Chemistry

Corresponding Member of the Academy of Sciences of the USSR A. P. Terent' ev, R. A. Gracheva, and L. M. Volkova

1961

SovietRxiv

Abstract

Full Text

Chemistry

Corresponding Member of the Academy of Sciences of the USSR A. P. Terent' ev, R. A. Gracheva, and L. M. Volkova

SYNTHESIS OF SUBSTITUTED PYRROLIDINECARBOXYLIC ACIDS THROUGH FURAN DERIVATIVES

α-Pyrrolidinecarboxylic acid (proline) is one of the principal amino acids that form protein molecules. To study its biological role, it is very important to be able to replace proline by its homologues or analogues. We have developed a general method for the synthesis of various pyrrolidinecarboxylic acids by oxidation of the benzoyl derivatives of the corresponding furylpyrrolidines. The latter are obtained by stepwise synthesis from furfural or acetylfuran. By this method, if desired, a labeled carbon atom can be introduced into any position of the pyrrolidine ring.

General scheme for the synthesis of pyrrolidinecarboxylic acids:

$$
\begin{gathered}
\mathrm{R{-}C(=O){-}CH{=}CH{-}R'} \quad (I)\\
\xrightarrow{\mathrm{HCN}} \qquad \mathrm{R{-}C(=O){-}CH_2{-}CH(CN){-}R'} \quad (II)\\
\xrightarrow{\mathrm{CH_3NO_2}} \mathrm{R{-}C(=O){-}CH_2{-}CH(CH_2NO_2){-}R'} \quad (III)\\
(II) \xrightarrow[\mathrm{CH_3COOH}]{\mathrm{Zn}} (\mathrm{IV}) \qquad (II) \xrightarrow{\mathrm{H_2}} (\mathrm{IV})\\
(\mathrm{IV}) \xrightarrow{\mathrm{LiAlH_4}} (\mathrm{V}) \longrightarrow \text{N-benzoyl derivative}\\
\xrightarrow{\mathrm{KMnO_4}} \left\{\begin{array}{ll} \text{HOOC-pyrrolidine derivative} & (VIa),\\ \text{pyrrolidine-COOH derivative} & (VIb). \end{array}\right.
\end{gathered}
$$

R or R$'$ = C_4H_3O, is converted by oxidation into carboxyl. VIa, b (R = R$'$ = C_6H_5).

By reductive cyclization over Raney nickel, β-ketonitriles are converted into furylpyrrolines. The latter, on reduction with lithium aluminum hydride, give furylpyrrolidines. By benzoylation of the furylpyrrolidines and oxidation of their benzoyl derivatives, we obtained 1-benzoylpyrrolidinecarboxylic acids.

In one of our works we described the synthesis of racemic proline (VIa, where R$'$ = H) (^{1}). The required nitrile was obtained by aminomethylation of acetylfuran, followed by replacement of the dimethylamino group by nitrile (^{2}):

$$\text{furyl}-\text{CO}-\text{CH}_3 \longrightarrow \text{furyl}-\text{CO}-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2\cdot\text{HCl} \longrightarrow \text{furyl}-\text{CO}-\text{CH}_2\text{CH}_2\text{CN}$$

Furoylpropionitrile was subjected to reductive cyclization over Raney nickel in ethyl alcohol at room temperature, and 2-furylpyrroline was obtained in 87% yield (^{3}). The latter is reduced in 85% yield by lithium aluminum hydride to 2-furylpyrrolidine. After oxidation of the benzoyl derivative with potassium permanganate and removal of the benzoyl protecting group, we obtained proline. The overall yield of the last two stages is 61.7%.

