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An efficient chemical fixation of nitric oxide: convenient and practical synthesis of 1,2,3-oxadiazole 3-oxides†

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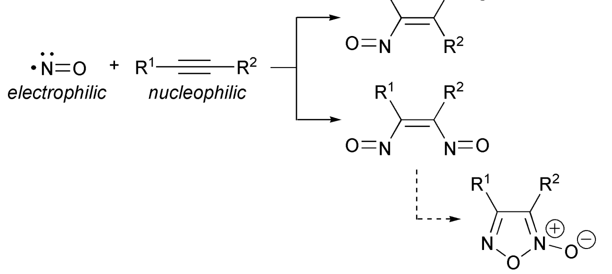
Nitric oxide reacts efficiently with alkynyllithium at low temperature producing 1,2,3-oxadiazole 3-oxides in good yields.

Nitric oxide (NO) is stable paramagnetic gas, which is an atmospheric pollutant, and also plays a fundamental role in biochemical processes.[1] While a number of approaches to directly fix nitric oxide into organic molecules have been investigated for one and half centuries,[2–4] the yields of the nitrogen-containing products and reproducibility of the reactions are usually low to moderate, which is probably due to the high reactivity of nitric oxide. Nonetheless, the controlled fixation of nitric oxide could lead to direct new routes to amino acids, alkaloids, and heterocyclic compounds, important classes of medicinal products. We have therefore investigated the development of reliable methods of fixation of nitric oxide into organic molecules.

Nitric oxide readily reacts with oxygen to produce dinitrogen trioxide and nitrogen dioxide, which are used as sources of nitrosonium and nitronium ions in organic syntheses.[5,6] Since nitric oxide itself is an electrophilic radical, it can in principle reacts with nucleophilic reagents such as alkynes (Scheme 1). However, the reaction has not been reported previously. Thus, we started to screen the reaction of nitric oxide gas with various alkynes. The results are summarized in Table 1.

First, when nitric oxide gas was bubbled through a THF solution of 1-(4-methoxyphenyl)-3-pentyne **1a** at 20 °C, **1a** was decomposed to give a complex mixture (entry 1). When the reaction was performed at −78 °C, starting **1a** was recovered (entry 2). Whether using the internal (**1a**), terminal (**1b**), and silylated alkynes (**1c**), the same results were obtained, that is no reaction at −78 °C and decomposition at room temperature (entries 1–5). On the other hand, when alkynylmagnesium bromide **1d** was used in place of **1a–c**, a clean reaction proceeded to give both the 1,2,3-oxadiazole 3-oxide **2a** in 13% yield along with 74% of **1b**, most likely arising from recovery of the starting material (entry 6). By using alkynyllithium **1e**, the yield of **2a** was dramatically improved up to 82%, and furthermore the reaction was reproducible (entry 7).[7] The structure of **2a** was confirmed by X-ray crystallography (Fig. 1).[8] Replacing H_2O by D_2O during the work-up procedure provided **2b** with more than 97% deuterium incorporation at the 4-position (entry 8), and use of chlorotrimethylsilane (2.0 equiv.) as quenching agent gave the corresponding **2c** in good yield (entry 9). Thus, the reaction is considered to start from nucleophilic attack of or one-electron transfer from alkynyllithium **3** to nitric oxide to produce unstable **5** (Scheme 2). The adduct **5** may isomerize to **6** to reduce electronic repulsion between nitrogen and oxygen atoms followed by 5-*endo*-digonal-mode cyclization[9] to give **7**. Since the reactions with alkyl- and alkenyllithium gave complex mixtures even at −78 °C, trapping the oxy-anion in **6** seems to be important for successful fixation. In the present case, the formation of a stable molecule, the heteroaromatic compound **7**, might also help the reaction to proceed smoothly and efficiently.

