STEREOSELECTIVE SILVER TRIFLATE-MEDIATED IODOCYCLIZATION OF CARBAMATES

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Summary: Iodocyclization of carbamates involving electron-deficient olefins, (i.e. α , β -unsaturated esters) is greatly facilitated by the use of silver(I) triflate and proceeds with excellent *trans* ring stereoselectivity. During this process, the resultant iodides can undergo epimerization, the rate of which is solvent-dependent.

lodocyclization of carbamates, which is a well-documented method^{1,2} for the heterofunctionalization of alkenes, involves the addition of electrophilic iodine and a pendant nucleophilic carbamate across a double bond. In most of these examples, however, the clefins undergoing functionalization are electron-rich, a feature which should facilitate electrophilic iodine addition and thus enhance the rate of cyclization in comparison to electron-deficient alkenes, such as those found in α ,β-unsaturated carbonyl systems 1. Although examples³ of iodocarbamation of the latter are rare, the resultant α -iodoesters 2 are of particular interest as substrates in the radical-mediated reductions⁴ and alkylations⁵ currently being investigated in this laboratory. We report herein the use of silver(I) triflate to enhance the rate of iodocyclization involving electron-poer olefins and describe a systematic study of factors governing the stereoselectivity of this process.



Shown in Scheme 1 is the preparation of the requisite carbamates 1 from commercially available amino acids. Thus the N-Cbz- α -amino acids 3 are reduced (LiAlH₄, THF, 0=25°C) to their corresponding alcohols. Oxidation (pyr·SO₃, CH₂Cl₂, 0=25°C) followed by Wittig reaction (Ph₃P=CHCO₂Et or Ph₃P=CH(Me)CO₂Et, CH₂Cl₂, 25°C) of the resultant aldehydes 4 afford 3 the desired carbamates 1.

Initial attempts to effect iodocyclization of these carbamates employing literature³ conditions (I₂, NaHCO₃, THF or MeCN) were problematic; long reaction times of up to several days and poor yields were not unusual. However, a dramatic rate enhancement was observed when the reaction was conducted in CCI₄ and in the presence of three to five equivalents of silver(I) triflate (Tatle 1, entries 1-4).^{6,7} When R₁=Me the transformations proceed with excellent *trans* ring stereoselectivity to afford predominantly **5**⁸ regardless of the nature of alkyl substituent R as shown by entries 5-8.

OEt Bn н a,b 0 Ē Ē R R. 3 d OEt OEt OEt HN HN P R R. 5 7 6

Scheme 1

Reagents: a) LiAlH₄, THF, $0 \Rightarrow 25^{\circ}$ C; **b)** pyr SO₃, DMSO, iPr₂NEt, CH₂Cl₂, 0°C; **c)** Ph₃P=CHCO₂Et or Ph₃P=CH(Me)CO₂Et, CH₂Cl₂, 25^oC.; **d)** I₂, AgOTt, NaHCO₃, CCl₄, 25^oC.

Interestingly, a minor product becomes more prominent when smaller allylic substitutents are used (entries 9-11). This byproduct was not the expected *cis*-4,5-disubstituted oxazolidinone **6**, but rather compound **7**⁹ in which the *trans* orientation of the oxazolidinone substituents is retained and the iodine is epimeric to that found in **5**. This minor component appears to arise from iodoepimerization of the initially formed product **5**. Indeed, subjection of **5** to cyclization conditions (i.e. I_2 , AgOTf, NaHCO₃, MeCN or CCI₄) leads to iodoepimerization over several hours with good recovery of **5** and **7** (Table 1, entries 13-16). This epimerization is not only time-dependent, but also solvent-dependent and proceeds faster in MeCN. After 4 hours, the epimerization of **5**b in CCI₄ gives a ratio of 14:1 of **5b:7b**, whereas a ratio of 6:1 is obtained in MeCN (cf. entries 14 and 17). This correlates with the ratios obtained when the iodocyclization of **1g** is conducted in CCI₄ and in MeCN (cf. entries 11,12). A study of the mechanism of epimerization has been initiated.

Our results have shown that for these carboethoxy olefins in which R_1 =Me, the iodocyclization proceeds in fair to good yields with **exclusive** *trans* ring selectivity regardless of the steric bulk at R; the minor product, if formed, also has *trans* ring geometry. In contrast, the iodocyclization exhibits much less *trans* selectivity in the absence of a *cis* olefinic methyl substituent (cf. entries 18,19). The rationale for this is evident from an analysis of the possible transition states (Scheme 2). In the presence of a *cis* substituent (i.e. R_1 =Me), the process is highly *trans*-selective since the *cis*-predictive transition states D and C are destabilized substantially by 1,3-allylic strain¹⁰ and bisecting 1,3-allylic interactions¹¹ respectively. These interactions are greatly diminished in the absence of a *cis* substituent (i.e. R_1 =H) such that reaction through either C or D is more viable and consequently more *cis* ring product is observed.



