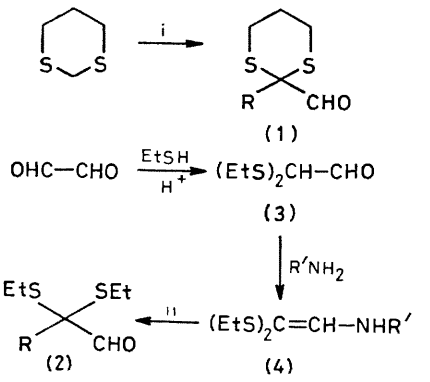
Alkylation of Enamines of Bis(ethylthio)acetaldehyde: Synthesis of Norpyrenophorin

By GORDON S BATES* and S RAMASWAMY
(*Department of Chemistry, University of British Columbia, Vancouver, B C , Canada* V6T 1Y6)

Summary Alkylation of the potassium anion of the glyoxal derivatives (**4**) with halides and sulphonate esters, followed by acidic hydrolysis, provides good yields of the corresponding pyruvaldehyde α-thioacetals

AN important structural feature of many natural products (*e g* cytochalasin A, and the diolides pyrenophorin, norpyrenophorin, and vermiculin) is the presence of a 4-oxoalk-2-enoic ester linkage A number of syntheses[1] of natural

products which contain the above combination of functional groups[2] have made use of the aldehydes (**1**).[3] These compounds, which have been prepared using the method outlined below, may be elaborated readily into the desired 4-oxoalk-2-enoic esters. Several drawbacks to the more widespread, general application of (**1**) in organic synthesis include (a) use of dithian, a relatively expensive starting material, (b) use of 2 equiv. of an organolithium reagent, (c) the need for scrupulously anhydrous *NN*-dimethylformamide, and (d) the facilities for maintaining constant low temperatures (−78 to −25 °C) for extended periods of time (12—60 h).[1c]



SCHEME 1. *Reagents:* i, a Bu^{n}Li, b RX, c Bu^{n}Li, d *NN*-dimethylformamide; ii, a KH, b RX, c H_3O^+.

We here report a simple, high-yielding synthesis of (**2**; R = alkyl), compounds synthetically equivalent to (**1**), *via* a sequence involving inexpensive and readily available starting materials, 1 equiv. of a base, and a convenient room-temperature alkylation.

Bis(ethylthio)acetaldehyde[4] (**3**), readily prepared from glyoxal and ethanethiol,† was condensed (2M CH_2Cl_2, −10 °C, 3 h) with t-butylamine, isopropylamine, cyclohexylamine, and aniline to give the enamines (**4**)‡ (*ca.* 90% yield). The alkylation[5] of various salts (cations: Li, Na, K, Mg) derived from the above enamines was studied in order to determine the variation in yield, rate, and site-specificity of alkylation, and subsequent ease of hydrolysis to the aldehydes (**2**). The optimum system for alkylation was found to be the potassium salt of the cyclohexyl enamine derivative (**4**; R′ = c-C_6H_{11}).§ The alkylations were monitored by t.l.c. or g.l.c. and were generally complete in 2—5 h at room temperature. With hindered alkylating agents (see below) overnight refluxing of the reaction mixture was required. The resulting alkylated cyclohexyl imine was hydrolysed readily in 2—3 h at room temperature by the direct addition of aqueous 2 N HCl. The desired aldehyde was isolated by a standard work-up and was sufficiently pure for use in subsequent reactions; further purification could be accomplished by chromatography on Florisil.