To obtain other substituted pyrrolidinecarboxylic acids, the above-described route to β-ketonitriles proved unsuitable—the Mannich reaction, as applied to ketones of the furan series (except acetylfuran), proceeds in very low yields. A simpler and more convenient synthesis of the required β-ketonitriles of the furan series is by addition of hydrocyanic acid to α,β-unsaturated ketones—furan analogs of chalcone:

$$\underset{\text{(I)}}{\text{RCOCH}{=}\text{CHR}'} \xrightarrow{\text{HCN}} \underset{\text{(II)}}{\text{R}-\text{CO}-\text{CH}_2-\text{CH}(\text{CN})-\text{R}'}$$

As a source of hydrocyanic acid we used readily available acetone cyanohydrin in the presence of soda. In addition to hydrocyanic acid, we also added nitromethane to furan chalcones. The nitro ketones obtained gave, on reduction with zinc in acetic acid, the same substituted pyrrolines:

$$\underset{\text{(I)}}{\text{RCOCH}{=}\text{CHR}'} \xrightarrow{\text{CH}_3\text{NO}_2} \underset{\text{(III)}}{\text{RCOCH}_2-\text{CH}(\text{CH}_2\text{NO}_2)-\text{R}'}$$

In the present work we synthesized, in the form of benzoyl derivatives, the following two pyrrolidinecarboxylic acids.

4-Phenylproline (VIa; $R' = \text{C}_6\text{H}_5$). From benzylideneacetylfuran, through the β-ketonitrile (IIa) and the nitro ketone (IIIa), 2-furyl-4-phenylpyrroline was obtained, which, according to the scheme described above, was converted into 1-benzoyl-4-phenylproline.

5-Phenylpyrrolidine-3-carboxylic acid (VIb, $R = \text{C}_6\text{H}_5$). By addition of hydrocyanic acid and nitromethane to furfurylideneacetophenone, the corresponding β-ketonitrile (IIb) and nitro ketone (IIIb) were obtained, which, according to the scheme described above, were converted into 1-benzoyl-5-phenylpyrrolidine-3-carboxylic acid.

The method presented can be applied to the synthesis of other substituted prolines and its structural analogs.

Experimental Part

Furan Chalcones (I)

Benzylideneacetofuran (Ia). To a mixture of 31.8 g (0.3 mole) of benzaldehyde, 30 ml of alcohol, and 40 ml of 12% NaOH solution at −15°, 16.5 g (0.15 mole) of acetylfuran was added dropwise with stirring. After stirring for half an hour, the precipitated solid was filtered off and washed with a small amount of alcohol. 14 g of Ia was obtained, yield 72%, m.p. 87-88°. Literature data: m.p. 87-88° (4).

Furfurylideneacetophenone (Ib). Similarly, from 82.5 g (0.86 mole) of freshly distilled furfural and 52 g (0.43 mole) of acetophenone in the presence of 130 ml of 12% NaOH solution, 55 g of Ib was obtained, yield 70%, b.p. 174° (6 mm). Literature data: b.p. 181-183° (9 mm) (5).

Nitriles (II)

To a solution of the furan chalcone in methyl alcohol, an excess of acetone cyanohydrin and 10% soda solution were added. The mixture was heated on a water bath for 4 hours, then boiled with activated charcoal. The filtrate was cooled; the precipitate was filtered off and washed with a small amount of alcohol.

2-Phenyl-3-furoylpropionitrile (IIa). From 13.7 g (0.07 mole) of Ia, 21.3 g (0.25 mole) of acetone cyanohydrin, and 20 ml of 10% soda solution, 11 g of IIa was obtained, yield 69%, m.p. 89-90° (from ethyl alcohol).

