Tetrahedron Letters, Vol. 34, No. 19, pp. 3087-3090, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

FREE RADICAL CHAIN REACTIONS OF 3-FLUORO-3-IODO-β-LACTAMS

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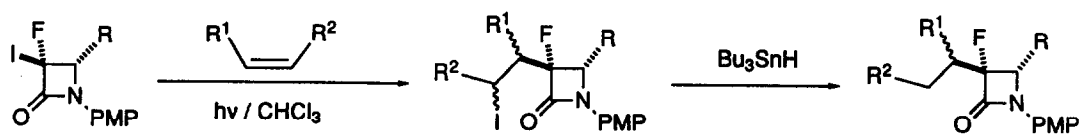
Abstract: The iodine atom transfer addition reaction of 3-fluoro-3-iodo-β-lactams under photolytic conditions was found to be a convenient and stereoselective method for functionalization at the C-3 position. The cyclization leading to 1-fluoro-3,6-diazabicyclo[3.2.1]octan-2-one derivatives was achieved using allylamine as an olefin.

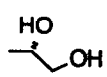
Free radical reactions have recently proven to be a very useful tool for the stereoselective synthesis of cyclic and acyclic systems.[1] The understanding of substituent and polar effects in this type of transformation enables successful planning and optimizing of the organic synthesis. The chemistry of α-monofluoro-radicals[2] has not been explored as much as one would expect based on the importance of fluorine containing molecules in medicine and commerce. In the course of our investigation of the reactivity of fluorine substituted β-lactams, we have found that optically active 3-fluoro-2-azetidinones, easily prepared via imine - ketene condensation,[3] are useful starting materials for synthesis of fluoro-compounds. The functionalization of the C-3 atom of the fluoro-β-lactam, performed by alkylation of the lactam enolate, is limited to alkylating agents that contain no other reactive functionalities. Radical type addition is an alternative approach to the preparation of 3-substituted derivatives.

Irradiation of the 3-iodo-β-lactam derivatives[4] **1** with UV light in the presence of olefins results in an iodine atom transfer addition reaction. The adducts **2**, *cis* substituted β-lactams, were formed in good yield and with excellent stereoselectivity (Table 1). In a typical experiment the solution of 3-iodo-β-lactam **1** (0.6 mmol) and olefin (3-4 mmol) in chloroform (3 mL, not degassed, stabilized with ethanol) was irradiated for 14 hours with UV medium pressure mercury lamp (450 W) at room temperature in quartz tube equipped with cooling finger. The products were purified by column chromatography on silica gel. In the case of disubstituted olefins, the resultant iodides were reduced with Bu_3SnH.[5]



1a R = 

1b R = Ph

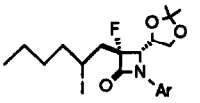
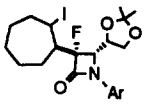
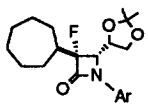
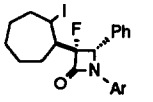
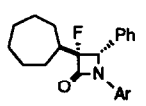
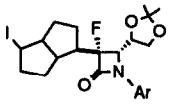
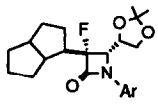
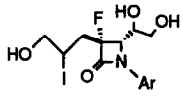
1c R = 

2

3

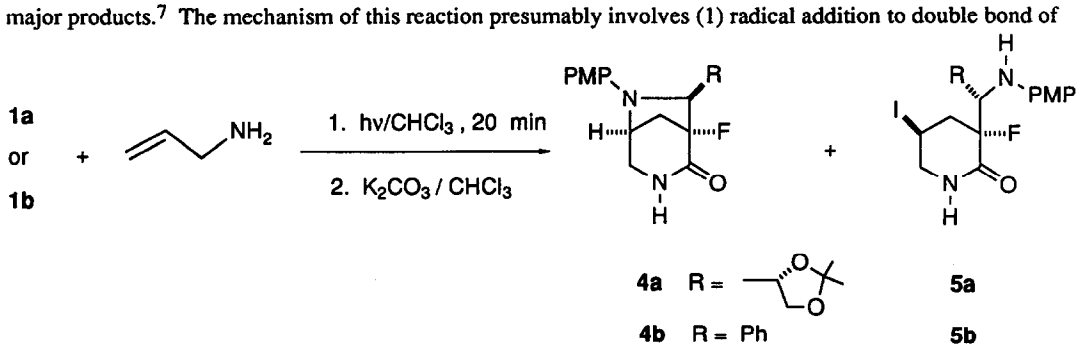
PMP = *p*-methoxyphenyl

Table 1. Iodine atom transfer addition reactions of 3-fluoro-3-iodo-β-lactams.

