Pergamon

Tetrahedron Letters 39 (1998) 19–22

TETRAHEDRON LETTERS

The Tetrazolylmethyl and Related Radicals: A Convenient Access to Tetrazoles and Other Heterocyclic Derivatives

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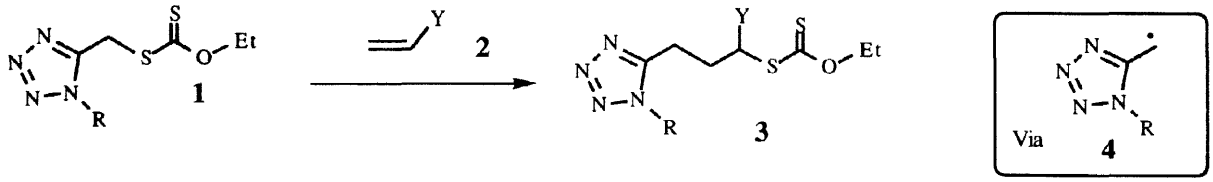
Received 1 October 1997; accepted 22 October 1997

Abstract : The tetrazole unit can be simply introduced by addition of the 5-tetrazolmethyl radical to a variety of terminal olefins using the xanthate transfer technology; the same principle can be applied to other heterocyclic systems such as imidazoles and benzothiazoles.

A tetrazole unit is not only comparable to a carboxylic acid moiety both in size and in acidity, but is is also metabolically more stable; it has thus been used as a carboxylic acid mimic in a wide number of compounds of biological interest such as antagonists of angiotensin II.[1] The stepwise building of these azole rings onto the substrate, usually by the addition of an azide under one form or another to a nitrile, remains a privileged strategy, especially in the case of aromatic tetrazole derivatives.[2] Only a few methods allow the direct introduction of the preformed heterocyclic ring and essentially all of the approaches are based on ionic processes. For example, Huff and co-workers[3] very recently applied the known but little used chemistry of the 5-tetrazolmethyl anion to construct a number of tetrazole containing structures. In contrast, as far as we know, the corresponding radical (**4**) does not seem to have been examined as a synthetic intermediate in this area. As part of our interest in the radical chemistry of xanthates,[4] we have found that such radicals can indeed be easily generated and captured to give a variety of highly functionalised and otherwise inaccessible structures. Moreover, the same approach can be extended to other equally important heteroaromatic systems such as imidazoles and benzothiazoles.



Scheme 1

The general outline of the method is displayed in scheme 1. The use of xanthate precursors such as **1** offers several major advantages over more traditional approaches: a) the process is cheap and convenient since no toxic heavy metal is involved; b) the method is compatible with a wide variety of functional groups and applicable to non activated but unhindered olefins; c) the final product is itself a xanthate and thus allows a great diversity of further modifications, either by another radical sequence or through the immensely rich chemistry of sulfur.

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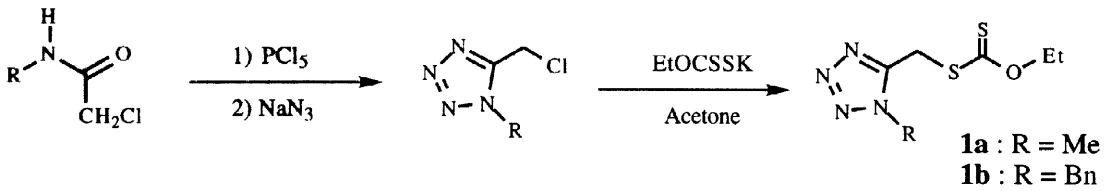
0040-4039/98/$19.00
PII: S0040-4039(97)10457-9

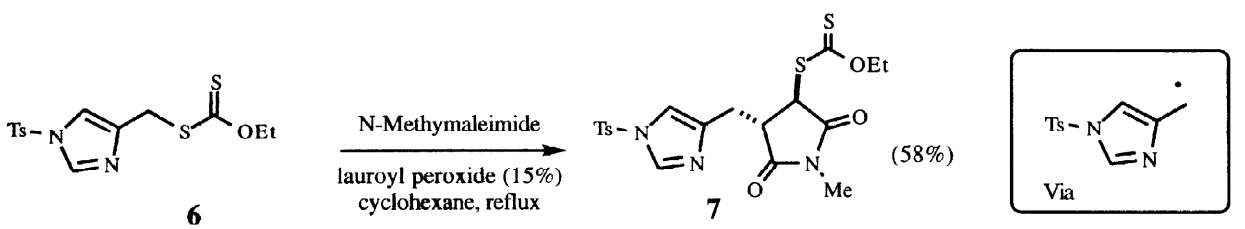
The requisite tetrazole xanthates are readily accessible and two such reagents, **1a** and **1b**, were prepared according to the sequence displayed in Scheme 2. Exposure of the imidoyl chloride derived from the appropriate chloroacetamide with sodium azide following the literature procedure[5] provided the two 5-chloromethyl tetrazoles which were then subjected to the action of potassium O-ethyl xanthate in acetone.



