Pergamon

Tetrahedron Letters 42 (2001) 6041–6044

TETRAHEDRON LETTERS

Influence of *N*-substituted lactams on acyclic free radical based hydrogen transfer

Yvan Guindon[a,b,*] and Mohammed Bencheqroun[a]

[a]*Institut de recherches cliniques de Montréal (IRCM), Bio-organic Chemistry Laboratory, 110, avenue des Pins Ouest, Montréal, Québec, Canada H2W 1R7*

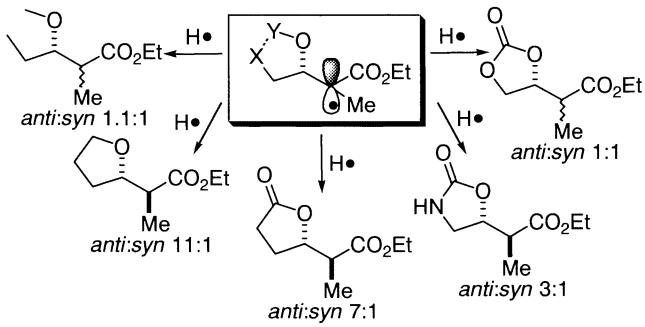
[b]*Department of Chemistry and Department of Pharmacology, Université de Montréal, C.P. 6128, succursale Centre-Ville, Montréal, Québec, Canada H3C 3J7*

Received 15 May 2001; accepted 5 July 2001

Abstract—*anti* Relative stereochemistry is achieved in the hydrogen-transfer reaction of a lactam adjacent to the carbon-centered radical. The sense of diastereoselectivity is reversed using *N*-substituted lactams, and optimal results favoring *syn* reduced products are obtained with an α-methylbenzyl group and a Boc group. © 2001 Elsevier Science Ltd. All rights reserved.

Carbon-centered free radicals on acyclic molecules[1] have started to receive considerable attention from organic chemists since it was found that significant diastereocontrol or enantiocontrol could be achieved in reactions involving these chemical intermediates. Our group has been particularly interested in the use of carbon-centered free radicals flanked by an ester and a stereogenic center bearing a heteroatom such as an oxygen or a fluorine.[2] Hydrogen-transfer reactions of such radicals have given high *anti* diastereoselectivity, particularly when the oxygen heteroatom is embedded in a ring.[2b,c] The increase of *anti* diastereoselectivity observed in the latter case is known as 'the exocyclic effect'.[2b,c] Scheme 1 shows a hydrogen-transfer reaction involving tributyltin hydride (Bu_3SnH) that gives an *anti*:*syn* ratio of 11:1 when a tetrahydrofuran ring is present adjacent to the carbon-centered radical. This result betters significantly the 1.1:1 ratio achieved with the acyclic counterpart. For the cyclic analogs, a decrease in diastereoselectivity is noted when X (Scheme 1) is an electron withdrawing group. In this scenario, the carbamate offers better diastereoselectivity than the carbonate, but the lactone gives the best result of the three, the *anti*:*syn* ratios being 3:1, 1:1, and 7:1, respectively. The results shown in Scheme 1 were rationalized using arguments such as minimization of allylic 1,3-strain, minimization of the dipole effect, and stabilization of the low-energy SOMO radical through hyperconjugation[3] (see the *anti*-predictive transition state **A**, Fig. 1).

The present study addresses two questions: (1) whether a nitrogen can be used as a heteroatom to replace the oxygen on the stereogenic center adjacent to the carbon-centered radical in order to give *anti* relative stereochemistry in hydrogen-transfer reactions as depicted by transition state **B** (R = H, Fig. 1); (2) whether the presence of a substituent (R group) on the nitrogen can reverse the radical facial preference of the hydrogen-transfer reaction to give the *syn* product. As seen in Fig. 1, the presence of an R group on the nitrogen may render more difficult the attack of Bu_3SnH from the bottom face of the radical and raise the energy of *anti*-predictive transition state **B**. As a consequence, a less energy demanding attack from the top face of the



Scheme 1.

Keywords: *N*-substituted lactams; hydrogen transfer; free radical; diastereoselectivity.

