The Journal of
Organic Chemistry

VOLUME 56, NUMBER 14 JULY 5, 1991

Communications

Radical Translocation Reactions of *o*-Iodoanilides: The Use of Carbon–Hydrogen Bonds as Precursors of Radicals Adjacent to Carbonyl Groups

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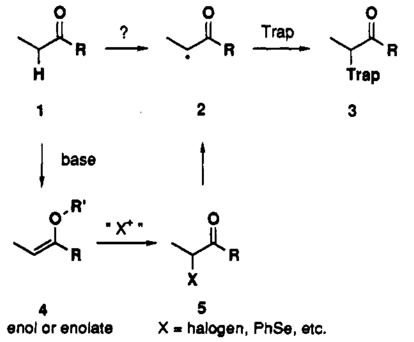
Received April 9, 1991

Summary: The treatment of *o*-iodoanilides with tributyltin hydride results in radical generation followed by rapid translocation to produce radicals adjacent to carbonyls. These radicals participate in cyclization and asymmetric addition reactions.

The formation of carbon–carbon bonds adjacent to carbonyl groups is one of the most important transformations in organic synthesis. These bonds are often formed through the intermediacy of enols or enolates, but the generality of such bond-forming methods is limited by the conditions that are required. In principle, carbon–carbon bonds adjacent to carbonyls can be formed under strictly neutral conditions by using radical reactions (see eq 1, **1** → **2** → **3**).[2] In practice, there is a severe limitation:



(1)

radical precursors are almost always formed in the step preceding the radical reaction,[3] and these precursors are formed by standard reactions of enols or enolates (**1** → **4** → **5**). The most economical solution to this limitation is to directly use a C–H bond adjacent to the carbonyl as a radical precursor;[3b] however, known C–H abstraction reactions of this type are limited to the simplest of carbonyl compounds because selectivities in bimolecular hydrogen-abstraction reactions are very poor.[4] In contrast, intramolecular hydrogen-transfer reactions are considerably faster and more selective than their bimolecular counterparts, and they provide a means for translocating a radical from one site to another prior to a carbon–carbon bond forming reaction.[5] We now report preliminary results showing that radicals adjacent to carbonyl groups are rapidly formed from C–H bonds by radical translocation reactions of *o*-iodoanilides.

o-Iodoanilides **6** are readily available by standard reactions for formation of tertiary amides. We suspect that

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[1] Dreyfus Teacher–Scholar, 1986–91; NIH Research Career Development Awardee, 1987–92.

[2] Illustrative examples of radical carbon–carbon bond forming reactions adjacent to carbonyls: (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (b) Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533. (c) Toru, T.; Yamada, Y.; Ueno, T.; Maekawa, E.; Ueno, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4815.

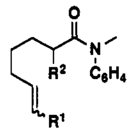
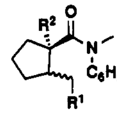
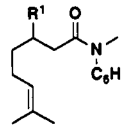
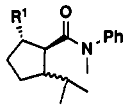
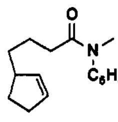
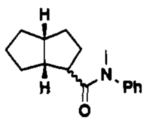
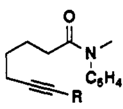
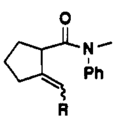
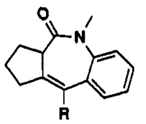
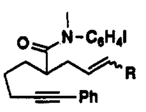
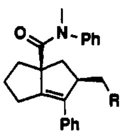
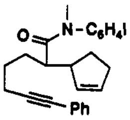
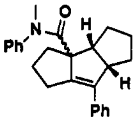
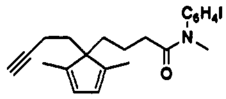
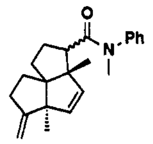
[3] (a) This problem is bypassed in certain sequential radical reactions where radicals adjacent to carbonyls are generated by prior radical addition or cyclization reactions. For examples, see: Curran, D. P.; Kuo, S. C. *Tetrahedron* **1987**, *43*, 5653. Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. (b) A second general strategy involves oxidation of highly enolizable carbonyl compounds. Carbon–hydrogen bonds are used as radical precursors, although a C–H abstraction is not involved. Leading reference: Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427.

