A New Synthesis of 4,5,6,7-Tetrahydrofuro[2,3-*c*]pyridines and Furo[2,3-*c*]pyrrolidines

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New syntheses of 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines and furo[2,3-*c*]pyrrolidine derivatives, starting from furan-3-carboxaldehyde, are reported.

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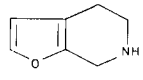
In order to further pursue one aspect of our continuing research program, we desired to obtain certain 2-hydroxymethyl-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines as well as furo[2,3-*c*]pyrrolidines. A few syntheses of 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines **1** have been reported in the literature. Two such syntheses start from readily available furfural, and complete the route by ring closure with the formation of the 3a-4 bond. The first of these routes [1] features as ring closure at the furo[2,3-*c*]pyridine oxidation level followed by catalytic hydrogenation of the pyridine ring. Ring closure in the second route [2,3] was performed at the oxidation level of a 4-oxodihydropyridine. The reported difficulties in the Wolff-Kishner reduction of the 4-oxo group in the latter case [2] were confirmed by us. Reduction of the 4-oxo group *via* treatment of the corresponding tosylhydrazone with catecholborane was also unsuccessful, as well as dehydration of the 4-hydroxy derivative [3]. A recently reported synthesis of furo[2,3-*c*]pyridines [4] demonstrates furan annulation onto 4-piperidone *via* rearrangement of an ethynyl epoxide. Similarly, ring closure of 4-phenacyl-3-piperidone to give 2-phenyl-substituted derivatives has been reported [5].

Block 1



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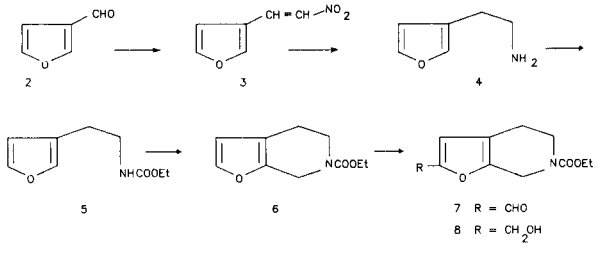
Since none of the preceding synthetic procedures was completely satisfactory for our purposes, we explored the possibility of forming the tetrahydropyridine ring by a route which included a Mannich reaction starting from furan-3-ethanamine.

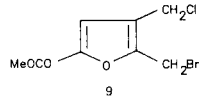
Block 2



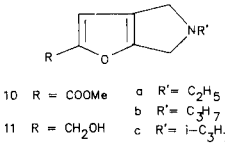
Condensation of 3-furancarboxaldehyde (**2**) with nitromethane easily afforded the nitrovinyl derivative **3**, which was reduced with lithium aluminum hydride to furan-3-ethanamine (**4**). This compound is quickly oxidized in the air, and cannot be distilled without extensive decomposition. For this reason, the crude product **4** was converted to the stable *N*-carbethoxy derivative **5**. Condensation of **5** with paraformaldehyde in the presence of *para*-toluenesulfonic acid completed the synthesis of the ring. Vilsmeier-Haack formylation of **6** gave the aldehyde **7**, which, by reduction with lithium aluminum hydride, afforded the desired compound **8**.

For the furo[2,3-*c*]pyrrolidine series, the only examples which have been previously reported in the literature [6] are the 2-carbomethoxy- or 2-hydroxymethyl-*N*-alkyl derivatives **10-11**, which were prepared from the furan **9** [7] by reaction with the appropriate amines. In our hands, the reaction of **9** with methylamine gave only the 2,3-bis-(dimethylaminomethyl)furan derivative **12a** [8], whereas with isopropylamine, perhaps due to steric reasons, a certain amount of the bicyclic product **10c** was obtained.

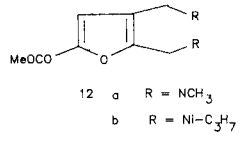
Block 3



9



10 R = COOMe a R' = C_2H_5
b R' = C_3H_7
11 R = CH_2OH c R' = i-C_3H_7



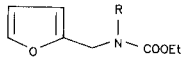
12 a R = NCH_3
b R = Ni-C_3H_7

Since the starting materials for the synthesis of 5-unsubstituted furans are not readily available, we attempted a more general synthetic procedure similar to that used for the corresponding furo[2,3-*c*]pyridines, *i.e.*, starting from 2- or 3-substituted furans. The Mannich reaction starting with *N*-carbethoxy-2-furanmethanamine **13** failed to give the desired intermediate for ring closure. Likewise, treatment of the isolated *N*-hydroxymethyl derivative **14** with

boron trifluoride etherate or *para*-toluenesulfonic acid were unsuccessful, perhaps due to the acid-sensitivity of the furan ring and the low reactivity of the C-3 position of the furan ring towards electrophilic attack.

