Highly Diastereoselective Formation of Substituted Indolizidines and Quinolizidines by Radical Cyclization

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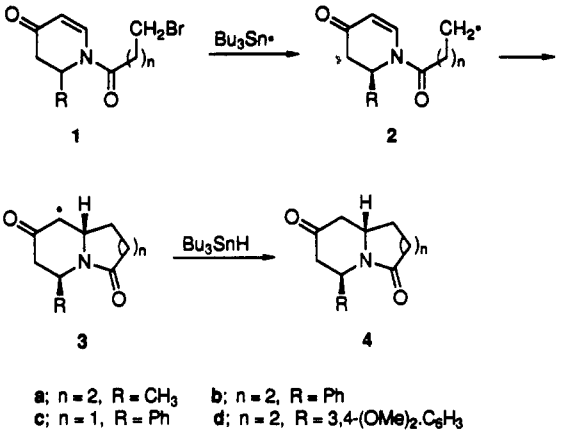
Summary: 2-Substituted 2,3-dihydro-4-pyridinones (e.g., **1a**) bearing an (ω-bromoacyl)-, (*o*-bromoaroyl)-, or (*o*-bromophenyl)acetyl group on nitrogen, when treated with tributylstannane, undergo highly diastereoselective cyclization by intramolecular homolytic addition anti to the substituent at C-2; molecular mechanics calculations support the view that the diastereoselectivity arises from the nonbonded interaction between the substituent and the amide carbonyl group.

The stereochemistry of annelation of carbocyclic compounds by radical cyclization onto a suitably disposed double bond is controlled primarily by stereoelectronic factors which require the approach of the radical center to be in a plane orthogonal to the nodal plane of the π system and to pass through a transition structure in which the new bond is relatively long (*ca.* 2.3 Å) and forms an angle with the double bond close to the tetrahedral angle.[1] This imposes almost exclusive cis stereochemistry on the newly formed ring junction.[2,3] Consequently, the stereochemistry of the new bond with respect to substituents (other than those at the radical center or on the double bond) is defined by their relationship to the side chain in the uncyclized radical. However, in species such as **2** (*n* = 1 or 2) where the radical chain is attached to a nitrogen atom which is planar, or can undergo rapid inversion,[4] the stereoelectronic requirements can be satisfied by radical addition to either face of the existing ring. The aim of the present work was to determine to what extent substitution at C-2 in **2** will affect the direction of intramolecular radical addition and hence control the diastereoselectivity of cyclization.

Previous work[5] has shown that the alkyl substituents in *N*-acyl-2-alkylpiperidines and related compounds preferentially assume an axial orientation. Nevertheless, *intermolecular polar addition* to substituted *N*-acyldihydropyridones occurs mainly on the same face as the substituent to afford cis-disubstituted products.[6] We have now found that in species such as **2** *intramolecular holmolytic addition* occurs with very high diastereoselectivity on the opposite face to the substituent at C-2 to afford products in which the newly formed bond is trans to the substituent. Not only do the reactions described in this paper provide further information about the factors affecting the diastereoselectivity of radical processes, but they should also be useful for the straightforward but highly diastereoselective syntheses of a number of important indolizidine and quinolizidine alkaloids. Herein, the preparation of the simple alkaloids (±)-myrtine (**15**) and (±)-lasubine-I (**16**) provide illustrative examples.

In a typical experiment, the bromide **1a**, obtained in 92% overall yield from 4-methoxypyridine by the general procedure previously described by Comins,[6,7] was heated in refluxing benzene under nitrogen while tributylstannane and a catalytic amount of AIBN in benzene were added slowly from a syringe pump. Chromatography of the



a; n = 2, R = CH_3 **b**; n = 2, R = Ph
c; n = 1, R = Ph **d**; n = 2, R = 3,4-$(OMe)_2$-C_6H_3

product afforded the quinolizidinedione **4a** in 91% yield and its diastereoisomer in 4% yield. The stereochemistry assigned to the products was based on the previous observation that in compounds of this type the proton at the ring junction of the trans isomer resonates at lower field than does that in the cis isomer.[8] It was confirmed by reduction of **4a** with lithium aluminum hydride followed by oxidation of the alcohol so formed to give (±)-myrtine (**15**) with spectral characteristics identical to those previously reported.[9] The reaction of **1b** with tributylstannane gave solely **4b** (89%) and appeared to be completely diastereoselective. Formation of the indolizidine derivative **4c** (80%) from **1c** was equally selective.

Reactions proceeding by aryl radical cyclization were also highly diastereoselective. Thus, treatment of the aryl bromide **5a** with tributylstannane gave solely **6a** (91%); no other product could be detected. The stereochemistry of **6a** was determined by X-ray crystallography[10] which also showed that the phenyl substituent occupies a

(1) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874.
(2) For some examples see: Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811. Wolf, F.; Agosta, N. C. *J. Chem. Res., Synop.* **1981**, 78. Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. Mohammed, A. Y.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 588.
(3) For discussions of the diastereoselectivity of some radical annelation reactions see: (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (c) Stork, G. In *Selectivity—A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Basel, 1984; p 281.
(4) Examples of the inversion of a bridgehead nitrogen atom during the course of free radical annelation are given in: Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269.
(5) Aripovskii, A. V.; Sakharovskii, V. G. *Russ. J. Phys. Chem.* **1989**, *63*, 754. Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(6) See, for example: Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549.
(7) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315.
(8) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445.
(9) Slosse, P.; Hotele, C. *Tetrahedron Lett.* **1979**, *20*, 4587; *Tetrahedron* **1981**, *37*, 4287.
(10) X-ray diffraction data will be published in *Crystallogr. Acta* and deposited with the Cambridge Crystallographic Data Centre.