TABLE. Reactions of the cyclohexyl enamines (**4**; R′ = c-C_6H_{11}) to give the aldehydes (**2**) (Scheme 1).[a]

Entry	R-X	Time/h	% Yield[b]
1	EtI	2	75
2	EtBr	2	75
3	EtOTs[c]	2	81
4	Bu^{n}Br	4	75
5	Bu^{n}OTs	4	77
6	Pr^{i}OBs[d]	6	76
7	c-C_6H_{11}OBs[d,e,f]	18	67
8	c-C_5H_9OBs[d,f,g]	18	63
9	CH_2=$CHCH_2$Br	2	85
10	$PhCH_2$Br	2	75

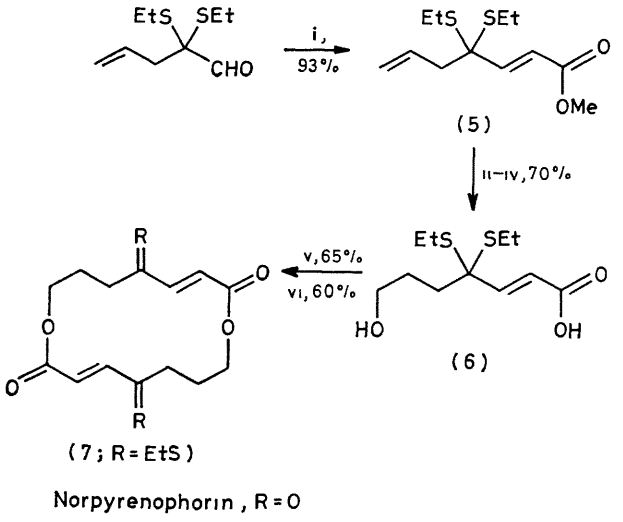
[a] All reactions used 0·1 M reagents in tetrahydrofuran at 25 °C. [b] Purified isolated material. All compounds had ^{1}H n.m.r., i.r., elemental analysis, and exact mass spectrum measurements fully consistent with the proposed structures. [c] Ts = *p*-$MeC_6H_4SO_2$. [d] Bs = $PhSO_2$. [e] c-C_6H_{11} = cyclohexyl. [f] Reaction carried out at 67 °C. [g] c-C_5H_9 = cyclopentyl.

The Table summarizes various alkylation reactions, and shows that halides, toluene-*p*-sulphonates, and benzenesulphonates all alkylate the potassium salt of (**4**; R′ = c-C_6H_{11}) in good yield. In marked contrast with the alkylation of the dithian system,[6] even alkylation with secondary alkylating agents[7] proceeds well (entries 6—8). The slightly lower yields obtained with cyclohexyl (entry 7) and cyclopentyl (entry 8) benzenesulphonates were undoubtedly due to competing elimination reactions, although no attempt was made to isolate the resulting alkenes. The relatively good yield of substitution products in these two cases was surprising with ring systems so extremely prone toward elimination. Benzenesulphonates are superior to toluene-*p*-sulphonates in cases where alkylation is sluggish (entries 7 and 8) and elevated temperatures are required to drive the reaction to completion in a reasonable time.

† A mixture of 1 M aqueous glyoxal, 2 equiv. of EtSH, and 0·05 equiv. of *p*-$MeC_6H_4SO_3H$ was vigorously stirred or shaken at room temperature for 6—12 h. The crude product was dried ($MgSO_4$) and distilled (b.p. 67 °C at 0·4 Torr) to give the desired aldehyde in 50—55% yield. The use of 1 M glyoxal here avoids the formation of 1,1,2,2-tetra(ethylthio)ethane. The reaction has been carried out on 10—500 mmol scales with equal success. The use of propane-1,3-dithiol results in formation of an intractable, presumably polymeric, material.

‡ No imine signals are observable in the ^{1}H n.m.r. spectrum (**4**).

§ A typical procedure is as follows. Under N_2 (or Ar) 10 mmol of the freshly distilled cyclohexyl enamine (**4**) (Kugelrohr distillation: 90 to 100 °C at 0·1 Torr) was added to a suspension of oil-free (hexane washed) KH (10 mmol) in anhydrous tetrahydrofuran (100 ml). After the H_2 evolution had ceased, allyl bromide (11 mmol) was added to the bright yellow solution of the anion. After 2 h at 25 °C, aqueous 2 N HCl (5 ml) was added and the mixture stirred at 25 °C for a further 2 h. After extraction with ether the extract was dried ($MgSO_4$) and evaporated. The crude product was distilled to yield 2,2-bis(ethylthio)pent-4-enal (8·5 mmol) (Kugelrohr distillation: 60 °C at 0·1 Torr).



