Tetrahedron Letters No. 44, pp 4193 - 4196.

0040-4039/78/1029-4193$02.00/0

γ-ALKYLATION OF LITHIUM DIENOLATES DERIVED FROM 3(2H)-FURANONES AND RELATED α,β-UNSATURATED CARBONYL COMPOUNDS

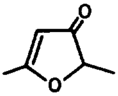
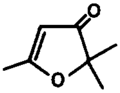
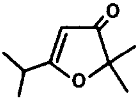
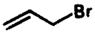
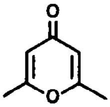
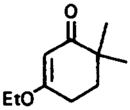
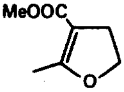
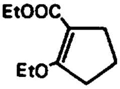
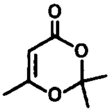
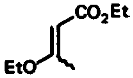
Amos B. Smith, III* and Robert M. Scarborough, Jr.
The Department of Chemistry, The Monell Chemical Senses Center and
The Laboratory for Research on the Structure of Matter
The University of Pennsylvania
Philadelphia, Pennsylvania, 19104

Although it is now generally accepted that lithium dienolates undergo near exclusive alkylation at the α rather than the γ carbon,[1] we will demonstrate in this letter that, at least, for some β-alkoxy-α,β-unsaturated carbonyl compounds, subtle structural features can markedly effect the α-selectivity. Our interest in the alkylation of β-alkoxy-α,β-unsaturated carbonyl compounds arose in connection with our studies directed at devising approaches to antitumor agents such as jatrophone,[2,3] which possess the 3(2H)-furanone ring system. The results of this study are illustrated in Table I.

Initially we examined the alkylation of the kinetic enolate derived from 2,5-dimethyl-3(2H)-furanone (**1**) via treatment with LDA in THF at -76°C. As expected alkylation occurred exclusively at the α′-position.[4] To our surprise however, alkylation of dienolates derived from 3(2H)-furanones (i.e. **2** and **3**) fully substituted in the α′-position afforded in excellent yield[5,6] *exclusive* γ-alkylation. To our knowledge the only previous example of selective γ-alkylation of a β-alkoxy-α,β-unsaturated ketone is 2,6-dimethyl-γ-pyrone (**4**).[7,8] However, the aromatic nature of **5** undoubtedly makes this doubly vinylogous ester a special case. From a synthetic point of view, significant here is the fact that alkylation of 3(2H)-furanones appears to be insensitive to the degree of substitution at the site of alkylation.

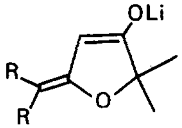
Since the above results were in direct contrast with the exclusive α-alkylation observed by deGroot and Hansen[9] for the closely related vinylogous ester **5**, we repeated their work. As reported only α-alkylation occurred.

Table 1: Alkylation of 3(2H)-Furanones and β-Alkoxy-α,β-unsaturated Carbonyl Compounds

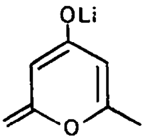
Entry	*Substrate*	*R-X*	*Alkylation distribution (percent)*		*Yield (percent)*	*Product*
			α	*γ*		
1[10]		MeI	100 (α')	0	73	10
			100 (α')	0	81	11
2[11]		MeI	0	100	85	12
			0	100	80	13
3[12]		MeI	0	100	93	14
			0	100	92	15
			0	100	83	16
		PhSeBr	0	100	75	17
4[7]		MeI	0	100	58	18
5[9]		MeI	100	0	61	19
6[13]		MeI	34	66	74	20, 21
7[14]		MeI	100	0	91	22
8			33	67	86	23, 24
9			100	0	88	25

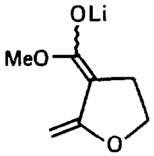
In an attempt to define further the apparent subtle structure features present in the dienolate which govern α vs γ selectivity, we examined a series of related β-alkoxy-α,β-unsaturated carbonyl compounds. Ideal candidates for this purpose appeared to be β-alkoxy-α,β-unsaturated esters since α′-alkylation would no longer be a concern. Furthermore, Katzenellenbogen and Crumrine[15] recently demonstrated the propensity of a wide variety of copper dienolates, derived from simple α,β-unsaturated esters to undergo selective γ-alkylation. To this end unsaturated esters 6-9 were prepared via know procedures, deprotonated in THF at -78°C with the LDA-HMPA complex prepared according to the method of Rathke[16] Schlessinger,[17] and the resultant lithium dienolate trapped either with methyl iodide or n-pentyl iodide. Under these conditions 6 and 8 afforded a mixture of α and γ alkylated products, the γ-products predominating 3:2 over that of the α. Esters 7 and 9 on the other hand afforded only α-alkylation.

