New α-Keto Acid Synthon; Alkylation of the Potassium Dianion of Bis(ethylthio)acetic Acid

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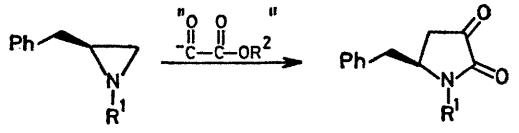
Summary The easily prepared, thermally stable, tetrahydrofuran-soluble potassium dianion of the glyoxylic acid derivative (**7**) was readily alkylated by halides, tosylates, epoxides, and *N*-tosyl-aziridines.

IN connection with a preliminary investigation directed at a synthesis of cytochalasin B,[1] we required a glyoxylic acid (ester) anion equivalent. Alkylation of such a synthon by an aziridine unit (**1**) incorporating the chirality at



(1)

C-3 of the cytochalasin, followed by lactam formation, would lead to a precursor containing an oxygen function at what would eventually become the C-9 position of the target molecule. The monoanions of the glyoxylic ester derivatives (**2**)—(**6**)[2] appeared to be possible synthons. However, when we attempted to open the aziridine derivative (**1**; $R^1 = p\text{-}MeC_6H_4SO_2$–) with the anions of any of the above compounds, either starting material was recovered or an unidentifiable mixture was obtained. Assuming that the problem was the instability of the ester anions (loss of OR^2– produces a keten derivative), we reasoned that the dianions of the corresponding carboxylic acids[3] should be much more stable, and also the dianion should be more reactive than the monoanion. Although the alkylation of acetic acid dianions stabilized by α-thio(alkyl)aryl groups has been reported[4] and although various thioacetals of glyoxylic acid[5,6] are known, we found no reference to the dianions of the latter compounds. We thus studied dianions derived from (**7**) and (**8**). The former acid was conveniently prepared by cautious addition of dichloroacetic acid to a tetrahydrofuran (THF) suspension of 3 equiv. of sodium hydride, followed by addition of an excess of ethanethiol. The mixture was stirred overnight at room temperature and normal work-up provided a quantitative yield of (**7**). Compound (**8**) was prepared by alkaline hydrolysis (aq. KOH–Bu^tOH, 1 h) of the corresponding ester.[2e]

Optimum alkylation conditions were established by varying the solvent, reaction temperature, base (*i.e.* gegenions present), *etc.* Table 1 shows that the dianion derived from (**8**) is more reactive than that derived from (**7**). This difference may be attributed to a directed anion at C-1 of the dithian ring of the dianion[6] of (**8**) or simply to steric reasons.

TABLE 1

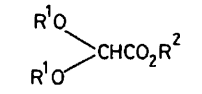
$$(RS)_2CHCO_2H \xrightarrow{\text{i, ii, iii}} (RS)_2C(CH_2Ph)CO_2H$$

i, 2 equiv. Bu^nLi; ii, $PhCH_2Cl$; iii, H_3O^+

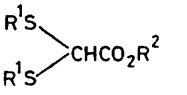
Acid substrate	Solvent (25 °C)	Time/h	Yield/%
(**7**) (R = Et)	THF	18	*ca.* 0
	THF–HMPA[a]	18	*ca.* 65
(**8**) (R = $-[CH_2]_3-$)	THF	3	100

[a] HMPA = $(Me_2N)_3PO$.

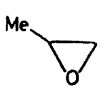
Although the use of dianions derived from (**8**) is recommended in cases of alkylating agents with low reactivity, we optimized alkylation conditions for the more readily obtainable and less expensive (**7**). The best conditions found were the reaction of 2 equiv. of potassium bis(trimethylsilyl)amide[7] with (**7**) in THF at 0 °C to generate the soluble potassium dianion species. Alkylations were then carried out with a variety of substrates (Table 2). Although most reactions were complete in < 1 h at 25 °C the mixtures were left for 2·5 h since their mixing efficiencies decreased with time owing to the precipitation of the insoluble potassium monoanion of the alkylated product. Of particular note are entries 4, 7, and 8 which show that tosylates[8] cleanly alkylate the dianion in good yield, entry 12 which illustrates the site-specific opening of an epoxide and, most importantly, the almost quantitative cleavage of the aziridine ring (entry 13) to the desired α-keto acid equivalent, a transformation which we were unable to achieve using existing methods.[9]