A more rewarding route was realized starting with 3-furancarboxaldehyde (**2**). Sodium cyanoborohydride reduction of 3-furancarboxaldehyde in the presence of ammonium acetate gave a crude mixture which, when reacted with ethyl chloroformate, appeared to yield the expected **15** along with the double condensation product **16**. Hydroxymethylation of **15** gave **17**, which was treated with formic acid in cyclohexane to give the desired compound **18**, in 20% yield.

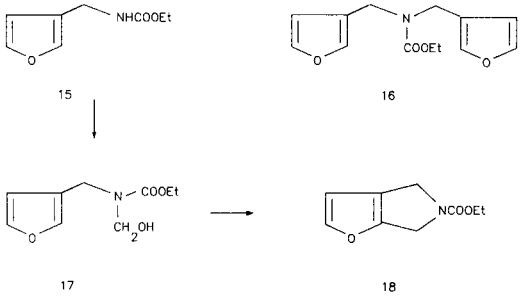
Block 4



13 R = H

14 R = CH_2OH

Block 5



EXPERIMENTAL

Melting points are uncorrected. The ^1H nmr spectra were measured in deuteriochloroform with a Bruker WP-80 spectrometer; chemical shifts (δ) were measured using tetramethylsilane as an internal standard. Mass spectra were taken with a Finnigan 4021 spectrometer. Flash column chromatography was performed using Merck 60 silica gel.

3-Nitrovinylfuran (**3**).

A mixture of 0.56 ml (10.4 mmoles) of nitromethane and 0.9 ml (10.4 mmoles) of 3-furancarboxaldehyde in 2.1 ml of toluene was cooled in an ice bath and 1.08 ml of 10 *N* sodium hydroxide was added dropwise, keeping the reaction temperature below 10°. After 15 minutes, 7 ml of iced water were added, and the mixture was added dropwise into 5.2 ml of 15% hydrochloric acid. The yellow precipitate was filtered and crystallized from ethanol to give 0.97 g (67%) of compound **3**, mp 101-103°; ir (nujol): 1640 (C=C), 1380 (C-NO_2) cm^{-1}; ^1H-nmr: δ 6.55 (m, H-4), 7.50 (m, H-2), 7.80 (m, H-5), 7.37 and 7.92 (AB, J = 15 Hz, CH=CH).

Anal. Calcd. for $C_6H_5NO_3$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.58; H, 3.71; N, 9.99.

Furan-3-ethanamine (**4**).

To a suspension of 1.6 g (42 mmoles) of lithium aluminum hydride in 40 ml of tetrahydrofuran was added 3 g (21 mmoles) of **3** during a 1.5 hour period. After stirring for 30 minutes, ethyl acetate and ethanol were added to destroy the excess of hydride reagent. The mixture was filtered and the residue was washed with boiling ethyl acetate. The combined organic phases were extracted with 2*N* hydrochloric acid, the extract made alkaline with 10*N* sodium hydroxide, and extracted with ethyl acetate. Drying and evaporation of the solvent gave a crude product (*ca.* 60% yield) which could neither be distilled nor chromatographed without decomposition; ms: m/z 111 (M^+), 94 (M^+-NH_3), 82.

3-(2-Ethoxycarbonylaminoethyl)furan (**5**).

A solution of 0.5 ml of crude **4** and 0.69 ml of triethylamine in 6.12 ml of dichloromethane was cooled in an ice bath, treated dropwise with 0.46 ml (4.9 mmoles) of ethyl chloroformate, and stirred at room temperature for 1 hour. After adding water, acidifying with hydrochloric acid and extracting with dichloromethane, the organic layer was washed with water, dried, and the solvent evaporated. Column chromatography using hexane:ethyl acetate 8:2, gave 0.3 g (23% from **3**) of compound **5** as an oil; ^1H nmr: δ 1.15 (t, Me), 2.55 (m, $ArCH_2$), 3.70 (t, CH_2N), 4.10 (q, CH_2O), 4.9 (br s, NH), 6.28 (m, H-3), 7.25 and 7.35 (2m, 2 x 1H, H-2 and H-5).