Scheme 2

Upon addition of a small quantity of lauroyl peroxide to a refluxing solution of tetrazolyl xanthate **1a** and allyl acetate in benzene, a smooth reaction occured to give the expected adduct **5a** in 72% yield after purification by chromatography.[6] As illustrated by the examples collected in the Table, a variety of tetrazole derivatives are easily accessible by simply modifying the olefinic trap. 1,2-Dichloroethane was used in place of benzene and yields were in general good; moreover, both electon-rich and electron-poor olefins such diethyl vinylphosphonate could be used, even though the tetrazolylmethyl radical would be expected to be electrophilic in character, by analogy with an α-alkoxycarbonylmethyl radical ($ROCOCH_2^{\bullet}$). This reflects in a sense the relative long life of the intermediate radicals when generated by the xanthate transfer method, thus allowing the inherently ambiphilic nature of radicals to be revealed. In other words, the addition of an electrophilic radical to an electrophilic olefin is slower than to an electron-rich olefin (other factors —e.g. steric— being equal) but occurs nevertheless.[7]

As a consequence of the mild and neutral reaction conditions, many of the commonly encountered functional groups are tolerated. Highly functionalised structures can therefore be rapidly assembled, the example involving the elaboration of a β-lactam or a latent amino acid being especially illustrative in this respect. In the former example, the reaction was performed on a rather small scale, which necessitated the use of greater amounts of initiator (36%) and did not proceed to completion (73% is the yield based on recovered starting material). Finally, the methyl group on the tetrazole moiety can be replaced by a benzyl group which can be in principle removed at a later stage if a naked tetrazole is the desired final product.

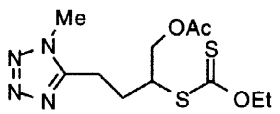
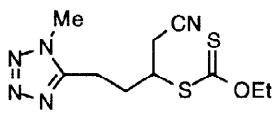
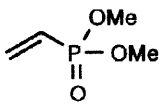
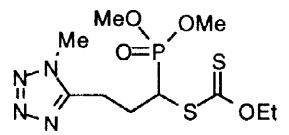
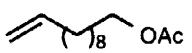
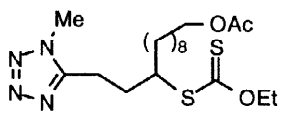
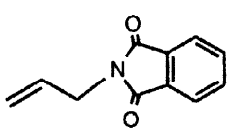
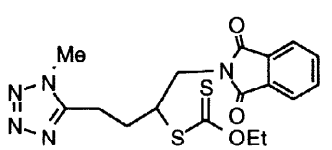
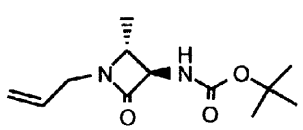
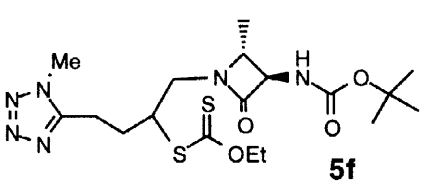
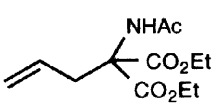
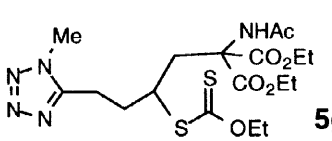
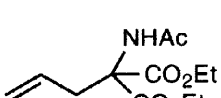
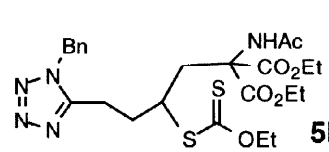


