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COBALT-MEDIATED REACTIONS. A NEW SYNTHETIC APPROACH TO β-, γ - and δ-LACTAMS

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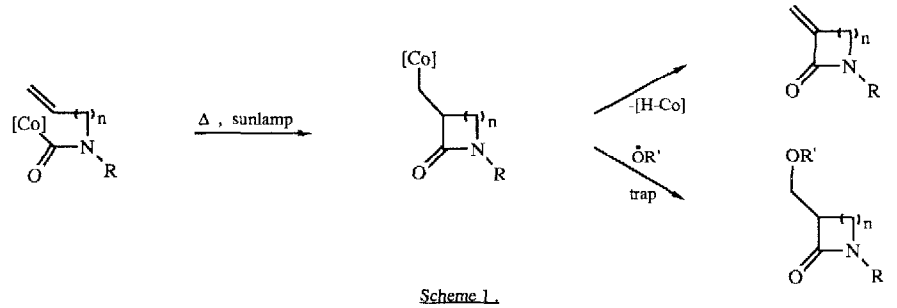
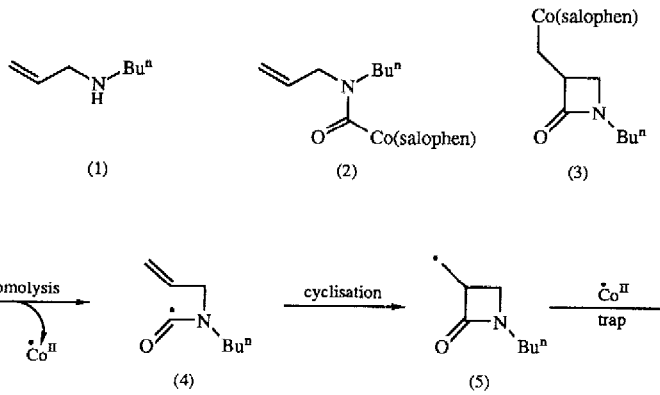
Summary: Unsaturated carbamylcobalt salophens, e.g. (2), undergo homolytic cleavage (Δ, sunlamp) producing carbamyl radicals, viz (4) which then undergo cyclisation, accompanied by trapping (with Co^{II} or TEMPO) or dehydrocobaltation, leading to functionalised β-, γ-, and δ-lactams e.g. (3), (6), (8), (11), (13) and (16).

The β-lactam family of antibiotics has acquired a status of unparalleled importance and significance in chemotherapy in recent years.[1] It is not surprising therefore that this class of compound has attracted considerable attention from both the synthetic chemist, with regard to the design of new apporaches to β-lactams, and the medicinal chemist in the search for novel, more active analogues.[2] Although less well investigated, 5- and 6-membered lactams are also of interest, particularly those α-methylene derivatives[3] which relate to the analogous and well-known naturally occurring anti-tumoral α-methylene-γ-butyrolactones.[4] In recent studies of cobalt-mediated radical reactions we have demonstrated the facile homolytic cleavage of a range of alkyl and acyl cobalt salophen reagents, and the oxidative additions of the resulting carbon centred radicals to C→C double bonds.[5] We now describe the extensions of this work to the synthesis of unsaturated carbamyl cobalt salophens, and the applications of these reagents in the synthesis of substituted β-lactams, and also 5- and 6-ring lactams (Scheme 1).



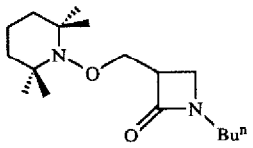
Scheme 1.

Thus, acylation of N-butyl-2-propenamine (1) with triphosgene (C_6H_6, N_2 C_5H_5N, 48h) first produced the corresponding carbamyl choride,[6] which was immediately reacted with sodium cobalt salophen reagent (THF, N_2, dark)[5] leading to the carbamyl cobalt salophen (2), as deep red crystals in 54% overall yield.[7] Irradiation of a solution of the cobalt salophen (2) in methylene dichloride, using light from a conventional 300W sunlamp (N_2, 48h), followed by work-up, chromatography and crystallisation, then led to the cobalt salophenmethyl substituted β-lactam (3) which was obtained as deep green crystals, m.p. 101°C (decomp), in 45% yield. The β-lactam (3) is produced from (2) by the now familiar sequence: (i) homolytic cleavage to the carbamyl radical (4), (ii) 4-exo-trig cyclisation, followed by (iii) trapping of the product radical centre (5) with Co^{II}; i.e. overall cyclisation accompanied by cobalt group transfer.[5] When a solution of the β-lactam cobalt salophen (3) was subsequently heated under reflux in dry toluene in the presence of tetramethylpiperidine oxide (TEMPO, 2 equivs.), a 71% yield of the adduct (6) was produced, which on hydrogenolysis (10% Pd-C, MeOH) gave the α-hydroxymethyl substituted β-lactam (7).[8]



