A New Highly Efficient Method for the Synthesis of *trans*-Tetrahydro-3,4-furandiamine

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A new four-step, highly efficient synthesis of *trans*-tetrahydro-3,4-furandiamine is described. Nitromercuration of 2,5-dihydrofuran with sodium nitrite and mercuric chloride in aqueous solution followed by base catalyzed elimination yielded 3-nitro-2,5-dihydrofuran which was aminated with ammonium hydroxide to give *trans*-tetrahydro-4-nitro-3-furanamine. Catalytic reduction of this material afforded the desired product **5** in 37% overall yield.

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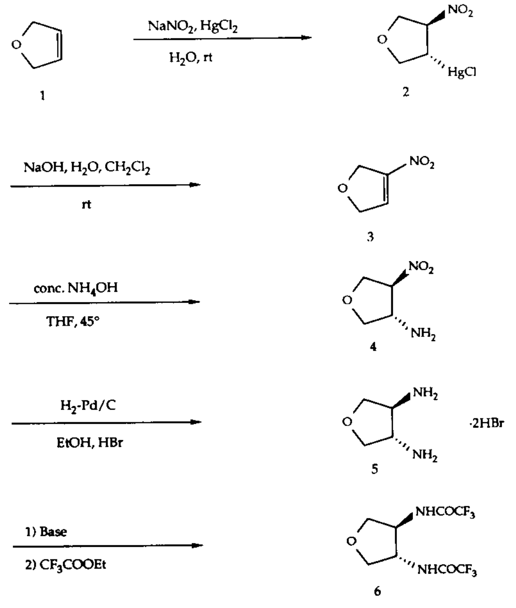
The *trans*-tetrahydro-3,4-furandiamine **5** can be prepared [1,2] from *dl*-1,3-butadiene diepoxide by a time consuming eight-step synthesis in 11% overall yield.

We now report a new four-step synthesis of **5** utilizing synthetic methodology developed by Corey and co-workers [3,4].



Reaction of commercially available 2,5-dihydrofuran **1** with two equivalents of sodium nitrite and one equivalent of mercuric chloride yielded the *trans*-nitromercurial **2** in 54% yield. Treatment of **2** with one equivalent of aqueous sodium hydroxide in methylene chloride for 20 minutes at room temperature followed by acidification, removal of the metallic mercury and concentration of the organic phase produced pure 2,5-dihydro-3-nitrofuran **3** in 77% yield. Reaction of **3** with concentrated ammonium hydroxide in tetrahydrofuran in a pressure bottle at 45° for 25 hours afforded the *trans*-tetrahydro-4-nitro-3-furanamine **4** in 93% yield. This oily crude material was immediately dissolved in ethanol containing two equivalents of 48% aqueous hydrogen bromide and 10% palladium-on-carbon catalyst and the mixture was reduced in Parr-Shaker to produce the *trans*-tetrahydro-3,4-diaminofuran **5** in 95% yield. Conversion of **5** to the free base and reaction with ethyl trifluoroacetate [5] yielded crystalline *trans-N,N'*-(tetrahydro-3,4-furandiyl)bis(2,2,2-trifluoroacetamide) **6**. Intermediates **2**, **3** and **4** are not very stable and should be treated with special care. However, they can be stored at lower temperatures for a few days without decomposition. All intermediates and the final product were supported by ^{1}H nmr and elemental analysis. The diaminofuran **5** was found to be identical by ^{1}H nmr to the one synthesized by the literature procedure [1] and it is racemic.

The *trans*-tetrahydro-3,4-diaminofuran **5** is a key intermediate for the synthesis of water soluble platinum complexes [6].

Table 1

^{1}H NMR Measurements of Products **2** through **6**

Product	Solvent	^{1}H NMR in δ (ppm)	
2	DMSO-d$_6$	2.7-2.9	(m, 1H, CHNO$_2$)
		3.7-4.2	(m, 4H, CH$_2$O)
		5.5-5.7	(m, 1H, CHHg)
3	CDCl$_3$	5.0	(s, 4H, CH$_2$O)
		7.1	(s, 1H, CH=C)
4	CDCl$_3$	1.6	(bs, 2H, NH$_2$)
		3.4-3.6	(m, 1H, CHNO$_2$)
		3.9-4.3	(m, 4H, CH$_2$O)
		4.6-4.9	(m, 1H, CHN)
5 (free base)	CDCl$_3$	1.5	(bs, 4H, NH$_2$)
		3.1-3.3	(q, 2H, CHO)
		3.4-3.7	(m, 2H, CHO)
		4.0-4.2	(m, 2H, CHN)
5 (HBr salt)	DMSO-d$_6$	3.6-4.2	(m, 6H, 4CH$_2$ & 2CH)
		8.3	(bs, 6H, NH$_3^+$)
6	CDCl$_3$	3.5-3.7	(m, 2H, CHO)
		3.9-4.2	(m, 2H, CHO)
		4.3-4.6	(m, 2H, CHN)
		9.1-9.5	(m, 2H, NHCO)

