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ASYMMETRIC SYNTHESIS OF PYRROLIZIDINONES BY RADICAL CYCLIZATION OF N-ALLYLIC PYROGLUTAMATES [1a]

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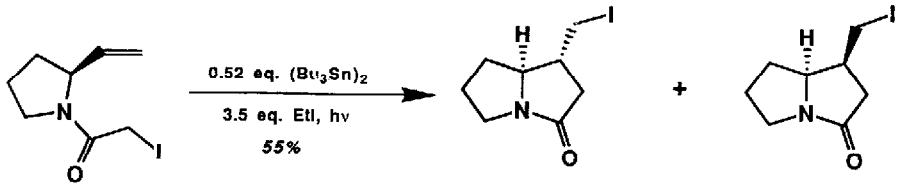
Abstract: Ethyl *S*-pyroglutamate is converted to *N*-allylic-*S* C_5 -iodomethyl-2-pyrrolidinone. Facile radical cyclization on treatment with AIBN and tributyltin hydride in refluxing benzene gives good yields of the C_6 substituted pyrrolizidin-2-one with excellent diastereoselectivity.

Radical cyclization of haloalkenes is an important tool for construction of carbocyclic rings in natural product synthesis.[2] An intermediate alkenyl radical is generated by treatment of haloalkenes with a radical initiator such as *azo-bis*-isobutyronitrile (AIBN) or by photochemical methods. Tributyltin hydride (Bu_3SnH) is usually added to transfer an hydrogen atom to the cyclized radical product. 1-Azabicyclo[m.n.0]alkanes are an important class of naturally occurring alkaloids of great interest to synthetic chemists.[3] The pyrrolizidine alkaloids (m = n = 1), for example, possess important biological activities ranging from insect attractants or defensive substances[3b] to anticholenergic[3b] or antineoplastic activity.[3b] Most of the synthetic routes to 1-azabicyclo[m.n.0] alkaloids rely on nucleophilic ring closures using Dieckmann or Aldol condensations.[3] A few strategies use acid catalyzed ring closure routes. 3+2 Cycloadditions with nitrone derivatives also lead to efficient syntheses of these alkaloids.[3] Radical cyclization has been applied sparingly to alkaloid syntheses but pyrrolizidines are well suited to this strategy.

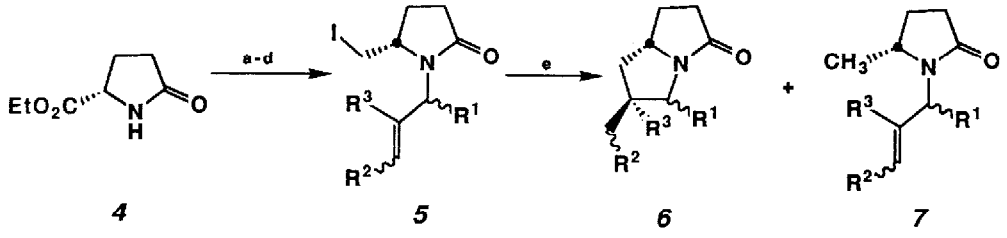
Radical cyclization of heteroatom containing substrates is known for many alkenyl halides[2,4] and two radical cyclization strategies have been used to construct pyrrolizidines. In the first Hart cyclized 5-thiophenyl-N-alkenyl-2-pyrrolidinones with AIBN and Bu_3SnH,[5] but produced mixtures of pyrrolizidines and indolizidines with poor diastereoselectivity and no asymmetric induction. More recently, Hart reported an asymmetric synthesis of (-)-swainsonine by radical cyclization of an asymmetric *N*-alkynyl-5-thiophenyl precursor.[6] The chiral succinimide precursor was prepared from tartaric acid, and radical cyclization gave excellent diastereoselectivity and a 70% yield of the desired indolizidinone products. In a recent prolinol based strategy,[7] Livinghouse prepared **1** via Wittig reaction with a BOC-protected prolinal. [8] Cyclization with Bu_3SnH/AIBN gave poor yields of the pyrrolizidine, but radical generation with *n*-$(Bu_3Sn)_2$/hν gave a 65:1 mixture of **2** and **3** in 58% yield.[7] Pyrrolizidin-2-one **2** was converted to (-)-trachelanthamidine in two steps.[7] Other non-radical prolinol strategies, involving intramolecular cyclization via carbanionic intermediates have been reported for the asymmetric synthesis of 'izidine' alkaloids such as septicine.[9]



