model CHI 760B), which was connected to a PC with the Origin 6.0 software. One Pt flag was used as the working electrode, another Pt flag as the auxiliary electrode, and $HgCl_2$/Hg as the reference electrode. $NaClO_4$ was applied to a background electrolyte.

SAFETY CAUTION: Perchlorates are explosive compounds and appropriate caution should be taken including the avoidance of evaporation to dryness of perchlorate-containing residues.

Spectral data for the products: **2a,** reddish solid, m.p. 92–93°C; IR (KBr) ν_{max} 2955, 2846, 1759, 1629, 1599, 1569, 1487, 1306 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.97 (d, 2H, *J* = 9.0 Hz), 7.41–7.48 (m, 3H), 7.66–7.69 (dd, 2H, *J* = 7.5 Hz, *J* = 2.0 Hz), 8.19 (dd, 2H, *J* = 8.1 Hz, J = 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 86.9, 92.3, 113.9, 120.4, 128.6, 130.2, 130.5, 131.9, 132.9, 164.5, 176.6; MS (EI) *m/z* 236 (M^+, 47), 208 (91), 193 (69), 165 (42), 149 (12) 129 (100), 105 (34), 75 (34); HRMS (ESI) *m/z* calcd. for $C_{16}H_{12}O_2 + H^+$: 237.0910; found: 237.0910. **2b**, all its characteristic data are consistent with those in ref. 8. **2c**, pale yellow solid, m.p. 101–102°C (lit.); IR (KBr) ν_{max} 3051, 2731, 1761, 1631, 1529, 1481, 1242, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.50 (m, 5H), 7.68 (dd, 2H, *J* = 7.2 Hz, *J* = 1.8 Hz), 8.15 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.8, 93.9, 120.1, 129.0, 129.2, 131.1, 131.2, 133.3, 135.5, 141.0, 176.9; MS (EI) *m/z* 240 (M^+, 2.2), 212 (2.9), 176 (0.9), 149 (0.5), 139 (0.6),129 (9.5), 111 (2.3), 79 (100); HRMS (ESI) *m/z* calcd. for $C_{15}H_9OCl + H^+$: 241.1547; found: 241.1552. **2d**, pale yellow solid, m.p. 120–121°C; IR (KBr) ν_{max} 2198, 1635, 1614, 1528, 1435, 1344, 1292 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.54 (m, 3H), 7.72–7.76 (m, 3H), 8.46–8.54 (m, 2H), 9.05 (t, 1H, *J* = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.2, 95.3, 119.3, 124.5, 128.2, 128.8, 129.9, 131.4, 133.3, 134.6, 138.0, 148.4, 175.4; MS (EI) *m/z* 251 (M^+, 31), 223 (20), 176 (52), 129 (63), 101 (47), 89 (19), 77 (100), 46 (23); HRMS (ESI) *m/z* calcd. for $C_{15}H_9O_3N + H^+$: 252.0655; found: 252.0658. **2e**, white solid, m.p. 83–84°C; IR (KBr) ν_{max} 2961, 2929, 1726, 1671, 1589, 1570, 1365, 1311 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 2H), 7.35–7.39 (m, 5H), 7.46–7.50 (m, 3H), 7.54–7.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5, 86.3, 90.5, 125.7, 127.9, 128.4, 128.6, 129.1, 129.3, 130.7, 133.1, 173.5; MS (EI) *m/z* 220 (M^+, 1.4), 207 (3.9), 192 (5.9), 178 (1.3), 149 (1.8), 129 (100), 91 (8.2), 77 (3.1); HRMS (ESI) *m/z* calcd. for $C_{16}H_{12}O + H^+$: 221.0958; found: 221.0949. **2f**, colourless oil, IR (KBr) ν_{max} 3428, 2924, 1726, 1588, 1525, 1450, 1366, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96–1.07 (m, 6H), 2.24–2.32 (m, 1H), 2.54 (d, 1H, *J* = 6.9 Hz), 3.12 (d, 1H, *J* = 6.9 Hz), 7.44–7.61 (m, 5H); ^{13}C NMR (75 MHz, CDCl3) δ 22.4, 27.7, 49.9, 54.4, 84.8, 90.4, 126.0, 128.5, 130.6, 133.0, 175.3; MS (EI) *m/z* 186 (M^+, 14), 171 (6.1), 158 (9.1), 145 (8.9), 129 (100), 115 (7.3), 85 (5.2), 77 (34); HRMS (ESI) *m/z* calcd. for $C_{13}H_{14}O + H^+$: 187.1117; found: 187.1116. **2g**, all its characteristic data are consistent with those in the ref. 9.

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