EXPERIMENTAL

The ^1H nmr measurements were obtained on a Varian Model FT-80 spectrometer and chemical shift values are reported in δ downfield from tetramethylsilane internal standard.

(R^*,R^*)-*trans*-Chloro(tetrahydro-4-nitro-3-furanyl)mercury (**2**).

The sodium nitrite (27.6 g, 0.4 mole) was dissolved in water (200 ml) and the mercuric chloride (54.3 g; 0.2 mole) was added. To the resulting bright yellow solution was added with good mechanical stirring the 2,5-dihydrofuran (14 g, 0.2 mole). The white thick suspension was stirred overnight at room temperature and the solid was filtered, washed with water, ethanol, ether and dried to give 38.2 g (54%) of **2** as white crystals.

Anal. Calcd. for $C_4H_6ClHgNO_3$ (352.16): C, 13.64; H, 1.71; N, 3.97. Found: C, 13.49; H, 1.51; N, 3.75.

2,5-Dihydro-3-nitrofuran (**3**).

The nitromercurial **2** (17.61 g, 0.05 mole) was slurried in methylene chloride (1 liter) and water (400 ml) and to the suspension was added with good stirring 5*N* sodium hydroxide (10 ml, 0.05 mole). The reaction mixture was stirred for 20 minutes at room temperature and acidified with concentrated hydrochloric acid to *p*H 3.0. The metallic mercury was removed and the organic phase was separated and evaporated under reduced pressure to give 4.43 g (77%) of **3** as a colorless oil at room temperature which solidified at ice bath temperature.

Anal. Calcd. for $C_4H_5NO_3$ (115.09): C, 41.74; H, 4.37; N, 12.17. Found: C, 41.93; H, 4.47; N, 11.98.

trans-Tetrahydro-4-nitro-3-furanamine (**4**).

The solution of nitroolefin **3** (3.07 g, 0.027 mole) and concentrated ammonium hydroxide (15.53 molar, 6.9 ml, 0.107 mole) in tetrahydrofuran (100 ml) was heated in a pressure bottle at 45° for 24 hours. It was then evaporated under reduced pressure to give 3.31 g (93%) of light yellow oil which was used immediately for the reduction step without further purification.

trans-Tetrahydro-3,4-furandiamine Dihydrobromide (**5**).

The crude **4** (11.5 g, 0.087 mole) was dissolved in ethanol (75 ml) and 48% hydrobromic acid (20 ml) and the 10% palladium-on-carbon catalyst (1.5 g) was added. The mixture was reduced overnight in a Parr-Shaker apparatus. The catalyst was filtered and the filtrate was concentrated under reduced pressure to give 20.9 g (95%) of **5**, which was crystallized as the dihydrobromide salt with 48% hydrobromic acid from a methanolic solution.

Anal. Calcd. for $C_4H_{10}N_2O \cdot 2HBr$ (263.98): C, 18.20; H, 4.58; N, 10.61; Br, 60.55. Found: C, 18.21; H, 4.39; N, 10.47; Br, 60.89.

trans-*N*,*N*'-(Tetrahydro-3,4-furandiyl)bis(2,2,2-trifluoroacetamide) (**6**).

The product **5** (1.8 g, 0.005 mole) was first converted to free base by dissolving it in water and adjusting the *p*H to 9.5 with sodium hydroxide. The free base was extracted with chloroform which was removed under reduced pressure and the resulting free amine was dissolved in ethyl trifluoroacetate (10 ml). The solution was heated under reflux for one hour leaving after evaporation 1.1 g (75%) of **6**.

Anal. Calcd. for $C_8H_8F_6N_2O_3$ (294.16): C, 32.66; H, 2.74; N, 9.52; F, 38.75. Found: C, 32.34; H, 2.85; N, 9.43; F, 38.90.

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[6] A manuscript on water soluble platinum complexes is currently being written.