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Improved synthesis of V-PYRRO/NO, a liver-selective nitric oxide prodrug, and analogues

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ABSTRACT

The reported synthesis of O^2-vinyl 1-(pyrrolidin-1-yl)diazen-1-ium-1,2-diolate (V-PYRRO/NO), a hepatoprotective agent, was cumbersome and limited by a poor overall yield of 4% from sodium 1-(pyrrolidin-1-yl)diazen-1-ium-1,2-diolate (PYRRO/NO). We report an improved synthesis of V-PYRRO/NO in two steps with a significantly higher overall yield of 40% from PYRRO/NO. Using this protocol, a number of structural analogues of V-PYRRO/NO were prepared in good yields.

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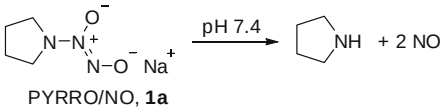
Nitric oxide (NO) prodrugs of the diazeniumdiolate class such as PYRRO/NO (**1a**) dissociate in aqueous buffer to release up to 2 mol of NO (Eq. 1):[1,2]



(1)

The O^2-vinyl derivative of PYRRO/NO, V-PYRRO/NO (**2a**, Scheme 1), has demonstrated promising pharmacological utility in a number of studies.[3–19]

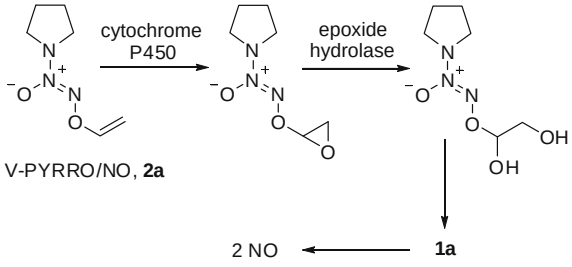
For example, V-PYRRO/NO protected the liver from ischemia-reperfusion injury during liver transplantation.[5] V-PYRRO/NO was found to be metabolized by cytochrome P450 isoforms 2E1 and 3A4;[17] the presumed mechanism for release of nitric oxide from V-PYRRO/NO involves epoxidation followed by hydrolysis to generate the anion of **1a**, which then spontaneously decomposes to form NO and pyrrolidine (Scheme 1).[3,17]

V-PYRRO/NO was previously reported to be synthesized in 4% overall yield by hydroxide-induced dehydrobromination of **3a**, which was in turn synthesized from **1a**.[3] The low yields of these reactions precluded the facile preparation of structural analogues of V-PYRRO/NO (Scheme 2). Herein, a protocol for the improved synthesis of V-PYRRO/NO and related vinylated diazeniumdiolates is described.

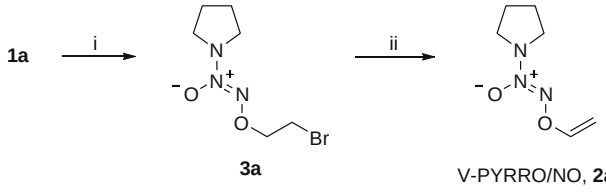
Recently, we reported the synthesis of V-PROLI/NO (**2c**) in three steps from diazeniumdiolated prolinol (**1b**, Scheme 3).[20] 2-Bromo-1-(trifluoromethanesulfonyloxy)ethane (**4**)[21] was used instead of 1,2-dibromoethane; the reaction of **4** with **1b** formed **3b** in 48% yield.[20]

Applying this procedure in an effort to improve the yield of **3a**, **1a** was reacted with **4** to form **3a** in the presence of 15-crown-5 in THF; work-up and silica gel chromatography afforded O^2-(2-bromoethyl) PYRRO/NO (**3a**) in 49% yield (Table 1).[22]

The reaction of a number of other diazeniumdiolate salts (**1d–h**) with **4** afforded the corresponding O^2-(2-bromoethyl) diazeniumdiolates (**3d–h**) in moderate to good yields (Table 1). For example, the reaction of **1h** with **4** produced **3h** in 69% yield.



Scheme 1. Proposed mechanism of NO release from V-PYRRO/NO.[17]



Scheme 2. Reported synthesis of V-PYRRO/NO.[3] Reagents and conditions: (i) $BrCH_2CH_2Br$, THF, 8%; (ii) NaOH, THF, H_2O, reflux, 54%.

