## ATOM TRANSFER CYCLIZATION REACTIONS OF α-IODO CARBONYLS

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Abstract: The free radical isomerization of unsaturated  $\alpha$ -iodo carbonyls to cyclic  $\gamma$ -iodo carbonyls is described. Iodine atom abstraction from the starting iodide by the cyclic radical is the key chain transfer step.

Halogen atom transfer addition and cyclization reactions are free radical processes which have received little attention as useful methods for formation of carbon-carbon bonds in organic synthesis.<sup>2</sup> The direct or metal-promoted addition reactions of polyhalo alkanes (i.e.  $CCl_3Br$ ) to alkenes have been most well studied.<sup>3</sup> Multiple halogen substitution expedites the abstraction of a halogen atom in the key chain transfer step, but the remaining halogen(s) must usually be removed in a subsequent step. Following the early report of Kharasch, Skell and Fisher,<sup>4a</sup> the addition of  $\alpha$ -halo esters to alkenes has been studied by several groups.<sup>4b-f</sup> We now report that  $\alpha$ -iodo carbonyls are excellent substrates for atom transfer cyclization reactions in which the key chain transfer step involves iodine atom abstraction from the starting iodo carbonyl by the cyclic radical.

Standard deprotonation of methyl 6-heptenoate with LDA, followed by reverse quench of the intermediate anion into iodine/THF, provided iodo ester 1a in 80% yield.<sup>5</sup> Isomerization to a mixture of 2a and 3a occurred upon heating of 1a in benzene under a variety of conditions as summarized in Table 1 (entries 1-3). While the use of a catalytic amount of tri-n-butyltin hydride was less efficient, heating of 1a with AIBN, either alone or in the presence of hexamethylditin, provided a slow but smooth conversion to cyclic products. Within experimental error, the product ratios were independent of the method of initiation. While a useful preference for 5-exo products 2 over 6-endo products 3 is observed, there is only a slight preference for formation of 2a-cis over 2a-trans.



A standard chain reaction is proposed for the isomerization of 1a to 2a and 3a.<sup>4a</sup> Stabilized radical 5, generated in an initiation step, can close via either 5-exo or 6-endo modes. The chain is then transferred by abstraction of an iodine atom from the starting iodide 1a by the cyclic radical. This exothermic step, illustrated in Eq. 2 for the 5-exo product 4, is driven by the formation of the stabilized radical 5.



The iodine donor capability of the iodo ester is a key to the success of the reaction. Attempted cyclization of the corresponding  $\alpha$ -bromo ester by heating of 1b in benzene in the presence of hexamethylditin, benzoyl peroxide or di-t-butyl peroxide was not successful. However, irradiation of a solution of 1b and 10% hexamethylditin with a 275w sunlamp<sup>2a</sup> did result in slow formation of the corresponding cyclic bromides 2b/3b (Table 1, entry 4) in modest yield. Other  $\alpha$ -iodo carbonyls including the t-butyl ester 1c and the phenyl-1d and t-butyl ketones 1e (Table 1, entries 5–7) were isomerized in a matter of minutes to the cyclic iodides by the sunlamp irradiation method.

Entry	starting halide	initiator	reaction method /time <sup>a</sup>	products (ratio %) 5-exo (2) 6-endo (3) Cis trans Cis trans		) ndo (3) trans	yield <sup>b</sup> %	
1	1a	n-Bu <sub>3</sub> SnH	A/5 h	48	45	2.3	4.7	48
2	1a	с	A/24 h	49	43	2.7	5.3	78
3	1a	Me <sub>6</sub> Sn <sub>2</sub>	A/16 h	53	40	2.4	4.6	83
4	1b	n-Bu <sub>6</sub> Sn <sub>2</sub>	B/24 h	50	40	3.6	6.4	42
5	1c	Me <sub>6</sub> Sn <sub>2</sub>	B/10 min	44 <sup>d</sup>	49	2.2	4.8	74
6	1d	Me <sub>6</sub> Sn <sub>2</sub>	B/10 min	21°	54	7.6	17.4	68
7	1e	Me <sub>6</sub> Sn <sub>2</sub>	B/10 min	20 <sup>e</sup>	54	8.7	17.3	63

Table 1Atom Transfer Cyclization of α-Halo Carbonyls

Footnotes: a) Method A, 5-10% initiator and AIBN each added in two separate portions at 1h intervals, benzene, reflux; Method B, 7-10% initiator, benzene, reflux, 0.3-0.5M, 275w sunlamp. b) combined isolated yield of purified products. c) AIBN was the only additive. d) 2,6-di-t-butyl pyridine was added to inhibit HI-promoted lactonization of the products. e) The 5-exo cis product was observed in the proton NMR spectrum of the crude reaction mixture but was not stable to chromatographic purification. The formation of this product is not reflected in the total mass balance.