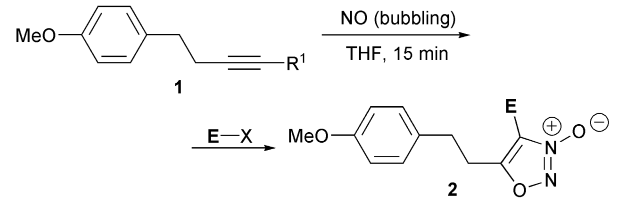


Scheme 1

As shown in Table 2, the reaction is general and can be applied to functionalized alkynyllithiums, such as those containing alkene, internal alkyne, ether, and sulfonamide in the side chain.

Although 1,2,3-oxadiazoles are reliable candidates for drug frameworks, their availability is somewhat low.[10] The present

Table 1 Reaction of nitric oxide with various alkynes



Entry	Substrate		Temp./°C	E–X	Product	Yield[a] (%)
	1	R1				
1	**a**	Me	25	**H**–OH	mixture[b]	—
2	**a**	Me	−78	**H**–OH	**1a**	97
3	**b**	H	25	**H**–OH	mixture[b]	—
4	**b**	H	−78	**H**–OH	**1b**	92
5	**c**	$SiEt_3$	−78	**H**–OH	**1c**	99
6	**d**	MgBr	−78	**H**–OH	**2a**	13[c]
7	**e**	Li	−78	**H**–OH	**2a**	82
8	**e**	Li	−78	**D**–OD	**2b**	79[d]
9	**e**	Li	−78	$\mathbf{Me_3Si}$–Cl	**2c**	85

[a] Isolated yield. [b] A complex mixture was produced. [c] **1b** was also obtained in 74% yield. [d] Deuterium was incorporated in more than 97% yield.

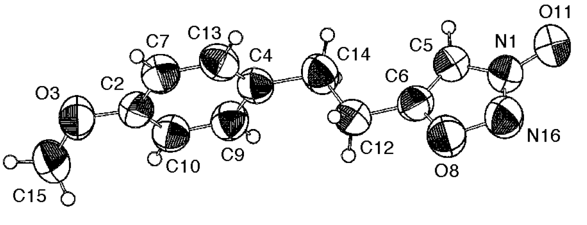


Fig. 1 The ORTEP view of **2a**. Selected bond lengths (Å) and angles (°): N(1)–O(11) 1.270(2), N(1)–N(16) 1.295(3), N(1)–C(5) 1.381(3), C(5)–C(6) 1.329(3), C(6)–O(8) 1.353(2), C(6)–C(12) 1.481(3), O(8)–N(16) 1.386(3), N(1)–C(5)–C(6) 105.85(19), N(1)–N(16)–O(8) 104.13(17), C(5)–N(1)–O(11) 126.86(19), C(5)–N(1)–N(16) 112.54(18), C(5)–C(6)–C(12) 135.45(19), C(5)–C(6)–O(8) 107.59(18), C(6)–O(8)–N(16) 109.88(16), O(8)–C(6)–C(12) 116.95(18), O(11)–N(1)–N16) 120.59(18).

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† Electronic supplementary information (ESI) available: crystal and molecular structure of **2a**. See http://www.rsc.org/suppdata/cc/b3/b311382e/

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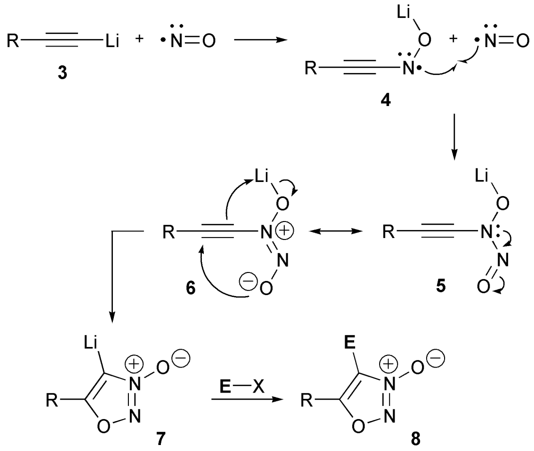
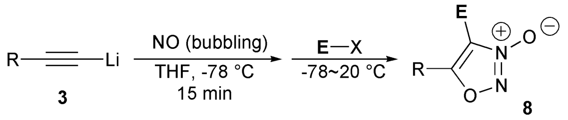