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.24; H, 7.22; N, 7.58.

6-Carbethoxy-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine (**6**).

A mixture of 0.3 g (1.3 mmoles) of **5**, 65 mg of paraformaldehyde and 16 mg of *para*-toluenesulfonic acid in 13 ml of toluene was refluxed 1 hour whereby water was removed by azeotropic distillation. The reaction mixture was cooled, washed successively with 5% sodium bicarbonate and water, dried and evaporated. Chromatography with hexane:ethyl acetate 9:1, gave 0.22 g (69%) of compound **6** as an oil; ms: m/z 195 (M^+), 166 (M^+ -C_2H_5), 150 (M^+ - OC_2H_5), 122 (M^+ - $COOC_2H_5$); ^1H nmr: δ 1.32 ppm (t, Me), 2.52 (m, CH_2-4, decoupled by irradiation of CH_2-7), 3.73 (t, CH_2-5), 4.18 (q, CH_2O), 4.50 (m, CH_2-7, decoupled by irradiation of CH-2), 6.25 (m, H-3), 7.26 (m, H-2).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.73; H, 6.79; N, 7.31.

6-Carbethoxy-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-2-carboxaldehyde (**7**).

The Vilsmeier reagent, which was prepared by adding 0.32 ml (3.5 mmoles) of phosphorus oxychloride to 0.27 ml of ice-cooled dimethylformamide (3.5 mmoles) and kept 20 minutes at 0°, was added to 0.68 g (3.5 mmoles) of **6** in 0.5 ml of dimethylformamide, and the temperature was kept below 20°. The mixture was stirred 1 hour at 0°, and 1 hour at room temperature, then poured into 3 ml of iced water. The resulting mixture was neutralized with 1 g of sodium carbonate, left overnight, and extracted with ether. The organic layer was evporated, and chromatographed with hexane:ethyl acetate 7:3, to give 240 mg (68%) of **7**, mp 88-90°; ^1H nmr: δ 1.32 (q, Me), 2.65 (m, CH_2-4), 3.83 (t, CH_2-5), 4.25 (q, CH_2O), 4.60 (broad s, CH_2-7), 7.23 (H-3), 9.61 (CHO).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.29; H, 5.94; N, 6.25.

6-Methyl-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine-2-methanol (**8**).

A solution of **7** (0.3 g, 1.26 mmoles) in 3 ml of tetrahydrofuran was added dropwise to an ice-cooled suspension of 65 mg of lithium aluminum hydride in 3 ml of tetrahydrofuran. The mix-

ture was refluxed for a half hour and then cooled. After addition of 40% aqueous ammonium chloride and extraction with ethyl acetate, the organic layer was dried and evaporated to give 120 mg (58%) of **8**, mp 77-78°; ^{1}H nmr: δ 2.40 (s, N-CH_3), 2.4-2.6 (4H), 3.4 (m, CH_2-7), 4.4 (s, CH_2OH), 6.05 (H-3).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.46; H, 7.92; N, 8.34.

Methyl 3,4-Bis(methylaminomethyl)furan-2-carboxylate (**12a**).

Into a solution of 0.5 g (1.87 mmoles) of **9** in 55 ml of acetonitrile, an excess of gaseous methylamine was bubbled, and the mixture left 2 hours at room temperature. Evaporation of the solvent followed by addition of dichloromethane gave a creamy solid (260 mg). The solid was dissolved in water, treated with sodium hydroxide to *p*H 9, and extracted with dichloromethane to give 170 mg of **12a** as an oil; ^{1}H nmr: δ 2.40 and 2.44 (s of 3H each, Me), 3.60 (s, 2H), 3.77 (s, 2H), 3.87 (s, OMe), 7.15 (H-5).

Methyl 5-Methylethylfuro[2,3-*c*]pyrrolidine-2-carboxylate (**10c**) and Methyl 3,4-Bis(methylethylaminomethyl)furan-2-carboxylate (**12b**).

A solution of 0.5 g (1.87 mmoles) of **9** and 0.48 ml (5.6 mmoles) of isopropylamine in 56 ml of acetonitrile was stirred 5 hours at room temperature. After evaporation of the solvent and dissolving the residue in dichloromethane, the solution was poured into aqueous 5% sodium bicarbonate, extracted with dichloromethane and chromatographed with dichloromethane:methanol, 97:3 to give 220 mg of **10c**, mp 72-74°; ^{1}H nmr: δ 1.15 ppm (d, Me_2, J = 6), 2.8-3.1 (m, CH), 3.75-3.95 (4H), 3.91 (OMe), 7.07 (H-3).

