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Copper mediated cyclization of 1-substituted enamides, dienamides and trienamides: regiochemistry, indigoid formation and methyl migration-aromatisation

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ABSTRACT

Copper mediated cyclization of activated 1-substituted enamides occurs via a 5-endo radical-polar crossover process. Trichloroacetyl derivatives can undergo further reactions post cyclization (elimination of HCl or dimerization potentially via copper carbenoids intermediates). Reaction of α-halo trienamides derived from β-ionone furnish either β- or γ-lactams via 4-exo or 5-exo cyclizations respectively depending upon the enamide tautomer undergoing reaction. For the less reactive dichloroacetamide derivative a competing regioselective methyl migration–aromatization prior to cyclization is observed.

1. Introduction

The copper-mediated cyclization of α-haloenamides has attracted considerable interest in recent years. The regioselective outcome of cyclization is primarily dependent upon the substitution of the alkene. Thus, for 1 (R1 = H and R2, R3 ≠ H), 4-exo atom transfer cyclization is the major pathway, while for 3 5-endo cyclization to give 4 predominates, via a radical-polar crossover pathway. That enamides like 3 can undergo 5-endo-trig radical cyclization processes with ease has recently been attributed to their ground state conformations. Enamides prefer the E-amide rotamer and exhibit transient axial chirality on the NMR timescale. The twisting of the N-alkenyl bond away from planarity favours cyclization as it positions the reacting radical in the correct geometry to interact with the alkene π* orbital. Copper mediated cyclization of 1-functionalised enamides (1 R2, R3 = H) has received less attention. While cyclization of 1a failed with a range of copper catalysts, cyclization of the more reactive enamides 5 or 6 with Cu[bipy]Cl produced 7. Both 5 and 6 were found to be interconverting under the reaction conditions and cyclization appeared to preferentially proceed via the more substituted 6. Replacing the 1-alkyl group in 1a with a group capable of stabilizing thermodynamically (captodatively) the cyclized radical will facilitate 5-endo cyclization.

Cyclizations of 8a-b using Bu3SnH were found to be acyl group dependent, with 8a providing better yields than 8b.

Scheme 1. Radical cyclization of enamides

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Elimination with DBU furnished the N-unsubstituted enamine which after deprotonation (LDA) and further acylation furnished 13b. Compounds 13a and 13c exhibited broad peaks in their NMR spectra, indicative of slow rotation about the C-N bond of the enamide functionality.\textsuperscript{5b-c}

Scheme 3. Preparation and cyclization of 13a-c.

Efficient cyclization of 13a was achieved using 50 mol% Cu[TPMA]Cl in refluxing toluene for 2 hours, while 13b required longer (6 hours). Both produced the expected cyclized lactams 16a-b which could be deprotected to 17 in high yields \textsuperscript{17a} (TFA, reflux, 2 h, 72%), \textsuperscript{17b} (91 TFA:H\textsubscript{2}O, rt, 0.5 h, 97%). By analogy we expected that cyclization of the derivative 13c would lead to the dichloro derivative 20. However, heating 13c for 5 hours under the same conditions as before led to a dark purple product, identified as the indigoid derivative 18 in 34% yield (as a single isomer around the central tetrabutylstibutylalkene).\textsuperscript{11} Attempts to increase the yield by varying the amount of CuCl or the reaction time failed, and the rest of the mass balance was uncharacterized baseline material. Possible mechanisms for the formation of 18 are outlined in Scheme 4. Reaction of 13c with Cu[TPMA]Cl generates the initial radical which undergoes 5\text-superscript{-endo} cyclization to give the captodative radical 19. Oxidation of this captodative radical to the cation followed by elimination of a proton furnishes 20 while regenerating Cu[TPMA]Cl. At this point, the gem dichloride 20 may react rapidly with Cu[TPMA]Cl to furnish the copper carbonyl species 21 which undergoes dimerization to the observed product 18.\textsuperscript{12} This potentially represents a formal
radical-polar-carbene triple crossover reaction. However, it proved impossible to determine the stereochemistry of the tetrasubstituted alkene component of 18 directly, as suitable crystals for X-ray determination could not be obtained.

Scheme 4. Possible mechanisms for the formation of 18.

Structurally related molecules, such as trichotamine, have been reported to possess the (E)-geometry and have been accessed by dimerization of appropriate α-keto carbene-carbenoid precursors, (e.g. copper assisted thermolysis of azo lactams 24a or carbene mediated olefination of keto lactams 24b using trimethylphosphite). Similarly, CuCl mediated carbene formation / dimerization of structurally related α,α-dichloroesters have been reported to provide mainly (E)-isomers. Compounds of the indigo group, which have the same [3,3']-bipyrrolidene-2,2-dione core as 18, have been reported in the literature as highly coloured dyes. Thus, in the absence of X-ray data we tentatively assigned the central alkene geometry of 18 as (E). Molecules of this type have shown promise in molecular bulk heterojunction solar cell devices. An alternative mechanism for the generation of 18 from 20 can be envisaged where Cu[TPMA]Cl generates the radical 22 which after dimerization to 23 and CuCl mediated elimination of chlorine provides the observed product 18.

Scheme 5. Cyclization of dienamide 25a

Dienamides and trienamides: Dienamides 25a-b were prepared by acylation of the benzyl imine of trans-4-phenyl-3-but-2-enone. Cyclization of the more reactive substrate 25a occurred with 30 mol% Cu[TPMA]Cl exclusively in a 5-exo manner via the intermediacy of a benzyl radical, followed by elimination of HCl to give 26. Cyclization was also possible using a polystyrene bound solid supported catalyst based upon the hexamethyl triethylenediamine ligand (albeit in a slightly lower 61% yield in 5 hours). Reaction of bromide 25b under either conditions led to decomposition of the starting material and a complex mixture of unidentified products.