In contrast to alkyl-substituted hexenyl radicals,<sup>6</sup> little is known about the regio- and stereochemistry of cyclization of stabilized radicals. Relative to simple alkyl-substituted analogues,<sup>7</sup> the ester-substituted radicals show a reduced but still useful 5-exo selectivity. In the formation of the 5-exo products, the esters show a low cis-selectivity while trans products are actually preferred with the more stable ketone analogues. Also, ketone-substituted radicals 1d and 1e provide considerably more 6-endo products than their ester counterparts.

It is of interest to ascertain whether the reactions are under kinetic control. The early work of Julia has shown that stabilizing groups can promote the equilibration of intermediate cyclic radicals.<sup>8</sup> We were not able to obtain any evidence for equilibration in these systems. In a reaction which has synthetic utility, prolonged heating of **2a-cis** (benzene, 2 d), either with or without an initiator, produced only lactone **6** (Eq. 3). Neither **2a-trans** nor **3** were detected. Stereoisomer **2a-trans** was stable to these reaction conditions. Not surprisingly, the t-butyl ester **2c-cis** lactonized much more readily.<sup>4c,d</sup> Irradiation of pure iodo ketone **2d-trans** resulted only in slow decomposition over several hours. Tri-n-butyltin hydride treatment (0.02M, benzene) of several of the cyclic iodides resulted in direct reduction with no detectable crossover. Finally, it is informative to note that iodide **1a** and bromide **1b** provided nearly the same ratio of products. Since bromine atom transfer must be much slower than iodine atom transfer (Eq. 2), more 6-endo products should have been produced in the case of **1b** were the cyclic radical (Eq. 2) is more rapid than ring opening of the cyclic radical.



The formation of fused bicyclic systems by this iodine atom transfer cyclization is a particularly useful reaction as illustrated in Eq. 4. Isomerization of iodomethyl ketone 7a produced cis-fused 8a as a 3/1 mixture of exo- and endo-iodides in 83% yield. Detectable amounts of the bridged bicyclic system which would have formed by 6-endo cyclization were not obtained. The slow cyclization reactions of radicals derived from  $\alpha$ -halo allyl esters led Stork and Ueno to develop a general alternative based on tin hydride cyclization of unsaturated halo acetals.<sup>9</sup> We now find that such slow cyclizations may indeed occur using the atom transfer method since there is no overt H-atom donor (i. e. Sn-H) to intercept intermediate radicals. For example, treatment of iodo ester 7b with 1 eq. of tri-n-butyltin hydride under standard conditions (benzene, 0.02M) produced no cyclic lactone 9b. Cyclohexenyl acetate was the only detectable product. In contrast, ditin-initiated cyclization of 7b produced 8b in 58% isolated yield (4/1, exo/endo iodide). Direct addition of one equivalent of tri-n-butyltin hydride to the reaction mixture and re-initiation resulted in the formation of 9b in 55% yield.<sup>10</sup> This one-pot conversion of 7b to 9b is conducted at high concentration (0.5M) and requires less than two hours total reaction time. Thus, even when the iodine atom is not desired in the final product, the iodine atom transfer method may prove superior to the tin hydride method for certain cyclizations.



Alkynes also provide excellent acceptors for the isomerization reaction. Sunlamp irradiation of terminal alkyne **10a** and hexamethyl ditin for 10 min (Table 1, conditions B) provided **11a** (2.4/1; E/Z) and **12a** in a ratio of 94/6 in 85% isolated yield (Eq. 5). Similar treatment of trimethylsilyl alkyne **10b** provided only 5-exo product **11b** (1/1; E/Z) in 81% yield.



In summary, sunlamp irradiation of unsaturated  $\alpha$ -iodo carbonyls in the presence of a hexaalkylditin promotes rapid isomerization to cyclic  $\gamma$ -iodo carbonyls. In addition to providing functionalized products for further synthetic transformations, the reaction should be a valuable alternative to the tin hydride method for the cyclization of stabilized radicals. Parenthetically, we note that our results on the cyclization and lactonization of iodo esters **1a** and **1c** strongly support the mechanism recently proposed by Maillard, Kraus and coworkers<sup>4d</sup> for the related stannyl iodo ester additions to alkenes.<sup>4c</sup>

Acknowledgement. We thank the National Institutes of Health (GM 31678) for funding of this work. We also thank American Cyanamid, Merck, and Eli Lilly for unrestricted support.

## **References and Notes**

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- 7) For comparison, the unsubstituted hexenyl radical shows a 50/1 preference for 5-exo over 6-endo closure. See ref. 6.
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- 10) Cyclohexenyl acetate is also isolated in 15% yield despite the absence of an overt H-atom donor. Likely hydrogen atom sources include allylic and ketonic hydrogens and alkyl hydrogens β to the tin. It can be concluded that the cyclization of the radical derived from 7b is slow enough to be comparable with the lifetime of the radical in solution.

(Received in USA 17 March 1987)