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RADICAL CYCLIZATIONS OF α-FLUORO-α-IODO AND α-IODO ESTERS AND AMIDES.[1]

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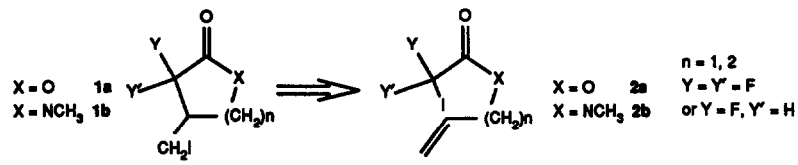
Abstract: The free radical cyclization of various unsaturated α-fluoro-α-iodo and α-iodo esters and amides is described. Unusual 12-membered dilactones and 18-membered trilactones were obtained under the standard atom transfer cyclization reaction conditions.

Free radical cyclizations of olefins have been used increasingly for the construction of 5- and 6-membered rings.[3] However, to our knowledge, the cyclization of radicals bearing α-fluoro substituents has not been reported. In connection with our interest in the preparation of biologically active fluorinated molecules, we have explored the possibility of applying this methodology to the synthesis of α-fluoro lactones (**1a**) and lactams (**1b**) from the corresponding α-fluoro-α-iodo esters (**2a**) and amides (**2b**).

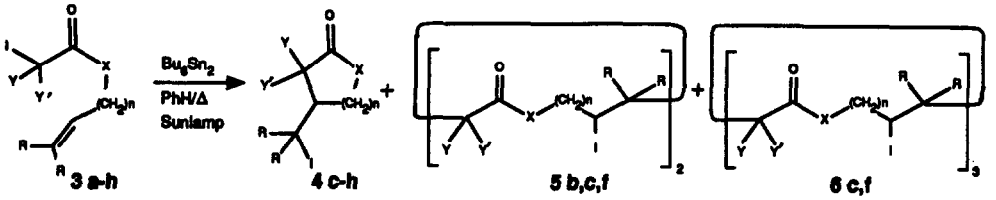


Since initial attempts to cyclize (**2a**) using Bu_3SnH gave only reduction products, the radical cyclization reactions were carried out using the atom transfer method.[4] Extensive studies by Curran[4] have shown this technique to be particularly useful for the cyclization of stabilized radicals. When a benzene solution of the difluoro ester (**3a**)[5,6] and 0.1 eq. of hexabutylditin was irradiated with a sunlamp, only the starting material was recovered. Interestingly, under the same conditions, the monofluoro ester (**3b**) produced an unusual 12-membered dilactone (**5b**) in 31% yield, with none of the anticipated 5-membered lactone (**4b**).

To our knowledge, the formation of a dilactone of this type through a free radical cyclization reaction has not been previously reported.[7] This observation prompted us to investigate the "ditin" initiated radical cyclization of various α-iodo esters and amides, and the results are summarized in Table 1.

Irradiation of allyl ester (**3c**) gave a mixture of products from which the expected 5-membered lactone (**4c**) was isolated in 11% yield along with the dilactone (**5c**) and trilactone (**6c**) in 15% and 17% yields, respectively.[8] In contrast, cyclization of the dimethylallyl esters (**3d**) and (**3e**) proceeded smoothly to give the corresponding lactones (**4d**) and (**4e**) in 68% and 62% yields, respectively. On the other hand, the homoallylic ester (**3f**) gave predominantly the dilactone (**5f**) (Table 1, entry 8).

The proposed pathways leading to the formation of dilactone (**5c**) and trilactone (**6c**) are outlined in Scheme 1.



X = O, n = 1, R = H
a: Y = Y′ = F
b: Y = H, Y′ = F
c: Y = Y′ = H

X = O, n = 1, R = CH_3
d: Y = Y′ = H
e: Y = H, Y′ = F

X = O, n = 2, R = H
f: Y = Y′ = H

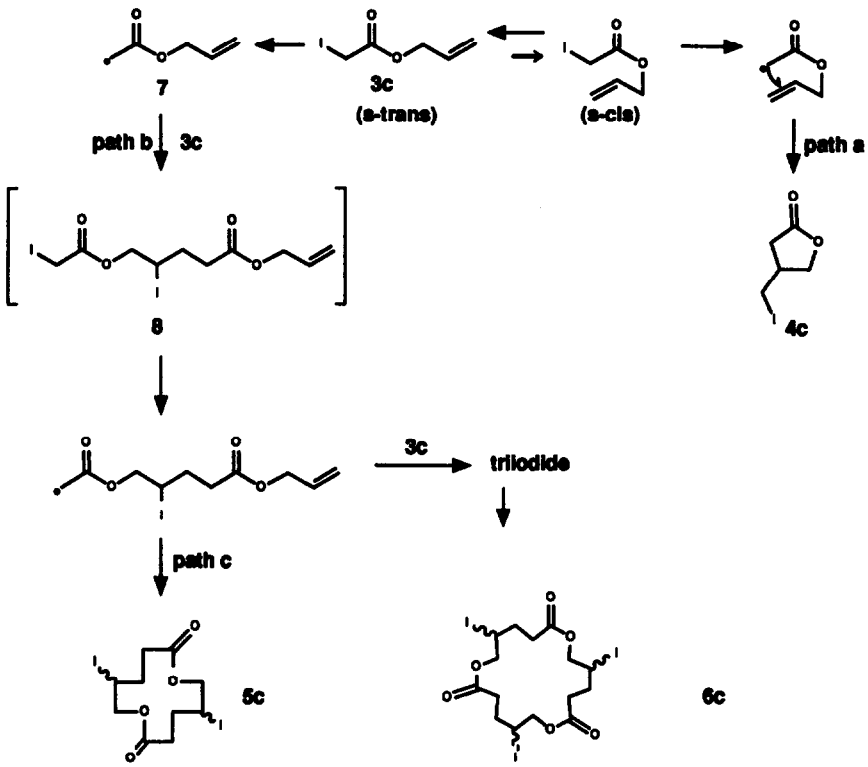
X = NCH_3 n = 1, R = H
g: Y = Y′ = H
h: Y = H, Y′ = F