SCHEME 2 *Reagents* I, $(MeO)_2POCH_2CO_2Me$, NaH, II, 9-borabicyclo[3 3 1]nonane, III, Me_3NO, IV, KOH, V, $EtO_2CN{=}NCO_2Et$, Ph_3P, VI, HgO, $BF_3{\cdot}Et_2O$

The synthetic utility of this new reagent is illustrated by the following synthesis of norpyrenophorin, a physiologically active diolide A Wittig–Horner reaction with (**2**, R = allyl) gave the $\alpha\beta$-unsaturated ester (**5**) in 93% yield The crystalline hydroxy-acid (**6**) (m p 86—87 °C) was obtained in 70% yield from (**5**) by a sequence of hydroboration with a subsequent oxidative work-up[8] followed by an alkaline hydrolysis Dimerization of (**6**) to give the crystalline diolide (**7**) (m p 85—86 °C) was achieved in 65% yield (plus 25% of higher oligomers) by stirring a dilute toluene solution of (**6**) with diethylazodicarboxylate and triphenylphosphine[9] at −40 °C to room temperature over 60 h Finally, the thioacetals present in (**7**) were hydrolysed (60% yield) to give norpyrenophorin in an overall yield of over 20% from the cyclohexyl enamine (**4**)

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[1] (a) E W Colvin, T A Purcell, and R A Raphael, *J Chem Soc, Perkin Trans* 1, 1976, 1718, (b) K F Burri, R A Cardone, W Y Chen, and P Rosen, *J Am Chem Soc*, 1978, **100**, 7069, (c) B Seuring and D Seebach, *Justus Liebig's Ann Chem*, 1978, 2044

[2] For other approaches to this system see H M Walton, *J Org Chem*, 1957, **22**, 308, M Kuchar, B Kakac, and O Nemecek, *Coll Czech Chem Commun*, 1972, **37**, 3950, P L Stotter and J B Eppner, *Tetrahedron Lett*, 1973, 2417, H Lerche, D Konig, and T Severin, *Chem Ber*, 1974, **107**, 1509, P A Bartlett, *J Am Chem Soc*, 1976 **98**, 3305 H Gerlach, K Oertle, and A Thalmann, *Helv Chim Acta*, 1977, **60**, 2860, E J Corey, R H Wollenberg, and D R Williams, *Tetrahedron Lett*, 1977, 2243, P Bakuzis, M L F Bakuzis, and T F Weingartner, *ibid*, 1978, 2371

[3] E J Corey and D Seebach, *Angew Chem, Internat Edn Engl*, 1965, **4**, 1077

[4] W Ando, J Suzuki, T Arai, and T Migita, *Tetrahedron*, 1973, **29**, 1507, D L Rakhmankulov N E Maksimova R A Karakhanov, E A Kantor, M Bartok, and S S Zlotskii, *Acta Phys Chem*, 1975, 177 (*Chem Abs*, 1976, **85**, 94290z), M Nakane and C R Hutchinson, *J Org Chem*, 1978, **43**, 3922

[5] G Stork and S R Dowd, *J Am Chem Soc*, 1963, **85**, 2178, T Cuvigny, H Normant, and P Hullot, *Bull Soc Chim Fr*, 1970, 3976, T Cuvigny and H Normant, *Organomet Chem Synth*, 1971, **1**, 237

[6] B-T Grobel and D Seebach, *Synthesis*, 1977, 357

[7] Secondary halides lead to significantly more elimination than the corresponding sulphonate esters P Veeravagu, R T Arnold, and E W Eigenmann, *J Am Chem Soc*, 1964, **86**, 3072, R C Bingham and P v R Schleyer, *ibid*, 1971, **93**, 3189

[8] G W Kabalka and H C Hedgecock, Jr, *J Org Chem*, 1975, **40**, 1776

[9] T Kurihara, Y Nakajima, and O Mitsunobu, *Tetrahedron Lett*, 1976, 2455