* Corresponding author. Fax: (514) 987-5789; e-mail: guindoy@ircm.qc.ca

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)01213-8

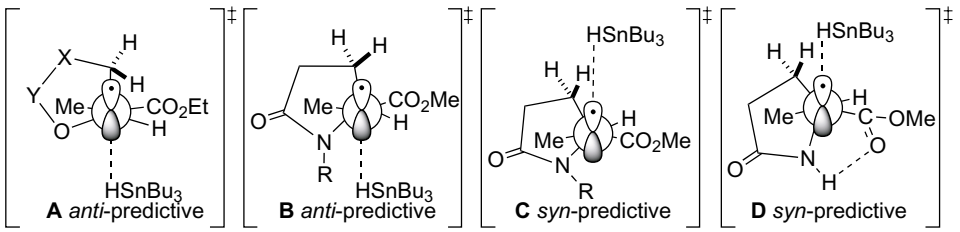
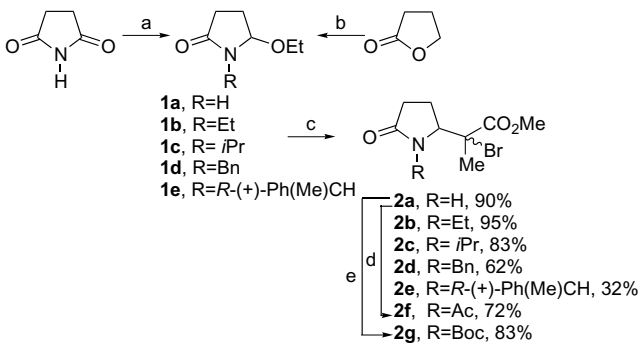


Figure 1. Proposed transition states for the hydrogen transfer step.

radical may be favored as shown in *syn*-predictive transition state **C**.

Lactam **2a** was chosen for the realization of the first part of this study. The idea behind this choice of substrate was that the presence of a carbonyl adjacent to the NH could impede the putative hydrogen bond between the NH and the carbonyl of the ester[4] (see *syn* competitive transition state **D**) that would otherwise complicate the interpretation of the results. The lactam was prepared by $NaBH_4$/HCl reduction of succinimide in EtOH to give the 5-ethoxy-2-pyrrolidinone **1a** in nearly quantitative yield.[5] The desired diastereoisomeric bromoester mixture **2a**[6] was obtained via a Mukaiyama reaction using bromo silyl ketene acetal[7] and ω-carbinol lactam **1a**.

A series of *N*-(substituted) lactams bearing different R groups was used for the second part of the study. The lactams were prepared via a general approach involving the reaction of different lithium aluminum amides with γ-butyrolactone[8] to afford corresponding hydroxy amides which were then converted to ω-carbinol lactams **1b**–**1e** using Swern oxidation conditions followed by treatment with HCl in EtOH (Scheme 2). The desired bromoesters **2b**–**2e** were obtained via Mukaiyama reactions with the appropriate ω-carbinol lactams **1b**–**1e**. The *N*-(Ac) **2f** and *N*-(Boc) **2g** derivatives of lactam **2a** were prepared using acetic anhydride and di-*tert*-butyl dicarbonate, respectively.[9] The resultant diastereomeric bromides were purified by flash chromatography, and the free-radical hydrogen-transfer reactions were then performed using the diastereoisomeric mixture.

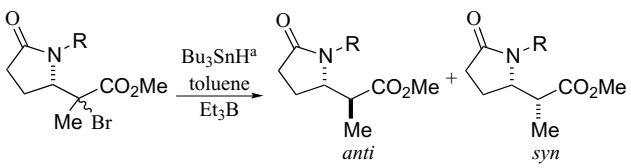


Scheme 2. *Reagents and conditions*: (a) (i) $NaBH_4$, EtOH; (ii) HCl 2N (pH 2), EtOH; (b) (i) $LiAlH_4$, Et_2O, then RNH_2 in Et_2O, 16 h; (ii) $(COCl)_2$, DMSO, Et_3N; (iii) HCl 2N (pH 2), EtOH; (c) $TiCl_4$, Me(Br)C=C(OMe)OTMS, CH_2Cl_2, −78°C; (d) $(Ac)_2O$, Et_3N, DMAP, CH_2Cl_2, 25°C, 6 h; (e) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, 25°C, 8 h.

As seen in Table 1, entry 1, the reaction of lactam **2a** with Bu_3SnH in the presence of Et_3B gave a result that was, in terms of preferred *anti* diastereoselectivity, similar to that obtained with the lactone (Scheme 1). This suggested that the NH could indeed replace the oxygen as the heteroatom on the stereogenic center even with the dipole effect between the C–N bond and the ester being less pronounced than in the case of the C–O bond (Fig. 1).

