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STEREOSELECTIVE RADICAL-MEDIATED REDUCTION AND ALKYLATION OF α-HALO ESTERS

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Abstract: Radical-mediated reduction and alkylation of ß-alkoxy-α-halo esters could be achieved with good stereoselection at low temperature.

We have reported recently[2] the stereoselective radical-mediated reduction of acyclic α-bromo ester **1** to give **2** in a *threo/erythro* ratio of 32:1 in good yield (Table I, entry 1). An electronegative group (e.g. OMe) α to the stabilized radical[3] was shown to be critical for the induction of stereoselectivity in these hydrogen transfer reactions. This influence was enhanced particularly by using low reaction temperatures and photochemical means to induce radical formation.

Owing to the scarcity of reports on stereoselective reactions involving acyclic radicals[4] it was desirable to: a) evaluate the scope of this reductive transformation by application to other systems of synthetic interest, and b) evaluate the capacity of such radicals for stereoselective carbon-carbon bond formation. Another objective was to better define the transition state models that could account for the observed stereoselectivity.

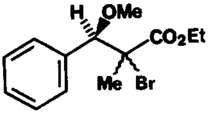
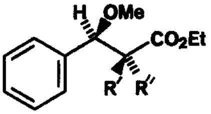
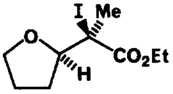
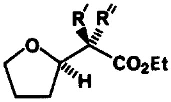
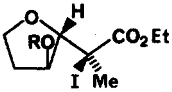
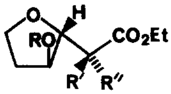
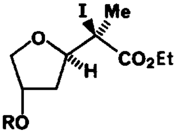
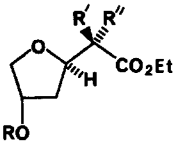
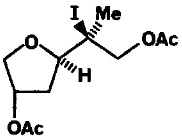
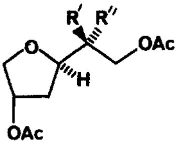
Our attention was first directed to the application of these radical-mediated transformations to the synthetically useful 2-substituted tetrahydrofuran[5] derivative (Table I, entry 2). Similar to **1**, this derivative embodies the requisite features of a tertiary halide which would give rise to a radical flanked by an ester and an electronegative group (i.e. ring C-O bond in **4**) on the adjacent carbon. It was of interest to see whether the hydrogen transfer reaction involving these substrates would demonstrate the remarkable stereoselectivity observed for **1**.

Indeed the reduction of **4**[6] with tributyltin hydride in the presence of a catalytic amount of AIBN in toluene at 50°C exhibited modest *threo* stereoselectivity (i.e. 8:1). In contrast, when the reaction was conducted at -78°C and a sunlamp was used in combination with AIBN as initiator, a dramatic increase in the *threo* diastereoselectivity was observed, yielding a ratio of 20:1[7].

Under similar conditions, other tetrahydrofuran derivatives[6] were studied in order to ascertain the influence of ring substituents on the stereochemical outcome. At 50°C it appears that the effects of ring substituents were negligible since the reduction of the 3-substituted (Table I, entries 3,4) and 4-substituted derivatives (entries 5, 6) demonstrated stereoselectivities[8] (ranging from 5:1 to 10:1) which were comparable to that of the unsubstituted analogue **4**. However, these effects were more pronounced at a lower reaction temperature (i.e. -78°C). The presence of a siloxy substituent appeared to be beneficial at -78°C (entries 4 and 6), especially in the reduction of **10**, for which a ratio 75:1 was observed. When esters were used as ring substituents, only modest increases in stereoselectivity were seen at -78°C[9] (entries 3 and 5) in comparaison to those obtained at 50°C. Entry 7 demonstrates the importance of the ester α to the radical for the maintenance of the stereoselection, a feature which was previously reported[2].

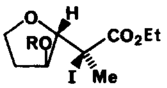
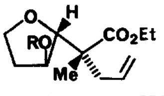
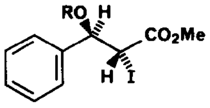
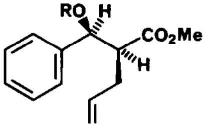
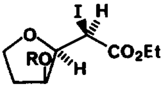
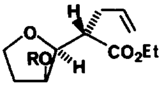
At this point, it was of interest to discover whether the high stereoselectivity demonstrated in these radical-mediated reductions would lend itself to carbon-carbon bond formation involving acyclic radicals. As shown in Table II, entry 1, reaction of tertiary iodide **10** with allyl tributyltin in combination with AIBN at 60°C gave the tertiary

