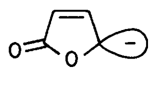
# Regioselective Alkylation of 2-Trimethylsiloxyfuran; Direct Access to 4-Substituted But-2-en-4-olides

**Charles W. Jefford, Adam W. Sledeski, and John Boukouvalas**

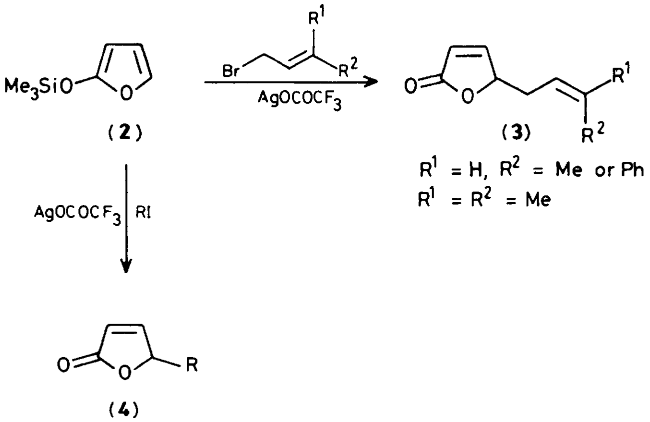
*Department of Organic Chemistry, University of Geneva, 1211 Geneva 4, Switzerland*

Primary iodides alkylate 2-trimethylsiloxyfuran in the presence of a molar excess of silver trifluoroacetate to give the 4-alkylbut-2-en-4-olides in 55—81% yield; as an illustration of the method, the cytotoxic marine sponge constituent, 4-(methoxycarbonylmethyl)but-2-en-4-olide was prepared in 79% yield in one step.

4-Substituted but-2-en-4-olides have attracted much interest on account of their diverse biological activities[1] and the utility of some of them as intermediates.[2] Although syntheses of butenolides abound,[3] methods that exploit the regioselective alkylation of an operational equivalent of the γ-anion of furan-2(5*H*)-one (**1**) are not common.[4] A promising reagent which behaves like (**1**), is 2-trimethylsiloxyfuran (**2**). We recently showed that 3-methyl and phenyl derivatives of prop-2-enyl bromide react with (**2**) in the presence of silver trifluoroacetate to give exclusively the least substituted 4-derivatives of but-2-en-4-olide (**3**) in high yield.[5] We now report that alkylation can be induced to proceed with the same regioselectivity with halides which are solvolytically inert. Such halides, in general, fail to react with silyl enol ethers and ketene silyl acetals on catalysis with Lewis acids.[6] Nevertheless, we believe that (**2**) should be significantly more nucleophilic than the usual enol ethers[7] and therefore susceptible to alkylation by primary halides, especially if activated by a silver salt.[5]



(**1**)



$R^1$ = H, $R^2$ = Me or Ph
$R^1$ = $R^2$ = Me

**a**; R = Et
**b**; R = $Pr^n$
**c**; R = $Bu^n$
**d**; R = n-Pentyl
**e**; R = n-Nonyl
**f**; R = $CH_2CN$
**g**; R = $CH_2CO_2Me$
**h**; R = $CH_2CO_2Et$

After trying several primary and secondary alkyl bromides and iodides in the presence of a molar excess of silver trifluoroacetate, it was found that only primary alkyl iodides were able to react with (**2**). Alkylation was regioselective and gave the corresponding 4-alkylbut-2-en-4-olides in substantial yields† (Table 1, entries 1—5). The by-products were the

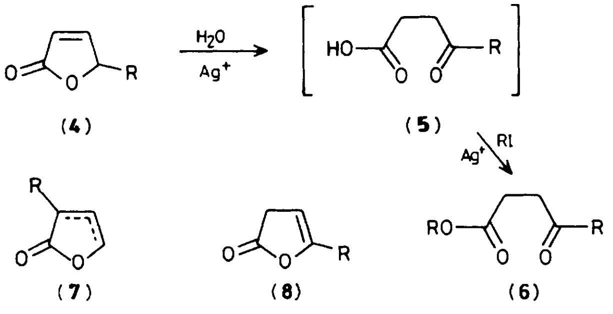
---

† In a typical experiment (**2**) (2 mmol) and $Bu^nI$ (2.6 mmol) were added to a suspension of $AgOCOCF_3$ (2.6 mmol) in dry $CH_2Cl_2$ (5 ml) with stirring under argon at −78 °C. The temperature was slowly increased to 20 °C over 4 h and the mixture was filtered through celite. Purification by flash chromatography ($SiO_2$, eluent: AcOEt/hexane) gave 4-n-butylbut-2-en-4-olide (**4c**) in 76% yield (Table 1, entry 3).

