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The Stereoselective Synthesis of 3-Fluoro-azetidinones

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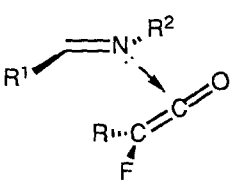
Abstract: 3-Fluoro-azetidinones were prepared by both the enolate-imine and ketene-imine condensation reactions. The reactions of fluorinated ketenes with imines were remarkably stereoselective forming products derived from *lk* reaction topicity.

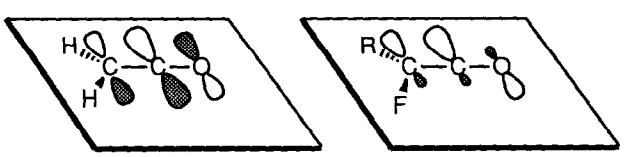
The stereoselective synthesis of fluorinated materials is important not only for the preparation of biologically active substances[2] or for the construction of novel ferroelectric devices[3] but also as test of synthetic strategy. 3-Fluoro-azetidinones derivatives may be employed not only as synthetic intermediates for the preparation of fluorinated β-lactam antibiotics but also as building blocks for carbohydrates and amino acids, however only limited reports have been made of the synthesis of these compounds [4] Now we describe two approaches to the construction of 3-fluoro-β-lactams using the ketene-imine condensation method[5] or the enolate-imine condensation method.[6]

We employed enolates prepared from the appropriate 2,4,6-trimethylphenyl (TMP) esters based upon our previous experience with these enolates.[7] Unfortunately these enolates did not exhibit stereoselectivity in the enolate-imine condensation even under a variety of experimental conditions. (Table 1)

In contrast the ketene-imine condensation to form 3-fluoro-azetidinones was highly stereoselective, forming only a single detectable diastereomer in all cases but one.[8] This selectivity may result from selective reaction of fluoroketene,[9] formed by treatment of the required acid chloride with triethylamine. The fluoroketene must react from the face opposite fluorine, this selectivity may be derived from simple dipolar effects or secondary orbital interactions,[10] but is likely not related to steric effects as the selectivity is retained even in the reactions of ketenes with a more bulky substituent on the α-carbon. However it may be possible that the intermediate zwitterion is undergoing equilibration to form the product lactam selectively.

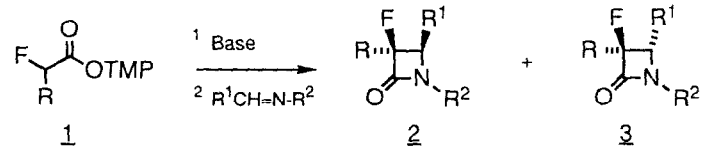


Dipolar Effects



Secondary Orbital Effects on LUMO

The involvement of ketenes in the ketene-imine condensation process has recently been established by IR spectroscopy.[11]



1 2 3

Table 1 Formation of 3-Fluoro-azetidinones via Enolate-Imine Condensation

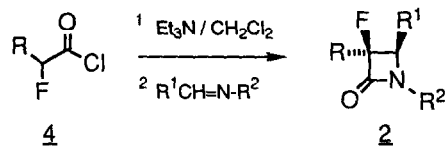
Ester 1	R	R^1	R^2	Method	Ratio 2 . 3	Yields[a]
a	Me	Ph	4-$MeOC_6H_4$	A	1 . 0 9	32%
a	Me	Ph	4-$MeOC_6H_4$	C	1 3.5	68%
b	Et	Ph	4-$MeOC_6H_4$	A	1 · 3	12%
b	Et	Ph	4-$MeOC_6H_4$	B	1 · 0 8	35%
c	Ph	Ph	4-$MeOC_6H_4$	A	1 : 2.5	26%
d	Ph	CO_2Et	4-$MeOC_6H_4$	A	1 · 3 6	48%
e	Me	CO_2Et	4-$MeOC_6H_4$	B	1 0.9	34%
f	Me	Ph	Ph	A	1 · 2 1	59%
f	Me	Ph	Ph	B	1 · 1.8	93%
g	Et	Ph	Ph	A	1 1	20%
g	Et	Ph	Ph	B	1 : 0.3	80%
h	Ph	Ph	Ph	A	1 : 0 4	70%

a. Each diastereomer was purified by chromatography Yield reported is that of the combined purified diastereomers

