Generation of aminoacyl radicals from 1-carbamoyl-1-methylcyclohexa-2,5 dienes: a new tin-free homolytic route to b**- and** g**-lactams**

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Radical induced homolyses of 1-carbamoyl-1-methylcyclohexa-2,5-dienes took place cleanly to yield aminoacyl radicals, with no competition from the alternative dissociation to methyl radicals: b**- and** g**-lactams were obtained from ring closures of suitably unsaturated model compounds.**

The quest for 'cleaner' free-radical precursors, independent of tin and other toxic metal involvement, and hence suitable for pharmaceutical syntheses,1 was aided by the discovery that esters of 1-methylcyclohexa-2,5-diene-1-carboxylic acid and of 2,5-dihydrofuran-2-carboxylic acid selectively furnished alkyl radicals on induced homolysis.2 These reagents were employed with moderate success in benign chain alkylations of olefins, and in cyclisations, affording product yields in the range 35–65%.3 The main limitation to the scope of their deployment was unwanted competition from an alternative dissociation of intermediate 1-methyl-1-carboxylatocyclohexadienyl radicals, that generated methyl radicals and benzoate esters as byproducts. These findings triggered the idea that analogous amides **1** might function as sources of aminoacyl radicals **3**. It was anticipated that the greater stability of aminoacyl radicals, in comparison to alkoxyacyls, would favour the desired dissociation of the delocalised radical **2** to aminoacyl **3**, over the alternative dissociation to Me **·** and amide **4** (Scheme 1). Moreover, it was expected that aminoacyls would not decarbonylate at moderate temperatures and hence could be incorporated in free-radical chain cyclisations.

To test this possibility, amide **7** was prepared as illustrated in Scheme 2. Benzylimine **5** was reduced to *N*-but-3-enylbenzylamine **6** with sodium borohydride and hence, by reaction with 1-methylcyclohexa-2,5-diene-1-carbonyl chloride,3 to amide **7**. Preliminary observations were carried out using EPR spectroscopy to monitor radical intermediates generated on photolysis of a solution of **7** in di-*tert*-butyl peroxide (DTBP) as initiator (In). Below about 30 $^{\circ}$ C the EPR spectrum showed a single radical with hyperfine splittings (hfs) and *g*-factor entirely as expected for cyclohexadienyl radical **8**; and similar to parameters previously reported for related radicals.3,4 Above this temperature the spectrum of radical **8** weakened and by about 60° C was entirely replaced by a new spectrum consisting of a simple nitrogen triplet ($g = 2.0018$, $a(N) = 2.21$ mT, $DH_{\text{pp}} =$ 0.24 mT). These EPR parameters are very similar to those of archetype aminoacyls *e.g.* EtNHC**·** (O) (*trans*-radical: *g* = 2.0018, $a(N) = 2.24$ mT)⁵ and we attribute the spectrum to radical **9**. Clear-cut spectroscopic evidence for the ring closed radical **11** was not forthcoming; partly because of sample boiling and weak spectra at higher temperatures.

Photolysis of a solution of amide **7** in DTBP with unfiltered light from a 400 W medium pressure Hg lamp at 50 °C for 8 h

afforded γ -lactam 12 as the main product (53%) together with smaller amounts of formamide **10** (37%) from direct reduction. Similar results were obtained simply by heating **7** with dibenzoyl peroxide (1.5 equiv.) in benzene for 24 h. Acyl radicals often cyclise in the *endo* mode6 and, in the case of **9**, this would have produced 1-benzylpiperidin-2-one containing a 6-membered ring. However, spectral evidence was unequivocal in support of structure **12** and none of the piperidine derivative was perceptible under our conditions.⁷ Most significantly, none of the aromatic amide of type **4** was detectable, even by GC-MS, and hence the adverse dissociation of delocalised radical **8** to Me**·** was negligible. This implied that amides of type **1** had high potential as clean aminoacyl radical sources, with promise of considerable generality for syntheses of a variety of lactams.

Carbapenems and nocardicins are important monocyclic antibiotic classes containing smaller, β -lactam rings that might, therefore, be accessible starting from appropriate amidocyclohexadienes. Radical cyclisations to afford 4-membered rings *via* 4-*exo-trig* ring closures are not generally favoured, but instances leading to β -lactams have been reported.⁸⁻¹¹ Suitably unsaturated aminoacyl radicals were generated from amides **13** and **17a**,**b**. EPR spectroscopic observations with amide **13** followed the same pattern as with amide **7** *i.e.* on photolysis with DTBP the spectrum showed the cyclohexadienyl radical at lower temperatures and aminoacyl radical **14** at higher temperatures $(z \text{ ca. } 40 \text{ °C})$. In preparative scale experiments at 60 °C, carbapenem derivative **15** was isolated as the major product (34%) along with formamide **16** (31%). Analogous aminoacyl radicals containing propargyl and cyanomethyl chains were generated from amides **17a** and **17b**. However, the formamides **18a**,**b** were the major products isolated. Neither of these radicals underwent efficient 4-*exo*-ring closure, pre-

Scheme 3

sumably because of the extra strain involved in forming 4-membered rings containing exocyclic double bonds.

In summary, therefore, radical induced homolyses of cyclohexadienyl amides of type **2** took place cleanly to yield aminoacyl radicals, with no competition from the alternative dissociation to methyl radicals. Model β - and γ -lactams were obtained from ring closures of alkenylaminoacyl radicals. Consequently, these amides, which are easily prepared from unsaturated amines and 1-methylcyclohexa-2,5-diene-1-carboxylic acid, furnish mild, tin-free routes to small, and probably medium ring lactams, eminently suitable for conversion to useful biologically active compounds.

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- 7 For example: carbamoylcyclohexadiene **7** (0.5 g, 1.8 mmol) in DTBP (1.3 cm³) was photolysed in a quartz tube at 60 °C for 6 h with light from a 400 W medium pressure Hg lamp. Remaining DTBP was evaporated and the residue chromatographed to give γ -lactam **12** (0.18 g, 53%); δ_H 1.25 (3H, d, *J* = 7 Hz), 1.55–1.65 (2H, m), 2.52 (1H, sextet, *J* = 7 Hz), 3.20 (2H, m), 4.48 (2H, AB), 7.2–7.4 (5H, m); δ_c 16.4 (CH₃), 27.1 (CH₂), 36.8 (CH), 44.6 (CH₂), 46.8 (CH₂), 127.5 (CH), 128.1 (CH), 128.6 (CH), 136.7 (C), 177.4 (C=O). Found: M⁺, 189.1158. C₁₂H₁₅NO requires *M*, 189.1154. Formamide derivative **10** (0.12 g, 37%) was also isolated.
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