A New Synthesis of Methyl α-Acetolactate based on Thiazolium Chemistry and modelled on the Enzymatic Synthesis of α-Acetolactate catalysed by Acetolactate Synthase

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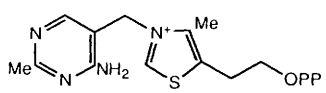
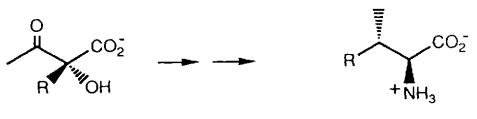
Methyl α-acetolactate [methyl 2-hydroxy-2-methyl-3-oxobutanoate (**13**)] has been synthesised *via* a series of adducts with benzothiazole in a manner analogous to the enzymatic reaction catalysed by acetolactate synthase.

Since the pioneering studies of Breslow[1] on the mechanism of enzymatic reactions in which thiamine pyrophosphate (**1**) acts as cofactor, organic chemists have been aware of the possibility of using the thiazolium system to catalyse acyloin condensations in the laboratory. This has led to the development of simple methods for the synthesis from aldehydes of acyloins.[2] The approach has been extended to the synthesis of optically active acyloins using chiral thiazolium salts[3] and to methods for the conjugate addition of acyl anion equivalents to α,β-unsaturated systems.[4] A macromolecular system to hold a thiazolium catalyst of the benzoin condensation has been described.[5]



(**1**)

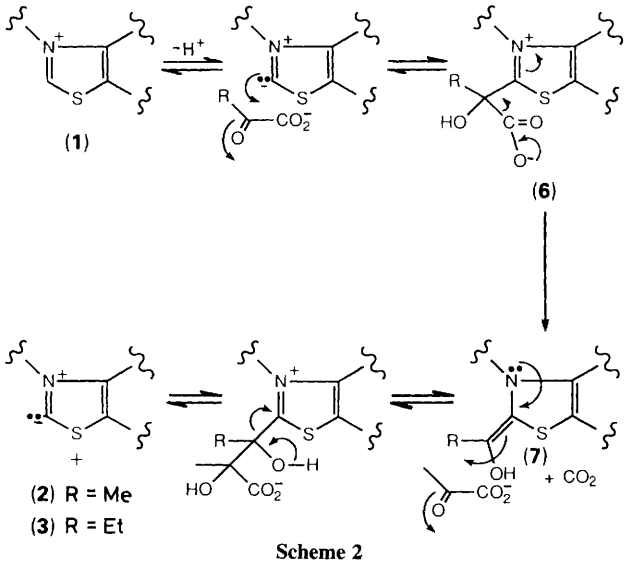
An important enzymatic reaction catalysed by a thiamine pyrophosphate-dependent enzyme is that of α-acetolactate (**2**) and α-acetohydroxybutyrate (**3**) synthesis. These compounds are precursors of valine (**4**) and isoleucine (**5**) respectively (Scheme 1). The condensing enzyme, acetolactate synthase [acetolactate pyruvate-lyase (carboxylating), EC 4.1.3.18] is the target for a range of powerful herbicides[6] and has therefore been the object of much recent attention.