Scheme 3

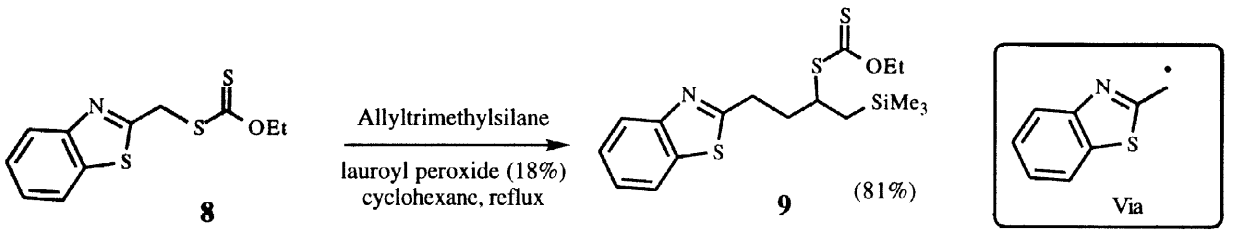
This new way of constructing tetrazole containing building blocks was easily extended to other heterocyclic systems. This is shown by the radical addition of the imidazole derived xanthate **6** to N-methylmaleimide to give compound **7** in 58% yield (scheme 3). Xanthate **6** was obtained in two steps from commercially available 4-hydroxymethylimidazole. First, 4-chloromethyl-1-*N*-tosylimidazole was prepared by tosylation and *in-situ* displacement of the labile tosylate group by a chloride ion and then treated with ethyl potassium xanthate in acetone to give **6** quantitatively.

It appears however that in this case an electrophilic trap is needed since the intermediate imidazolylmethyl radical failed to add to allyl acetate. A modification of the substitution pattern on the imidazole ring might be necessary to enhance its reactivity towards simple unactivated olefins.

Table. Radical addition of xanthates **1a** and **1b** to various olefins.

Substrate	Xanthate	% Initiator	Product	(Yield)
	**1a**	12%	 **5a**	(72%)
	**1a**	13%	 **5b**	(69%)
	**1a**	9%	 **5c**	(88%)
	**1a**	9%	 **5d**	(66%)
	**1a**	9%	 **5e**	(65%)
	**1a**	36%	 **5f**	(46%;73%)
	**1a**	9%	 **5g**	(73%)
	**1b**	12%	 **5h**	(74%)

In contrast, the benzothiazolylmethyl radical derived from **8**[8] added readily to the electron rich trimethylallylsilane to give the usual addition product **9** in 81% yield, as shown in scheme 4.



Scheme 4

In summary, the possibility of capturing the intermediate radicals in an *intermolecular* fashion using the present xanthate based approach allows an expedient, yet flexible and efficient, elaboration of a great diversity of complex structures starting from simple, readily available precursors. Tetrazoles, imidazoles, benzothiazoles and certainly many other heterocyclic systems which may be of pharmaceutical or agrochemical interest can be introduced under mild conditions without the need for toxic or expensive heavy metals.

Acknowledgements: We wish to thank Hoechst Marion Roussel and the Société de Secours des Amis des Sciences for very generous financial support (J.-B. S. and T. B.) and Mr Benoît Sortais for the preparation of compound **8**.

References and notes

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4. For a review of this work, see: Zard, S. Z. *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 672-685.
5. Uchida, M.; Komatsu, M.; Morita, S.; Kanbe, T.; Nakagawa, K. *Chem. Pharm. Bull.* **1989**, *37*, 322-326.
6. Typical experimental procedure : A solution of the xanthate (1 mmol) and olefinic trap (3 mmol) in degassed 1,2-dichloroethane (4 ml) is heated to reflux under argon with periodical addition of lauroyl peroxide (2-3% every 1.5-2 hrs) until consumption of the starting material. The solvent is distilled off under reduced pressure, and the residue purified by column chromatography on silica gel. The reaction can be run under more concentrated conditions (1 mmol of xanthate in 2ml (example **5f**) or even 1ml (example **9**) of solvent or the ratio of xanthate to olefin reversed as for example **5f** and **7** where 1mmole of olefin was used for 2 mmol of xanthate.
7. (a) Curran, D. P. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 4, pp 715-831. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986.
8. Made by treating benzothiazolylmethyl chloride (Samat, A.; Gugliemetti, R.; Metzger, J. *Helv. Chim. Acta.* **1972**, *55*, 1782-1801) with ethyl potassium xanthate in acetone.