Scheme 2

Table 2 Reaction of nitric oxide with various alkynyllithiums



Entry	Substrate		E–X	Product	Yield[a]
	3	R		**7**	(%)
1	**a**	*n*-C_8H_{17}	**H**–OH	**a**	84
2	**a**	*n*-C_8H_{17}	**D**–OD	**b**	82
3	**a**	*n*-C_8H_{17}	**Me$_3$Si**–Cl	**c**	88
4	**b**	Ph	**H**–OH	**d**	72
5	**b**	Ph	**Me$_3$Si**–Cl	**e**	78
6	**c**	$CH_2CH_2CH_2OBn$	**H**–OH	**f**	80
7	**c**	$CH_2CH_2CH_2OBn$	**Me$_3$Si**–Cl	**g**	79
8	**d**	CH_2OCH_2CCPh	**H**–OH	**h**	72
9	**d**	CH_2OCH_2CCPh	**Me$_3$Si**–Cl	**i**	88
10	**e**	CH_2N(*p*-Ts)CH_2CHCH_2	**H**–OH	**j**	82

[a] Isolated yield.

method can provide a wide variety of 1,2,3-oxadiazole 3-oxides, which are much more stable than the 1,2,3-oxadiazoles themselves,[11] in short and high-yielding steps.

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7 A typical experimental procedure: nitric oxide gas was bubbled through a solution of 4-(4-methoxyphenyl)-1-butynyl-1-lithium **1e**, which was prepared *in situ*, by treatment of 1-(4-methoxyphenyl)-3-butyne **1b** (800 mg, 5.00 mmol) in THF (45 mL) with *n*-butyllithium (1.60 M in hexane; 3.20 mL, 5.12 mmol) at 0 °C for 15 min, at −78 °C for 15 min. After stirring the solution at −78 °C for an additional 15 min, argon was bubbled through followed by addition of water (2.0 mL), and then the reaction mixture was warmed up to room temperature. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash silica gel column chromatography gave **2a** (903 mg, 82%), prism (colorless: AcOEt–*n*-hexane). Mp 76 °C. IR (neat) 1628, 1612, 1584, 1514, 1435, 825 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.9–3.15 (m, 4 H), 3.80 (s, 3 H), 6.85 (d, $J = 8.8$ Hz, 2 H), 6.93 (s, 1 H), 7.08 (d, $J = 8.8$ Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.66, 30.97, 54.89, 113.95, 117.48, 129.00, 130.05, 158.34, 169.60. High-resolution MS calcd. for $C_{11}H_{13}N_2O_3$ $[M + 1]^+$ 221.0926, found 221.0924.

8 Crystal data of **2a**: $C_{11}H_{12}N_2O_3$, $M = 220.23$, monoclinic, $P2_1/c$, $a = 5.6130(4)$, $b = 8.9250(5)$, $c = 22.154(2)$ Å, $\beta = 95.563(3)°$, $V = 1104.60(13)$ Å^3, $T = 298$ K, $Z = 4$, $D_x = 1.324$ Mg m^{-3}, Mo Kα radiation, $\lambda = 0.71073$ Å, $\theta = 25.78°$, $\mu = 0.098$ mm^{-1}, 1863 reflections measured, 1417 were used in all calculations. $R = 0.0674$, $\omega R = 0.1580$, $S = 1.065$. CCDC 220238. See http://www.rsc.org/suppdata/cc/b3/b311382e/ for crystallographic data in CIF or other electronic format.

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11 After refluxing a solution of **2a** in xylene for 10 h under argon atmosphere, the starting **2a** was recovered in almost quantitative yield.