Tetrahedron Letters No.23, pp. 1847-1852, 1965. **Pergamon Press Ltd.**
Printed in Great Britain.

A NOVEL PROCEDURE FOR THE SYNTHESIS OF 2,3-DIHYDROFURANS

M. A. Gianturco*, P. Friedel and V. Flanagan

Fundamental Research Dept. of The Coca-Cola Company
Linden, New Jersey, USA

(Received 19 March 1965; in revised form 12 April 1965)

2,3-Dihydrofurans are potentially useful intermediates for the synthesis of a variety of substances, among which are γ-hydroxyaldehydes and γ-hydroxyketones, γ-lactones, furans, cyclopropyl aldehydes and ketones, and hydroxy-aminoacids**. The usefulness of these compounds for the production of polymers, pharmaceutical products and pesticides has also been indicated in the patent literature (5). However, no direct synthetic method of general applicability seems to be available for 2,3-dihydrofurans. Indeed, compounds of this type have generally been prepared from not too accessible γ-hydroxycarbonylic substances (6) - or potential γ-hydroxycarbonylic substances, such as γ-acetylenic alcohols (7) - and by base-catalyzed isomerization of 2,5-dihydrofurans (8,9).

The 2,5-isomers have, in turn, been obtained from the cis-olefinic diols that result from the stereospecific hydrogenation of 1,4-acetylenic

---

*To whom inquiries concerning this paper should be addressed.

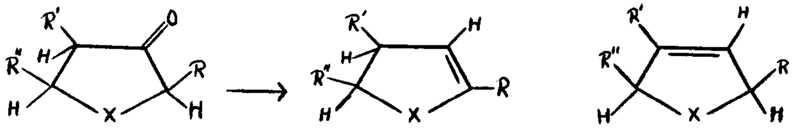
**The conversions of dihydrofurans to γ-lactones and to furans will be described in a forthcoming communication from this laboratory. Rearrangements of 2,3-dihydrofurans to cyclopropane derivatives have been observed (1,2,3). The syntheses of DL-ornithine, DL-proline and DL-α-amino-δ-hydroxyvaleric acid from 2,3-dihydrofurans have been described (4).

diols (10,11). Some simple 2,3-dihydrofurans have also been prepared by catalytic dehydrogenation-dehydration of butane-1,4-diols (12) or by dehydrochlorination of chlorotetrahydrofurans (13).

We wish to report that the Bamford-Stevens reaction (14,15), when applied to the p-toluensulphonylhydrazones of the now easily available tetrahydrofuran-3-ones (16), affords a very convenient synthetic route to 2,3-dihydrofurans. To effect this conversion, the appropriate tosylhydrazone (0.03 moles) was dissolved in 60 ml ethylene glycol to which sodium (0.06 gram-atoms) had been previously added and the mixture was quickly heated to 140-170°. The dihydrofurans, generated in good yields in the course of this rapid reaction, were directly distilled from the mixture in a stream of nitrogen. Even though the prompt removal of the volatile products should not favor their equilibration, 2,3-dihydrofurans were the predominant products in all the cases investigated.

The reaction proceeded with good yields also when applied to the tosylhydrazone of tetrahydrothiophen-3-one.

In this manner, the following transformations could be easily effected: (a) Tetrahydrofuran-3-one (Ia) ⟶ 2,3-dihydrofuran (IIa) and 2,5-dihydrofuran (IIIa); (b) 2-Methyltetrahydrofuran-4-one (Ib) ⟶ 2-methyl-2,3-dihydrofuran (IIb) and 2-methyl-2,5-dihydrofuran (IIIb); (c) 2-Methyltetrahydrofuran-3-one (Ic) ⟶ 2-Methyl-4,5-dihydrofuran (IIc) and 2-methyl-2,5-dihydrofuran (IIIc=IIIb); (d) 3-Methyltetrahydrofuran-4-one (Id) ⟶ 3-methyl-2,3-dihydrofuran (IId) and 3-methyl-2,5-dihydrofuran (IIId); (e) Tetrahydrothiophen-3-one (Ie) ⟶ 2,3-dihydrothiophene (IIe) and 2,5-dihydrothiophene (IIIe). The yields of isolated products and the ratios of the isomers are indicated in Table I.



