Tetrahedron Letters,Vol.25,No.40,pp 4451-4454,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

FURANS IN SYNTHESIS 4.[1]

SILYL FURANS AS BUTENOLIDE EQUIVALENTS

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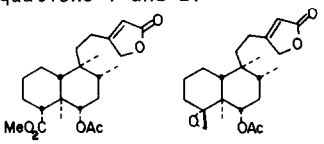
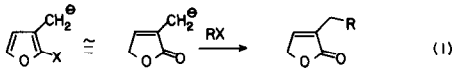
Summary: The preparation and utilization of butenolide anion equivalents 5 and 6 in alkylation sequences is described. Treatment with CH_3CO_3H unmasks a latent butenolide moiety providing a general route to 3- and 4-alkyl 2(5H)-furanones.

The butenolide moiety is present in numerous biologically active natural products, such as in the highly active neo-clerodanes ajugarins IV and V.[3,4] As part of a general program in furan chemistry, we were interested in developing substituted isoprenoid furyl synthons 1 and 3 as the operational equivalents of butenolide anions 2 and 4 in the alkylation sequences outlined in equations 1 and 2.

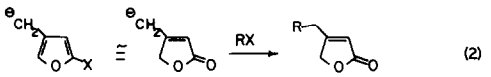


Ajugarin-IV Ajugarin-V



(1)

1 2



(2)

3 4

In principle, the direct oxidation of a 3-substituted furan would provide the corresponding butenolide;[5] however, regiochemical ambiguities render this approach questionable. A more suitable solution to this problem is the unraveling of an appropriate 2- and 5-substituted-3-alkyl furan. As has been demonstrated by Kuwajima,[6a] and recently employed by Schultz,[6b] Goldsmith and Liotta[6c] the trimethylsilyl group will serve to regio-specifically direct the introduction of oxygen (1 and 3, X=Me_3Si) providing the corresponding 3- or 4-alkyl 2(5H)-furanones (eqs. 1 and 2).[7,8]

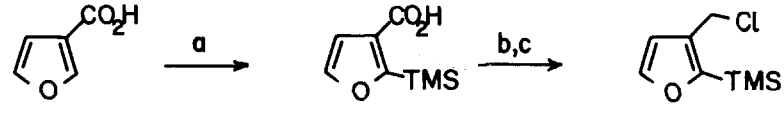
With this design concept in mind, the requisite 2- and 5-TMS-3-chloromethyl furans 5 and 6 were prepared as outlined in Schemes I-III. Regiospecific generation[8] and silylation of the dianion derived from 3-furoic acid provided the corresponding 2-trimethylsilyl--3-furoic acid (Scheme I, 92%).[8b] Reduction and chlorination[9] gave the desired chloromethyl furan 5 (77%).[10] The regioisomeric 5-TMS-3-chloromethyl furan 6 can be obtained as indicated in Scheme II. Treatment of furan-3-methanol with nBuLi followed by addition of φssφ afforded an 82% yield of a mixture (1:4) of furans 7 and 8. Furan 8, after purification (prep HPLC) and silylation,[11] was converted to the corresponding 2-φS-5-TMS-furan-3-methanol 9 (42% over 3 steps). Removal of the 2-φS-group was then effected with Raney nickel to give furan 10 (56%). Chlorination of 10[9] provides the target 5-TMS-3-chloro methyl furan 6[10] in 77% yield. Although this procedure is virtually identical to that reported by Goldsmith and Liotta,[6c] in our hands it provides lower yields and is more tedious than the alternative outlined in Scheme III. Direct bromination of 3-furoic acid (Scheme III) affords bromo-furoic acid 11 (60%).[12] Treatment of 11 with 2.2 eq. of nBuLi and TMSCl gave silyl acid 12 (63%), which led to furan-methanol 10 (81%) after reduction. Overall, the Scheme III approach provides 10 in 31% yield (3-steps) versus 16% (Scheme II).

