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# Stereoselective Radical-Mediated Cyclization of Norephedrine Derived α-Iodoamides: Experiments and TS-Modelling

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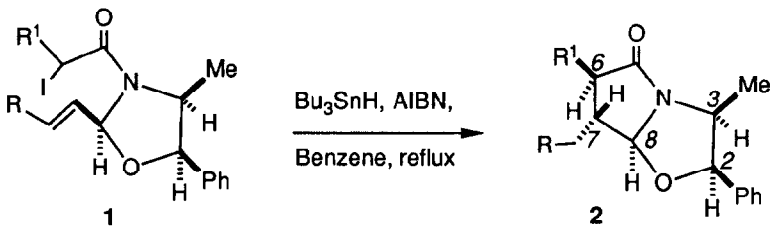
***Abstract:*** *Radical-mediated cyclization of norephedrine derived α-iodoamides 1 was found to be highly stereoselective (≥97:3) favouring diastereoisomer 2. Transition state modelling with a force field developed* ad hoc, *nicely predicts the stereochemical results.*

The understanding of the factors that control relative stereochemistry in radical cyclization reactions is a topic of continuous interest.[1] As part of a long term project aimed at investigating the stereodirecting effects of allylic stereocentres in addition reactions (e.g. nucleophilic[2] and electrophilic[3]) to π-systems,[4] we report in this Letter on the stereoselectivity of radical additions to double bonds[5] (Scheme 1).

**Scheme 1. Radical mediated cyclizations.**




R = H, Me, COOMe; $R^1$ = H
R = H; $R^1$ = Me

α-Iodoamides **1** were synthesized as outlined in Scheme 2. Norephedrine **3** was treated with the suitable α-chloroacyl chloride (Shotten Baumann) to give the α-chloroamide. Subsequent reaction with α,β-unsaturated dimethylacetals [refluxing benzene, pyridinium tosylate (Py-Ts), 4-Å mol. sieves] gave the corresponding oxazolidines in very good yield and high *cis* selectivity (Table 1).[6] Substitution of the chloride with iodide (NaI, acetone) gave oxazolidines **1** in good overall yield.

Slow addition (6 hr) of a 0.08 M solution of Bu3SnH (1.1 mol.eq.) in benzene containing a catalytic amount of AIBN (0.05 mol.eq.) to a 0.02 M refluxing benzene solution of α-iodoamide **1** (1 mol.eq.) gave, after work-up (KF-$H_2O$) and chromatography, bicyclic compounds **2** (Table 2).[7,8,9]

The stereostructure of bicyclic compounds **2** was proved by careful analysis of the $^1H$ coupling constants, and by n.O.e. difference experiments [particularly between C2-*H*, C8-*H*, and C7-C*H*$_2$R]. The electrophilic nature of the α-carbamoyl radicals, in analogy with all radicals α-substituted with electronwithdrawing groups,[1b] is well documented by the low cyclization yield in the case of the electron-poor olefin **1** [R=$CO_2$Me, $R^1$=H (Table 2, Entry 4)]. It is worth noting that the secondary radical generated from a racemic α-iodopropionate tether (Scheme

1, $R^1$=Me) undergoes stereocontrolled cyclization to give γ-butyro lactam **2** [R=H, $R^1$=Me (Table 2, Entry 3)] in which the newly formed stereogenic centre (C-6) bearing the original propionate methyl group is of high stereochemical purity (≥ 97% *si* face selectivity).[5c]

**Table 1.** ***Cis-trans*** **ratios and yields of Py-Ts mediated cyclizations [3→1].**

| Entry | Compound **1** | *cis:trans* (C-2/C-4) ratio[a] | cyclization yield (%) |
|---|---|---|---|
| 1 | R=H; $R^1$=H | ≥95:5[b] | 90 |
| 2 | R=Me; $R^1$=H | 80:20[c] | 80 |
| 3 | R=H; $R^1$=Me | ≥95:5[d] | 90 |
| 4 | R=$CO_2$Me; $R^1$=H | ≥95:5[e] | 80 |

[a]see footnote 6. [b]benzene, reflux, 10 hr, 0.25 mol.eq. Py-Ts. [c]benzene, reflux, 13 hr, 0.25 mol.eq. Py-Ts. [d]benzene, reflux, 14 hr, 0.25 mol.eq. Py-Ts. [e]benzene, reflux, 70 hr, 0.40 mol.eq. Py-Ts.