1 *2* *3*

S-Ethyl pyroglutamate (*4*) is prepared in high yield by reaction of glutamic acid with thionyl chloride and heating in ethanol[10]. Alkylation of *4* with a variety of allylic halides required 1.5 equivalents of powdered KOH, 20 mol% of Bu_4NBr as a phase transfer catalyst (analogous to the work of Takahata)[11] in THF but gave yields of only 5-10%. Sonication (ultrasonic cleaning bath) during the reaction led to good to excellent yields of the desired *N*-substituted lactams (81% with allyl bromide). The alkylation reaction did not racemize the C_5 hydrogen.

Standard $LiBH_4$ reduction of the ester gave only 0-10% yield of the requisite hydroxymethyl lactam. Reduction with lithium aluminum hydride on anhydrous silica gel,[12] however, gave 70-85% of the alcohol.[13] Conversion of the hydroxymethyl moiety to the mesylate (one equivalent of CH_3SO_2Cl and one equivalent of alcohol in CH_2Cl_2 were treated with 1.1 equivalents of triethylamine at -78°)[14] allowed formation of the iodomethyl derivative by Finkelstein exchange (10 equivalent of sodium iodide in refluxing acetone for 1 hour). In sharp contrast to the cyclization of *1*, treatment of one equivalent of *5* with 2 equivalents of Bu_3SnH (5-10 mol% AIBN in refluxing benzene [5-25 mM], 4-12 hours) gave good yields of cyclized product, *6* (see Table 1). Iodolactam *5a* gave *6a* in 70% yield.[15] In all cases except *5d*, *7* (resulting from hydrogen transfer to the intermediate radical) was the only other product. Identification of *6* was straightforward via NMR and capillary GC/Mass spectral analysis.



4 *5* *6* *7*

(a) $R^2CH=C(R^3)CHR^1Br$ /THF/**sonication**/Bu_4NBr/KOH (b) $LiAlH_4/SiO_2$ (c) CH_3SO_2Cl/NEt_3
(d) NaI/acetone (e) AIBN/ Bu_3SnH /PhH/reflux

As an example, asymmetric induction in *6a* was confirmed ($[\alpha]^D_{25}$ = +20.8 [EtOH, c. 0.0288 g/mL]) and NMR analysis clearly showed the C_6 methyl group to be *cis*- to the hydrogen at C_{7a} (*exo*-methyl). The proton at C_{7a} appears at 4.04 ppm; the methyl group at 1.09 ppm; the *exo*- proton at C_5 at 3.81 ppm and the *endo*-hydrogen at C_5 at 2.42 ppm. The COSY spectrum shows strong coupling of the methyl group and C_6 hydrogen, which appears at 2.33 ppm, but no coupling of the C_{7a} and C_6 hydrogens. Enhanced long range coupling (W-type) in the COSY for the C_{7a} hydrogen and the *exo*-C_5 hydrogen is apparent. Similar long range coupling for the C_6-C_{7a} hydrogens was absent, strongly suggesting the methyl

group is *exo* (*cis*-) to the C_{7a} hydrogen. There was no enhancement for these signals in the NOESY spectrum.

Similar *exo*-selectivity was observed in the prolinol based system.[2] Models show a steric interaction of the alkenyl moiety with the pyrrolidinone ring in the *endo*-transition state which is absent in the *exo*- transition state. No significant interaction of the C_{7a} hydrogen was apparent in any transition state leading to cyclized product. Although the energy differential between these rotamers may be small, the diastereoselectivity for the *exo*-transition state was clear. A single product was detected in the ^{1}H NMR and by GC/MS analysis. Further analysis by HPLC (C_{18}-reverse phase, acetonitrile) showed less than 1% of a peak which *may* be the *endo*- diastereomer. Analysis by GC/MS showed that no indolizidin-2-one was formed in the cyclization of ***5a***.[16] The diastereoselectivity of this reaction appears comparable to that of the prolinol-based cyclization.