The introduction of an alkyl group on the nitrogen, in all cases, resulted in a reversal of diastereoselectivity from the *anti* isomer preference to a *syn* isomer preference (cf. entry 1 with entries 2–7). Ratios ranging from 1:3 to 1:8 were obtained for the Et, *i*Pr, and Bn substrates (entries 2–4). Interestingly, an impressive ratio >20:1 in favor of the *syn* product was obtained for *N*-(α-methylbenzyl) substrate **1e** (entry 5). The latter result can be accounted for by the sp^2 character of the C–N bond of the amide, which can impose a barrier of rotation (allylic 1,3-strain) that increases the rotamer population wherein the hydrogen on the stereogenic

Table 1. Radical-mediated reduction of lactams



Entry	Lactam	*anti*:*syn*		Yield (%)[c]
		Product	Ratio[b]	
1	**2a**, R = H	**3**:**4**	7:1	91
2	**2b**, R = Et	**5**:**6**	1:3	73
3	**2c**, R = *i*Pr	**7**:**8**	1:7	71
4	**2d**, R = Bn	**9**:**10**	1:8	91
5	**1e**, R = (R)-Ph(Me)CH-	**11**:**12**	1:>20	75
6	**2f**, R = Ac	**13**:**14**	1:5	78[d]
7	**2g**, R = Boc	**15**:**16**	1:>20	99[d]

[a] Conditions: To a cold solution (−78°C) of lactam (0.1 M) in toluene were added 2 equiv. of Bu_3SnH and 0.2 equiv. of Et_3B.
[b] Ratios of crude mixture products were determined by ^1H NMR.
[c] Isolated yields of reduced products.
[d] The reaction was performed in Cl_2Cl_2.

center of the α-methylbenzyl group is planar to the carbonyl of the amide. This conformation forces the two substituents (methyl and benzyl) to be quasi orthogonal to the heterocycle making even more difficult the bottom face trajectory of the Bu_3SnH (Fig. 2).

The reduction of *N*-(Acyl) bromo lactams was also considered in this study. As seen in entry 6, the *N*-(Ac) substrate gave a 5:1 ratio in favor of the *syn* product, while an excellent ratio >20:1 was obtained for the *N*-(Boc) derivative. Our rationale for the latter result is that the two carbonyls take on a *synperiplanar* or *synclinal*[10] conformation that positions the *tert*-butyl group in the trajectory of the bottom face Bu_3SnH attack (Fig. 2). The conformational arguments considered herein have been shown to be applicable to early transition states, which are normally invoked when free-radical intermediates are involved.[11] Of additional interest is that the mild basic treatment of the *N*-(Boc) reduced lactam **16** [MeONa, MeOH, 0°C, 10 min, 80%] led exclusively to an acyclic β-*N*-(Boc)-amino ester,[12] which belongs to a family of compounds with a large range of biological activity.

Literature suggests that the relative configuration of the reduced products can be established by the correlation of NMR chemical shifts.[13] In this study, the resonance of the methyl group adjacent to the ester function for the *syn* compounds was slightly downfield relative to that of the *anti* isomers as already seen in previously published results.[2] The NMR assignments were verified by X-ray crystallographic structure of the reduced *N*-benzylated *syn* product **10** (Fig. 3) and were further verified through a series of chemical transformations. Benzylation of the major reduced product **3** (entry 1) gave a compound identical to the minor *N*-(benzylated) product **9** (entry 4), confirming the *anti* relative diastereoselectivity obtained for the reduction of lactam **2a**. Similarly, Boc cleavage of the major reduced product **16** (entry 7), having given a product that was the same as the minor reduced lactam **4** (entry 1), corroborated that the reduction of *N*-(Boc) bromo lactam **2f** had in fact led to the formation of the *syn* product.

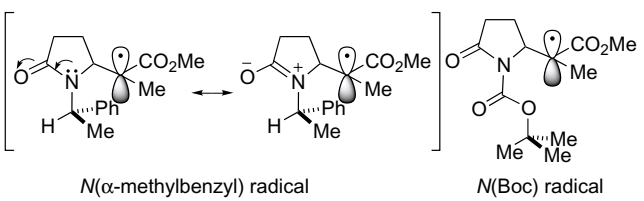


Figure 2.

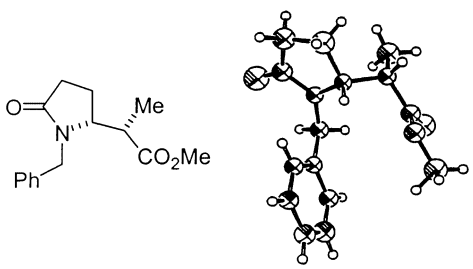


Figure 3. X-Ray crystallographic structure of **10**.

