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1,4-Diaminobutanes From Furans: A New Synthetic Approach to Substituted Putrescines

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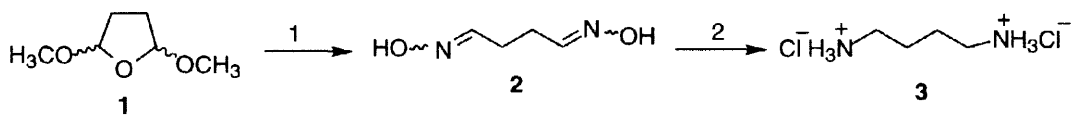
Abstract: A novel approach for the synthesis of (hydroxymethyl)- and (aminomethyl)-putrescines starting with furanmethanols and aminomethyl-furanmethanols is reported. The furans were converted to their 2,5-dimethoxy-tetrahydrofuran derivatives and the latter were ring-opened in acid media. The resulting carbonyl derivatives were isolated as their dioximes and the latter were then reduced to the corresponding amino alcohols.

In our continuous search for new synthetic analogs[1] of the naturally occurring polyamines[2], we examined the possibility of preparing putrescine (1,4-diaminobutane) derivatives substituted with hydrophylic hydroxymethyl residues starting with furan derivatives. We had already shown[3,4] that alkylpyrroles are good synthons for the preparation of hydrophobic alkylputrescines, as the pyrroles can be ring-opened by reaction with hydroxylamine. We report below that putrescine dihydrochloride (**3**) can be prepared in 50% overall yield from 2,5-dimethyoxytetrahydrofuran (**1**) when the latter is ring-opened in acid medium, the resulting succinic dialdehyde is trapped as its dioxime **2**, and the latter is reduced to **3** (Scheme 1).



1) i) 50% AcOH, 1h, 80 ^{0}C; ii) $HONH_2.HCl$, NaOAc, 24h, 20 ^{0}C; iii) ext. EtOAc
2) i) 50% Raney Ni, 2N NaOH/EtOH 1:1, 2h, 25 ^{o}C; ii) ext. Cl_3CH; iii) CH_3OH/HCl

Scheme 1

Although this synthetic sequence is very likely no more advantageous than the orthodox approach to **3**,[5] it becomes very useful when the above mentioned diamino alcohols are needed. The synthesis of 2,5-diaminopentanol (ornithinol **9a**) from furfuryl acetate **4a** is outlined in Scheme 2. N-substituted derivatives of **9a** have been prepared by reduction of N-substituted ornithines.[6-8] To obtain **9a** itself, **4a** was submitted to a Clauson-Kaas reaction[9] using bromine in methanol over potassium carbonate, and the expected mixture of diastereoisomers **5a**[10] was obtained in 78% yield. Reduction of **5a** to the corresponding tetrahydrofuran derivatives **6a**[11] was achieved in 95% yield by catalytic hydrogenation over 5% Rh on alumina in the presence of 1% triethylamine. If the latter was omitted, partial hydrogenolysis of the 2-methoxy residue took place to give **7a** as a subproduct of the reaction. The hydrogenolysis of ketals in the presence of 5% Rh on alumina and traces of acid has been reported.[12] Hydrolysis of the cyclic diacetal **6a** was achieved by using 50% acetic acid at 80°C[13] and the ketoaldehyde was isolated as its dioxime **8a**[14] (68%) by addition of hydroxylamine to the reaction mixture. Reduction of **8a** to 2,5-diaminopentanol (**9a**)[15] was best achieved using Raney Ni in a50% ethanol-2N sodium hydroxide solution. The ester bond was saponified (60%) during the course of the reaction. Extraction

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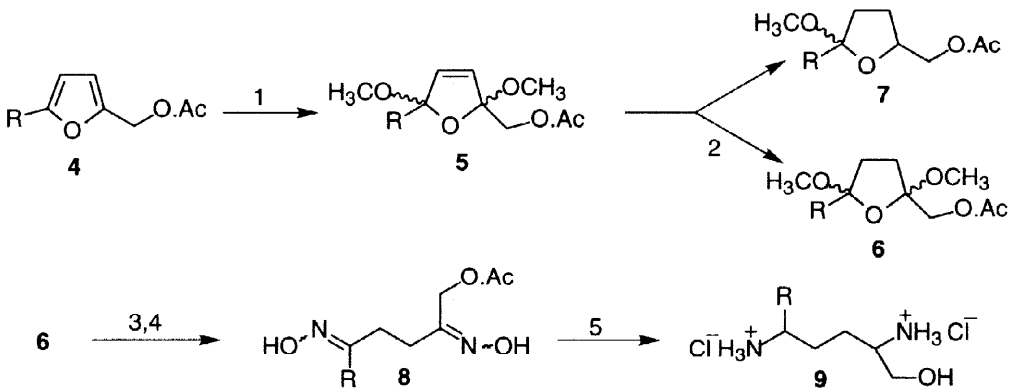
of **9a** into chloroform gave the free base which was transformed into its dihydrochloride by dissolution in methanol-HCl. Reduction attempts of **8a** using catalytic hydrogenation over Pd/C or Rh/Al_2O_3, or Zn in acetic acid, or sodium in ethanol failed to give **9a** in good yields.

