Highly Accelerating Effect of Lewis Acids on Ruthenium(II)-Catalyzed Radical Addition Reactions

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Received November 12, 2001; accepted December 4, 2001

The intramolecular ruthenium(II)-catalyzed radical addition of the trichloroacetyl pendant group to the 2-oxazolone skeleton is greatly enhanced in the presence of catalytic Lewis acids including rare earth metal triflates, thus providing a convenient route to a highly potential chiral synthon for vic-amino alcohols.

Key words 2-oxazolone; radical addition; ruthenium(II) complex; Lewis acid; accelerating effect

Vicinal amino alcohol functions are structural units which are contained in a substantial number of bioactive compounds as well as in chiral sources which are widely used for asymmetric synthesis.1) We have previously demonstrated versatile synthetic routes for chiral vic-amino alcohols, which involve, as a key step, the highly efficient chiral functionalization of a simple 2-oxazolone heterocycle.2) Among these, the intramolecular RuCl₂-catalyzed radical addition of α-chloroacetyl pendant groups including trichloroacetyl and 2,2-dichloropropionyl groups as in compounds 1a—d to the 2-oxazolone skeleton proceeds with perfect regio- and diastereo-selectivity to give the 12-membered macrolides 2a—d, respectively, which, in turn, represent good precursors for the versatile synthesis of chiral 2-amino alcohols.3—5) This methodology was successfully applied to chiral synthesis of 2,2-dichlorodifluoro (3) and 2,2-difluorostatine derivatives (4),3) and the unusual amino hydroxy acids 55) and 65) with three contiguous chiral centers, which are key components of cyclosporins and bleomycins, respectively (Chart 1). There is still an ongoing need, however, to improve this radical addition which proceeds quite sluggishly and requires a reaction period in excess of 72 h to obtain reasonable yields. We have now found that the addition of Lewis acidic compounds such as lanthanoid triflates as additives results in a considerable reduction in reaction time. This paper describes the promising effects of Lewis acid additives on the remarkable acceleration of this type of Ru(II)-catalyzed radical cyclization reaction.

In a typical experiment, a solution of the 3-(1-apocamphane-carbonyl)-2-oxazolone (1a) bearing a trichloroacetyl pendant group, which is readily obtainable from DPPOx 6) (7) and the carboxylic acid (8), in benzene was refluxed in the presence of RuCl₂(PPh₃)₃ (0.1 eq) with La(OTf)₃ (0.1 eq) to give excellent yields of the sole cycloaddition product (2a) with excellent diastereoselectivity (above 99% de) within half an hour, as seen in Fig. 1. In the absence of La(OTf)₃, only an 11% yield of the macrolide was obtained, which was configurationally identical with 2a and which could be unequivocally determined by conversion to the authentic 4-methoxy compound (11) (Chart 2). This suggests that similar confor-
motions such as 10 with the anti-coplanar carbonyls due to dipole repulsion are operative at the transition states for both cyclizations, i.e., with or without Lewis acids.

As seen in Table 1, the Lewis acidic additives examined in this study involve the rare earth metal triflates as well as conventional Lewis acids such as BF₃ and ZnCl₂. All of the lanthanoid triflates examined as additives were highly effective, apparently independent of the Lewis acidity of the lanthanoid complexes. The other reagents, BF₃·OEt₂, Zn(OTf)₂, ZnCl₂ and EtAlCl₂ were equally useful. A minimal amount of La(OTf)₃ up to 0.05 equimolar amounts was sufficiently effective to result in a moderate acceleration (Fig. 1).

The exclusive cyclization to the 5-position of 2-oxazolone heterocycle may be rationalized by assuming the favored conformation (10) with the anti-coplanar amido carbonyls based on an intramolecular steric and electrostatic interaction, which leads to the less strained 12-membered ring structure. It seems likely that coordination of the Lewis acids to carbonyl groups and chlorine atoms would be responsible for the enormous acceleration observed, but the details of this are not presently clear.

When the 2-oxazolone derivative (1c) with a 2,2-dichloropropionyl pendant group in place of the trichloroacetyl group was applied to this Lewis acid mediated intramolecular cyclization, the cycloaddition proceeded in a similar manner to give the diastereomeric mixture of cyclic adduct (2c), as has been previously reported for the reaction performed in the absence of a Lewis acid. No apparent acceleration, however, was observed in this reaction which gave only a 34% yield even for a prolonged reaction time of over 70 h. The structure of 2c was confirmed by stereoselective conversion to the reductively dechlorinated 12 on treatment with tris(trimethylsilyl)silane in the presence of triethylborane at 78 °C.

The Ru(II)-catalyzed radical addition, as aided by lanthanoid triflates was explored for the intermolecular addition of carbon tetrachloride to 3-acyl-2-oxazolones (13a, b). The reaction resulted in the exclusive formation of trans-4-chloro-5-trichloromethyl-2-oxazolidinone derivatives (14a, b), but the acceleration effect of the triflates was only moderate (Table 2).