[4] Intramolecular hydrogen atom transfer is a fundamental radical reaction. Reviews: Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 161. Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, p 333.

[5] (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (b) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896. (c) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron Lett.* **1990**, *31*, 6911. (d) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181.

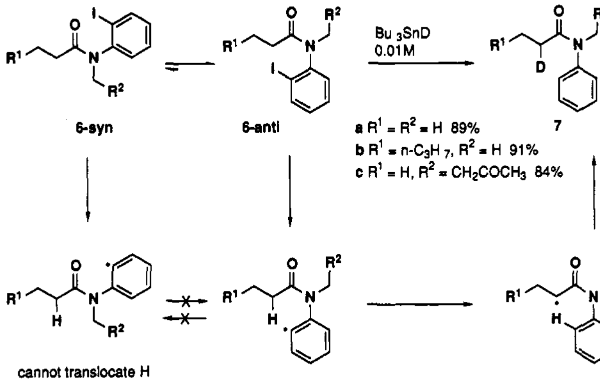
0022-3263/91/1956-4335$02.50/0

Table I. Radical Cyclization Reactions of Unsaturated *o*-Iodoanilides

entry	*o*-iodoanilide[a]	products (cis/trans)[b]	yield[c]
			
a	**8a** $R^1 = R^2 = H$	**9a**	h
b	**8b** $R^1 = CO_2Et, R^2 = H$	**9b** (2.1/1)	94%
c	**8c** $R^1 = CO_2Et, R^2 = Me$	**9c** (1.4/1)	80%
d	**8d** $R^1 = Ph, R^2 = H$	**9d** (1.3/1)	83%
e	**8e** $R^1 = Me, R^2 = H$	**9e** (1.3/1)	67% (18%[d])
			
f	**8f** $R^1 = H$	**9f** (1.2/1)	81%
g	**8g** $R^1 = Me$	**9g** (1/1)[e]	84%
			
h	**8h**	**9h** (1.2/1)[f]	60% (21%[d])
		 + 	
i	**8i** R = H	**9i** **10i**	h
j	**8j** R = Ph	**9j** (1/1.3) **10j**	52%
			
k	**8k** R = H	**9k**	62%[i]
l	**8l** R = Me	**9l** (8/1)	71%
			
m	**8m**	**9m**	35%[g]
			
n	**8n**	**9n** (1/1)[f]	75%

[a] Prepared by acylation of an acid chloride with *o*-iodoaniline ($BrCCl_3$, Ph_3P) and then *N*-methylation (see Supplementary Material for details). [b] Ratio of stereoisomers as determined by integration of the crude ^1H NMR spectra. [c] Yield after purification by flask or medium-pressure liquid chromatography. [d] Yield of reduced, uncyclized side product. [e] Only two isomers are formed, assignment is tentative. [f] Stereochemistry not assigned. [g] The starting material was a 1/1 mixture of diastereoisomers, but only one tricyclic product was isolated. The stereochemistry of amide-bearing stereocenter is not known with certainty; several minor adducts were found, but these were not isolated. [h] Chains do not propagate efficiently, and complex mixtures of products were formed. [i] Only one isomer was isolated.

a favorable rotamer population of 6 is critical for the success of the radical translocation because a radical derived from 6-syn cannot translocate a hydrogen atom,[6] and it does not live long enough to rotate.[5b] We were therefore pleased to learn from NMR experiments that *o*-iodoanilides like 6 exhibit a healthy preference for the anti rotamer (6-anti).[7] As best we ascertain, all *o*-iodoanilides prepared in this study have an anti/syn rotamer population of >95/5.



(2)

When we reduced propionanilide **6a** with tributyltin deuteride (2 equiv) under standard conditions (0.01 M, benzene, 80 °C, AIBN), we isolated the reduced product **7a** in 89% yield. According to mass spectral analysis, **7a** was completely monodeuterated (>98%), and a ^2H NMR spectrum indicated that most of the deuterium label (≥95%) was located adjacent to the carbonyl.[8] We observed similar results upon tin deuteride reduction of pentanoyl anilide **6b**; the deuterium atom was located adjacent to the carbonyl (a 1,5-hydrogen transfer), and there was no evidence for 1,6- or 1,7-hydrogen transfer products. To separate the radical stabilizing effects of the amide from effects caused by its geometry, we prepared anilide **7c**. Although this compound has two pairs of secondary C–H bonds adjacent to carbonyls that are situated for 1,5-hydrogen transfer, we again observed >95% deuterium transfer adjacent to the amide (**7c**). These results indicate that the translocation reactions of radicals derived from *o*-iodoanilides are fast[9] and selective thanks to the geometry of the amide connector.