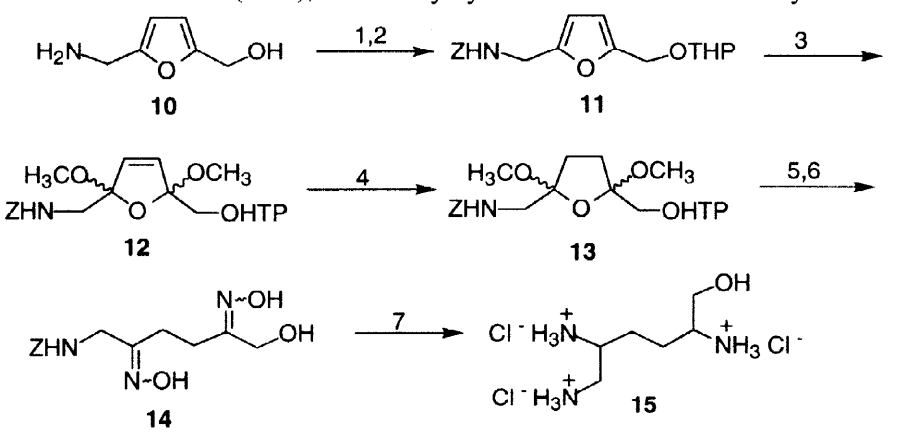


a: R = H; b: = CH_2Ac; c: R = CH_2OH

1) i) CH_3OH, K_2CO_3; ii) Br_2, CH_3OH. 2) THF, 5% Rh/Al_2O_3, H_2, TEA, 50 psi, 2h. 3) 50% AcOH, 1h, 80 ^{0}C. 4) $HONH_2.HCl$, NaOAc, 24h, 20^{0}C, ext. EtOAc. 5) i) Raney Ni/2N NaOH, EtOH, 2h, 25^{0}C; ii) ext. Cl_3CH, then CH_3OH/HCl.

Scheme 2

The synthetic outline depicted in Scheme 2 was also used to prepare 2,5-diamino-1,6-hexanediol (**9c**) from 2,5-furanedimethanol (Aldrich) by first converting it into its diacetate **4b**[16] and then into the isomer mixture of the dihydrofurans **5b** (91%). Reduction of **5b** to **6b**[17] (95%) was followed by ring opening of **6b** to the syn/anti mixture of dioximes **8b**[18] (50%), and finally by reduction of **8b** to **9c**[19] dihydrochloride (60%).



Z= $O.CO.CH_2C_6H_5$

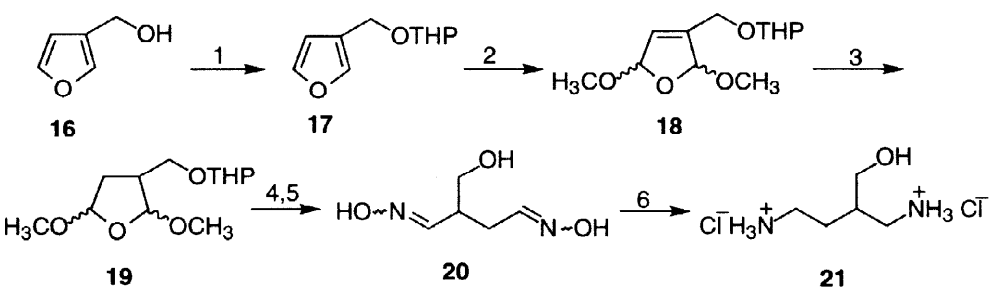
1) i) CH_2Cl_2, DHP, pTS, 5h; ii) 5% $NaCO_3H$, ext. Et_2O, 98%.2) Cl_3CH, 10% NaOH, $BnCO_2Cl$, 18h, 70%; 3) i) CH_3OH, K_2CO_3; ii) Br_2, CH_3OH, 83%; 4) THF, 5% Rh/Al_2O_3, H_2, 50 psi, 2h, 90%; 5) 50% AcOH, 1h, 80 ^{0}C; 6) $HONH_2.HCl$, NaOAc, 24h, 20 ^{0}C, ext. EtOAc 7) i) Raney Ni/2N NaOH, EtOH, 2h, 25 ^{0}C; ii) ext. Cl_3CH, then CH_3OH/HCl.

