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STEREOSELECTIVE REDUCTION OF ACYCLIC α-BROMO ESTERS

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Abstract: Radical-based reduction of β-methoxy- or β-fluoro-α-bromo esters could be achieved with good stereoselection at low temperatures. A systematic evaluation of this reaction is presented and possible transition state models are discussed.

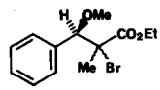
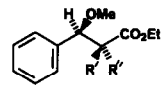
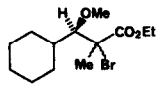
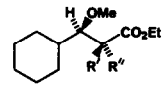
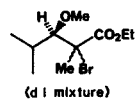
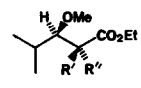
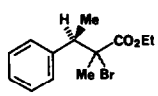
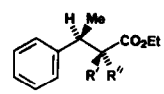
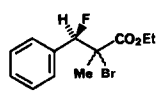
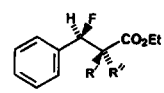
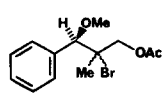
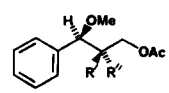
Although radical-based reactions have attracted considerable interest in the last decade and important advances have been made in this field of research[1], the problem of stereoselection in reactions involving acyclic radicals remains largely to this date unsolved, a topic on which we would like to report herein.

During the course of our work involving the use of β-alkoxy-α-halo esters as intermediates in the synthesis of natural products[2], we were intrigued by the modest *threo*[3] stereoselectivity demonstrated by the reduction of β-alkoxy-α-bromo ester **1** (Table 1, entry 1) with tributyltin hydride and a catalytic amount of AIBN in toluene at 50°C. Since there are few reports of stereoselective reactions[4] involving acyclic radicals, we initiated a systematic study of this radical-mediated reduction in an effort to optimize the preponderance of the major product and to understand the origin of this phenomenon.

The turning point of this study came when the reaction temperature was lowered and photochemical techniques were used in combination with AIBN to initiate the reaction. When the reduction of **1** (1:1 diastereomeric mixture) was conducted at temperatures between -10° and -78°C and a sunlamp (CGE 275-watt bulb) was used in combination with tributyltin hydride and AIBN, a dramatic increase in the diastereomeric excess (de) was observed (entries 2-4). That is, the stereoselectivity of this reduction improved as the reaction temperature was lowered. Thus a ratio of 32:1 for the preferential formation of isomer **2** was obtained when the reaction was performed at -78°C, compared to 7:1 at 50°C.

The influence of steric and electronic factors on stereoselection is demonstrated by entries 5 to 8. First, replacement of the phenyl group in **1** by cyclohexyl (entry 5) or isopropyl residues (entry 6) gave poorer stereoselectivity even when the reaction temperature was -78°C. These results reflect the importance of steric factors at the position α to the radical. Secondly, to investigate the effect of electronic factors at the same centre, the methoxyl group in substrate **1** was replaced by methyl or fluoride residues. The stereoselectivity (32:1) could be abolished completely (2:1) by the substitution of the methoxyl (entry 4) for a methyl group (entry 7). When the substitution at this position was made with fluoride (entry 8), the tributyltin hydride

TABLE I

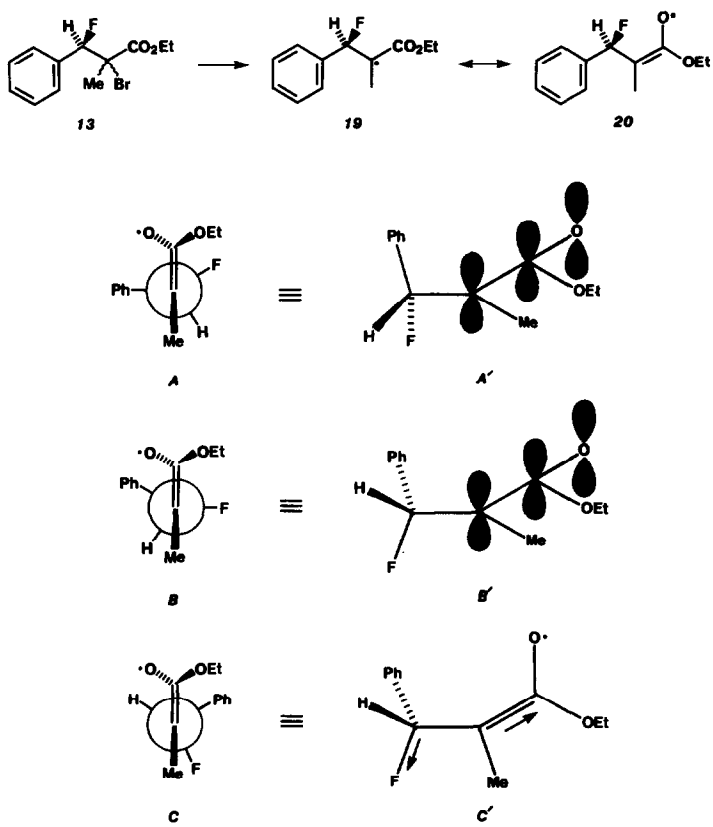
ENTRY	SUBSTRATE	REACTION CONDITIONS [a] (TEMP.°C)	PRODUCTS (RATIO) [b]	YIELD (%)[c]
1	 (d l mixture) *1*	*A* (50°C)	 *2* R′=H, R″=Me *3* R′=Me, R″=H *(2/3 = 7/1)*	78
2	*1*	*B* (-10°C)	*2+3* *(2/3 =11/1)*	92
3	*1*	*B* (-45°C)	*2+3* *(2/3 =20/1)*	86
4	*1*	*B* (-78°C)	*2+3* *(2/3 =32/1)*	90
5	 (d l mixture) *4*	*B* (-78°C)	 *5* R′= H, R″= Me *6* R′= Me, R″= H *(5/6 = 12/1)*	75
6	 (d l mixture) *7*	*B* (-78°C)	 *8* R′=H, R″= Me *9* R′= Me, R″= H *(8/9 =8/1)*	86
7	 (d l mixture) *10*	*B* (-78°C)	 *11* R′= H, R″= Me *12* R′= Me, R″= H *(11/12 =2/1)*	85
8	 (d l mixture) *13*	*B* (-78°C)	 *14* R′= H, R″= Me *15* R′= Me, R″= H *(14/15 = 20/1)*	88
9	 (d l mixture) *16*	*B* (-78°C)	 *17* R′= H, R″= Me *18* R′= Me, R″= H *(17/18 = 1/1)*	70