(**2**) R = Me
(**3**) R = Et

(**4**) R = Me
(**5**) R = Et

Scheme 1



Scheme 2

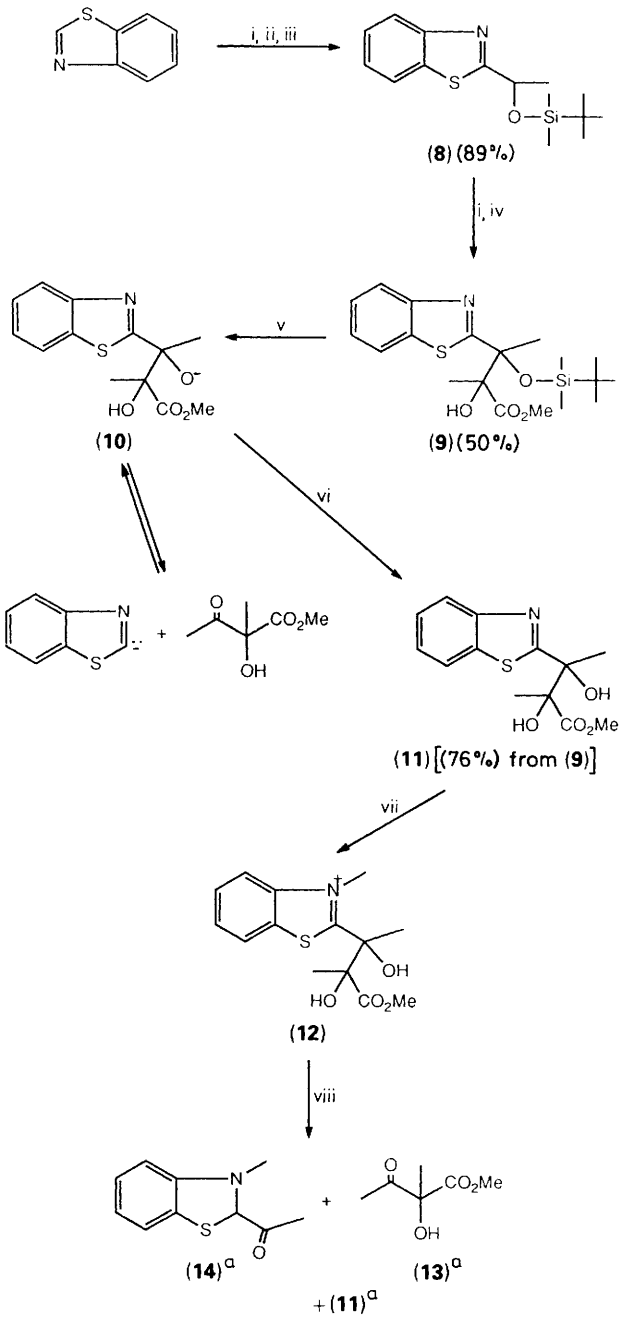
Table 1. Product distribution (% yield) on decomposition of the diastereoisomers of (**12**).

	Diastereoisomer of (**12**)	
Product	(2*R*,3*S* + 2*S*,3*R*)	(2*R*,3*R* + 2*S*,3*S*)
(**13**)	15	27
(**11**)	27	37
(**14**)	10	9

The mechanism of action of acetolactate synthase (Scheme 2) inspired the development of an analogous laboratory route (Scheme 3) which permits participation by two different carbonyl compounds in an acyloin condensation in a controlled manner.

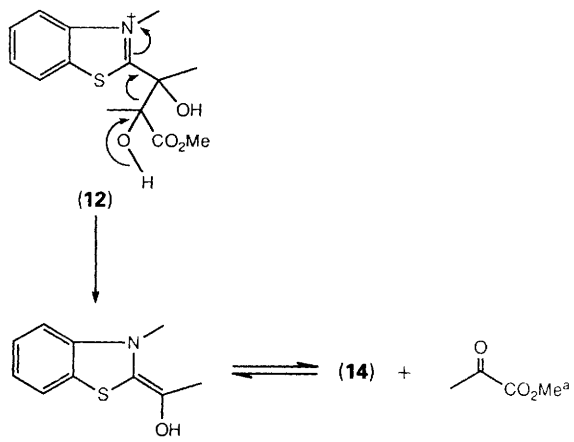
The attack by the thiazolium anion on pyruvate in the enzymatic reaction was paralleled by an attack of the C-2 anion of benzthiazole on acetaldehyde (step i, Scheme 3). The product was trapped as the t-butyldimethylsilyl derivative. In the enzymatic reaction, the corresponding initially formed adduct (**6**) undergoes decarboxylation to the acyl anion equivalent (**7**). In the synthetic route, this species was simulated by deprotonation of the derivative (**8**)[7] which was treated with methyl pyruvate to give a mixture of diastereoisomeric products (**9**). One of these diastereoisomers crystallised from the mixture and was shown by *X*-ray crystallography to be the (2*R*,3*R* + 2*S*,3*S*) racemate.[8] Since the chirality at C-3 is lost later in the sequence, this diastereoisomerism is of no significance from the synthetic point of view.