Scheme 3

An analogous synthetic sequence allowed the preparation of putrescine substituted with hydroxymethyl and aminomethyl residues; e.g. (2,5-diamino)-6-amino-1-hexanol **15** (Scheme 3). Starting with the known 5-aminomethylfurfuryl alcohol **10**[20], the hydroxymethyl residue was protected by reaction with dihydropyran to

give the tetrahydropyranyl derivative; the latter was then protected on its aminomethyl end by converting it into its benzyl carbamate. The resulting furan **11**[21] withstood the release of acid during the Clauson-Kaas reaction without cleavage of the tetrahydropyranyl acetal and **12**[22] was obtained in 83% yield. It was reduced to **13**[23] with hydrogen over Rh/Al_2O_3 (90%), the tetrahydrofuran ring of **13** was ring opened by acid treatment with 50% acetic acid that also cleaved the tetrahydropyranyl acetal and the resulting diketone was isolated as its dioxime **14**[24] in 50% overall yield. On reduction of the latter with Raney Ni the oxime groups were reduced to the secondary amines and the benzyloxycarbonyl protecting group was cleaved to give **15**[25] (30%) that was isolated as its trihydrochloride.

An analogous series of reactions yielded 2-hydroxymethylputrescine **21** from 3-hydroxymethylfuran **16** (Aldrich) (Scheme 4), thus broadening the scope of synthetic sequence outlined in Scheme 1 to include -substituted furans. The alcohol group was protected as its tetrahydropyranyl derivative **17**[26] by reaction of **16** with dihydropyran. The tetrahydropyranyl acetal residue was not affected by the Clauson-Kaas reaction and **18**[27] was obtained in good yields. It was reduced to **19**[28] by catalytic hydrogenation over 5% Rh/Al_2O_3. The hydrolysis of the cyclic acetal **19** also cleaved the tetrahydropyranyl group. The resulting 2-hydroxymethyl-succinaldehyde was isolated as its dioxime **20**. The latter had to be separated from the oxime of 5-hydroxypentanal originated in the cleavage of the tetrahydropyranyl group, and this was achieved by chromatography on silica gel using 10% methanol in chloroform as eluant. The syn/anti mixture of dioximes **20** was reduced to the dihydrochloride **21**[29] following the procedure described for **9**.



1) i) CH_2Cl_2, DHP, pTS, 5h; ii) 5% $NaCO_3H$, ext. Et_2O,98%. 2) Br_2, CH_3OH, K_2CO_3 ,95%. 3) 5% Rh/Al_2O_3, THF, H_2, 50 psi, 2h, 90%. 4) 50% AcOH, 1h, 80°C. 5) $HONH_2$.HCl, NaOAc, 24h, 20°C, 80%. 6) i) Raney Ni/2N NaOH, 2h, 25°C. ii) CH_3OH/HCl, 61%.

Scheme 4

The experimental results reported above show the usefulness of substituted furans as synthons to obtain substituted putrescines.

