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REGIOSPECIFIC ALKYLATION OF β-KETOTHIOESTERS AND USE IN THE SYNTHESIS OF ACYL-TETRONIC ACIDS

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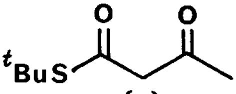
Summary: Anions of t-butylacetothioacetate (1) react with alkylhalides and carbonyl compounds in a regiospecific manner to afford products which are versatile synthetic intermediates as exemplified by short syntheses of the mold metabolites carolic acid (2) and carlosic acid (3).

The utility of thioesters in organic synthesis is well known[1]. They are of particular value in the formation of large ring lactones[2]. Similarly, β-ketoesters have been shown to be versatile synthetic intermediates[3]. It is reasonable therefore to expect that β-ketothioesters, and especially t-butylacetothioacetate (1) might well combine the myriad properties of the two systems.

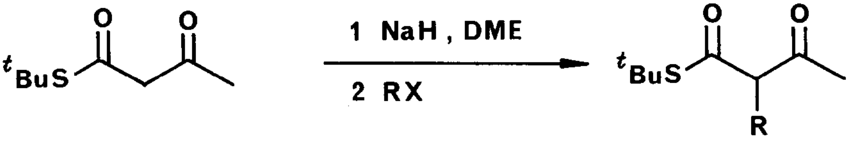


(1)

Compound (1) was prepared in 65% yield by treatment of diketene with sodium t-butylthiolate in T.H.F. Use of the thiolate anion in this manner circumvents the addition of thiol to the double bond of diketen noted elsewhere.[4]

Alkylation of (1) at the 2-position was achieved by anion formation with sodium hydride in 1,2-dimethoxyethane (D.M.E.) at 0°C followed by reaction with the alkyl halide at room temperature (Scheme 1).

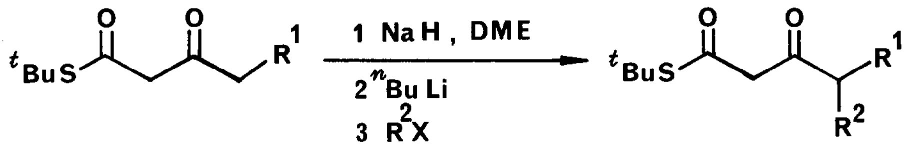
Scheme 1



Entry	R	X	Yield %
1	$CH_2=CH.CH_2$	Br	46
2	CH_3	I	65

Generation of the dianion from (1) involved sequential treatment with sodium hydride (at 0°C) and n-butyl lithium in DME (at -20°C). Reaction of this dianion, and others, with alkyl halides gave the alkylated products in moderate to good yields (Scheme 2).

Scheme 2

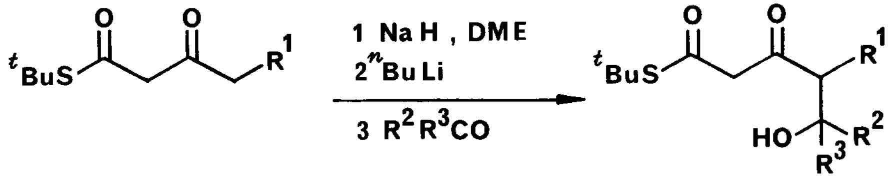


Entry	R^1	R^2	X	Yield %
1	H	CH_3	I	78
2	CH_3	CH_3	I	69
3	$(CH_3)_2$	CH_3	I	34
4	H	$CH_2{=}CH.CH_2$	Br	70
5	H	$CH_2CH_2OSiMe_2{}^tBu$	I	63
6	H	$(CH_2)_2CHCH_3$ $OSiMe_2{}^tBu$	I	53
7	H	$(CH_2)_4CHCH_3$ $OSiMe_2{}^tBu$	I	59
8	H	Me $(CH_2)_8C\text{-}CO_2Me$ OLi	I	56

Use of solvents other than D.M.E., e.g. T.H.F., led to very low yields and many unwanted side products. The entries in Scheme 2 demonstrate, as expected, that alkylation yields decrease as the steric congestion at the reacting centre increases.