Nr.	β-Lactam 1	Olefin	Adduct 2	Yield, %	Product 3	Yield, %
1	**1a**[a]			67	—	—
2	**1b**[b]		reaction very slow			
3	**1a**[a]			67		70
4	**1b**[b]			71		79
5	**1c**[a]		reaction very slow			
6	**1a**[a]			74		71
7	**1c**[a]			25	—	—

a) Optically pure; b) racemic.

The addition proceeds with very good stereochemical control, providing only *cis* - substituted β-lactam derivatives.[6] The observed stereoselectivity can be rationalized by the steric influence of the substituent at C-4. This substituent also seems to be very important to the reactivity of the studied process. The 4-phenyl substituted β-lactam **1b** is less reactive than **1a**. In experiments with cycloheptene (Table 1, entry 4), 24 hours of irradiation was necessary for complete conversion of starting material. Also the epimerization of **1b** at C-3, that takes place during irradiation, is slower than in **1a**. A very interesting transformation was observed while using allylamine as an olefin. The 1-fluoro-3,6-diazabicyclo[3.2.1]octan-2-one derivatives **4** were found as major products.[7] The mechanism of this reaction presumably involves (1) radical addition to double bond of



the allylamine and transfer of the iodine, (2) formation of the δ-lactam and (3) formation of the second ring by the S_N2 substitution of iodine. First two steps are fast (20 min of irradiation is enough to consume the starting material) but the crude reaction mixture contains each of the intermediates. Heating under reflux with K_2CO_3 accelerates the last cyclization step. The diastereoisomer of iodo-δ-lactam **5**, not suitable for such cyclization, was found as a byproduct. In the case of nonfluorinated carbonyl compounds, the addition of initiators like Bu_6Sn_2 was necessary to drive the radical process to completion.[8] However, the cyclization of 3-iodo-4-phenyl-2-azetidinone with allylamine did not occur even with Bu_6Sn_2 as an additive.

3-Alkyl substituted derivatives of the β-lactam **6** were also obtained using tributyltin hydride mediated addition to activated olefins.[1] The "Tin Method" has previously been reported with nonfluorinated β-lactams (6-bromopenicillanate).[9] When two equivalents of Bu_3SnH were introduced directly to the reaction mixture, the addition product **6** was obtained as a single *cis* diastereoisomer[10] (Table 2, method "A"). However the major product of this reaction was the reduced β-lactam **7**. The slow addition of tributyltin hydride solution via syringe pump, improved the yield of desired adduct but at the expense of the formation of numerous polymerization byproducts (Table 2, method "B").

In the case of reduction of the iodide **1a**, as well as 3-bromo derivative, with Bu_3SnH, a 3 : 1 mixture

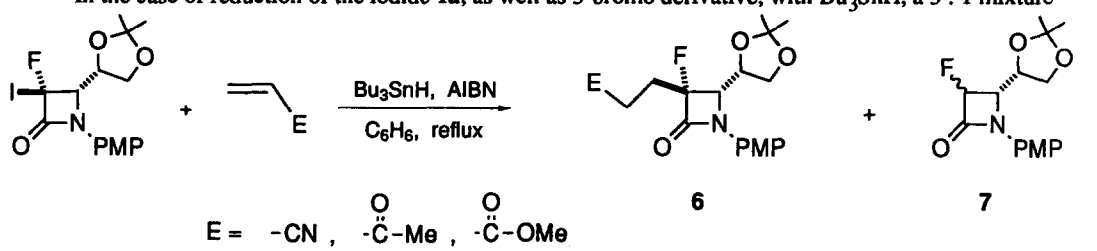


Table 2. Free radical additions to olefins using "Tin Method".

Entry	Olefin	Method[a]	Product	Yield, %	Ratio[b] **6** : **7**
1	CH_2=CH-CN	A	**6a**	16	1 : 5.2
2	CH_2=CH-CN	B	**6a**	48	1 : 0.8
3	CH_2=CH-C(O)Me	A	**6b**	22	1 : 3.5
4	CH_2=CH-C(O)Me	B	**6b**	22	1 : 0.4
5	CH_2=CH-C(O)OMe	A	**6c**	37	1 : 1.7
6	CH_2=CH-C(O)OMe	B	**6c**	41	1 : 0.6

a) **Method A**: Bu_3SnH (2 eq.), AIBN (cat.), C_6H_6, reflux 6-8 h; **Method B**: Bu_3SnH (2 eq.) - added via syringe pump, AIBN (cat.) ,C_6H_6, reflux 6-8 h; b) Determined from ^{19}F NMR.

of *cis* and *trans* diastereoisomers was obtained. This indicates that the abstraction of the hydrogen from tin hydride by α-fluororadical must be a much more facile process than hydrogen abstraction in the case of alkyl radicals.[11]

Acknowledgements. Financial support of this work by the National Science Foundation Grant number CHE-8901986, and DARPA Contract DAAL 0398KO198 is gratefully acknowledged.