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10. **5a**:^{13}CNMR (20 MHz, $CDCl_3$) 19.27, 19.38 (CH_3), 48.32, 48.87, 53.81, 54.76 (OCH_3), 65.10, 65.28 (OCH_2), 106.54, 107.58 (C=C), 110.63, 111.67 (C_2), 130.09, 130.56 (C=C), 131.75, 131.87 (C_5), 169.10 (CO). MS-EI (m/z) 202 (M^+).
11. **6a**:^{13}CNMR (20 MHz, $CDCl_3$) 19.59 (CH_3), 30.32, 30.51, 30.82 (CH_2), 48.14, 48.44, 53.64, 54.37 (OCH_3), 63.70, 64.14 (OCH_2), 105.03, 105.58 (C_5), 107.04, 107.51 (C_2), 169.25 (CO). MS-EI (m/z) 204 (M^+).
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14. **8a**:^{13}CNMR (20 MHz, $CDCl_3$) 21.79 (CH_3), 22.63, 24.73, 24.82, 27.15, 29.58 (CH_2, mixture of syn/anti), 63.34, 63.58 (OCH_2), 154.23, 154.39, 154.95 (C=NOH), 170.53 (CO).
15. **9a**:^{13}CNMR (20 MHz, $CDCl_3$) 24.06, 24.45 (CH_2), 40.40 (CH), 46.94 (CH_2N), 62.50 (CH_2OH). MS-EI (m/z) 118 (M^+), 100 (M^+–H_2O), 83 (M^+–H_2O–NH_3).
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17. **6b**:^{13}CNMR (20 MHz, $CDCl_3$) 19.78 (CH_3), 31.85, 32.02 (CH_2), 48.39, 48.98 (OCH_3), 63.03, 63.27 (CH_2O.), 107.45, 107.77 (C_2, C_5), 169.68 (CO).
18. **8b**:^{13}CNMR (20 MHz, $CDCl_3$) 20.36 (CH_3), 27.07 (CH_2), 58.49 (CH_2O), 153.59 (C=NOH), 170.01 (CO). MS-EI (m/z), 260 (M^+), 140 (M^+–$2CH_3CO_2H$, 100%).
19. **9c**:^{13}CNMR (20 MHz, D_2O) 24.63 (CH_2), 37.59 (CH^+NH_3), 63.01 (CH_2O). MS-MALDI (m/z), 149 (M^++1).
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21. **11**:^{13}CNMR (20 MHz, $CDCl_3$) 18.11, 24.49, 29.34 (THP), 37.27 (CH_2N), 60.73, 65.65, 68.57 (CH_2O), 96.24 (O-CH-O), 106.76, 109.05 (furan-C), 126.98, 127.18, 127.41, 134.44 (Ph), 150.36, 151.28 (furan-C), 155.37 (CO).
22. **12**:^{13}CNMR (20 MHz, $CDCl_3$) 18.93, 24.83, 29.96 (THP), 45.40, 45.51 (CH_2N), 49.74, 49.91 (CH_3O), 61.95, 64.01, 66.03 (CH_2O), 93.74 (O-CH-O), 98.67, 98.79 (C=C), 110.53, 111.70, 127.32, 127.54, 127.69, 132.66, 156.03 (CO).
23. **13**:^{13}CNMR (20 MHz, $CDCl_3$) 18.97, 18.75, 24.90, 29.77, 30.01 (CH_2), 33.62, (CH_2N), 45.47 (CH_3O), 61.44, 64.01, 69.02, 97.22, 110.53, 111.70, 127.32, 127.55, 127.67, 135.60, 154.46.
24. **14**:^{13}CNMR (20 MHz, $CDCl_3$) 22.39, 28.74 (CH_2), 31.30, 31.60 (CH_2N), 61.57, 66.73 (CH_2O), 127.67, 127.76, 128.75, 135.97 (Ph), 151.66, 152.02 (C=NOH), 156.61 (CO).
25. **15**:^{13}CNMR (20 MHz, D_2O): 22.86, 27.30 (CH_2), 31.53 (CH_2N), 40.33, 49.83 (CHN), 62.23 (CH_2OH). MS-MALDI (m/z), 148 (M^++1).
26. **17**:^{13}CNMR (20 MHz, $CDCl_3$): 18.82, 25.18, 60.10 (THP), 59.47, 61.00 (CH_2O), 96.98 (O-CH-O), 110.00, (C_3), 122.09 (C_2), 140.22, 142.72 (C_1, C_4).
27. **18**:^{13}CNMR (20 MHz, $CDCl_3$): 18.71, 18.85, 24.71, 29.67, 30.00 (CH_2), 52.79, 53.26 (CH_3O), 51.77, 60.59 (CH_2O), 96.90, 97.66 (O-C-O), 105.64, 107.53 (C_2, C_5), 124.75, 125.28 (CH=C), 141.82, 142.44 (C=CH).
28. **19**:^{13}CNMR (20 MHz, $CDCl_3$): 18.69, 24.99, 29.93 (THP), 43.43, 43.96 (CH_2), 52.65 (CH), 53.91 (CH_3O), 60.81, 65.52, 67.60 (OCH_2), 98.96 (O-CH-O), 105.11, 107.78 (C_2, C_5).
29. **21**:^{13}CNMR (20 MHz, $CDCl_3$): 27.28 (CH_2), 40.02 (CH-NH_2), 46.18, 48.32 (CH_2N), 63.12 (CH_2O). MS-EI (m/z) 118 (M^+), 100 (M^+–H_2O).