o-Iodoanilides are valuable precursors for carbonyl-substituted hexenyl radical cyclizations. Table I summarizes the results of a series of experiments conducted under the standard conditions. Several generalizations can be drawn from these experiments. The cyclizations proceed with excellent efficiency provided that the acceptor has at least one terminal substituent. The terminal alkene (entry a) and the terminal alkyne (entry i) did not propagate chains efficiently and provided complex mixtures of products that were not characterized. The cyclization of the phenyl-substituted alkyne (entry j) provided a possible clue to failures of entries a and i; in addition to the ex-

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(6) Cohen, T.; McMullen, C. H.; Smith, K. *J. Am. Chem. Soc.* **1968**, *90*, 6866.

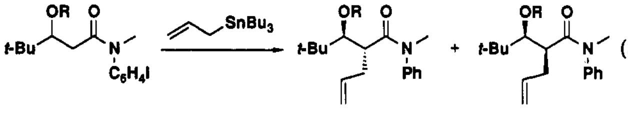
(7) Evidence from ^2H and ^{13}C NMR spectra of all the anilides indicated that mainly one rotamer is present. Accurately quantifying the percentage of the minor rotamer was not easy. In several cases, a small *N*-methyl singlet was observed slightly downfield of the major *N*-methyl singlet. Typical ratios of these two singlets were 97/3 at 25 °C in $CDCl_3$. Heating of one sample resulted in disappearance of the minor resonance, which we tentatively attribute to coalescence. For assignments of amide rotamers by NMR experiments, see: Lewin, A. H.; Frucht, M. *Org. Magn. Reson.* **1975**, *7*, 206.

(8) Because of broader peaks and reduced sensitivity, ^2H NMR is not as useful as ^1H NMR in quantifying minor products. We feel that as much as 3–4% of a minor deuterium-labeled product could have gone undetected.

(9) Beckwith has estimated that aryl radicals abstract hydrogen from tin hydride with a $k_H \approx 10^8\ M^{-1}\ s^{-1}$ (see: Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072). By using this rate constant, we can estimate $k_{1,5} \geq 10^8\ s^{-1}$ for radicals derived from *o*-iodoanilides.

pected product **9j**, a side product **10j** resulting from further addition of the cyclic radical to the anilide ring formed.[10] Fortunately, the poor yields of desired products seem limited to the simplest of substrates; as the complexity of the precursors increased, so did the yields. Generally, the reduced, cyclized products **9** were isolated in high yields, although in two cases (entries e and h) significant amounts of the products of simple reductive deiodination (not shown) formed. Assuming that these simple reduction products form because cyclization is not rapid enough, their yields could be decreased by lowering the tin hydride concentration. The cis/trans ratios of product **9** are uniformly low, as is typical for simple carbonyl-substituted radicals.[2] In contrast, a side-chain substituent apparently provides a good level of asymmetric induction (entry g). Only two of the four possible products are formed from the cyclization of **8g**, and their configurations are assigned from Beckwith's guidelines.[11] *o*-Iodoanilides are also good precursors for tandem radical cyclizations (entries k–n). Cyclization of **8n** provides of striking example of conducting a new type of tandem cyclization through a cyclopentadiene, which we hope will be useful for a synthesis of the crinipellin family of tetraquinanes.[12]

o-Iodoanilides also offer interesting possibilities for conducting radical addition reactions. We have conducted a variety of bimolecular radical allylations with allyltributylstannane, and we illustrate this type of reaction by the two intriguing examples in eq 3. Radical allylation of β-hydroxy anilide **11a** under Keck's standard thermal conditions (80 °C)[13] provided an inseparable mixture of isomers **12a**-anti/syn in a ratio 86/14.[14] By using Keck's standard photolytic conditions[14] (25 °C), the **12a**-anti/syn ratio increased to 93/7 (64% isolated yield). In sharp contrast, allylation of the β-acetoxy anilide **11b** under the photolytic conditions provided **12b**-anti/syn in a reversed ratio of 15/85 (41% isolated yield). Similar trends were observed in deuterium trapping experiments with tributyltin deuteride.[15] These preliminary results hold forth the promise that radical addition reactions are suitable for dictating 1,2-asymmetric induction in acyclic systems[16] and that the stereochemical outcome can be reversed by simple adjustments of substituents. Indeed, recent studies from our lab[17a] and Giese's[17b] have already led to the formulation of a transition state model that will be detailed in a forthcoming joint paper.