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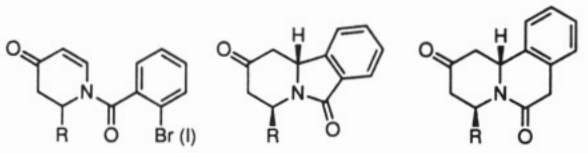
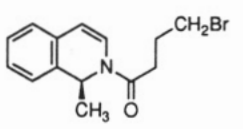


5a; R = Ph
5b; R = CH_3

6a; R = Ph
6b; R = CH_3

7a; R = Ph
7b; R = CH_3



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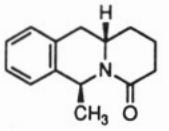

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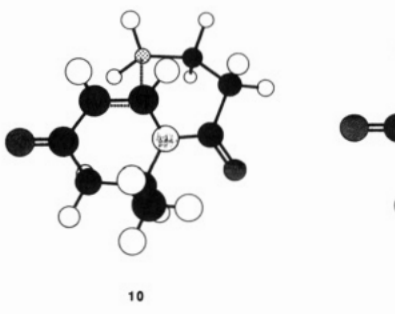
pseudoaxial position. Similar treatment of the appropriate bromides gave the indolizidine **6b** (86%) and the quinolizidine derivatives **7a** (72%) and **7b** (82%). Radical ring closure in substituted dihydroisoquinolines occurs with equally high diastereoselectivity.[11] The only detectable isomer obtained from **8** was **9** (90%) the stereochemistry of which was confirmed by X-ray crystallography.[10]

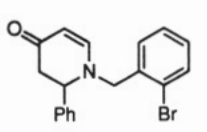
For the cyclization of **2a**, molecular mechanics[12,13] was used to model the two possible transition structures **10** and **11** in which the reactive centres form a triangular array orthogonal to the nodal plane of the π system. Figure 1 depicts these structures from above the plane of the ring. When the approach of the radical center is from below, the methyl substituent in **10** assumes a pseudoaxial position, whereas attack from the opposite side leads to a transition structure **11** in which the methyl is pseudoequatorial. The strain energy of structure **10** leading to the preferred product, **4a**, was found to be almost 3 kcal/mol less than that of the alternative structure, **11**. The calculations indicate that in the higher energy structure **11** there is a serious nonbonded interaction between the pseudo equatorial methyl group and the amide oxygen atom. This is not present in **10** where the substituent is pseudoaxial. In accord with this rationale, cyclization of the bromide **12** lacking an amide oxygen atom shows poor diastereoselectivity (3:1) in favor of the diastereomer **13**.[14] In this case molecular mechanics calculations gave an energy difference of only 0.4 kcal/mol between the trans transition structure leading to **13** and its cis isomer.

Although these experiments were conducted mainly to explore the factors affecting the diastereoselectivity of radical cyclization and to show that they can be rationalized by molecular mechanics calculations, they also provide useful general methods for the preparation of substituted indolizidines and quinolizidines. As a simple example of the application of the method to more complex systems we have prepared (±)-lasubine I (**16**) in five steps in good overall yield. The compound **1d**, prepared in one step from 4-methoxypyridine, gave the cyclized product **4d** (91%) when treated with tributylstannane in the usual way. Reduction of **4d** with LAH gave **14** oxidation of which with PCC followed by reduction with $NaBH_4$ gave **16**[16] in 91% yield from **4d**.



10 **11**

Figure 1. MMX-minimized transition structures for the cyclization of **2a** viewed from above the plane of the ring.



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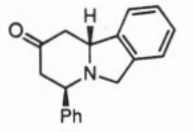

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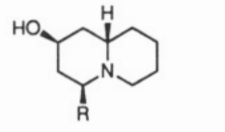
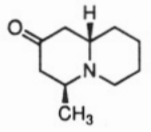


14; R = 3,4-$(OMe)_2$.C_6H_3



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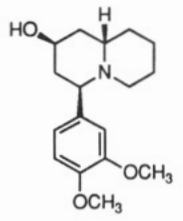

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Since this work was completed (−)-lasubine I has been prepared by a very short and efficient sequence.[17] However, in view of the very high chemoselectivity of the radical reactions described above they should provide a useful alternative to more conventional approaches to highly functionalized systems. Relevant studies are in hand.

Supplementary Material Available: Experimental procedure and compound characterization data (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) The cyclization of aryl radicals onto the dihydroisoquinoline nucleus has previously been described by: Yamaguchi, R.; Hamasaki, T.; Utimoto, K. *Chem. Lett.* **1988**, 913.

(12) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. See also: Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(13) Calculations were performed with Macromodel V3.5x and the MM2* force field: Mohamadi, F.; Richards, N. G. T.; Guida, W. C.; Liskamp, R.; Camfield, C.; Chang, G.; Hendrikson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(14) It has been reported (ref 15) that radical cyclization of an *N*-alkyldihydropyridone gives only one diastereomer. We are currently examining the reasons for the difference between that result and the behaviour of **12**.

(15) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976.

(16) Fuji, K.; Yasmada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515.

(17) Comins, D. L.; LaMungan, D. H. *J. Org. Chem.* **1992**, *57*, 5807.