Fluoride ion deprotection of the crystalline diastereoisomer of (**9**) obtained led to a mixture of all four diastereoisomers of the diol (**10**), owing to the reversibility of the cleavage reaction in which methyl α-acetolactate is released (Scheme 3). Accordingly, the benzothiazole system was brought closer in reactivity to the thiamine pyrophosphate system by quaternisation of the nitrogen to give the salt (**12**) as a mixture of diastereoisomers. The salt mixture was decomposed without delay (methanol–triethylamine) to give as major products, methyl α-acetolactate (**13**), the diol mixture (**11**), and the 2-acetyl derivative (**14**) of *N*-methyldihydrobenzothiazole.



Scheme 3. *Reagents and conditions:* i, BuLi, −78 °C; ii, MeCHO; iii, $Me_2NCH_2CH_2NMe_2$, $Bu^tSi(Me)_2Cl$; iv, $MeCOCO_2Me$; v, Bu_4NF_4; vi, H^+; vii, Me_3OBF_4; viii, MeOH, Et_3N. [a] Yields from (**11**) are given in Table 1.

The diastereoisomeric mixture of diols (**11**) could be separated by chromatography. One of the diastereoisomers crystallised and was shown by *X*-ray crystallography to have the configuration (2*S*,3*R* + 2*R*,3*S*).[8] When the two diols (**11**) were separately taken through the remaining part of the synthetic sequence, the isolated yields of the three identified products were as given in Table 1. It is evident that release of methyl α-acetolactate competes with *N*-demethylation and retro-aldol cleavage, the latter process (Scheme 4) leading to the acetyl derivative (**14**). It also appears that the behaviour of the diastereoisomers of the diols towards product release is



Scheme 4. [a] Not identified.

significantly different. The acetyl derivative (**14**) is the benzothiazole analogue of 'active acetaldehyde' [(**7**), Scheme 2]. Corresponding compounds (as the hydroxyethylthiazolium species) are readily prepared from thiamine pyrophosphate.[9] The enzymatic route was thus successfully mimicked. Further development of the method is in hand.

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References

1 R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719.
2 H. Stetter, R. Rämsch, and H. Kuhlmann, *Synthesis*, 1976, 733; W. Tagaki and H. Hara, *J. Chem. Soc., Chem. Commun.*, 1973, 891.
3 J. Sheehan and T. Hara, *J. Org. Chem.*, 1974, **39**, 1196; W. Tagaki, Y. Tamura, and Y. Yano, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 478.
4 H. Stetter and H. Kuhlmann, *Chem. Ber.*, 1976, **109**, 2890; *Tetrahedron Lett.*, 1974, 4505; H. Stetter, W. Basse, and J. Nienhaus, *Chem. Ber.*, 1980, **113**, 690.
5 H.-D. Lutter and F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1125.
6 R. S. Chaleff and T. B. Ray, *Science*, 1984, **223**, 1443; R. A. LaRossa and J. V. Schloss, *J. Biol. Chem.*, 1984, **259**, 8753; D. L. Shaner, P. C. Anderson, and M. A. Stidham, *Plant Physiol.*, 1984, **76**, 545; T. B. Ray, *ibid.*, 1984, **75**, 827.
7 H. Chikashita, S. Ikegami, T. Okumura, and K. Itoh, *Synthesis*, 1986, 375; F. Jordan, Z. H. Kudzin, and C. B. Rios, *J. Am. Chem. Soc.*, 1987, **109**, 4415.
8 N. W. Alcock, D. H. G. Crout, G. Pike, and E. R. Lee, unpublished.
9 R. Kluger, K. Karimian, G. Gish, W. A. Pangborn, and G. T. DeTitta, *J. Am. Chem. Soc.*, 1987, **109**, 618.