During some experiments involving thermolytic cleavage of (3) in the presence of TEMPO, we also isolated small amounts (~4%) of the α-methylene-β-lactam (8)[9] in addition to (6). Usefully, when the carbamyl cobalt salophen (2) was heated in toluene alone, the product (8) of cyclisation followed by dehydrocobaltation was the main compound isolated (~25%). α-Methylene β-lactams have been prepared previously,[10] and they are of considerable use as Michael acceptors in reactions with a variety of nucleophiles, leading to a range of useful 3-substituted β-lactams. The new and specific synthesis of 3-hydroxymethyl substituted β-lactams from carbamylcobalt salophens by the cyclisation-trapping methodology, summarised above, might have relevance in new approaches to thienamycin (9) and related important antibiotics.

In parallel investigations, we have also studied the radical initiated cyclisations of 3-butenyl and 4-pentenyl substituted carbamyl cobalt salophens, viz (10) and (15), with a view to the synthesis of γ- and



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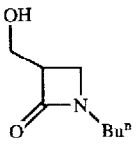

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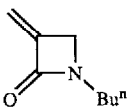

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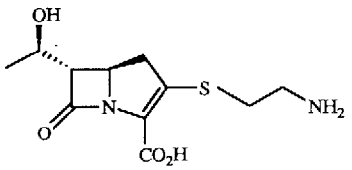

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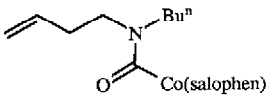

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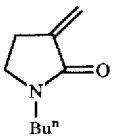

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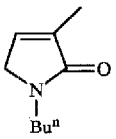

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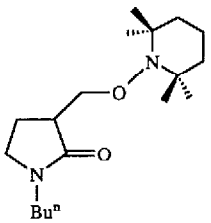

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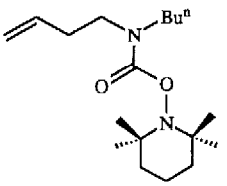

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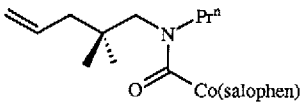

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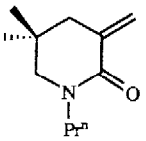

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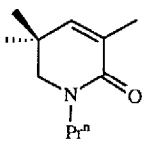

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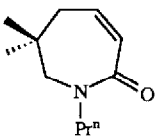

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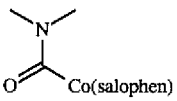

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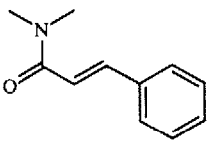

(20)

δ-lactams. Thus, when a red solution of the carbamylcobalt salophen (10) prepared from N-butyl-4-pentenamine, in toluene was heated under reflux for 50h, chromatography gave the α-methylene-γ-lactam (11) and the isomeric pyrrolidinone (12) products expected from 5-exo-trig cyclisation accompanied by dehydrocobaltation from (10), in a combined yield of 62%.[11] In addition, when (10) was irradiated in methylene dichloride in the presence of TEMPO, a satisfying 59% yield of the TEMPO-trapped cyclised material (13) was obtained, together with a 23% yield of the acylic adduct (14). A similar thermolysis of the 4-pentenyl substituted carbamylcobalt salophen (15) led to largely (16; 51%) and (17; 7%), but in this instance we were also able to isolate small amounts (∿7%) of the seven ring-lactam (18) resulting from 7-endo-trig cyclisation of (15).

The aforementioned oxidative cyclisations of terminal alkenyl substituted carbamylcobalt reagents can also be effected in an intermolecular sense using deactivated (electrophilic) C→C double bonds. Thus the carbamyl cobalt salophen (19) for example, reacts smoothly with styrene (10 equivs., Δ, C_6H_5Me) leading to the E-cinnamamide (20) in approximately 50-60% yield.

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