Method A: To a tetrahydrofuran solution (5 mL) of diisopropylamine (0.37 mL, 2.6 mmol) was added dropwise 2.5 M *n*-butyllithium in hexane (1.0 mL, 2.5 mmol) at -20 °C with stirring. The solution was stirred for 10 min. at -5 °C, and cooled to -90 to -100 °C. To this solution was added dropwise a tetrahydrofuran solution (3 mL) of the appropriate ester (2.5 mmol) at a rate such that the temperature did not exceed -90 °C and immediately was added dropwise a tetrahydrofuran solution (3 mL) of the appropriate imine (2 5 mmol) below -90 °C. The reaction mixture was allowed to warm up gradually to room temperature and stirred overnight Then dichloromethane (30 mL) and water (25 mL) were added and the organic layer was separated, washed with water, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with an appropriate ethyl acetate-*n*-hexane mixture) to give the corresponding β-lactam derivatives All compounds gave the desired spectral and elemental microanalytical data

Method B· All operations were identical with method A except 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (N,N'-dimethyl-propyleneurea, DMPU) (1 mL, 8 3 mmol) was added prior to addition of ester.

Method C. All operations were identical with method A except hexamethyldisilazane (2 6 mmol) was employed in place of diisopropylamine



4 2

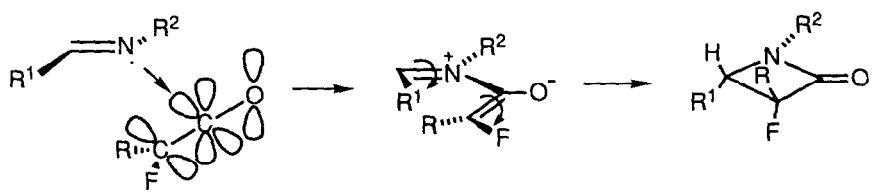
Table 2. Formation of 3-Fluoro-azetidinones via Ketene-Imine Condensation

Acyl Chloride 4	R	R^1	R^2	Yield[a]
c	Ph	Ph	-4-(MeO)C_6H_4	16%
d	Ph	CO_2Et	-4-(MeO)C_6H_4	48%
h	Ph	Ph	Ph	51%
i	Ph	Ph	Et	40%
j	Ph	Ph	Me	10%
k	Ph	Ph	CH_3 C-Ph (*S*)	10%[b]
l	H	Ph	Me	33%
m	H	Ph	Ph	70%
n	H	Ph	-4-(MeO)C_6H_4	70%
o	H	PhCH=CH	-4-(MeO)C_6H_4	15%
p	Ph	PhCH=CH	-4-(MeO)C_6H_4	25%
q	H	CO_2Et	-4-(MeO)C_6H_4	66%[c]

[a] Yield chromatographically pure product. Only a single diastereomer was formed unless otherwise noted. [b] No asymmetric induction observed. [c] 19 : 1 mixture of 2 to 3.

The following procedure was utilized for the ketene-imine condensation method. Under an argon atmosphere, to a dichloromethane solution (15 mL) of 6.8 mmol imine and 6.8 mmol triethylamine was added dropwise a dichloromethane solution of 6.8 mmol α-fluorocarboxylic acid chloride[12] at ambient temperature with stirring. The reaction mixture was stirred overnight. The reaction mixture was washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with an appropriate ethyl acetate-*n*-hexane mixture) to give the corresponding 3-fluoro-β-lactam derivative.

The *lk* topicity of lactam formation which selectively creates the diastereomer found experimentally, follows from the required conrotatory motion of the ring closure.[13]



Further studies of the synthetic utility of these potential building blocks are in progress.

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8. Assignment of stereochemistry is based upon fluorine-proton coupling constants where smaller dihedral angle between proton and fluorine in **3** results in the larger coupling constant, eg , **2a** ^{1}H NMR ($CDCl_3$) δ 4 98 (d, $J_{4,F}$ = 3 9, 1H, H-4) 3 73 (s, 3H, OCH_3) 1 81 (d, $J_{CH_3,F}$ = 21 6, 3H, CH_3); **3a** ^{1}H NMR ($CDCl_3$) δ 5 17 (d, $J_{4,F}$ = 12 0, 1H, H-4) 3 74 (s, 3H, OCH_3) 1.25 (d, $J_{CH_3,F}$ = 22 8, 3H, CH_3) 6.83 (d, 2H, Ar) 7.2 - 7.4 (m, 7H, Ar)
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12. **Caution**· Sodium-fluoroacetate and fluoroacetyl chloride are fatal poisons affecting the central nervous system causing epileptic convulsions. α-Fluorocarboxylic acid chlorides were handled with extreme caution in an efficient fume hood.
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