(3)

11a R = H

11b R = Ac

12a-anti 80°C, 86/14 **12a-syn**
25°C, 93/7

12b-anti 25°C, 15/85 **12b-syn**

In summary, *o*-iodoanilides are easily introduced, stable precursors that permit the use of C–H bonds as precursors for radical formation adjacent to carbonyl groups in functionalized molecules. The intramolecular hydrogen-transfer reactions of these precursors are exceedingly rapid, and the resulting radicals can be used for standard radical addition and cyclization reactions. Finally, although removal is clearly a matter of concern, we have not yet extensively investigated the excision of the anilide auxiliary from the product. In two cases (Table I, entries d and n), we successfully hydrolyzed the products to carboxylic acids under standard conditions (NaOH, THF/water, 100 °C, 12 h). In the long run, we believe that the design of modified *o*-iodoanilides will result in groups that are even easier to remove.

Acknowledgment. We thank the National Institutes of Health and ICI Pharmaceuticals for funding of this work. We are grateful to Dr. C. Eric Schwartz for conducting the cyclization of **8n** and to Dr. Philip Yeske for conducting the hydrolysis of **9n**.

Supplementary Material Available: Representative experimental procedures and copies of ^{13}C and ^{1}H NMR spectra and mass spectra of all new products (71 pages). Ordering information is given on any current masthead page.

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(10) Consistent with the proposed pathway, the ratio **9j**/**10j** increased as a function of increasing tin hydride concentration. We speculate that the cyclohexadienyl radicals formed by additions to the aromatic ring might not react rapidly with tin hydride at low concentrations, but might instead react by other pathways. This could explain both the difficulties in maintaining chains for entries a and i, and also the lack of clean formation of reduced products.

(11) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(12) Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272.

(13) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

(14) Samples **12a**/**12b** were correlated by the following reactions:

$$\textbf{12a}\text{-syn/anti} \underset{\text{L-Selectride}}{\overset{\text{acetyl chloride}}{\rightleftharpoons}} \textbf{12b}\text{-syn/anti}$$

Stereostructures were assigned by standard ^{1}H and ^{13}C NMR trends for β-hydroxy carbonyls. See: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984: Vol. 3, Chapter 2.

(15) Reduction of **11a** with Bu_3SnD (25 °C) gave an 88/12 ratio of anti/syn deuteration, while reduction of **11b** gave a 23/77 ratio. Deuteration ratios were determined by ^{2}H NMR, and proton assignments were made by the standard trends $J_{anti} > J_{syn}$ (see ref 14).

(16) (a) Related allylations of β-alkoxy esters have just recently appeared. Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* 1991, *32*. 27. All five examples reported gave syn selectivity. (b) For recent observations of related group (thiopyridyl) and atom (H) transfer reactions, see: Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-G. *J. Am. Chem. Soc.* **1990**, *112*, 6741. Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallée, J.-F. *Tetrahedron Lett.* **1990**, *31*, 2845.

(17) (a) Ramamoorthy, P. S., unpublished results. (b) Giese, B.; Bulliard, M.; Zeitz, H.-G. *Synlett*, in press.

A New Vinylsilane Substitution Reaction with Glyoxylate: Asymmetric Synthesis of α-Hydroxy β,γ-Unsaturated Esters

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Received April 24, 1991

Summary: The vinylsilane substitution reaction with glyoxylate and the asymmetric version thereof are described. These new reactions provide α-hydroxy β,γ-unsaturated esters of biological and synthetic importance in high enantiomeric and geometric purity.

The development of efficient methods for the regio- and stereocontrolled formation of carbon–carbon bonds, especially in the asymmetric cases, is the subject of intense current study. Vinylsilanes are well-known to undergo substitution reactions with a wide range of electrophiles

0022-3263/91/1956-4337$02.50/0