I II III

a: X=O; R=R'=R''=H
b: X=O; R=R'=H; R''=CH_3
c: X=O; R=CH_3; R'=R''=H
d: X=O; R=R''=H; R'=CH_3
e: X=S; R=R'=R''=H

TABLE I. REACTIONS OF TOSYLHYDRAZONES OF Ia-Ie.
WITH SODIUM IN ETHYLENE GLYCOL

Products	ex Tosylhydrazone of	Isolated Yields*	II: III**
IIa & IIIa	Ia	80%	94:6
IIb & IIIb	Ib	73%	96:4
IIc & IIIc	Ic	58%	89:11
IId & IIId	Id	73%	67:33
IIe & IIIe	Ie	66%	65:35

Preparation of Tosylhydrazones. The derivatives of Ia-Ie (16) were obtained by refluxing for 1-1/2 to 2 hours a solution of ketone (0.02M) and p-toluensulphonylhydrazine (0.02M)⊛ in ethanol (20 ml). The tosylhydrazones separated on cooling in yields exceeding 70% and no attempts were made to obtain further crops of crystals from the mother liquors. The materials - as obtained - were suitable for the

---

*Calculated on the basis of tosylhydrazone employed.

**The percent areas in the vapor-phase chromatograms were taken to indicate percent composition.

⊛Available from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin, U.S.A.

Bamford-Stevens reaction. Samples recrystallized for analysis (EtOH) had the following m.p.s. From Ia. m.p. 147-148°. Found: N, 10.94. Calcd. for $C_{11}H_{14}N_2O_3S$: N, 11.02%. From Ib. m.p. 141-142°. Found: N, 10.41. - From Ic. m.p. 131-132°. Found: N, 10,47. - From Id. m.p. 139-140°. Found: N, 10.36. Calcd. for $C_{12}H_{16}N_2O_3S$. N, 10.44%. - From Ie. m.p. 161-162°. Found: N, 10.34. Calcd. for $C_{11}H_{14}N_2O_2S_2$: N, 10.36%.

Separation and Characterization of Dihydrofurans and Dihydrothiophenes. The various mixtures of compounds of type II and III were separated into their components by VPC, under the following conditions: 6mx0.25" column, packed with 15% phenylsilicone 550 on 60-80 mesh Diatoport S, 75°, 55cc He/min. The retention times, expressed in minutes, were as follows: IIa, 8.0; IIIa, 11.6 - IIb, 10.8; IIIb, 14.1 - IIc, 16.4; IIIc (=IIIb), 14.1. - IId, 10.9; IIId, 25.0. - IIe, 39.5; IIIe, 55.0.

Compounds IIc and IIIa were identified by comparison with commercial samples. The other dihydrocompounds were identified and characterized by their IR and mass spectra (easily identifiable parent peaks were present in all cases). Some NMR spectra were also recorded. IIa and IIb were characterized also by reaction with alcoholic 2,4-dinitrophenylhydrazine, which yielded derivatives analyzing correctly for the 2,4-dinitrophenylhydrazones of the appropriate γ-hydroxyaldehydes. The pertinent spectral data of the dihydrofurans and dihydrothiophens isolated in the course of this work are given below.*

IIa. IR: 3.22(w), 6.17(s), 6.26(sh), 8.78(s), 9.45(s)μ. Mass spectrum: m/e = 41 (100%), 39 (94%), 70 (molec. ion, 68%), 69 (42%), 42 (40%). NMR: Two identical quartets at 3.80 and 5.17τ and two triplets at 5.77 and 7.47τ (intensity 1:1:2:2). 2,4-Dinitrophenylhydrazone

---

*Only the most characteristic absorptions in the IR spectra (CCl_4) and the five most intense peaks in the mass spectra are recorded. The NMR spectra were determined in CCl_4 at 60 MC, tetramethylsilane as internal standard.

(of γ-hydroxybutanal), m.p. 121-122° [lit. (8), 120°]. Found: N,20.84. Calcd. for $C_{10}H_{12}N_4O_5$: N,20.89%.