Table 1 Atom Transfer Cyclization of α-Iodo Esters and Amides[a-c]

Entry	Substrate	Conc. (M)	Products (% Yield)[d] 4	5	6
1	3b	0.05	-	31[e]	-
2		0.008	-	56[e]	-
3	3c	0.5	11	15	17
4		0.076	19	38	17
5		0.008	64	22	-
6	3d	0.076	68	-	-
7	3e	0.076	62	-	-
8	3f	0.008	7	66	26
9	3g	0.076	61	-	-
10	3h	0.076	13[f]	-	-

a) 0.1 eq. of $(Bu_3Sn)_2$ was used for 3b-3f. b) Total 0.3 eq. and 0.5 eq. of $(Bu_3Sn)_2$ were used for 3g and 3h, respectively. c) All reactions were carried out in refluxing benzene and irradiation times for 3b-3f, 3g and 3h were 6h, 8h and 18h, respectively. d) Yields of products after purifiction by flash chromatography on silica gel. e) Two diastereomers of 5b in a ratio of 1:1 were isolated by chromatography. f) 79% of the starting material recovered.

Scheme I Proposed Pathways for the Formation of Dilactone (5c) and Trilactone (6c)



The intermolecular addition of the initial radical (7) to the starting olefin (3c) (path b) apparently competes favorably with a slow radical cyclization (path a), leading to the formation of the intermediate diiodide (8). The diiodide (8) then proceeds to give dilactone (5c) and trilactone (6c) as shown. The slow rate of cyclization to the monolactone is attributed to the unfavorable s-cis conformation associated with the ester[9] and the stability of the α-carbonyl radical. The greatly improved yield of (4c) observed for the cyclization of (3c) under the high dilution condition (8 mM)[10] presumably results from the reduced rate of the intermolecular addition (Table 1, entry 5). Introduction of terminal substituents on the olefin in the esters (3d) and (3e) suppresses the intermolecular addition, leading to the exclusive formation of lactones (4d) and (4e), respectively. Since the fluorine substituent further increases the stability of the α-carbonyl radical[11], no cyclization product (4b) is obtained from fluoro ester (3b).

In contrast to the findings obtained for α-iodo esters (3b) and (3c), cyclization of α-iodo amides (3g) and (3h) proceeded as expected to give the 5-membered lactams (4g) and (4h) in 60% and 13% yields, respectively.[12] No di- or trilactam was isolated.[13] This result is consistent with the relatively higher proportion of the required s-cis conformation in amides.[14]

References and Notes

1. Contribution No. 796 from the Institute of Organic Chemistry.

2. Syntex Postdoctoral Fellow 1988-1989.

3. (a) Curran, D.P. *Synthesis* **1988**, 417 and 489. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, Oxford, 1986.

4. Curran D.P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

5. The requisite α-fluoro-α-iodo esters were prepared from commercially available ethyl bromofluoroacetate and ethyl bromodifluoroacetate according to the following sequence: (i) NaI/acetone, (ii) $LiOH/CH_3OH/H_2O$, (iii) $SOCl_2$, (iv) $ROH/Et_3N/Et_2O$. The corresponding amides were prepared by amination of the acid chlorides obtained as above.

6. All new compounds were characterized by ^1H NMR and mass spectra. Satisfactory elemental analysis and/or high resolution mass spectra were also obtained.

7. It should be mentioned that radical cyclization has been utilized for the construction of a different type of macrocylic system. Porter, N. A. and Chang, V, H.-T. *J. Am. Chem. Soc.* **1987**, *109*,4976

8. Atom transfer cyclization of 2-cyclohexenyl iodoacetate has been reported by Curran.[3] However, no di- or trilactones were isolated.

9. Oki, M.; Nakanishi, H. *Bull. Chem. Soc. Japan* **1970**, *43*, 2558.

10. This concentration is considerably lower than that of standard atom transfer cyclization reactions (see reference 4).

11. Chambers, R.D. *Fluorine in Organic Synthesis*, Wiley-Interscience, New York, 1973.

12. Addition of 3.5 eq. of EtI to the reaction of (**3h**) did not improve the yield of (**4h**). Jolly, R.S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536.

13. Radical cyclization of *N*-allyl-*N*-methyl chloroacetamide using the $(n\text{-}Bu)_3SnH$ method has been recently reported. However, the expected lactam was obtained in only 24% yield along with 39% of the reduction product. Sato, T.; Wada, Y.; Nishimoto, M.; Ishibashi, H; and Ikeda, M. *J. Chem. Soc., Perkin. Trans. I*, **1989**, 879.

14. Stewart, W.E.; Siddall, T.H. III *Chem. Rev.* **1970**, *70*, 517.

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