References and Notes

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2. Perfluoroalkyl radicals were generated with SmI_2: a) Ma, S.; Lu, X. *Tetrahedron* **1990**, *46*, 357; Et_3B: b) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542; c) Takeyama. Y.; Ichinose, Y; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3159; Zn-$NiCl_2$ d) Yang, C.-Y; Burton D.J. *J. Chem. Soc. Chem. Commun.* **1992**, 233-234; e) Wang, Y.; Yang, Z.-H; Burton, D.J. *Tetrahedron Lett.* **1992**, *33*, 2137-2140 and references cited therein. Free radical cyclization of α-fluoro-α-iodoesters was performed using Bu_6Sn_2 / sunlamp irradiation: d) Barth, F.; O-Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121.
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4. The starting materials, 3-fluoro-3-iodo-2-azetidinones **1a, b**, were prepared via iodination of the enolate of 3-fluoro-β-lactams in THF at -70 °C using inverse addition technique. Compound **1a**: yield 62 %; de 85 % (*trans*); mp 143-144 °C; $[\alpha]_D$ +12.4 ° (c = 1.0, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ -132.7. Compound **1b**: yield 56 %; de 86 % (*trans*); mp 106-108 °C; ^{19}F NMR ($CDCl_3$) δ -129.2.
5. Better yields were obtained by additional hydrogenation on Pd/C in ethanol due to the reduction of unsaturated type byproducts.
6. Stereochemistry in the ring can be easily determined by inspection of vicinal coupling constant to hydrogen at C-4 in ^{19}F NMR. In *cis* substituted compounds this coupling constant is 2-3 Hz, while in *trans* about 12 Hz.
7. Compound **4a**: yield 40 %; oil; $[\alpha]_D$ - 21.8 ° (c = 4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.21 (s, 3H), 1.36 (s, 3H), 2.22 (d, 1H, *J* = 10.4), 2.48 (m, 1H), 3.45 and 3.58 (AB, 2H, *J* = 11.5), 3.75 (s, 3H), 3.93-4.15 (m, 4H), 4.25 (dd, 1H, *J* = 6.3, *J* = 8.8), 6.78 (m, 2H), 6.90 (br, 1H), 6.96 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.0, 26.2, 35.0 (d, *J* = 18), 50.4, 55.5, 61.8 (d, *J* = 8), 66.1 (d, *J* = 6), 67.9 (d, *J* = 25), 78.8, 94.7 (d, *J* = 205), 109.1, 113.7, 117.6, 143.2, 153.6, 169.8 (d, *J* = 25); ^{19}F NMR ($CDCl_3$) δ -182.1 br. Compound **4b**: yield 28 %; oil; ^1H NMR ($CDCl_3$) δ 2.40 (d, 1H, *J* = 10.4), 2.66 (m, 1H), 3.46 and 3.57 (AB, 2H, *J* = 10.9), 3.69 (s, 3H), 4.37 (m, 1H), 4.87 (d, 1H, *J* = 10.3), 6.42 (m, 2H), 6.74 (m, 2H), 6.84 (br, 1H), 7.21-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 35.8 (d, *J* = 18), 49.3, 55.6, 57.0 (d, *J* = 7), 69.9 (d, *J* = 27), 96.0 (d, *J* = 206), 113.6, 114.8, 126.3, 128.1, 128.6, 135.1, 139.9, 152.1, 169.2 (d, *J* = 25); ^{19}F NMR ($CDCl_3$) δ -182.9 br. Products **5** could not be isolated in pure form due to their instability.
8. Curran, D.P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140, Curran, D.P.; Kim, D.; Ziegler, C. *Tetrahedron* **1991**, *47*, 6189.
9. a) Sacripante, G.; Just, G. *J. Org. Chem.* **1987**, *52*, 3659; b) Hanessian, S.; Alpegiani, M. *Tetrahedron Lett.* **1989**, *45*, 941-950.
10. Compound **6a**: mp 78-79 °C; $[\alpha]_D$ + 65.8 ° (c = 0.1, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ -174.3 (t, *J* = 23), compound **6b**: mp 124-126 °C; $[\alpha]_D$ + 57.0 ° (c = 1.1, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ -172.7 (t, *J* = 20), compound **6c**: mp 108-109 °C; $[\alpha]_D$ + 67.0 ° (c = 1.0, $CHCl_3$); ^{19}F NMR ($CDCl_3$) δ -173.1 (t, *J* = 23).
11. For alkyl radicals this rate constants ($k_H = 2 \cdot 10^6\ M^{-1} \cdot s^{-1}$) is nearly independent on alkyl substitution. Chatgilialoglu, C.; Ingold, K.U.; Scaiano, J.C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

(Received in USA 20 January 1993; accepted 9 March 1993)