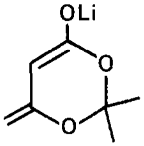
While no general rules can, as yet, be stated for the regioselectivity observed in the alkylation of β-alkoxy-α,β-unsaturated carbonyl compounds, we note that γ-alkylation was observed in all cases wherein the corresponding dienolate contains a double bond which is exocyclic to a ring as depicted below. No γ-alkylation occurred for substrates whose dienolate possessed an endocyclic or acyclic olefin.



(R = H or CH$_3$)







Clearly, extensive further structure-reactivity studies are required before the subtle nature of the α vs γ selectivity in the alkylation of β-alkoxy-α,β-unsaturated carbonyl compounds will be fully appreciated. Such studies are currently in progress in our laboratory.

Acknowledgment: It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (The National Cancer Institute) through Grant No. CA-22807. In addition, we thank Mr. S. T. Bella of the Rockefeller University for the microanalysis and the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania where the 220 and 360 MHz spectra were obtained.

References and Footnotes

1. (a) H. E. Zimmerman in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N.Y. 1963, p 345; (b) A. C. Cope, H. L. Holmes, and H. O. House, Org. React., 9, 102 (1957); (c) H. O. House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin Menlo Park, Calif., 1972, Chapter 9; (d) M. W. Rathke and D. Sullivan, Tetrahedron Lett., 4249 (1972); (e) J. L. Hermann, G. R. Kieczykowski, and R. H. Schlessinger, ibid., 2433 (1973); (f) S. A. G. de Graaf P. E. R. Oosterhoff, and A. van der Gen, ibid., 1653 (1974).

2. S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore, and R. F. Bryan, J. Am. Chem. Soc., 98, 2295 (1976).

3. In addition to jatrophone and increasing number of antitumor agents possessing the 3(2H)-furanone ring system have recently been uncovered, see for example R. F. Raffauf, Phi-Kuei C. Huang, P. W. Le Quesne, S. B. Levery and T. F. Brennan, J. Am. Chem. Soc., 97, 6884 (1975) and references cited therein.

4. R. Lantz, A. B. Harnfeldt, Chem. Scr., 10, 126 (1976), also see: G. Stork and R. L. Danheiser, J. Org. Chem., 38, 1776 (1973); and G. Stork, R. L. Danheiser and B. Ganem, J. Am. Chem. Soc., 95, 3415 (1973).

