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

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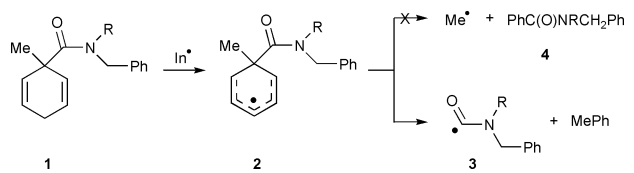
Radical induced homolyses of 1-carbamoyl-1-methylcyclohexa-2,5-dienes took place cleanly to yield aminoacyl radicals, with no competition from the alternative dissociation to methyl radicals: β- and γ-lactams were obtained from ring closures of suitably unsaturated model compounds.

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 by-products. 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.

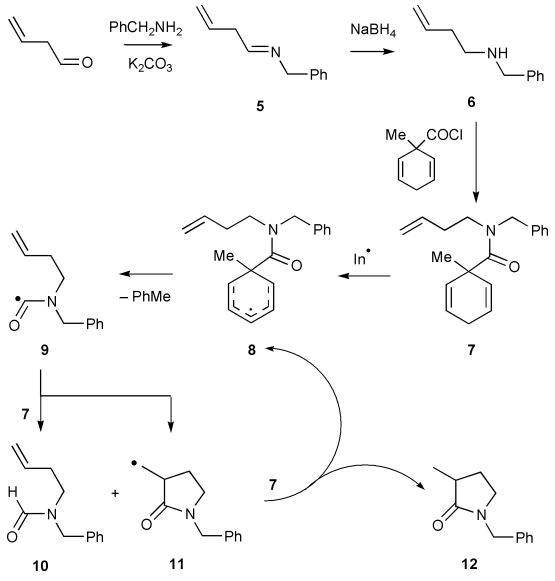
To test this possibility, amide **7** was prepared as illustrated in Scheme 2. Benzylimine **5** was reduced to *N*-but-3-enylbenzylamine **6** with sodium borohydride and hence, by reaction with 1-methylcyclohexa-2,5-diene-1-carbonyl chloride,[3] to amide **7**. Preliminary observations were carried 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 °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_{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* mode[6] 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 (> *ca.* 40 °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 1



Scheme 2

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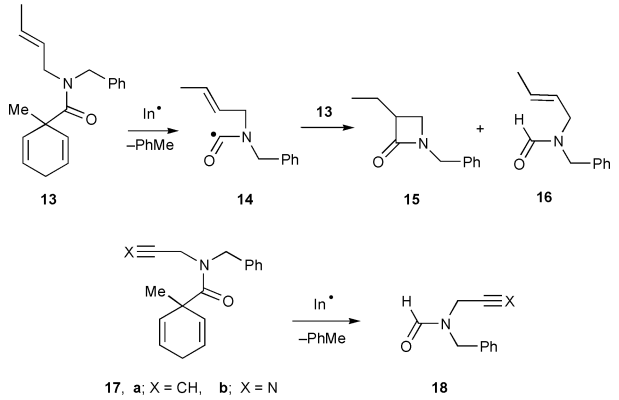

Scheme 3

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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Notes and references

1 P. A. Baguley and J. C. Walton, *Angew. Chem., Int. Ed.*, 1998, **37**, 3072.
2 G. Binmore, J. C. Walton and L. Cardellini, *J. Chem. Soc., Chem. Commun.*, 1995, 27.
3 G. Binmore, L. Cardellini and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1997, 757.
4 L. Lunazzi, G. Placucci and L. Grossi, *J. Chem. Soc., Perkin Trans. 2*, 1982, 875; R. H. Schuler, G. P. Laroff and R.W. Fessenden, *J. Chem. Phys.*, 1973, **77**, 456.
5 R. Sutcliffe and K. U. Ingold, *J. Am. Chem. Soc.*, 1981, **103**, 7868; H. Hefter and H. Fischer, *Ber. Bunsen-Ges. Phys. Chem.*, 1970, **74**, 493.
6 C. Chatgilialoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991.
7 For example: carbamoylcyclohexadiene **7** (0.5 g, 1.8 mmol) in DTBP (1.3 cm^3) 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 (CH_3), 27.1 (CH_2), 36.8 (CH), 44.6 (CH_2), 46.8 (CH_2), 127.5 (CH), 128.1 (CH), 128.6 (CH), 136.7 (C), 177.4 (C=O). Found: M^+, 189.1158. $C_{12}H_{15}NO$ requires M, 189.1154. Formamide derivative **10** (0.12 g, 37%) was also isolated.
8 G. B. Gill, G. Pattenden and S. J. Reynolds, *Tetrahedron Lett.*, 1989, **30**, 3229; G. B. Gill, G. Pattenden and S. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1994, 369.
9 H. Ishibashi, C. Kameoka, H. Iriyama, K. Kodama, T. Sato and M. Ikeda, *J. Org. Chem.*, 1995, **60**, 1276; H. Ishibashi, C. Kameoka, K. Kodama, T. Sato and M. Ikeda, *Tetrahedron*, 1996, **52**, 489.
10 A. J. Clark and J. L. Peacock, *Tetrahedron Lett.*, 1998, **39**, 1265.
11 L. Boiteau, J. Boivin, B. Quiclet-Sire and S. Z. Zard, *Tetrahedron*, 1998, **54**, 2087.