Trienamides 27a-c and 28a were prepared by acylation of the 4-methoxybenzyl imine of β-ionone. Reaction of β-ionone with 4-methoxybenzylamine in benzene at reflux, with 10 mol% ZnCl₂ for two days, furnished the imine in 80% yield. Acylation of the imine with either 2-bromo-2-methylpropionyl bromide, trichloroacetyl chloride or dichloroacetyl chloride and triethylamine in DCM furnished the desired enamides 27a-c and 28a. Acylation with either trichloroacetyl or dichloroacetyl chloride provided only one enamide regioisomer 27b-c while reaction with 2-bromo-2-methylpropionyl bromide furnished both regioisomers 27a and 28a in a 2:1 ratio. It was possible to separate both isomers by careful chromatography, although the sensitivity of the enamides led to low yields of purified compounds (12-30%).

Scheme 6. Cyclization of trienamides 27a-b and 28a.

Cyclization of the more substituted bromotrienamide 27a was attempted first by using 30 mol% Cu[TPMA]Br in toluene at reflux. After 5 hours no starting material remained and the β-lactam product 29a was isolated in 26% yield. No bromide 30a (X = Br) arising from atom transfer to the 4-exo cyclized radical was detected suggesting termination either occurred via oxidation to the allylic cation by Cu[TPMA]Br₂ followed by elimination, or by direct elimination of HBr from 30a at elevated temperature. No products arising from the alternative 5-exo or 5-exo cyclization modes were detected. The rest of the mass balance after chromatography was uncharacterized baseline material (presumably oligomeric products). Cyclization of the tautomerenic enamide 28a gave rise to the same β-lactam 29a (37%) and the three 5-exo products 31a-c in 84% combined yield (31a = 8%, 31b = 27%, 31c = 12%). No evidence of 6-exo, 7-exo or 8-exo cyclization was observed. NOE measurements confirmed the stereoselectivity of the alkenes in the products 31a-c. This suggests that 28a is converting to 27a under the reaction conditions and that 27a cyclizes exclusively in the 4-exo mode. Reacting the trichloroacetyl derivative 27b under the same conditions as 27a led to complete disappearance of starting material in only 3 hours and the chlorine atom transfer product 30b (X = Cl) was isolated as a 1:1 mixture of diastereomers (29%) along with the triene 29b (7%) arising from elimination of HCl from 30b. As for 27a, only 4-exo cyclization was observed, although in poor overall yield. The fact that atom transfer product 30b was isolated for 27b and not 27a suggests that the trienes 29a-b arise from elimination of HX from 30a-b rather
than Cu[TPMA]Cl₂ mediated oxidation of the resonance stabilized radical directly to a cation and loss of a proton.

Scheme 8. Cyclization of trienamide 27c.

Finally we investigated the cyclization of the substrate 27c. Reaction and cyclization of dichloroacetyl derivatives under atom transfer conditions are often problematic as both initiation and cyclization can be slow.¹⁸ Heating 27c with 30 mol% Cu[TPMA]Cl in toluene at reflux for 5 hours led to only recovered starting material. Heating for a further 6 days led to a complex mixture of products, but no starting material remained. The two products isolated pure enough for accurate identification (compounds 32 and 33) indicated that both oxidation of the cyclohexene ring and regioselective methyl migration had taken place. The stereochemistry of the β-lactam 33 was determined by NOE measurements. In this case initiation and cyclization are so slow that competing processes occur. Methyl migration and aromatization of conjugate carotenoid systems is important in the biosynthesis of aromatic carotenoids¹⁹ and the same rearrangement can be accomplished by reacting β-ionone with 2–4 equivalents CuCl₂ (30%) in DMF as solvent, albeit in low yields.²⁰ It is likely that any build-up of Cu[TPMA]Cl₂ in our reaction is responsible for this migration.

Conclusions

Copper mediated cyclization of activated 1-substituted enamides occurs via a 5-endο radical-polar crossover process. Trichloroacetyl derivatives can undergo further reactions post cyclization (elimination of HCl or dimerization potentially via copper carbenoid intermediates). Reaction of α-halo trienamides derived from β-ionone furnish either β- ϵ-y-lactams via 4-exo or 5-exo cyclizations respectively depending upon the enamide tautomer undergoing reaction. For the less reactive dichloroacetyl derivative a competing regioselective methyl migration-aromatization prior to cyclization is observed.

Acknowledgments

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References and notes


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   (f) m.p. 184.0–186.0°C. λmax (CHCl₃) 273 nm (ε = 29,853), 375 nm (ε = 6,931), 567 nm (ε = 11,018). vmax (film)/cm⁻¹ 2956, 1718, 1684, 1635, 1597, 1571 (400 MHz, CDCl₃) 7.78 (4H, d, J = 8.8 Hz), 7.12 (4H, d, J = 8.8 Hz), 7.08 (2H, s), 6.93 (4H, d, J = 8.8 Hz), 6.72 (4H, d, J = 8.8 Hz), 4.99 (4H, s), 3.89 (6H, s), 3.71 (6H, s); δC (125.8 MHz, CDCl₃) 186.3, 169.1, 164.3, 158.9, 147.4, 132.8, 129.3, 129.2, 132.3, 129.5, 114.0, 113.9, 111.5, 55.7, 55.2, 43.5, m/z 671 (MH⁺), 523, 460, 391, 341; [Found: (MH⁺) 671, 2388, C₅₆H₆₁O₁₂N₀ requires (MH⁺) 671, 2393]