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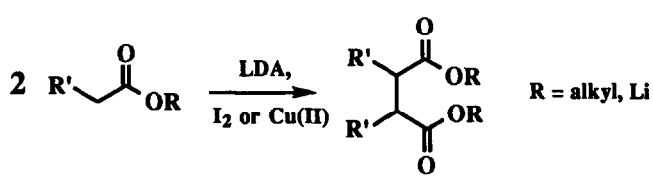
The Stereoselective Synthesis of Succinamide Derivatives *via* Enolate Oxidative Coupling

Ned A. Porter*, Qi Su, Jill J. Harp, Ian J. Rosenstein and Andrew T. McPhail
Department of Chemistry
Duke University
Durham, North Carolina, 27708

Abstract: *Enolates derived from optically pure oxazolidines couple with high stereoselectivity when oxidized with iodine or cupric salts.*

Although first reported in 1935 by Ivanoff,[1] the oxidative coupling of enolates has only found limited use for carbon-carbon bond formation during the past twenty-five years. The reaction proceeds to give good to excellent yields and has been utilized in the synthesis of a number of natural products.[2] Not only has its synthetic value been recently realized, but its mechanism has been the focus of a substantial research effort. Rathke[3] employed Cu(II) salts as oxidant and proposed a radical-radical coupling mechanism. Brocksom,[4] Belletire,[5] and Fox[6] have performed the reaction using I_2 as an oxidant.

Scheme 1



An electron transfer mechanism was postulated by Belletire who has also examined the stereoselectivity of the reaction and has observed a *dl*:*meso* ratio of 11:1 for the oxidative coupling of the dianion of phenylacetic acid while a 1:5 *dl*:*meso* ratio was found for the coupling of the enolate of ethyl phenylacetate.[5] It was also reported that the coupling of 3-phenylpropionic acid dianion gives mostly *dl* product. Although relative control of contiguous stereogenic centers is possible, there are no reports of control of absolute stereochemistry in this coupling reaction. We now report the synthesis of succinamide derivatives with excellent absolute stereocontrol *via* the coupling of chiral amide enolates.

The use of oxazolidines as chiral auxiliaries has proven successful for controlling the stereoselectivity of chemical reactions. Hegedus[7] has utilized oxazolidine auxiliaries in metal-carbene chemistry and we have

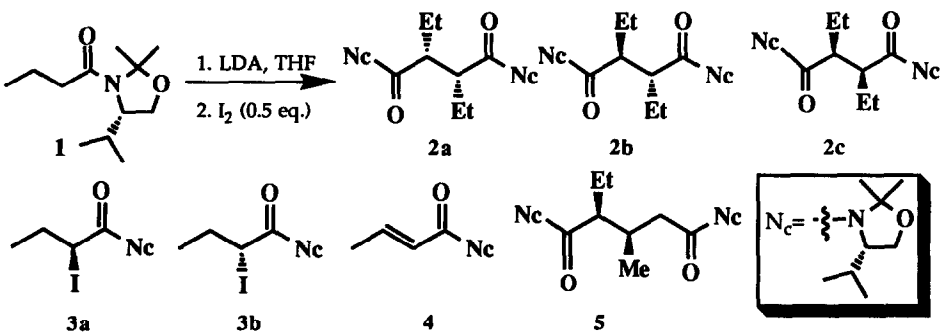
demonstrated control of stereochemistry in free radical addition and atom transfer reactions using oxazolidines, thiazolidines and substituted pyrrolidines as auxiliaries.[8] Thus, we decided to explore the possibility of utilizing the directing ability of the oxazolidine auxiliary for controlling the stereochemistry of the oxidative coupling reaction.

Oxazolidine **1** was readily synthesized in overall yield of 70% from commercially available valinol in two steps. This was achieved by reaction of valinol with acetone in the presence of $MgSO_4$ followed by subsequent acylation with butyryl chloride and N-methyl morpholine in methylene chloride **1**.

A typical procedure for the oxidative coupling of **1** follows. To a 0.3M solution of **1** in freshly distilled tetrahydrofuran at -78°C under an atmosphere of argon was added 1.1 eq. of lithium diisopropoylamide. The reaction mixture was kept at this temperature for 2.5h and subsequent inverse addition to a 0.5M solution of molecular iodine or $CuCl_2$ in tetrahydrofuran at -78°C *via* cannula was accomplished. The ice bath was removed after 30 min. and the reaction was allowed to warm to room temperature. Flash chromatography in 12.5% ethyl acetate/hexane separated the dimers from the other products. High performance liquid chromatography in 1% isopropanol/hexane gave complete separation of the dimers.