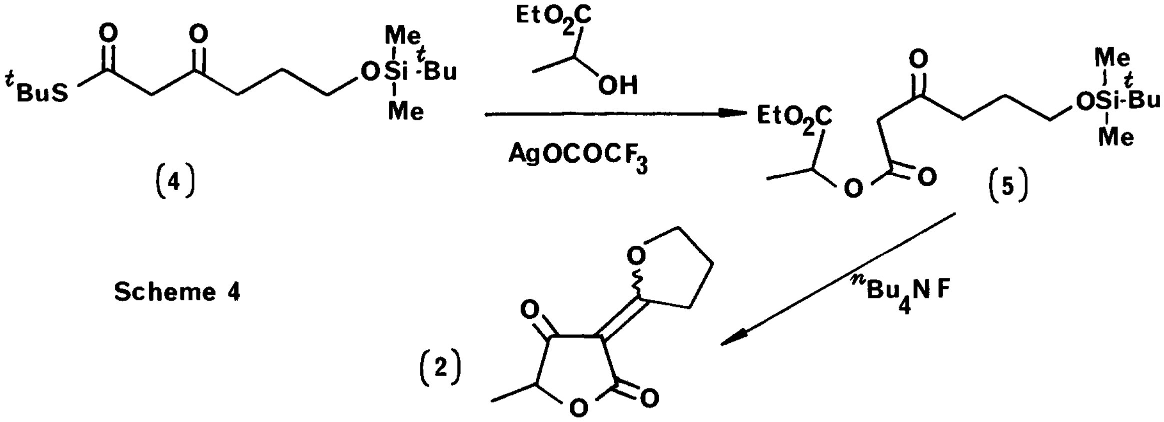
In a brief study, the t-butylacetothioacetate dianions were also shown to react with carbonyl compounds in good yield (Scheme 3). In entry 1 of the Scheme no diastereomeric preference of the product was observed.

Scheme 3

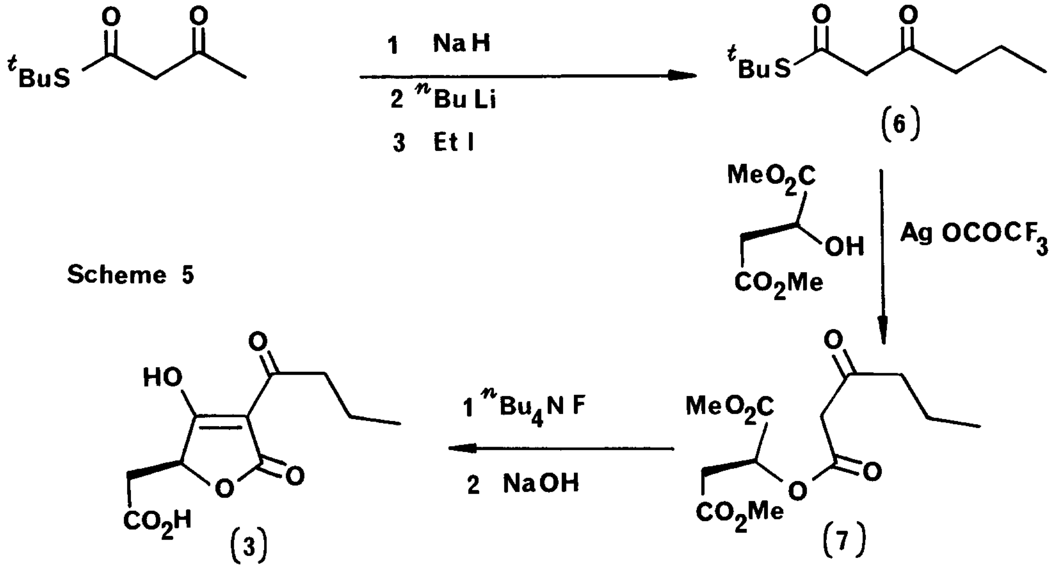


Entry	R^1	R^2	R^3	Yield %
1	CH_3	Ph	H	64
2	H	$R^2{=}R^3{=}$cyclohexyl		80
3	CH_3	$R^2{=}R^3{=}$cyclohexyl		73

β-Ketothioesters may be transesterified under very mild conditions to oxo-esters by reaction with alcohols under metal catalysis[5]. This reaction was used together with the previously described alkylations to effect very short syntheses of the mold metabolites, carolic acid (2) and carlosic acid (3) (Schemes 4 and 5).