**Table 1.** Alkylation of 2-trimethylsiloxyfuran (**2**) with primary alkyl iodides, α-iodo-acetonitrile, and α-iodoacetic esters (RI) to give 4-alkylbut-2-en-4-olides (**4**) and γ-keto carboxylates (**6**).

| Entry | RI (R =) | (**4**), % yield[a] | (**6**), % yield[b] |
|---|---|---|---|
| 1 | Et | (**4a**), 61 | (**6a**), 6 |
| 2 | $Pr^n$ | (**4b**), 74 | (**6b**), 5 |
| 3 | $Bu^n$ | (**4c**), 76 | (**6c**), 3[a] |
| 4 | n-Pentyl | (**4d**), 78[c] | (**6d**), 4 |
| 5 | n-Nonyl | (**4e**), 57 | (**6e**), 3 |
| 6 | $CH_2CN$ | (**4f**), 55 | (**6f**)<br>(**6g**)<br>(**6h**) 0 |
| 7 | $CH_2CO_2Me$ | (**4g**), 79 | |
| 8 | $CH_2CO_2Et$ | (**4h**), 81 | |

[a] Yields refer to products isolated. [b] Yields of (**6a**,**b**), (**6d**—**h**) were estimated from the 360 MHz $^1$H n.m.r. spectra of the crude reaction mixtures. [c] New compound; elemental analysis and spectral data consistent with structure (**4d**) were obtained.



volatile trimethylsilyl and alkyl trifluoroacetates, and the γ-keto esters (**6**) formed in negligible amounts. As silver trifluoroacetate is hygroscopic, it was difficult to exclude moisture completely. Consequently, some hydrolysis of (**4**) occurred. The resulting γ-keto carboxylic acid (**5**),[8] on esterification with alkyl iodide, undoubtedly accounted for (**6**).

Equally reactive towards (**2**) were α-iodoacetonitrile and ethyl α-iodoacetate. The 4-(α-acetyl)[9] derivatives (**4f**,**h**) were directly produced in passable yields (Table 1, entries 6 and 8). When methyl α-iodoacetate was used, the racemic butenolide (**4g**), recently isolated as a chiral isomer from the marine sponge *Xestospongia* sp,[10] was easily prepared (Table 1, entry 7).

Unlike other methods, the present procedure requires but a single step and is entirely regioselective. Neither 2-alkylated products (**7**) nor 4-alkylbut-3-en-4-olides (**8**) were observed.[11] Moreover, the formation of racemates, such as (**4a**,**g**), is no longer a major disadvantage as they can be simply and preparatively resolved by chromatography over cellulose triacetate.[12]

We thank the Swiss National Science Foundation (grant 2.812—0.85) for financial support.

*Received, 9th November 1987; Com. 1623*

## References

1 G. Ohloff, 'Progress in the Chemistry of Organic Natural Products,' Springer Verlag, Vienna, 1978, **35**, pp. 431–527; E. D. de Silva and P. J. Scheuer, *Tetrahedron Lett.*, 1981, **22**, 3147.
2 J. L. Herrman, M. H. Berger, and R. H. Schlessinger, *J. Am. Chem. Soc.*, 1979, **101**, 1544; G. Stork and S. D. Rychnovsky, *ibid.*, 1987, **109**, 1564; S. Hanessian and P. J. Murray, *J. Org. Chem.*, 1987, **52**, 1170.
3 For recent examples see: M. Pohmakotr and P. Jarupan, *Tetrahedron Lett.*, 1985, **26**, 2253; S. Hanessian, P. J. Hodges, P. J. Murray, and S. P. Sahoo, *J. Chem. Soc., Chem. Commun.*, 1986, 754; J. C. Carretero, S. De Lombaert, and L. Ghosez, *Tetrahedron Lett.*, 1987, **28**, 2135.
4 K. Tanaka, K. Ootake, K. Imai, N. Tanaka, and A. Kaji, *Chem. Lett.*, 1983, 633.
5 C. W. Jefford, A. W. Sledeski, and J. Boukouvalas, *Tetrahedron Lett.*, 1987, **28**, 949.
6 I. Fleming, *Chimia*, 1980, **34**, 265; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 96; P. Brownbridge, *Synthesis*, 1983, 1; 85; T. N. Wheeler, *J. Org. Chem.*, 1984, **49**, 706.
7 C. W. Jefford, D. Jaggi, and J. Boukouvalas, *Tetrahedron Lett.*, 1987, **28**, 4037; C. W. Jefford, D. Jaggi, G. Bernardinelli, and J. Boukouvalas, *ibid.*, 4041.
8 J. Cardellach, C. Estopa, J. Font, M. Moreno-Mañas, R. M. Ortuño, F. Sanchez-Ferrando, S. Valle, and L. Vilamajo, *Tetrahedron*, 1982, **38**, 2377.
9 M. Janda, E. Körblovà, and I. Stibor, *Coll. Czech. Chem. Commun.*, 1983, **48**, 96.
10 E. Quiñoà, E. Kho, L. V. Manes, P. Crews, and G. J. Bakus, *J. Org. Chem.*, 1986, **51**, 4260.
11 For the preparation of 4-substituted 3-buten-4-olides from furans see: A. Pelter and M. Rowlands, *Tetrahedron Lett.*, 1987, **28**, 1203.
12 E. Francotte and D. Lohman, *Helv. Chim. Acta*, 1987, **70**, 1569.