Found, %: C 74.67; 74.31; H 5.09; 5.06
$C_{14}H_{11}O_2N$. Calculated, %: C 74.65; H 4.92

2-Furyl-3-benzoylpropionitrile (IIb). Analogously to IIa, from 13.7 g (0.07 mole) of Ib, 21.25 g (0.25 mole) of acetone cyanohydrin, and 20 ml of 10% sodium carbonate solution, 13 g of IIb was obtained, yield 81.4%, m.p. 107.5-108.5° (from ethyl alcohol).

$$C_{14}H_{11}O_2N.$$

Found, %: C 74.33; 74.43; H 5.05; 5.12
Calculated, %: C 74.65; H 4.92

Nitro ketones (III)

To a solution, cooled to −10°, of 0.82 g-atom of sodium in 30 ml of absolute methyl alcohol, 0.12 mole of nitromethane was slowly added with stirring. The resulting suspension was poured at 40-50° into a well-stirred solution of 0.03 mole of I in 30 ml of absolute methyl alcohol. Heating was continued until the precipitate had completely disappeared, after which the reaction mixture was rapidly cooled to −15° and 10 ml of glacial acetic acid was added dropwise, and after 20 min, 100 ml of water. The precipitated solid was filtered off, washed with water and ethyl alcohol, and dried.

γ-Nitro-β-phenylbutyrofuran (IIIa). From 6 g (0.03 mole) of Ia, 6.8 g (0.12 mole) of nitromethane, and 1.9 g of sodium, 7 g of IIIa was obtained, yield 95%, m.p. 90-91° (from ethyl alcohol).

$$C_{14}H_{13}O_4N.$$

Found, %: C 64.57; 64.41; H 5.53; 5.34
Calculated, %: C 64.79; H 5.04

γ-Nitro-β-furylbutyrophenone (IIIb). Analogously to IIIa, from 35 g (0.18 mole) of Ib, 40 g (0.72 mole) of nitromethane, and 11 g of sodium, 35 g of IIIb was obtained, yield 80%, m.p. 49-50° (from methyl alcohol). Literature data: m.p. 49.5-50° (^{6}).

Pyrrolines (IV)

1) A suspension of 0.044 mole of ketonitrile (II) in 70 ml of 95% ethyl alcohol was hydrogenated in the presence of 2 g of Raney nickel. After uptake of 0.09 mole of hydrogen, the hydrogenation was stopped, the catalyst was filtered off and washed with 10 ml of ethyl alcohol. The solvent was distilled off, and the residue was distilled in vacuo.

2) To a solution of 0.05 mole of nitro ketone III in 150 ml of glacial acetic acid, with stirring over 30 min at 55°, 50 g of zinc dust was added. The mixture was kept for 15 min at 60°, cooled, the precipitate was filtered off and washed twice with acetic acid. The filtrate was made strongly alkaline and IV was extracted with benzene. After distillation of the benzene, the oily substance was distilled in vacuo.

2-Furyl-4-phenylpyrroline (IVa). 1) By hydrogenation of 10 g (0.044 mole) of IIa, 7 g of IVa was obtained, yield 75%, b.p. 144-145° (2 mm), n_D^{20} 1.5870, d_4^{20} 1.1337, MR_D 62.60, calculated 62.69. 2) From 13.5 g (0.052 mole) of IIIa, by reduction with zinc in acetic acid, 4 g of IVa was obtained, yield 53%, b.p. 142-143° (4 mm), n_D^{20} 1.5869, d_4^{20} 1.1335, MR_D 62.58, calculated 62.69.

3-Furyl-5-phenylpyrroline (IVb). 1) From 5 g (0.22 mole) of IIb, after absorption of 0.990 l (0.044 mole) of hydrogen, 4 g of IVb was obtained, yield 86%, b.p. 144-146° (2 mm), n_D^{20} 1.5657, d_4^{20} 1.1140, MR_D 62.28, calculated 62.69. 2) By reduction of 15 g (0.05 mole) of IIIb with zinc dust in acetic acid, 5.5 g of IVb was obtained, yield 54%, b.p. 154° (4 mm), n_D^{20} 1.5659, d_4^{20} 1.1138, MR_D 62.31, calculated 62.69.

