CHEMISTRY LETTERS, pp. 73-76, 1977. Published by the Chemical Society of Japan

A CONVENIENT METHOD FOR THE PREPARATION OF 3-SUBSTITUTED FURANS

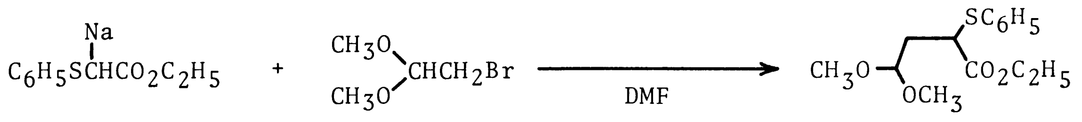
Hiroshi KOTAKE, Katsuhiko INOMATA, Shin-ichi AOYAMA, and Hideki KINOSHITA
Department of Chemistry, Faculty of Science, Kanazawa University, Kanazawa 920

It was found that ethyl 4,4-dimethoxy-2-phenylthiobutyrate is an useful reagent for the preparation of 3-substituted furans from alkyl halides. 3-Benzylfuran, 3-geranylfuran (nordendrolasin), and 3-octadecylfuran were prepared by the method in good yields.

In the preceding paper,$^{1)}$ it was reported that β-alkoxy-γ-bromoketones, prepared by the $TiCl_4$-promoted reaction of α-bromoacetals with silyl enol ethers, are readily converted to the corresponding furans on refluxing in toluene. It is known that a number of furan derivatives occurring in nature are 3-substituted furans$^{2)}$ such as perillene and dendrolasin, but we could not obtain 3-substituted furans in sufficient yields by the above method.

Although many methods for the preparation of furan derivatives were reported,$^{2-5)}$ there were only a few methods$^{5)}$ which could apply to the preparation of 3-substituted furans. In the present study, it was established that ethyl 4,4-dimethoxy-2-phenylthiobutyrate (III) is an useful reagent to prepare 3-substituted furans from alkyl halides as shown in the Scheme.

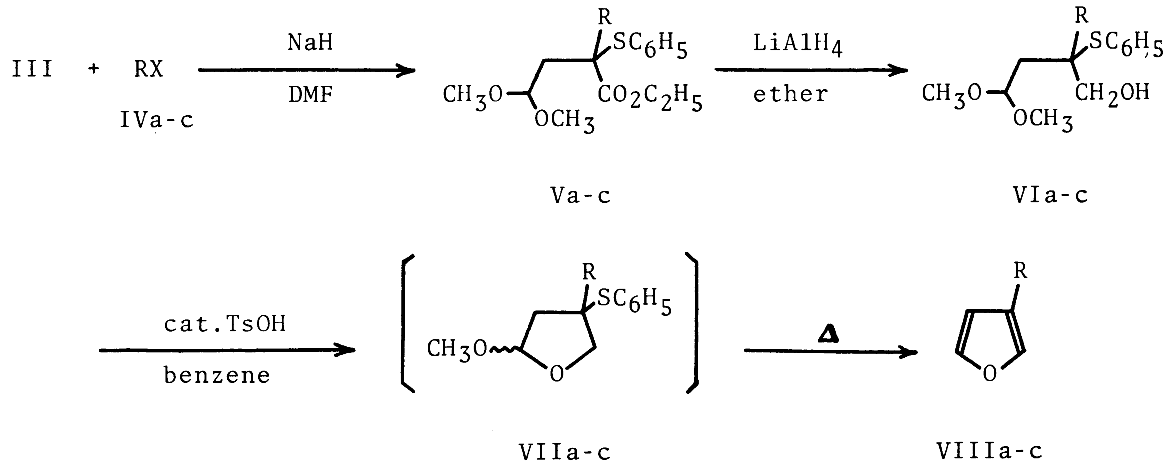
The starting material III was readily prepared by the reaction of sodium salt of ethyl phenylthioacetate (I) with α-bromoacetal (II) as follows: to a suspension of



I II III

sodium hydride[6] (1.60 g, 33 mmol) in DMF (20 ml) was added dropwise a DMF solution (10 ml) of ethyl phenylthioacetate (6.10g, 31 mmol) at room temperature under a nitrogen atmosphere. After 15 min, a solution of II (5.41 g, 32 mmol) in DMF (10 ml) was added to the solution at 60°C. The reaction mixture was then allowed to stand at 60°C for 3.5 hr. Precipitates were removed by filtration and the filtrate was concentrated on evaporation of the solvent under reduced pressure. The residue was treated with pH 7.2 buffer solution followed by extraction with ethyl acetate. The organic extract was dried over Na_2SO_4, concentrated, and distilled, giving 6.10 g (69%) of III: bp 138-141°C/1 mmHg.

Scheme



The following procedure is representative for the reaction of III with alkyl halide to synthesize 3-substituted furans. To a suspension of sodium hydride (60 mg, 1.25 mmol) in DMF (3 ml) was added dropwise a DMF solution (1 ml) of III (299 mg, 1.05 mmol) at 60°C under a nitrogen atmosphere. After 5 min, a solution of benzyl bromide (IVa, 180 mg, 1.06 mmol) in DMF (1 ml) was added to the solution at 60°C. The reaction mixture was then allowed to stand at 60°C for 3 hr and worked up exactly according to the above outlined procedure. The resulting residue was separated by preparative tlc to afford ethyl 2-benzyl-4,4-dimethoxy-2-phenylthiobutyrate (Va) in 82% (322 mg) yield.