IIb. IR: 3.22(w), 6.17(s), 6.25(sh), 8.74(s), 9.45(s)µ. Mass spectrum: m/e = 55(100%), 39(71%), 84(molec. ion. 69%), 41(66%), 27(64%), NMR: Two quartets at 3.88 and 5.28τ; two multiplets at 5.4-5.8 and 7.0-8.0τ and a doublet at 8.7τ (intensity 1:1:1:2:3). 2,4-Dinitrophenylhydrazone (of γ-hydroxypentanal), m.p. 133-134°. Found: N,19.92. Calcd. for $C_{11}H_{14}N_4O_5$: N,19.85%.

IIc. IR: 5.92(s), 8.02(s), 8.42(s), 9.82(s), 9.92(s)µ*.

IId. IR: 3.22(w), 6.18(s), 6.23(sh), 8.76(s), 9.93(s)µ. Mass spectrum: m/e = 69(100%), 41(69%), 39(57%), 84(molec. ion, 43%), 27(38%).

IIe. IR: 3.25(w), 6.27(s), 6.35(sh), 7.94(s), 10.0(s), 10.15(s), 10.98(s)µ. Mass spectrum: m/e = 85(100%), 86(molec. ion, 50%), 45(39%), 39(14%), 58(12%). NMR: Two multiplets centered at 3.92 and 4.50τ, and complex signal between 6.7 and 7.5τ (intensity 1:1:4).

IIIa. IR: 3.22(w), 9.20(s), 9.87(s), 10.17(s), 11.18(s)µ*.. Mass spectrum: m/e = 39(100%), 41(96%), 42(72%), 70(molec. ion, 59%), 29(36%).

IIIb+IIIc. IR: 3.23(w), 6.0(w), 9.0(s), 9.18(s), 9.38(s)µ. Mass spectrum: m/e = 28(100%), 43(74%), 69(57%), 39(40%), 41(38%), 84(molec. ion, 16%).

IIId. IR: 3.25(w), 5.97(m), 9.28(s), 10.27(s), 10.64(s), 11.12(s)µ. Mass spectrum: m/e = 41(100%), 39(90%), 69(82%), 27(50%), 29(45%), 84(molec. ion, 40%).

IIIe. IR: 3.25(w), 6.06(m), 8.13(s), 8.95(s), 10.46(s)µ. Mass spectrum: m/e = 85(100%), 86(molec. ion, 87%), 45(57%), 27(21%), 39(21%). NMR: Two singlets at 4.20 and 6.32τ (intensity 1:2).

---

*Available from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin, U.S.A. Purified by VPC.

REFERENCES

(1) H. Normant, Bull. soc. chim. France, (1951), C115.

(2) J. Wiemann, N. Thoai and F. Weisbuch, Compt. Rend. 256, 178(1963).

(3) C.L. Wilson, J. Amer. Chem. Soc. 69, 3002(1947).

(4) R. Gaudry, Can. J. Chem. 29, 544(1951).

(5) British Patent 846.192 and German Patent 1.064.957.

(6) J. Huet and J. Druex, Compt. Rend. 256, (18), 4570(1964).

(7) J. Colonge and R. Gelin, Bull. soc. chim. France, (1954), 799.

(8) R. Paul, M. Pluchaire and G. Collardeau, Bull. soc. chim. France, (1950), 668.

(9) J.C. Anderson, D.G. Lindsay and C.B. Reese, Tetrahedron, 20, 2091(1964).

(10) A. Valette, Ann. Chim. 12, 3, 664(1948).

(11) Yu. K. Yur ev, Ik, Korotbitsyna, R.D. Ben-Yakir, L.A. Savina and P.A. Akishin, Vestnik Moskov Univ., 6, No. 2, Ser. Fiz.-Mat. i Estesven. Nauk No. 1, 37(1951).

(12) P. Dimroth and R. Pasadach, Angew. Chem. 72, 866(1960).

(13) H. Normant, Chimie et Industrie, 63, No. 3, bis, 511(1950).

(14) W.R. Bamford and T.S. Stevens, J. Chem. Soc., 4735(1952).

(15) L. Caglioti and M. Magi, Tetrahedron, 19, 1127(1963) and Refs. therein.

(16) M. Gianturco, P. Friedel and A.S. Giammarino, Tetrahedron, 20, 1763(1964).