Pyrrolidines (V)

To a solution, cooled to −10°, of 0.05 mole of lithium aluminum hydride in 25 ml of absolute ether, a solution of 0.025 mole of IV in 30 ml of absolute ether was added dropwise with stirring. Cooling was removed, stirring was continued for another 30 min, and the reaction mixture was heated under reflux on

in a water bath for 3 hours. The excess lithium aluminum hydride was decomposed with a saturated aqueous solution of potash. The ether layer was separated and dried over potash. The residue after removal of the ether was distilled in vacuo.

2-Furyl-4-phenylpyrrolidine (Va). Reduction of 5.5 g (0.026 mole) of IVa with lithium aluminum hydride (2 g (0.052 mole)) gave 3.75 g of Va, yield 68%, b.p. 149–150°, n_D^{20}1.5650, d_4^{20}1.1071, MR_D 62.74, calculated 63.16.

Benzoyl derivative, yield 90%, m.p. 103–104° (from petroleum ether).

Found, %: C 78.91; 79.08; H 6.29; 6.11
$C_{21}H_{19}O_2N$. Calculated, %: C 79.47; H 6.03

3-Furyl-5-phenylpyrrolidine (Vb). From 5.8 g (0.027 mole) of IVb, reduction with lithium aluminum hydride (2.2 g (0.054 mole)) gave 4.75 g of Vb, yield 82%, b.p. 170° (2 mm), n_D^{20}1.5651, d_4^{20}1.0720, MR_D 62.55, calculated 63.16.

Found, %: C 78.16; 78.26; H 7.11; 7.05; N 6.83
$C_{14}H_{15}ON$. Calculated, %: C 78.74; H 7.09; N 6.56

Benzoyl derivative, yield 81%, m.p. 101–102° (from petroleum ether).

Found, %: C 79.08; 79.25; H 6.28; 6.25; N 4.40; 4.39
$C_{21}H_{19}O_2N$. Calculated, %: C 79.47; H 6.03; N 4.43

Benzoyl derivatives of pyrrolidinecarboxylic acids (VI). To a solution of 0.003 mole of the benzoyl derivative of pyrrolidine in 10 ml of acetone, 2–3 drops of 20% KOH solution were added. The mixture was cooled to 15° and, with stirring, a solution of 0.024 mole of potassium permanganate in 150 ml of water was gradually added. After decolorization, the precipitated manganese dioxide was filtered off and washed with hot water. The combined filtrates were evaporated to a volume of 20 ml, extracted twice with ether, and acidified with conc. HCl while cooling. The precipitated benzoyl derivative of pyrrolidinecarboxylic acid was filtered off, dried, and recrystallized from water.

1-Benzoyl-4-phenylpyrrolidine-2-carboxylic acid (VIa), yield 62%, m.p. 151–152° with decomposition.

Found, %: C 71.38; 71.45; H 6.03; 5.95
$2C_{18}H_{17}O_3N \cdot H_2O$. Calculated, %: C 71.05; H 5.96

1-Benzoyl-5-phenylpyrrolidine-3-carboxylic acid (VIb), yield 55%, m.p. 156–157°.

Found, %: C 72.80; 72.91; H 6.02; 6.11
$C_{18}H_{17}O_3N$. Calculated, %: C 73.20; H 5.76

Moscow State University
named after M. V. Lomonosov

Received
22 IV 1961

REFERENCES

1. A. P. Terent' ev, R. A. Gracheva, First All-Union Interuniversity Conference on the Chemistry of Furan Compounds, 1959, Saratov, 1959, p. 35.
2. E. Knott, J. Chem. Soc., 1947, 1180.
3. E. Knott, J. Chem. Soc., 1948, 186.
4. C. Weygand, F. Strobel, Ber., 68, 1839 (1935).
5. F. Semmler, Ber., 42, 2355 (1909).
6. N. Drake, H. Gilbert, J. Am. Chem. Soc., 52, 4965 (1930).

Note: Figure translations are in progress. See original paper for figures.