Table 1: Effect of Silver(I) Triflate on Iodocyclization of Carbamates^a

Entry	Substrate	R	R ₁	AgOTf (equiv)	Solvent	Time (h)	Yield (%) ^b	Ratio ^r 5:6:7
				_				
1	1a	c-C ₆ H ₁₁	Me	0	CCI4	0.75ª	0e	
2	1a	c-C ₆ H ₁₁	Me	1	CCl₄	0.75	5 ⁶	>20:0:1
3	1a	c-C ₆ H ₁₁	Me	2	CCI₄	0.75	17 0	>20:0:1
4	1a	c-C ₆ H ₁₁	Me	3	CCI₄	0.75	96 ^e	>20:0:1
5	1a	c-C ₆ H ₁₁	Me	5	CCI₄	4	57	>20:0:1
6	1Ь	iĔr	Me	5	CCI₄	4	75	>20:0:1
7	1c	tBu	Me	5	CCI	4	72	>20:0:1
8	1d	n-C ₆ H ₁₁	Me	5	CCI	4	73	>20:0:1
9	1e	Bn	Me	5	CCIA	4	71	10:0:1
10	1f	Et	Me	5	CCI	4	.65	17:0:1
11	1a	Me	Me	5	CCL	4	68	19:0:1
12	1g	Me	Me	5	MeCN	4	72	12:0:1
13	5Ď	iPr	Me	3	MeCN	1	98	18:0:1
14	5b	iPr	Me	3	MeCN	4	78	6:0:1
15	5b	iPr	Me	3	MeCN	12	94	4:0:1
16	5b	iPr	Me	3	MeCN	24	82	2:0:1
17	55	iPr	Me	ä	CCL	4	67	14.0.1
18	1h	CH ₂ (C-C ₂ H ₄₄)	Me	3	CCL	3	76	9:0:1
19	11	$CH_2(c-C_6H_{11})$	Н	3	CCl ₄	3	81	1:1:0

^aAll new compounds have been satisfactorily characterized. ^bIsolated yields. ^cRatios determined by ¹H nmr. ^dEvan after 4h, only starting material is recovered. ⁹Conversion of substrate to product, determined by ¹H nmr.

A typical protocol for iodocyclization in which iodoepimerization of the initial product is minimized involves the reaction of N-Cbz derivatives 1^{12} with I_2 (3 equiv), NaHCO₃ (3 equiv) and

AgOTf (3 equiv) in CCl₄ at room temperature. The reaction is quenched with aqueous $Na_2S_2C_3$ (0.2 M) after all substrate olefin has been consumed.

In summary, the use of silver(I) triflate offers dramatic rate enhancement of iodocyclizations involving electron-deficient alkenes (i.e. α , β -unsaturated esters). Furthermore, when these alkenes are terminally disubstituted (i.e. R_1 =Me), excellent stereoselectivity is observed for this process and is attributed to the minimization of 1,3-allylic strain to afford only *trans* ring geometry. The stereoselective radical-mediated reduction and alkylation of the resultant tertiary iodides are currently under study, the results of which will be published in due course.

References and Notes

- 1. For recent reviews, see: (a) Cardillo, G.; Orena, M.; Sandri, S. *Pure Appl. Chem.* **1988**, *60*, 1679; (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.
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- 5. Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D. Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27.
- Silver nitrate was initially used, but failed to enhance the rate of cyclization presumably due to its insolubility in THF. Silver (I) triflate, in contrast, is quite soluble in a variety of solvents. Silver nitrate has been reported to facilitate methoxybromination of electron-poor alkenes; see: Vishwakarma, L.C.; Walia, J.S. J. Indian Chem. Soc. 1976, 53, 156.
- 7. I₂/Ag⁺ has been used recently for the heterofunctionalization of an electron-rich alkene: see: Lipshutz, B.H.; Barton, J.C. *J. Am. Chem. Soc.* **1992**, *114*, 1084.
- 8. The relative stereochemistry of 5b was confirmed by x-ray crystallographic analysis.
- 9. The relative stereochemistry of 7 was deduced by subjecting both 5 and 7 to tributyltin hydride reduction, which afforded the same major product oxazolidinone. Presumably the stereoselective reduction proceeded through the same intermediary radical.
- For the effects of 1,3-allylic strain on conformation and stereoselectivity of reactions, see: (a) Johnson, F. Chem. Rev. 1968, 68, 375; (b) Hoffmann, R.W. Chem. Rev. 1989, 89, 1841.
- 11. The relative energies of 4-methyl-2-pentene conformers have been estimated.^{10b} The conformer corresponding to transition state **C**, in which the vinylic methyl group bisects the two allylic substituents (i.e. C-N and C-R bonds) may be destabilized by as much as 3.4 kcal/mol.^{10b}
- 12. N-Boc derivatives are susceptible to loss of the Boc group during iodocyclization conditions.

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