Tributyltin hydride-mediated tandem reactions of dehydroalanines leading to α-substituted pyroglutamates

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Tributyltin hydride-mediated cyclisation of dehydroalanines produces an intermediate captodative radical, which can be trapped by reaction with oxygen- or carbon-centred radicals or (principally) electron-poor alkenes, to provide a quick approach to a variety of α-substituted pyroglutamates.

One important method for preparing substituted pyrrolidinones of biological importance, centres on the radical cyclisation of unsaturated haloamides.[1] These reactions generally involve cyclisation of a carbamoylmethyl radical on to an *N*-allyl double bond, in a (favoured) 5-*exo-trig* pathway, and this has been shown to provide a mild and flexible approach to a variety of pyrrolidinones.[2] More recently, however, an alternative approach to pyrrolidinones has been developed, which centres on the 5-*endo-trig* radical cyclisation of halo-enamides bearing an *N*-vinyl double bond.[3] This cyclisation is unusual (disfavoured) in that the initial carbamoylmethyl radical reacts to form a 5- rather than a 4-membered (or β-lactam) ring. The 4-membered ring would normally be expected from a (favoured) 4-*exo-trig* cyclisation. We have recently demonstrated that this method of cyclisation can be used to prepare pyroglutamates **4** from halo-dehydroalanines of type **1** (Scheme 1).[4] The regioselective formation of a pyroglutamate ring could result from a reversible cyclisation, which leads to the predominant formation of captodative radical **3**.

As the radical cyclisation of **1** proceeds *via* captodative radical **3**, this offers a potential method for preparing α-substituted pyroglutamates in one-pot or tandem reactions. Following our studies on the intramolecular reaction of radicals of type **3**,[6] this paper reports the (entropically more difficult) intermolecular trapping of these types of radical to form conformationally restricted α-substituted pyroglutamates.[7] Radicals of type **3** are shown to react with carbon- or oxygen-centred radicals to yield α-substituted pyroglutamates, such as **7** and **25**, in 13 and 32% yield, respectively. Reactions with chiefly electron-poor alkenes, such as methyl methacrylate, allow the direct formation of C-2 alkylated pyroglutamates such as **16**. During the course of this work, an unusual intermolecular radical addition followed by intramolecular cyclisation sequence has been shown to provide a quick approach to oxo-azepane derivatives such as **18**. This involves regioselective addition of carbamoylmethyl radical **2** to methyl methacrylate, to form tertiary radical **20**, before a 5-*endo* cyclisation can take place (Scheme 5). Radical **20** then undergoes a 7-*endo-trig* cyclisation to produce captodative radical **21**, which leads to the formation of oxo-azepane **18** on hydrogen-atom abstraction from tributyltin hydride.

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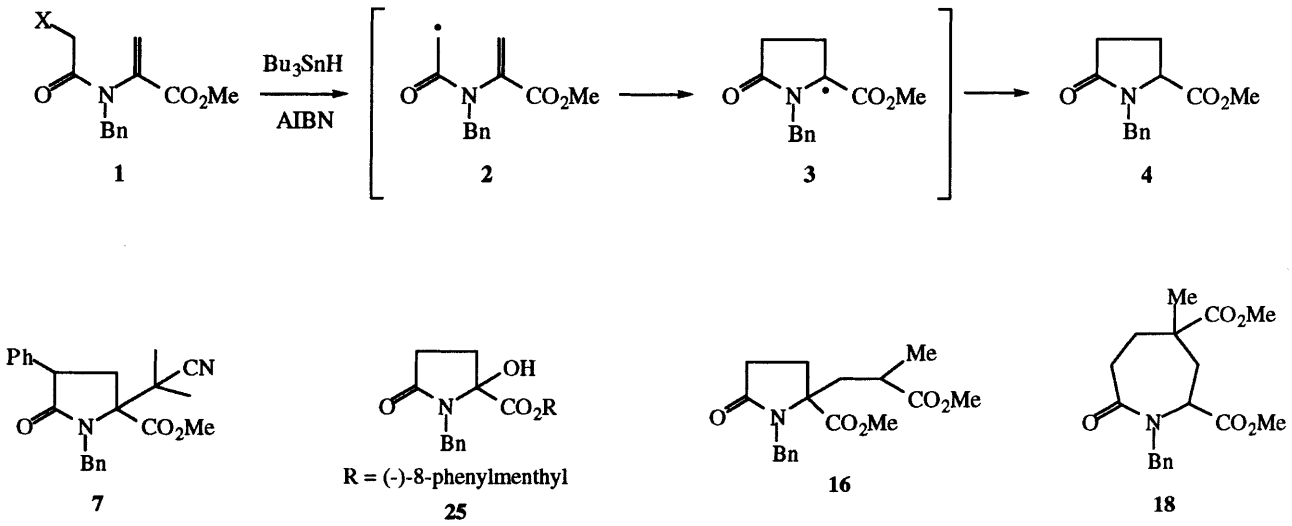
Techniques used: TLC, FTIR, ^{1}H and ^{13}C NMR, LRMS, HRMS

References: 12

Tables: 2

Schemes: 7



Scheme 1

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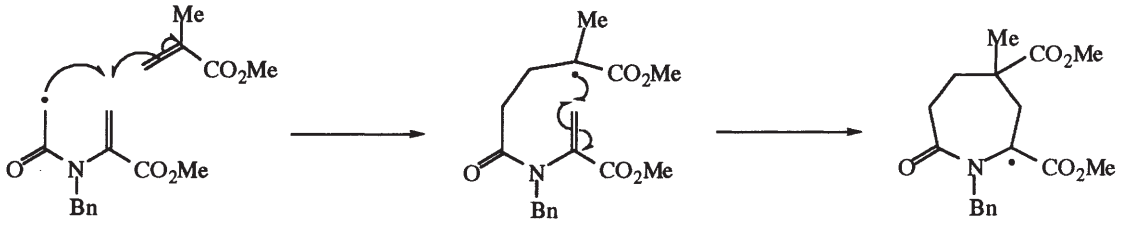

Scheme 5

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