Iodolactams ***5b*** and ***5c*** were cyclized to ***6b*** and ***6c***, respectively, under identical conditions (see Table 1) with *exo*-selectivity. Cyclization of ***5d*** introduced the problem of selectivity between the methylene and methyl moieties. A 30:70 mixture of ***6d*** and 6-methylindolizidin-2-one was isolated, the remainder of the product being ***7d*** although this was greatly diminished at concentrations of less than 5 mM. The product distribution suggests a slight preference for the rotamer with the methylene group *endo*-. The steric encumbrance inherent to an *endo*- methyl or methylene probably leads to a rotamer in which the terminal methylene carbon is exposed to attack, giving the six-membered ring. We did *not* observe indolizidin-2-one products in any other case[16] but ***7*** was the by-product in reactions of ***5a-f***.

Table 1. Radical Cyclization of N-Allylic-5-iodomethyl-2-pyrrolidinones.

5/6[a]	R^1	R^2	R^2	Time (hr)	Conc (mM)	% 6[a,b]
a	H	H	H	4	10	70
b	H	Ph	H	3	25	72
c	H	Me	H	12	3	52
d	H	H	Me	12	5	96[c]
e	Me	H	H	12	4.3	54
f	$-CH_2CH_2CH_2-$		H	12	6	58

[a] Satisfactory analysis for all new compounds [b] remaining product is ***7***
[c] a 70:30 mixture of 6-methylindolizidin-2-one and ***6d***

Substitution at the position α to the nitrogen, R^1 in ***5e*** and ***5f*** leads to the expected mixture of diastereomers. The methyl group at C_6 is *exo*- but the 70:30 diastereomeric mixture in ***5e*** is reflected in the cyclized product, ***6e***. The conformational bias for the *equatorial* isomer in ***5f*** leads to some selectivity for the *trans*-fused B-C ring in ***6e***. Only one product was easily discernible in the ^{1}H NMR but HPLC shows a 30:1 mixture of diastereomers for ***6f***.

The facility of the pyroglutamate based radical cyclization under milder conditions than the prolinol based cyclization is obvious from these results. The high preference for *exo*-substitution during the cyclization is apparent. COSY and NOESY are powerful tools for

determining the relative stereochemistry of substituents in these pyrrolizidinones. Modification of this pyroglutamate strategy to a C_5-alkenyl *N*-iodoethyl derivative is underway and will allow the asymmetric synthesis of a variety of naturally occurring pyrrolizidine alkaloids.

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15. Addition of 1.30 g (4.90 mmol) of **5a**, 0.45 g (9.80 mmol) of Bu_3SnH and 0.05 g (0.3 mmol) of AIBN in 500 mL of dry benzene was followed by reflux for 4 hours. The solution was cooled, concentrated *in vacuo* and chromatography (silica gel/ether) gave 0.48 g (3.45 mmol, **70%**) of **6a**: ^1H NMR ($CDCl_3$) δ 1.09 (d, 3H), 1.61 (m, 4H), 2.33 (m, 1H), 2.42 (m, 1H), 2.61 (m, 2H), 3.81 (dd, 1H) and 4.04 ppm (m, 1H); ^{13}C NMR ($CDCl_3$) : δ 19.6 (q), 28.3 (t), 34.5 (t), 34.9 (t), 39.7 (t), 49.3 (t), 60.2 (d) and 175.3 ppm (s); Mass spectrum (m/z, rel. intensity): 139 (P,50), 124 (3), 110 (2), 97 (100), 84 (12), 69 (50), 55 (40) and 41 (45).

16. Indolizidin-2-ones show a pronounced P-1 peak in the mass spectrum. This peak was missing in all pyrrolizidin-2-ones, allowing differentiation by GC/MS.

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