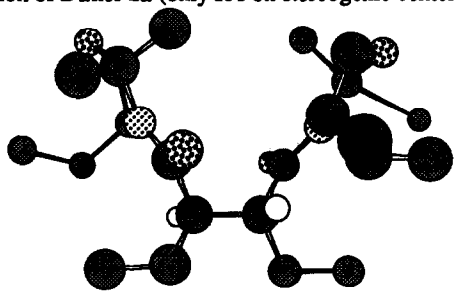
Oxidation of the enolate of **1** with molecular iodine at -78°C gave rise to the products, **2-5** (Scheme 2). All three possible diastereomers of the dimer **2** were formed in this reaction. The combined yield of the dimers was typically 40-50% after isolation by liquid chromatography. The ratio of *RR:RS:SS* i.e. **2a:2b:2c** was determined by gas chromatography to be 92:3:5 at -78°C and 80:14:6 at 0°C. The configurations of two of the diastereomers, **2a** and **2b**, were established by single crystal x-ray analyses.[9,10] The asymmetric crystal unit of the major diastereomer **2a** consists of two molecules with similar conformations; a view of the solid-state conformation of one of these molecules is presented in Figure 1. The other products of this reaction were the α-iodoamides **3a** and **3b**, the α,β-unsaturated amide **4** and the Michael adduct **5**. The ratio of **3a:3b** was 5:1 at -78°C. The configuration of **3b** and **5** were also determined by x-ray analysis.

Scheme 2

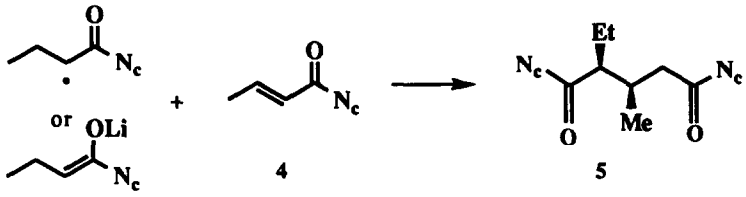


The addition of the radical or the enolate derived from **1** to amide **4** would explain the formation of **5** (Scheme 3). Only one stereoisomer of **5** was formed in this reaction. We note that Heathcock[11] and Yamaguchi[12] have shown that chiral enolates of amides add to α,β-unsaturated systems with a high degree of stereoselectivity.

Fig. 1 Solid-state Conformation of Dimer **2a** (only H's on stereogenic centers shown for clarity)



Scheme 3



When $CuCl_2$ was used in place of I_2, the ratio of **2a:2b:2c** was 98:1:1 for the reaction carried out at -78°C. The yield of the dimers was 50-55%. α-Chloroamides (the formation of which is similar to α-iodoamides **3a** and **3b**), were formed in an 11:1 ratio along with a small amount of **5**. The combined yields of **3a** and **3b** were 12% while that of **5** was 8%.

To test the possibility of an S_N2 pathway in the formation of **2a-c**, the enolate of **1** was allowed to react with the major iodide, **3a**. The dimer of the *RS* configuration should be the only isomer formed *via* a strict S_N2 mechanism. When this reaction was carried out, the products were **1**, α,β-unsaturated amide **4** and Michael adduct **5**. Again, only one stereoisomer of the Michael adduct was observed. No coupling products were seen in this reaction.[2] This suggests that an S_N2 pathway is not operative in the I_2 coupling since no dimers were formed in the model reaction.

The radical coupling mechanism was also tested. Reaction of the enolate of **1** with diphenyl-diselenide gave two α-phenylselenoamides in a ratio of 39:1. Photolysis of these phenylseleno compounds at 0° C in the presence of hexabutylditin gave **1**, **4**, and the dimers **2a:2b:2c** in a ratio of 5.5:6.1:1. The low stereoselectivity observed in this reaction, which we believe proceeds by an authentic radical coupling mechanism, suggests that the enolate oxidative coupling does not occur by encounter and coupling of free radicals. We note that these results do not exclude the intermediacy of a reactive radical pair that collapses with stereoselectivity. A mechanism involving a radical intermediate that undergoes addition to an enolate is likewise not excluded by the model studies.

The overall synthesis of the optically pure succinamide **3a** involves three steps from commercially available starting materials. Selectivity is excellent for the cupric salt catalyzed reaction and the *RR* product can be obtained pure by simple flash column chromatography. Although the mechanism of the coupling reaction remains in doubt, this report makes clear that absolute control of stereochemistry in enolate oxidative coupling is possible.

Acknowledgements

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9*Crystal Data* for **2a**: $C_{24}H_{44}N_2O_4$, M = 424.63, monoclinic, space group $P2_1$, a = 16.657(2) Å, b = 14.590(2) Å, c = 11.248(1) Å, β = 107.70(1)° (from 25 accurately centered reflections, 36°<θ<40°), V = 2604(1) Å^3, Z = 4, D_{calcd} = 1.083 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 5.5 cm^{-1}; crystal dimensions: 0.30 x 0.30 x 0.40 mm. Intensity data ($+h,-k,\pm l$; $\theta_{max.}$ = 75°; 5570 non-equivalent reflections) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-Kα radiation, graphite monochromator). The crystal structure was solved by direct methods (MULTAN11/82). Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, N, O; isotropic H) converged (max.shift:esd = 0.01) at R = 0.046 (R_w = 0.062) over 3332 reflections with $I > 3.0\sigma(I)$. Atomic coordinates, bond lengths, bond angles, and torsion angles for **2a** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

[10]The crystal structure analyses of **2b**, **3b**, and **5** will be reported elsewhere.

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