With the required silyl-3-chloromethyl furans 5 and 6 in hand, the coupling-oxidation sequences were examined as outlined in equations 3 and 4. Furan 5 is smoothly converted to the Grignard reagent, treatment with nonyl iodide and Li_2CuCl_4[1,9b,c] gave 2-TMS-3-decylfuran 13 (82%).[10] Oxidation of 13, by the method of Kuwajima[6a] yielded a 1:1 mixture of α,β-unsaturated and β,γ-unsaturated lactones 14[10] and 15,[10] respectively (78%). In a similar fashion, furan 6 (eq. 4) was coupled, via the Grignard reagent, with nonyl-iodide to provide 16[10] (77%). Oxidation of 16[6a] afforded the corresponding 4-decyl-2(5H) furanone 17[10] in 91% isolated yield.

Other representative examples designed to examine the relative rate of furan vs. remote olefin oxidation as a function of the degree of alkene substitutions are presented in Table I. As is obvious from Table I, good to excellent yields of coupled silyl furans are realized in all cases; and if the alkene is less than trisubstituted, the major or exclusive oxidation product is the result of attack at the furyl residue.

These results, when combined with our earlier reports on the synthesis of 3-substituted furans,[1,9b] demonstrate the utility of silyl furans 5 and 6 as the operational equivalents of butenolide anions 2 and 4. The application of this methodology to the synthesis of bioactive natural products is currently under way.

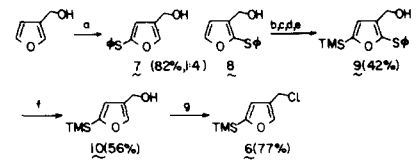
SCHEME I



92% 5 (62%)

a) i. LDA, THF, -78°; ii. TMSCl ; b) LAH, Et_2O; c) MsCl, LiCl, s-collidine, DMF

SCHEME II



7 (82%, I:4) 8 9 (42%)

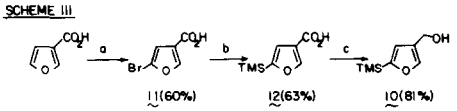
10 (56%) 6 (77%)

a) i. 2.2 eq nBuLi, TMEDA, 0°, ii. ΦSSΦ; b) prep. HPLC; c) tBuMe$_2$SiCl, DMF,  ,

d) i. nBuLi, Et$_2$O, 0-25°, ii. TMSCl, 0°, e) HOAc, THF, H$_2$O (1:3:1) 60°, 1h;

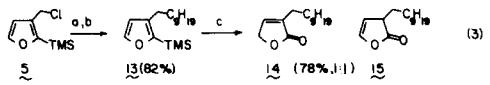
f) Raney-Nickel, EtOH, Δ; g) see Scheme I c

SCHEME III



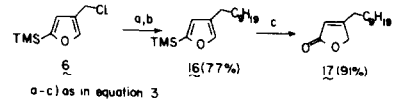
11 (60%) 12 (63%) 10 (81%)

a) pyr·HBr$_3$, HOAc; b) i. 2.2 eq nBuLi, Et$_2$O, -78°, 30 min; ii. TMSCl; c) LAH, Et$_2$O



5 13 (82%) 14 (78%, I:1) 15 (3)

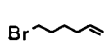
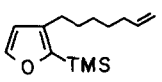
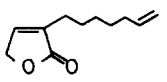
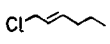
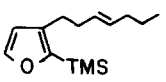
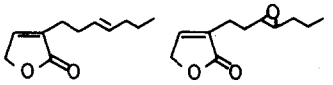
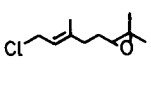
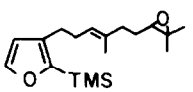
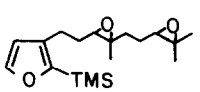
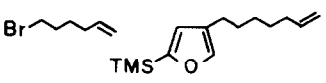
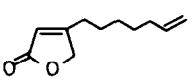
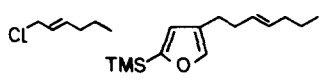
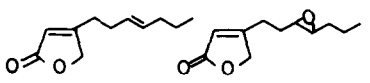
a) Mg, THF; b) nonyl-I, Li$_2$CuCl$_4$; c) CH$_3$CO$_3$H, NaOAc, CH$_2$Cl$_2$