**Scheme 2.** **Synthesis of α-iodoamides 1.**

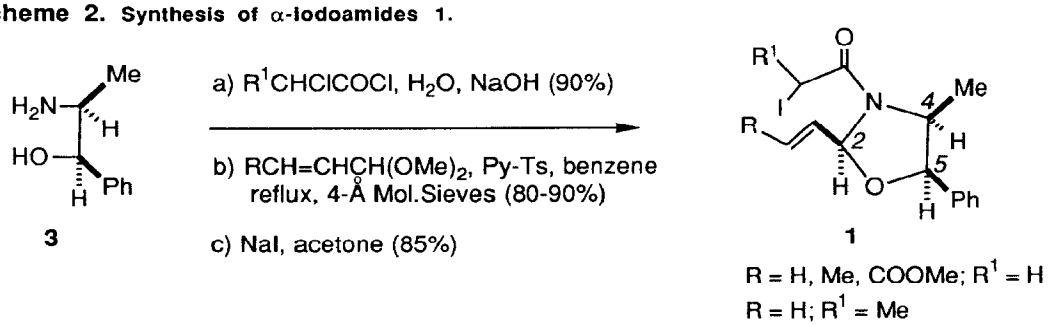



**Table 2.** **Diastereomeric ratios and yields of radical-mediated cyclizations [1→2].**[8]

| Entry | Compound **2** | *trans-cis* (C-7/C-8) ratio | *si-re* face (C-6) ratio | %yield |
|---|---|---|---|---|
| 1 | R=H; $R^1$=H | ≥97:3 | - | 55[8a] |
| 2 | R=Me; $R^1$=H | ≥97:3 | - | 60[8a,b] |
| 3 | R=H; $R^1$=Me | ≥97:3 | ≥97:3 | 80[8c] |
| 4 | R=$CO_2$Me; $R^1$=H | ≥97:3 | - | 32[8a] |

The stereoselectivity of the cyclization reactions was analyzed in detail with the application of MM-force field calculations to model transition structures.[10] The model was based upon MM-X force field,[11] with new parameters and constraints devised from the following considerations: (a) a C(radical)-C(olefin) distance = 2.5 Å was imposed, 17% longer than the *ab initio* calculated value for the malononitrile radical addition to ethylene (2.14 Å);[10g] (b) a rotational barrier (10.3 kcal $mol^{-1}$) was imposed around the C(radical)-C(carbonyl) bond[12a] to mimick the experimental restrained rotation of α-carbamoyl radicals;[12b,c] (c) a conformational preference was imposed[13a] for the rotamer with the double bond eclipsed with the allylic hydrogen.[13b]

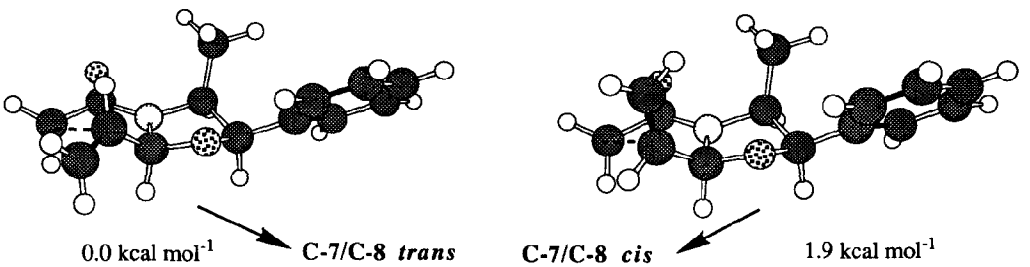
This model corresponds to an "early" transition state, with the radical and the olefin trigonal carbon atoms slightly pyramidalized, which retains the conformational preferences of the starting functional groups (α-carbamoyl radical and olefin).[15,16] Predictions of stereochemical ratios based on this model (Table 3) were in good agreement with the experimental results. It is interesting to observe that ground-state calculations (MM-X[11]

or MMOD[17]) on reaction products **2** (*trans*) and on their C-7 epimers (*cis*) predict almost no selectivity (ΔE ca. 0.4 kcal mol$^{-1}$ in favour of the *trans*). One example [R=H; R$^1$=H (Table 3, entry 1)] is shown in Schemes 3 and 4.