Scheme 4



Scheme 5

Thus, compound (4) (product from entry 5, Scheme 2) was transesterified with ethyl lactate using $AgOCOCF_3$ (2 eq, Et_2O, Na_2HPO_4 buffer) to afford (5) in 75% yield. Simultaneous Dieckmann cyclisation and deprotection of (5) was carried out by treatment with 3 eq of tetra-n-butylammonium fluoride to give carolic acid[6] (2) in 90% yield. In a similar way, alkylation of the dianion from (1) with ethyl iodide gave (6) in 70% yield. Treatment of (6) with (S)-dimethylmalate, in T.H.F., and with 1 eq. of $AgOCOCF_3$ afforded (7) in 75% yield. Dieckmann cyclisation was achieved using 1 eq tetra-n-butylammonium fluoride in T.H.F. followed by hydrolysis to give (S)-carlosic acid[6] (3) in 60% overall yield from (7). It is noteworthy that the use of bases other than $^nBu_4NF$ on similar malate derived systems led to dimethyl fumarate as the only identifiable product as a result of a facile β-elimination of the acetoacetate moiety[6]. Use of the conditions described above completely avoids these problems.

Use of other β-ketothioesters in the above reactions, for example phenylacetothioacetate, was much less satisfactory owing to instability of the resulting anions decomposing by loss of phenylthiolate. The reactions described with t-butylacetothioaceate (1), however, constitute a useful synthetic procedure as, in principle, it behaves as a synthetic equivalent to diketen.

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References

1. G.E. Wilson and A. Hess, J. Org. Chem., 1980, **45**, 2766 and references therein; (b) S. Motoki and T. Sato, Bull. Chem. Soc. Jap., 1969, **42**, 1322; (c) H. Gerlach and P. Künzler, Helv. Chim. Acta., 1978, **61**, 2503; (d) T. Wakui, H. Yamaguchi and S. Motoki, Bull. Chem. Soc. Jap., 1977, **50**, 1645; (e) H.-J. Liu, H.K. Lai and S.K. Attah-Poku, Tetrahedron Lett., 1979, 4121.

2. (a) H. Gerlach and A. Thalmann, Helv. Chim. Acta., 1974, **57**, 2661; (b) E.J. Corey and K.C. Nicolaou, J. Am. Chem. Soc., 1974, **96**, 5614; (c) E.J. Corey, D.J. Brunelle and P.J. Stork, Tetrahedron Lett., 1976, 3405; (d) E.J. Corey and D.J. Brunelle, Tetrahedron Lett., 1976, 3409; (e) S. Masamune, S. Kamata and W. Schilling, J. Am. Chem. Soc., 1975, **97**, 3515.

3. (a) L. Weiler, J. Am. Chem. Soc., 1970, **92**, 6702; (b) S.N. Huckin and L. Weiler, J. Am. Chem. Soc., 1974, **96**, 1082; (c) For further examples see: F.W. Sum and L. Weiler, Tetrahedron Suppl. No. 1, 1981, **37**, 303.

4. (a) J.G. Dingwall and B. Tuck, Angew. Chem. Int. Ed. Engl., 1983, **22**, 498; (b) see also: F. Duus, P. Jakobsen and S.-O. Lawesson, Tetrahedron, 1968, **24**, 5323, and reference 1b above.

5. S. Masamune, Y. Hayase, W.Schilling, W.K.Chan and G.S. Bates, J. Am. Chem. Soc., 1977, **99**, 6756.

6. J.L. Bloomer and F.E. Kappler, J. Chem. Soc., Perkin Trans. I, 1976, 1485 and references therein.

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