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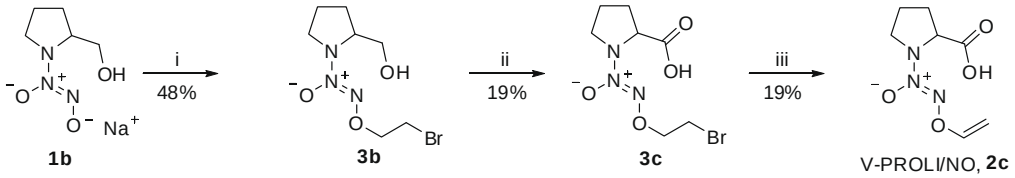
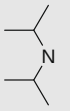
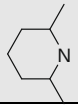


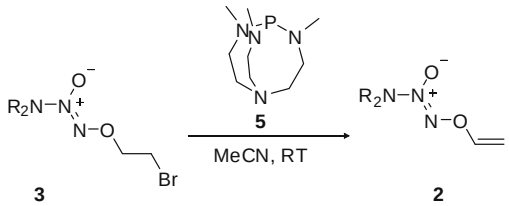
Scheme 3. Reported synthesis of V-PROLI/NO.[20] Reagents and conditions: (i) $BrCH_2CH_2OTf$ (**4**), THF, 15-crown-5, 48%; (ii) $RuCl_3$, $NaIO_4$, EtOAc, H_2O, MeCN, 19%; (iii) NaOH, THF, H_2O, reflux, 19%.

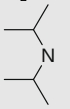
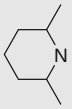
Table 1
Synthesis of O^2-(2-bromoethyl) diazeniumdiolate derivatives

Reactant	Product		Yield (%)
	R_2N	Compd no.	
PYRRO/NO, **1a**[a]		**3a**	49
DMA/NO, **1d**[b]	Me_2N	**3d**	55
DEA/NO, **1e**[c]	Et_2N	**3e**[d]	57
1f[e]		**3f**	31
1g[c]		**3g**	65
1h[e]		**3h**	69

[a] Ref. 3.
[b] Ref. 23.
[c] Ref. 24.
[d] Previously prepared in 17% yield by the reaction of **1e** and 1,2-dibromoethane in THF; Ref. 25.
[e] Ref. 26.

Table 2
Synthesis of some O^2-(vinyl) diazeniumdiolate derivatives



Reactant	Product		Yield (%)
	R_2N	Compd no.	
3a		**2a**[a]	81
3d	Me_2N	**2d**	64
3e	Et_2N	**2e**[b]	80
3f		**2f**	73
3g		**2g**	81
3h		**2h**	76

[a] Ref. 3.
[b] Previously prepared by the dehydrohalogenation of **3e** by NaOH in THF under refluxing conditions; Ref. 25.

Next, we proceeded to find a superior elimination method to prepare O^2-vinyl diazeniumdiolates from the corresponding bromide. 2,8,9-Trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (**5**) was reported by Verkade et al. to be an efficient base to carry out dehydrohalogenation reactions under mild reaction conditions.[27] Using a modified literature procedure, **3a** was reacted with **5** in acetonitrile at room temperature and V-PYRRO/NO **2a** was isolated in 81% yield (Table 2).[28,29] This yield was better than the previously reported yield of 54% using sodium hydroxide as the base under refluxing conditions (Scheme 2).[25]

The proazaphosphatrane-mediated dehydrohalogenation protocol was then applied to the bromides **3d**–**h** and the desired O^2-vinyl prodrugs were prepared in yields ranging from 64% to 81% (Table 2).[29]

The nitric oxide prodrugs, **1f** and **h**, were previously reported as excellent sources of NO and were proposed to have a favorable toxicological profile suggesting that compounds **2f** and **h** may have some advantages over V-PYRRO/NO.[26] The biological evaluation of these structural analogues is underway and the results will be published in due course.

Acknowledgments

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Supplementary data

Supplementary data (analytical data for new compounds and NMR spectra of **2d**, **2f**–**h**, and **3d**, **3f**–**h**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.103.

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22. To a slurry of **1a** (370 mg, 2.43 mmol) in THF (5 mL), **4** (750 mg, 2.92 mmol) and 15-crown-5 (100 μL) were added and stirred overnight at room temperature. The solvent was removed under reduced pressure and diluted with dichloromethane. The solution was washed with 10% NaOH and the organic layer was separated, dried (Na_2SO_4), and filtered through a plug of $MgSO_4$. The filtrate was concentrated under reduced pressure and the resulting oil was then purified by silica gel flash chromatography using a mixture of 12→75% EtOAc–hexanes to afford **3a** (0.28 g, 1.18 mmol, 49%) as an oil. The spectral features of this material were consistent with previously published values. Unless otherwise mentioned, this procedure was used for the syntheses of **3d**–**h**.
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29. To a solution of **3a** (270 mg, 1.14 mmol) in anhydrous acetonitrile (12 mL), **5** (491 mg, 2.27 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was removed and the resulting oil was purified using silica gel flash chromatography with a mixture of 12→75% EtOAc–hexanes to afford **2a** (145 mg, 0.92 mmol, 81%) as an oil. The spectral features of this material were consistent with previously published values. Unless otherwise mentioned, this procedure was used for the synthesis of **2d**–**h**.