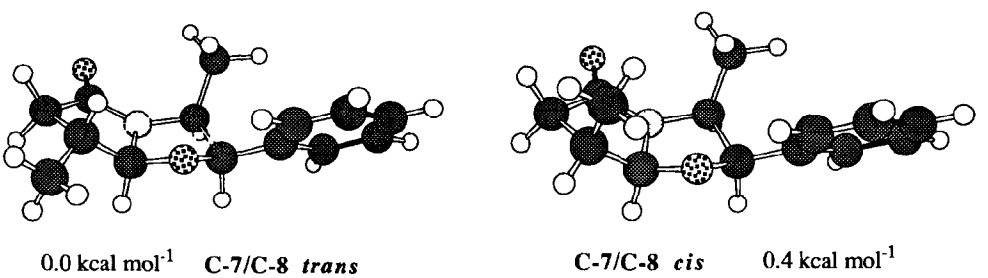
**Table 3. Prediction of diastereomeric ratios based on transition structure modelling.[14]**

| Entry | Compound **2** | *trans-cis* (C-7/C-8) ratio | *si-re* face (C-6) ratio |
|---|---|---|---|
| 1 | R=H; R$^1$=H | 94:6 [ΔE =1.9 kcal mol$^{-1}$] | - |
| 2 | R=Me; R$^1$=H | 93:7 [ΔE =1.8 kcal mol$^{-1}$] | - |
| 3 | R=H; R$^1$=Me | 94:6 [ΔE =1.9 kcal mol$^{-1}$] | 99:1 [ΔE = 3.3 kcal mol$^{-1}$] |
| 4 | R=$CO_2$Me; R$^1$=H | 90:10 [ΔE =1.5 kcal mol$^{-1}$] | - |

**Scheme 3.** Transition structure models of the radical cyclization leading to compound **2** [R=H; R$^1$=H (Table 3, entry 1)].




**Scheme 4.** Ground state models of compound **2** [R=H; R$^1$=H (*trans*)] and its C-7 epimer (*cis*).

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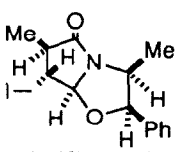
8. (a) In the case of $R^1$=H, the major side-products of the $Bu_3SnH$ mediated reaction at 80°C were the reduction products (acetamides). Acetamides were the only isolated products when the reaction was run at room temperature.

   (b) α-Iodoamide **1** [R=Me; $R^1$=H (Table 1, entry 2)] is a 80:20 (C-2/C-4) *cis:trans* mixture. The minor (C-2/C-4) *trans* isomer gave the cyclization product with high selectivity: *trans-cis* (C-7/ C-8) ≥97:3; 60% yield; absolute configuration 2R, 3S, 7S, 8R.

   (c) 1.5 mol.eq. of $Bu_3SnH$ was used for the cyclization of α-iodoamide **1** [R=H; $R^1$=Me (Table 2; entry 3)]. When 1.1 mol.eq. was used, variable amounts of compound **2'** were formed as by-product of the radical cyclization reaction.




**2'**

9. No *endo-(6)* ring closure product was observed, in contrast with the high *endo-(6):exo-(5)* ratios reported for the cyclization reactions of α-keto radicals (carbonyl group inside the forming ring), see: Curran, D.P.; Chang, C.-T. *J.Org.Chem.* **1989**,*54*,3140.
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11. MM-X Force Field from PC-Model-PI, version 3.2 (Copyright Serena Software). See also: *Advances in Molecular Modelling*, Vol. 2; Liotta, D., Ed.; JAI Press Inc., **1990**.
12. (a) The X-C(rad)-C(acyl)-Y torsional parameters were assigned values of $V_1$=0.0; $V_2$=2.9; $V_3$=0.0. (b) Strub, W.; Roduner, E.; Fisher, H. *J.Phys.Chem.* **1987**,*91*,4379. (c) Wu, L.-m.; Fisher, H. *Helv.Chim.Acta* **1983**,*66*,138.
13. (a) The H-C(stereocentre)-C(alkene)-C(alkene) torsional parameters were assigned values of $V_1$= -2.0; $V_2$=1.0; $V_3$=0.0. (b) The rotamer with the allylic hydrogen eclipsed with the double bond is usually the most stable conformer for alkenes, see: Bond, D.; Schleyer, P.v.R. *J.Org.Chem.* **1990**,*55*,1003. In 2-alkenyl-oxazolidines this rotamer is favoured both in the crystal structure (X-ray, see ref.6) and in $CDCl_3$ solutions (n.O.e. difference experiments).
14. Boltzmann distribution at 353°K (+80°C, refluxing benzene).
15. Because of the early transition state, factors that influence the ground-state alkene conformation would also be expected to influence the transition state in the addition reaction.
16. Details on the force field will be given in a full paper.
17. MacroModel (MMOD): Copyright Columbia University. See: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M .; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440.