TABLE I : TEMPERATURE EFFECT ON STEREOSELECTIVITY

ENTRY	SUBSTRATE	PRODUCTS	REACTION CONDITIONS[a]	RATIO[b]	YIELD[c] (%)
1	 1 (dl)	 2 R'=H, R''=Me 3 R'=Me, R''=H	A B	2/3 7/1 2/3 32/1	78 90
2	 4 (dl)	 5 R'=Me, R''=H 6 R'=H, R''=Me	A B	5/6 8/1 5/6 20/1	92 91
3	 7 R = Ac	 8 R = Ac, R'=Me, R''= H 9 R = Ac, R'=H, R''=Me	A B	8/9 5/1 8/9 8/1	81 96
4	10 R = TBS	11 R =TBS, R'=Me, R''= H 12 R =TBS, R'=H, R''= Me	A B	11/12 10/1 11/12 75/1	84 93
5	 13 R=Ac	 14 R= Ac, R'= Me, R''= H 15 R= Ac, R'= H, R''= Me	A B	14/15 6/1 14/15 9/1	88 80
6	16 R=TBS	17 R= TBS, R'=Me, R''= H 18 R = TBS, R'= H , R''= Me	A B	17/18 7/1 17/18 18/1	85 99
7	 19	 20 R'= Me, R''= H 21 R'= H, R'' =Me	A	20/21 1/1	81

a) All reactions were performed at a concentration of 0.1 M 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 at 50°C, with a reaction time of 1 h. Condition B: Initiation was accomplished by irradiation using a sunlamp (CGE 275 watt bulb) at −78°C, with a reaction time of 30 min. b) Ratios were determined by gas chromatographic or ^{1}HNMR analysis. c) Yields of isolated products.

TABLE II : RADICAL-MEDIATED CARBON-CARBON BOND FORMATION

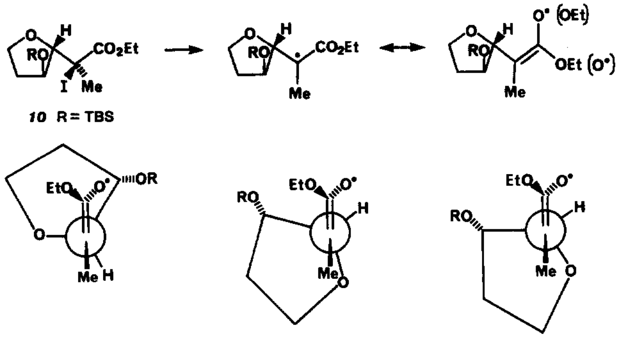
ENTRY	SUBSTRATE	ERYTHRO PRODUCT	REACTION CONDITIONS[a] (Rx time)	RATIO[b] erythro/threo	YIELD (%)[c]
1	 *10* R = TBS	 *22* R = TBS	*A* (9 h)	>30/1	55
			B	no Rx	—
2	 (dl) *23* R = Me	 *24* R = Me	*A* (5 h)	5/1	82
			B (6 h)	17/1	75
3	*25* R = Bn	*26* R = Bn	*A* (7 h)	5/1	73
			B (4 h)	22/1	87
4	 *27* R = TBS	 *28*	*A* (7 h)	>30/1	67
			B (7 h)	>30/1	67

a) All reactions were performed at a concentration of 0.1 M using 2.0 equiv. of allyltributyltin. Condition A: In refluxing hexane using AIBN as initiator (0.2 equiv. added every 3 h.) Condition B: In toluene at -78°C using Et_3B as initiator (0.2 equiv. added every 2 h . under a very slow stream of air). b) Ratios were determined by gas chromatographic or ^1HNMR analysis. c) Yields of isolated products.

methyl derivative **22**[10] in good yield and with an impressive ratio (>30:1). Interestingly, reaction of secondary iodides **23**, **25**[11] and **27** at 50°C exhibited modest to good stereoselectivities (i.e. 5:1, 5:1 and >30:1, respectively). These ratios could be improved[12] (i.e. 17:1, 22:1 and >30:1, respectively) by lowering the reaction temperature to -78°C and using Et_3B as an initiator[13]. The reaction times for these radical-mediated alkylations were longer than those required for the hydrogen transfer process, furthermore, tertiary iodides do not react well at -78°C.