In conclusion, the present study indicates that a nitrogen can replace an oxygen as the heteroatom in the hydrogen-transfer paradigm studied herein to give access to the *anti* product. Alternatively, the sense of diastereoselectivity can be reversed by adding substituents on the nitrogen, while the use of α-methylbenzyl and Boc groups in such reactions can provide optimal results favoring *syn* isomers.

Acknowledgements

This work was supported financially by NSERC. We thank Dr. Brigitte Guérin and Ms. LaVonne Dlouhy for their assistance in the preparation of this manuscript.

References

1. (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296; (b) Liotta, D. C.; Durkin, K. A.; Soria, J. J. *Chemtracts* **1992**, *5*, 197; (c) Miracle, G. S.; Cannizzaro, S. M.; Porter, N. A. *Chemtracts* **1993**, *6*, 147; (d) Smadja, W. *Synlett* **1994**, 1; (e) Giese, B.; Damm, W.; Batra, R. *Chemtracts* **1994**, *7*, 355; (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions–Concepts, Guidelines and Synthetic Applications*; VCH: New York, 1996; (g) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562; (h) *Radicals in Organic Synthesis*, 1st ed.; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH, 2001; Vol. 1.
2. (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845; (b) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166; (c) Guindon, Y.; Faucher, A.-M.; Bourque, É.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276 and references cited therein.
3. Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, É.; Jung, G. *J. Org. Chem.* **1995**, *60*, 288.
4. (a) Curran, D. P.; Abraham, A. C.; Liu, H.-T. *J. Org. Chem.* **1991**, *56*, 4335; (b) Kündig, E. P.; Xu, L.-H.; Romanens, P. *Tetrahedron Lett.* **1995**, *36*, 4047; (c) Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507.
5. Hubert, J. C.; Steege, W.; Speckamp, W. N.; Huisman, H. O. *Synth. Comm.* **1971**, *1*, 103.
6. Compound **2a**: (Less polar) mp 81°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (broad s, 1H), 3.82 (dd, J=8.0, 4.4 Hz, 1H), 3.82 (s, 3H), 2.43–2.30 (m, 3H), 2.19–2.12 (m, 1H), 1.85 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.26, 170.81, 61.83, 60.10, 53.45, 29.58, 23.08, 22.03. Anal. calcd for $C_8H_{12}BrNO_3$: C, 38.42; H, 4.84; N, 5.60.

Found: C, 38.32; H, 5.02; N, 5.58. (More polar) mp 130°C; ^{1}H NMR: 6.66 (broad s, 1H), 4.06 (dd, $J=5.2$, 1.3 Hz, 1H), 3.81 (s, 3H), 2.46–2.22 (m, 3H), 1.94–1.84 (m, 1H), 1.83 (s, 3H); ^{13}C NMR: 177.80, 170.50, 63.50, 60.50, 54.80, 30.00, 23.90, 23.80. Anal. calcd for $C_8H_{12}BrNO_3$: C, 38.42; H, 4.84; N, 5.60. Found: C, 3.32; H, 4.85; N, 5.57.3. ^{1}H NMR: 6.59 (broad s, 1H), 3.75 (q, $J=7.5$ Hz, 1H), 3.67 (s, 3H), 2.44 (qd, $J=7.0$, 1.5 Hz, 1H), 2.31–2.17 (m, 3H), 1.79 (m, 1H), 1.14 (d, $J=7.0$ Hz, 3H); ^{13}C NMR: 177.76, 174.72, 55.82, 51.91, 45.26, 29.78, 24.73, 12.94. Compound **4**: ^{1}H NMR: 6.88 (broad s, 1H), 3.90–3.83 (m, 1H), 3.66 (s, 3H), 2.45 (qd, $J=7.0$, 1.5 Hz, 1H), 2.31–2.17 (m, 3H), 1.79–1.70 (m, 1H), 1.17 (d, $J=7.0$ Hz, 3H); ^{13}C NMR: 178.27, 177.76, 55.53, 44.37, 29.69, 24.49, 12.55. Anal. calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.02; H, 7.60; N, 8.06.

7. Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554.
8. Solladié-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.* **1992**, *57*, 5831.
9. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.
10. See, X-ray structure of *N*-(BOC) protected pyroglutamic ester: Baldwin, J. E.; Miranda, T.; Moloney, M. *Tetrahedron* **1989**, *45*, 7459.
11. Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* **1993**, *34*, 5885. See Ref. 1e.
12. See Ref. 9. To explain the regioselectivity of the methanolysis, the authors contend that the *tert*-butyl group exerts a steric influence on the course of the reaction, thus rendering the *amide* carbonyl more susceptible to nucleophilic attack.
13. Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024–2030.