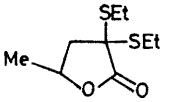
(2) $R^1=R^2=Me$
(3) $R^1=R^2=Et$



(4) $R^1=Et, R^2=Me$
(5) $R^1=-[CH_2]_2-, R^2=Et$
(6) $R^1=-[CH_2]_3-, R^2=Et$
(7) $R^1=Et, R^2=H$
(8) $R^1=-[CH_2]_3-, R^2=H$



(9)



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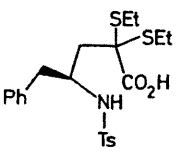

(11)

Ts = *p*-$MeC_6H_4SO_2$

The fact that somewhat lower yields were obtained with isopropyl derivatives (entries 5, 6, and 7) and cyclohexyl tosylate (entry 8) was undoubtedly due to competing elimination reactions. However, the significant decrease in elimination with isopropyl tosylate (entry 7) is in agreement with the well known greater reactivity of tosylates compared with halides in substitution reactions.[10] The relatively good yield of substitution product with cyclohexyl tosylate was surprising in a ring system so extremely prone to elimination.

The reactions were rapid, high yielding, and simple to carry out.† There was no need to remove the oil from the potassium hydride used to generate the potassium base, since the work-up included an extraction to yield essentially pure carboxylic acid. The trace of coloured material in the crude products could be removed by filtration through LH-20 Sephadex using chloroform as eluant (material balance is quantitative).

TABLE 2[a]

$$(EtS)_2CHCO_2H \xrightarrow{\text{i, ii, iii}} (EtS)_2CRCO_2H$$

i, 2 equiv. $KN(SiMe_3)_2$; ii, **R–X**; iii, H_3O^+.

	R–X	Yield[b]/%		R–X	Yield[b]/%
1	MeI	100	8	c-$C_6H_{11}OTs$[c,d]	64
2	EtI	100	9	$Me[CH_2]_3Br$	100
3	EtBr	100	10	$CH_2=CHCH_2Br$	100
4	EtOTs[e]	100	11	$PhCH_2Cl$	100
5	Pr^iI	50	12	(**9**)	95[e,f] as (**10**)
6	Pr^iBr	50	13	(**1**) R^1 = Ts[e]	93[f–h] as (**11**)
7	Pr^iOTs[e]	72			

[a] All reactions 0·1 M in carboxylic acid in THF at 25° C. [b] Purified, isolated material. All compounds had ^1H n.m.r., i.r., elemental analysis, and exact parent mass spectrum measurements fully consistent with the proposed structures. [c] Ts = *p*-$MeC_6H_4SO_2$. [d] c-C_6H_{11} = cyclohexyl. [e] Pure by gas chromatography (OV-17; OV-101). [f] Reaction time 18 h. [g] M.p. 151—152 °C (Et_2O–hexane). [h] Can be cyclised to the corresponding *N*-tosyl lactam with oxalyl chloride (75%).

† A typical procedure is as follows. Under N_2 (or Ar), $HN(SiMe_3)_2$ (22 mmol) was added to a suspension of KH (3·2 g; 25% in mineral oil) in anhydrous THF (100 ml) at 0 °C. After the H_2 evolution had ceased, a solution of (**7**) (10 mmol) in THF (10 ml) was added dropwise over 10 min with vigorous stirring. Any precipitate formed was allowed to dissolve before additional acid was added. Benzyl chloride (11 mmol) was added and the mixture was stirred at 25 °C for 2·5 h. Water was added to dissolve the precipitate and the THF was evaporated off. A solution of the residue in water was washed with hexane, acidified with 2N HCl, and extracted with ether. The ether extract was dried and evaporated to yield 2·70 g (100%) of the ethane dithioacetal of phenylpyruvic acid, m.p. 66–67 °C.

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