Although theoretical evaluation of this work is at an early stage, we would like to comment on some mechanistic aspects that could serve to rationalize the observed diastereoselectivity for both the hydrogen transfer and the alkylation reactions. Depicted in Scheme 1 are possible rotamers of the intermediary radical derived from **10** that would lead to the major product. The analysis is based on the following assumptions: a) the radical is not pyramidalized and b) the radical is delocalized through the carbethoxy group. Rotamers analogous to A and B have been previously discussed[2]. Although predictive of the stereoselection observed in the radical-mediated alkylation of **10**, rotamer A suffers from severe interaction between the ester appendage and the tetrahydrofuran ring residue. In comparison, rotamer B not only lacks such destabilizing interactions but the intramolecular electrostatic or dipole-dipole interactions between the two electronegative groups are alleviated through their *anti* orientation. Delivery of hydrogen or allyl group from the least hindered face of the radical would lead to the observed diastereoselection. In rotamer C, also consistent with the stereochemical outcome, the CHOR of the tetrahydrofuran ring is perpendicular to the plane of the delocalized radical[14]. The attack on the radical will once again occur on the least hindered face of the molecule. Calculations are being made to assess the validity of these transition models.

SCHEME 1



10 R = TBS

Rotamer A Rotamer B Rotamer C

In conclusion, we have shown that radicals which are both adjacent to an ester and α to an electronegative group react diastereoselectively to undergo C-H or C-C bond formation. Moreover, the stereoselectivity of such processes can be enhanced by using low reaction temperatures in combination with photochemical activation or Et_3B.

Acknowledgments

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3. Excellent reviews have been published recently. See for example:a) B. Giese, *Radicals in Organic Synthesis*, Pergamon Press, Oxford **1986**; b) B. Giese, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969.
4. See for example: a) D.J. Hart, H.-C. Huang, R. Krishnamurthy and T. Schwartz, *J. Am. Chem. Soc.* **1989**, *111*, 7507; b) N.A. Porter, D.M. Scott, B. Lacher, B. Giese, H.G. Zeitz and H.J. Lindner, *J. Am. Chem. Soc.* **1989**, *111*, 8311; c) D.P. Curran, W. Shen, J. Zhang and T.A. Heffner, *J. Am. Chem. Soc.* **1990**, *112*, 6738; d) N.A. Porter, E. Swann, J. Nally and A.T. McPhail, *J. Am. Chem. Soc.* **1990**, *112*, 6740; e) B. Giese, M. Zehnder, M. Roth and H.G. Zeitz, *J. Am. Chem. Soc.* **1990**, *112*, 6741.
5. For example see: Y. Guindon, P.C. Anderson, C. Yoakim, Y. Girard, S. Berthiaume and H.E. Morton, *Pure Appl. Chem.* **1988**, *60*, 1705.
6. Tertiary iodides were prepared using the iodoetherification reaction (I_2, $NaHCO_3$, THF) and were obtained as the major isomer. The products were charaterized as exemplified in a) M. Labelle, H.E. Morton, Y. Guindon and J.P. Springer,*J. Am. Chem. Soc.***1988**,*110*,4533;b)M. Labelle and Y. Guindon, *J. Am. Chem. Soc.* **1989**, *111*, 2204.
7. F.H. Gouzoules and R.A. Whitney, *J. Org. Chem.* **1986**, *51*, 2024.
8. The absolute stereochemistry of the products were confirmed through X-ray analysis of para-nitrobenzoate derivatives of the desilylated products derived from **11** and **17**.
9. A systematic evaluation of the stereoselectivity outcome based on various substituents on the tetrahydrofuran ring is presently underway.
10. Structure **22** was based on nOe experiments on the corresponding lactone. [1) 5%HF/ CH_3CN; 2) LiOH, H_2O-THF; 3) Ph_3P, DEAD, THF].
11. L.C. Vishwakarma and J.S. Walia, *J. Indian Chem. Soc.*, **1976**, *53*, 156.
12. The erythro stereochemistry of **26** was assigned from the coupling constant of the corresponding alcohol (derived through hydrogenation of **26**) see C.H. Heathcock, *Asymmetric Synthesis*, S.D. Morrison Ed., *Academic Press*, London, **1984**, *3*, 115; Methylation of the hydroxy compound allowed us to confirm structure **24**.
13. K. Miura,Y. Ichinose,K. Nozaki,K. Fugami,K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, **1989**, *62*, 143.
14. Rotamer C may be stabilized by hyperconjugation. That is, electron deficient radical having low somo energy would be stabilized by overlap with the sigma orbital of the adjacent carbon. This interaction should be optimal when the most electropositive group (i.e. CHOR or CH_2 for the derivatives lacking a substituant at C-3 of the tetrahydrofuran ring) is perpendicular to the π system of the radical. See: F. Bernardi, A. Bottoni, J. Fossey and J. Sorba, *Tetrahedron*, **1986**, *42*, 5567 and references therein.

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