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.85; H, 7.31; N, 6.41.

Chromatographic separation of the above reaction gave, in addition to **10c**, 400 mg of methyl 3,4-bis(methylethylaminomethyl)-furan-2-carboxylate (**12b**) as an oil, ^{1}H nmr: δ 1.47 (d, 2Me, J = 6), 1.52 (d, 2Me J = 6), 3.4-3.6 (m, 2CH), 3.90 (OMe), 4.32 (s, 2H), 4.51 (s, 2H), 7.45 (H-5).

5-Methylethylfuro[2,3-*c*]pyrrolidine-2-methanol (**11c**).

A solution of 0.84 g of **10c** in 4.7 ml of dry tetrahydrofuran was added dropwise to a suspension of 0.2 g of lithium aluminum hydride in 10 ml of tetrahydrofuran, and the mixture was refluxed for 2 hours. After cooling and adding ice, the mixture was treated with 1*N* sodium hydroxide, extracted with ethyl acetate and chromatographed with dichloromethane:methanol 95:5 to give 0.55 g of **11c**, mp 64-65°; ^{1}H nmr: δ 1.15 (d, 3H, Me J = 6), 2.90 (q, CH), 3.7-3.9 (4H), 4.52 (CH_2OH), 6.16 (H-3).

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.01; H, 8.41; N, 7.48.

3-*N*-Ethoxycarbonylaminomethylfuran (**15**).

A mixture of 7 g (0.07 moles) of 3-furancarboxaldehyde, 4.6 g (0.07 mole) of sodium cyanoborohydride and 54 g (0.52 mole) of ammonium acetate in 200 ml of methanol was stirred at room temperature for 2 days. After evaporation, the residue was taken up in ether and extracted with dilute hydrochloric acid. the aqueous layer was treated with 10% aqueous potassium hydroxide, saturated with sodium chloride, and extracted with ether to give a crude product, which was used for the following step without any further purification.

An ice-cooled solution of 4.5 g of the crude product and 3.7 ml of triethylamine in 25 ml of dichloromethane was added dropwise to 5 ml of ethyl chloroformate, then stirred for 1 hour at room temperature. Water was then added followed by hydrochloric acid, and the aqueous layer was extracted with dichloromethane. The combined organic layers were evaporated and chromatographed with hexane:ethyl acetate, 9:1 to give 1.1 g of **15** as an oil; ^{1}H nmr: δ 1.29 (t, Me), 4.18 (q, CH_2O), 4.22 (s, Ar-CH_2), 6.29 (H-4), 7.25-7.40 (H-2 + H-5).

3-(*N*-hydroxymethyl-*N*-ethoxycarbonyl)aminomethylfuran (**17**).

A mixture of 450 mg of **15**, 0.15 ml of 40% formaldehyde, 1 drop of 10% sodium hydroxide and 5 ml of methanol was stirred 3 hours at room temperature and then evaporated, the residue was taken up with water and ethyl acetate, and the extract chromatographed with hexane:ethyl acetate 7:3, to give 310 mg of compound **17** as an oil; ^{1}H nmr δ 1.26 (t, Me), 4.20 (q, CH_2O), 4.38 (Ar-CH_2), 4.79 (CH_2OH), 6.35 (H-4), 7.37 (H-2 and H-5). Compound **17** was too unstable to be purified sufficiently for elemental analysis.

5-Ethoxycarbonylfuro[2,3-*c*]pyrrolidine (**18**).

A mixture of 720 mg of **17**, 3.6 ml of 90% formic acid, and 15 ml of cyclohexane was stirred 10 minutes at room temperature, then diluted with water, neutralized with sodium bicarbonate and extracted with ethyl acetate. The extract was chromatographed with hexane:ethyl acetate 6:4, to give 125 mg (20%) of compound **18**, mp 182-184° (from ethyl acetate); nmr: δ 1.32 (t, Me), 4.10 (s, 2H), 4.26 (q, CH_2O), 4.31 (s, 2H), 6.28 (H-3), 7.40 (H-2).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.54; H, 6.18; N, 7.68.

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