a) All reactions were carried out at a concentration of 0.1M in toluene using 2.0 equiv of nBu_3SnH and a catalytic amount of AIBN (0.02 equiv.) Condition A: Initiation was accomplished by heating (50°C). Condition B: Initiation was accomplished by irradiation using a sunlamp (CGE 275 watt bulb). b) Ratios were determined by gas chromatographic or NMR analysis. c) Yields of isolated products.

reduction proceeded with good stereocontrol (20:1). Clearly these results demonstrate the strong influence of electronic effects on the substituent α to the radical[5]. Moreover, entry 9 shows that the presence of the ester α to the radical is crucial for stereoselective reduction in these examples.

Although theoretical evaluation of this work is at an early stage, we would like to comment on mechanistic aspects of the models proposed to account for the *threo* diastereoselectivity. Underlying this analysis are the following assumptions: a) the radical is not pyramidalized[6], and b) the radical is delocalized through the carbethoxy group. The possible reactive rotamers of the intermediary radical arising from bromide **13** are depicted in Scheme I. Rotamer A (or A') is derived from a transition state model proposed by Houk[7], and used recently by Hart[4a], for allylic asymmetric induction in radical addition to alkenes. In the Houk model[7], the bond bearing the largest allylic substituent is perpendicular to the π-system, while the smallest allylic substituent occupies a position that minimizes torsional strain created by the incoming radical. Unfortunately the reactive rotamer (A and A') based on this model neither accounts for the strong electronegative influence on the stereoselectivity, nor is predictive of the stereochemical outcome.

SCHEME I



In the transition state depicted as rotamer B (or B'), the perpendicular orientation of the polar

substituent to the π-system is reminiscent of the orientation found in the Felkin-Anh[8] model of nucleophilic attack on ketones. This rotamer (B or B') may be stabilized by a stereoelectronic effect which has been invoked by Giese to describe a radical of high SOMO energy interacting with the LUMO of a neighboring carbon-oxygen bond[9]. In contrast, the radical involved in the title reaction is α to an ester moiety and consequently has a low SOMO energy[10]. Nevertheless, this model is predictive of the *threo* bias and is consistent with the observed electronegative effects on the stereoselectivity.

The final transition state model C (and C'), also consistent with the stereochemical outcome, is analogous to the one proposed by Cornforth[11] for nucleophilic addition to carbonyl groups. In this proposed transition state model, the intramolecular electrostatic or dipole-dipole interactions between the two vicinal electronegative groups are alleviated through their *anti* orientation. In a non-ionic process such as a radical-based reaction, these destabilizing intramolecular interactions could well play a significant role in controlling the stereochemistry. Assuming that the attack of the trialkyltin hydride on this rotamer would be *anti* to the largest substituent β to the ester, one would predict an improvement in stereoselectivity as the steric factor increases. Calculations are presently being made to test the validity of the latter two transition state models.

In conclusion, this work has demonstrated the importance of an electronegative group α to a stabilized acyclic radical for the induction of stereoselectivity in hydrogen-transfer reactions. This influence can be enhanced particularly by using low reaction temperatures and photochemical procedures to induce the formation of the radical.

Acknowledgements

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5. Based on these observations, presence of other protective groups on the hydroxyl may affect the stereoselection by altering the polarity of the C-O bond.
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9. Pronounced conformational preference of pyranoses bearing a radical at C-1 have been observed by ESR. See ref. 1a, p.61 and 1b.
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