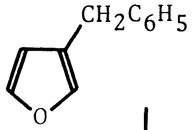
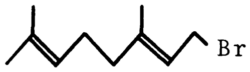
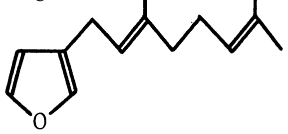
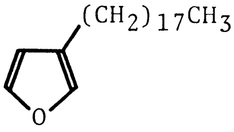
The ester Va (390 mg, 1.04 mmol) was then reduced with lithium aluminum hydride (38 mg, 1.00 mmol) in ether (7 ml) at room temperature for 30 min followed by treatment with conc. NaOH. An ethereal extract dried over Na_2SO_4 was evaporated and the residue was separated by preparative tlc to afford 2-benzyl-4,4-dimethoxy-2-phenylthiobutan-1-ol (VIa) in 98% (338 mg) yield.

Finally a benzene (11 ml) solution of the alcohol VIa (332 mg, 1 mmol) was refluxed in the presence of catalytic amount of p-toluenesulfonic acid for 2 hr. The reaction mixture was washed with 1N NaOH and dried over Na_2SO_4. After removal of the solvent, the expected 3-benzylfuran (VIIIa) was separated by preparative tlc in 91% (143 mg) yield. The product VIIIa showed a reddish purple color on Ehrlich reaction.[7)]

The cyclic intermediate (VIIa) was isolated from another experiment at lower temperature and confirmed by ir and pmr spectra.

By the similar procedure, 3-geranylfuran (VIIIb, nordendrolasin) and 3-octadecylfuran (VIIIc) were prepared by the reaction of III with geranyl bromide (IVb) and octadecyl iodide (IVc), respectively. The results are listed in the Table.

Table. The Synthesis of 3-Substituted Furans

RX		Isolated yield,[a)] %		
		Va-c	VIIIa-c[b)]	
IVa,	$C_6H_5CH_2Br$	82		89
IVb,		78		83
IVc,	$CH_3(CH_2)_{17}I$	82		83

a) All compounds exhibited ir and pmr spectral data[8)] in accordance with assigned structure.

b) Yield based on the corresponding esters Va-c. The alcohols VIb,c were not isolated.

REFERENCES

1) T. Mukaiyama, H. Ishihara, and K. Inomata, Chem. Lett., 1975, 527.

2) M. Kotake, Ed., "Dai yuki-Kagaku," Asakura, Vol. 14, Tokyo (1959), p. 1-37.

3) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, Inc., New York (1968), Chap. 4.

4) S. Coffey, Ed., "Rodd's Chemistry of Carbon Compounds," 2nd ed., Vol. IV A, Elsevier Scientific Publishing Co., Amsterdam (1973), Chap. 2.

5) J. ApSimon, Ed., "The Total Synthesis of Natural Products," Vol. 2, John Wiley and Sons, Inc., New York (1973), p. 159-165 and 227-233.

6) About 50% NaH in "Bayol 85" from Wako Pure Chem. Ind. Ltd..

7) To an alcohol solution (1 ml) of p-dimethylaminobenzaldehyde (50 mg) and a drop of sample was added a few drops of conc.HCl. The reddish purple coloration indicates the formation of furans.

8) Va: oil, ir 3040, 3010, 1718, 1595, 1575, 1235, 1182, 1115, 1070, 1040, 745, 740, 695, 685 cm^{-1}; pmr ($CDCl_3$) δ 1.17 (t, 3H), 2.14 (d, 2H), 3.27 (s, 2H), 3.31 (s, 3H), 3.37 (s, 3H), 4.03 (q, 2H), 4.88 (t, 1H), 7.32 (m, 10H).

Vb: oil, ir 3040, 1720, 1575, 1565, 1235, 1215, 1180, 1120, 1090, 1075, 1040, 745, 700, 685 cm^{-1}; pmr ($CDCl_3$) δ 1.17 (t, 3H), 1.57 (s, 6H), 1.66 (s, 3H), 2.04 (m, 6H), 2.41 (d, 2H), 3.17 (s, 6H), 4.00 (q, 2H), 4.60 (t, 1H), 5.04 (broad, 1H), 5.32 (t, 1H), 7.23 (m, 5H).

Vc: oil, ir 3040, 1725, 1580, 1460, 1250, 1145, 1020, 740, 681 cm^{-1}; pmr ($CDCl_3$) δ 1.17 (t, 3H), 1.22 (s, 37H), 2.03 (d, 2H), 3.21 (s, 6H), 4.01 (q, 2H), 4.67 (t, 1H), 7.23 (m, 5H).

VIIIa: oil, 3120, 3100, 3065, 3045, 3010, 1578, 1490, 1447, 1379, 1165, 1142, 1065, 1055, 1010, 868, 780, 755, 723, 700 cm^{-1}; pmr ($CDCl_3$) δ 3.61 (s, 2H), 6.08 (m, 1H), 7.05 (m, 1H), 7.07 (s, 5H), 7.16 (t, 1H).

VIIIb: oil, ir 3120, 1630, 1555, 1490, 1438, 1370, 1146, 1050, 1013, 863, 765, 710 cm^{-1}; pmr ($CDCl_3$) δ 1.62 (s, 3H), 1.67 (s, 6H), 2.08 (m, 4H), 3.17 (d, 2H), 5.25 (broad, 1H), 5.39 (t, 1H), 6.33 (m, 1H), 7.28 (m, 1H), 7.42 (t, 1H).

VIIIc: melts at near 35°C, ir 1555, 1492, 1460, 1153, 1055, 1019, 865, 767, 710 cm^{-1}; pmr (CCl_4) δ 1.28 (s, 35H), 2.46 (t, 2H), 6.40 (m, 1H), 7.39 (m, 1H), 7.52 (t, 1H).

(Received November 9, 1976)