In conclusion, the intramolecular Ru(II)-catalyzed radical addition of the trichloroacetyl pendant group to the 2-oxazolone ring, which is dramatically accelerated by the presence of catalytic amounts of Lewis acids including the rare earth metal triflates, represents a promising tool for the chiral synthesis of 2-amino alcohols with vicinal stereogenic centers, by virtue of perfect diastereoccontrol and high efficiency.

Experimental
General Methods Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP 370 polarimeter. ¹H-NMR spectra were recorded in CDCl₃ with tetramethylsilane as the internal standard on JEOL ALPHAS-500
(500 MHz) and JEOL JNM-GX400 (400 MHz) spectrometers. MS and high resolution (HR)-MS were obtained with a JEOL JMS-DX303HF mass spectrometer.

tert-Butyl (1S,2R,4R)-2-[(2-Hydroxyethoxy)-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]carboxylate To a solution of tert-butyl (2R)-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)carboxylate (1g) (400 MHz) andJEOL JNM-GX400 (400 MHz) spectrometers. MS and high resolution (HR)-MS were obtained with a JEOL JMS-DX303HF mass spectrometer.

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(5H, m), 2.41—2.46 (1H, m), 3.26 (3H, s), 3.34—3.42 (3H, m), 3.54—3.59 (1H, m), 4.70 (1H, dd, J = 3.7, 7.7 Hz), 6.79 (1H, d, J = 2.2 Hz), 7.29 (1H, d, J = 2.2 Hz). Anal. Calcd for C_{16}H_{23}NO_5: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.03; H, 7.40; N, 4.52.

trans-3-Acetyl-4-chloro-5-trichloromethyl-2-oxazolidinone (14a) A solution of 3-acetyl-2-oxazolone 12 (12a) (100 mg, 0.79 mmol) in CCl_{4} (5 ml) was refluxed in the presence of RuCl_{2}(PPh_{3})_{3} (76 mg, 0.08 mmol) and Tb(OTf)_{3} (5 mg, 0.008 mmol) for 1 h. The mixture was passed through a silica gel-pad with EtOAc as eluent. Evaporation of the eluate followed by chromatography on silica gel (hexane : CH_{2}Cl_{2} 5 : 1) afforded 3-acetyl-4-chloro-5-trichloromethyl-2-oxazolidinone (13a) (107 mg, 49%) as colorless crystals, mp 56 °C. 1H-NMR (500 MHz) δ: 2.58 (3H, s), 5.14 (1H, d, J = 1.2 Hz), 6.36 (1H, d, J = 1.2 Hz). This was identical with the reported compound.10)

trans-3-[(1S,2R,4R)-2-(2-Methoxyethoxy)-7,7-dimethylbicyclo[2.2.1]heptane-1-yl]-4-chloro-5-trichloromethyl-2-oxazolidinone (14b) In a manner similar to the above, this was obtained as a diastereomeric mixture (1 : 1) in 75% yield as colorless crystals. Diastereomer a: [α]_{D}^{27} +15.0° (c = 1.02, CHCl_{3}). 1H-NMR (500 MHz) δ: 1.12 (3H, s), 1.12—1.19 (1H, m), 1.34 (3H, m), 1.67—1.79 (4H, m), 1.93—1.97 (1H, m), 2.17—2.22 (1H, m), 3.34 (3H, s), 3.39—3.49 (1H, m), 3.58—3.62 (1H, m), 4.62 (1H, dd, J = 3.7, 4.3 Hz), 5.11 (1H, d, J = 1.2 Hz), 6.44 (1H, d, J = 1.2 Hz). HR-MS (FAB) Calcd for C_{17}H_{23}NO_5Cl_{4}Na (MNa): m/z 484.0272. Found: m/z 484.0228. Diastereomer b: [α]_{D}^{27} -25.2° (c = 1.00, CHCl_{3}). 1H-NMR (500 MHz) δ: 1.14 (3H, s), 1.15—1.28 (1H, m), 1.35 (3H, s), 1.68—1.93 (5H, m), 2.21—2.28 (1H, m), 3.26 (3H, s), 3.28—3.37 (3H, m), 3.41—3.46 (1H, m), 4.58 (1H, dd, J = 3.7, 4.3 Hz), 5.11 (1H, d, J = 1.2 Hz), 6.51 (1H, d, J = 1.2 Hz). HR-MS (FAB) Calcd for C_{17}H_{23}NO_5Cl_{4}Na (MNa): m/z 484.0228. Found: m/z 484.0228.

References and Notes
8) This conformation might be supported by X-ray crystal analysis of the closely related 3-[2(R)-(2-methoxyethoxy)bicyclo[2.2.1]heptane-1-carbonyl]-2-oxazolone.11)