6 16 (77%) 17 (91%) (4)

a-c) as in equation 3

Table I Alkylation and Oxidation of Silyl-Furans

Furan	RX	Product	Butenolide
5		 74%	 67%
5		 67%	 52% 36%
5		 93%	 93%
6		70%	 77%
6		60%	 51% 35%

Acknowledgement: We gratefully acknowledge support of this research by the Camille and Henry Dreyfus Foundation, the Research Corporation, the Petroleum Research Fund administered by the American Chemical Society and Michigan State University.

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1) For the previous report in this series, see: Tanis, S.P.; Herrinton, P.M., J. Org. Chem. 1983, 48, 4572.
2) Recipient of a Camille and Henry Dreyfus Grant for Young Faculty in Chemistry, 1980-84.
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10) All yields refer to isolated, purified products. Infrared, ^{1}H-NMR and mass spectra are fully consistent with the assigned structures. Following are IR, ^{1}H-NMR and mass spectral data for representative compounds:
5:(BP_8=75°);IR(neat):2960,1565,1450,1255,860CM^{-1};^{1}H-NMR(60MHzCDCl$_3$):δ=7.41(d,J=2H$_3$,1Hz), 6.35(d,J=2Hz,1H),4.50(S,2H),0.30(S,9H),EI-MS(70eV):188(M^+,91),173(65),153(base).
6:(BP_{10}=90°);IR(neat):2980,1600,1260,855cm^{-1};H-NMR(60MHz,CHCl$_3$):δ=7.55(S,1H),6.60(S,1H), 4.45(S,2H),0.25(S,9H);EI-MS(70eV):188(M^+,28),173(89),153(18).
13:IR(neat):2960,1580,1470,1400,1260,850CM^{-1};^{1}H-NMR(60MHz,CHCl$_3$):δ=7.45(d,J=2Hz,1H),6.20 (d,J=2Hz,1H),2.25(brt,J=6Hz,2H),1.35(brm,16H),0.90(m,3H),0.25(S,9H);EI-MS(70eV):280 (M^+,15.8),265(5),154(43).
14:IR(neat):2960,1760,1660CM^{-1};^{1}H-NMR(60MHz,CDCl$_3$):δ=7.20(M,1H),4.20(M,2H),2,40(brm,2H), 1.40(brm,16H),0.90(m,3H);EI-MS(70eV):224(M^+,15),195(2.5),179(5.3),98(base).
15:IR(neat):3350,2960,1790,1660CM^{-1};^{1}H-NMR(60MHz,CDCl$_3$):δ=6.80(brs,1H),6.10(brs,1H),5.55 (brm,1H),2.25(brm,2H),1.40(brm,16H),0.90(m,3H);EI-MS(70eV):224(M^+,27),195(9),179(2.5), 98(base).
16:IR(neat):2960,1450,1250,1075,840CM^{-1};^{1}H-NMR(60MHz,CDCl$_3$):δ=7.35(S,1H),6.45(S,1H),2.40 (t,J=6Hz,2H),1.40(brm,16H),0.90(m,3H),0.25(S,9H);EI-MS(70eV):280(M^+,3),265(2.2),154 (base).
17:IR(neat):2960,1785,1755,1650CM^{-1};^{1}H-NMR(60MHz,CDCl$_3$)δ=5.90(q,J=2Hz,1H),4.80(d,J=2Hz, 2H),2.50(m,2H),1.35(brm,16H),0.9(m,3H);EI-MS(70eV):224(M^+,0.2),195(0.4),164(2.8),98 (20),85(base).
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(Received in USA 27 April 1984)