5. Yield and product ratios were determined by analytical vapor phase chromatography (vpc); yield were not maximized.

6. The structure assigned to each new compound was in accord with its infrared and 220 MHz spectra Analytical samples of each new compound obtained by preparative vpc gave C and H combustion analysis within 0.4% of theory. The 60 and/or 220 MHz NMR Spectra (CCl_4,δ) for alkylation products 10-25 are recorded below: 10 (60 MHz) 1.25 (s, 6H), 2.16 (s, 3H), 5.20 (s, 3H); 11 (60 MHz) 1.20 (s, 3H), 1.30-2.10 (m, 6H), 2.11 (s, 3H), 4.70-5.15 (complex m, 2H), 5.20 (bs, 1H), 5.58 (m, 1H); 12 (220 MHz) 1.23 (s, 6H), 2.48 (m, 2H), 5.20 (s, 1H); 13 (220 MHz) 0.90 (t, J = 7.5 Hz, 3H), 1.27 (bs, 14H), 1.63 (m, 2H), 2.41 (t, J = 7 Hz, 2H), 5.18 (s, 1H); 14 (220 MHz) 1.25 (s, 9H), 1.32 (s, 6H), 5.20 (s, 1H); 15 (220 MHz) 1.20 (s, 6H), 1.29 (s, 6H),2.28 (d, J = 7 Hz, 2H), 4.96 (m, 1H), 5.04 (bs, 1H), 5.20 (bs, 1H) 5.61 (m, 1H); 16 (220 MHz) 0.88 (t, J = 7.5 Hz, 3H) 1.19 (s, 6H), 1.27 (s, 6H), 1.25-1.70 (m, 8H), 5.18 (s, 1H); 17 (60 MHz) 1.25 (s, 6H), 1.54 (s, 6H), 4.94 (s, 1H), 7.15-7.61 (m, 5H); 18 (60 MHz) 1.28 (t, J = 7 Hz, 3H) 2.20 (s, 3H), 2.51 (q, J = 7 Hz, 2H), 6.00 (bs, 2H); 19 (60 MHz) 1.15 (s, 6H), 1.32 (t, J = 6 Hz, 3H), 1.58 (t, J = 1.5 Hz, 3H), 1.75 (t, J = 6 Hz, 2H), 2.50 (br, t, J = 6 Hz 2H), 3.99 (q, J = 6 Hz, 2H); 20 (220 MHz) 1.43 (s, 3H), 1.84 (m, 1H), 2.59 (m, 1H) 3.68 (s, 3H), 3.84 (s, 1H),4.09 (m, 2H), 4.16 (s, 1H); 21 (220 MHz) 1.11 (t, J = 7 Hz, 3H), 2.62 (q, J = 7 H 2H), 2.84 (t, J = 10 Hz, 2H), 3.63 (s, 3H), 4.36 (t, J = 10 Hz, 2H); 22 (60 MHz) 1.21 (t, J = 7.5 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H), 1.30 (s, 3H), 1.60-2.51 (complex m, 4H) 3.78 (q, J = 7.5 Hz, 2H), 4.11 (q, J = 7.5 Hz, 2H), 4.50 (t, J = 2 Hz, 1H); 23 (220 MHz) 0.90 (t, J = 7.5 Hz, 3H), 1.22-1.56 (m, 6H), 1.65 (s, 6H), 2.00 (s, 3H) 2.25 (t, 7.5 Hz, 2H); 24 (220 MHz) 0.90 (t, 7.5 H, 3H), 1.25-1.63 (m, 8H), 1.70 (s, 6H), 2.22 (t, J = 7.5 Hz, 2H) 4.09 (q, J = 7.5 Hz, 2H), 25 (220 MHz) 0.89 (t, 7Hz, 3H) 1.31 (m, 12H), 2.25 (m, 5H), 3.93 (q, J = 7 Hz, 2H), 4.09 (q, J = 7 Hz, 2H).

7. M. Yamamoto and N. Sugiyama, Bull. Chem. Soc. Jap., 48, 508 (1975).

8. Regioselective γ-alkylation has been reported for vinylogous amides, see: M. Yoshimoto, N. Ishida and T. Hiraoka, Tetrahedron Lett., 39 (1973); and T. A. Bryson and R. B. Gammill, Tetrahedron Lett., 3963 (1974).

9. Ae. de Graaf and B. J. M. Jansen, Rec. Trav. Chim., Pays Bas. 93, 153 (1974), and 95, 81 (1976).

10. C. Venturello and R. D'Aloisio Synthesis, 754 (1977).

11. Prepared by alkylation of 1. For earlier preparation see: I. I. Nazarova, B. P. Gusev, and V. F. Kucherov, Isv. Akad. Nauk USSR., 729 (1965).

12. J. A. Rampes, S. Hoff, P. Montijn, L. Brandsma and J. F. Arens, Rec. Trav. Chim., 88, 1445 (1969).

13. F. Korte and H. Machleidt, Chem. Ber., 90, 2137 (1957).

14. Prepared using the method of Stork and Kraus see: G. Stork and G. A. Kraus, J. Am. Chem. Soc., 98, 2351 (1976).

15. J. A. Katzenellenbogen and A. L. Crumrine, J. Am. Chem. Soc., 96, 5662 (1974); also see J. A. Katzenellenbogen and A. L. Crumrine, J. Am. Chem. Soc., 98, 4925 (1976).

16. M. W. Rathke and D. Sullivan, Tetrahedron Lett., 4249 (1972).

17. J. L. Herrmann, G. R. Kieczykowski and R. H. Schlessinger, Tetrahedron Lett., 2433 (1973).

(Received in USA 22 August 1978)