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Radical cyclization of β-aminoacrylates: synthesis of bicyclic pyrrolidine derivatives

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Abstract

Radical cyclization of the β-aminoacrylate derived from 4-(2-bromoethyl)azetidin-2-one led to the stereoselective formation of a bicyclic β-lactam product, which may serve as a precursor for *cis*-2,5-disubstituted pyrrolidines.

Radical cyclization of β-aminoacrylates was shown to be a useful method in the preparation of azacyclic compounds.[1] β-Aminoacrylates prepared from primary amines carrying secondary alkyl groups were converted into pyrrolidine and piperidine derivatives, and a useful level of stereocontrol (~4:1) favoring *trans*-2,5-disubstituted pyrrolidine products was ascertained when the methanesulfonamide substrates were employed.[1a] In our continuing search for stereoselective conversions, we considered the use of β-lactam templates in radical cyclization reactions.

The known azetidin-2-one derivative **3**[2] may be synthesized from the carboxylic acid **1**[3] via the homologous alcohol **2**.[4] Reaction of the azetidin-2-one **3** with ethyl propiolate in the presence of tributylphosphine afforded the β-aminoacrylate **4**. Radical cyclization of **4** under the standard high dilution conditions led to the formation of the novel bicyclic β-lactam **5**[5] in 49% yield. An epimeric product **6** was isolated in 3% yield along with the simple reduction product 4-ethylazetidin-2-one (28%) (Scheme 1). The stereochemical assignment was confirmed by comparing proton NMR spectra of the *N*-benzyl derivatives of *cis*- and *trans*-2,5-bis(ethoxycarbonylmethyl)pyrrolidine, obtained from the reaction of **5** and **6** with sodium ethoxide in ethanol and then with benzyl bromide in acetone in the presence of K_2CO_3. The benzylic methylene protons exhibit a singlet signal (δ 3.78) for the *cis* isomer and an AB quartet (δ 3.64 and 3.85, $J = 14.3$ Hz) for the *trans* isomer.[6]

For further comparison studies, the β-aminoacrylate **8** was prepared from the known oxazolidinone **7**.[7] Radical cyclization of **8** in the presence of tributylstannane and AIBN resulted in the formation of an inseparable 3.3:1 mixture of the products **9** and **10** (Scheme 2). The mixture was reacted with trimethylsilyl phenylselenide in toluene under reflux in the presence of a catalytic

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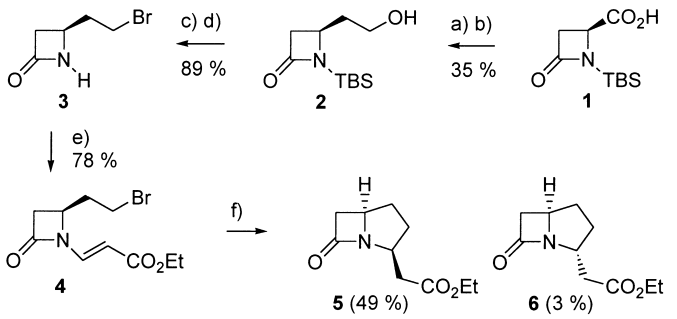
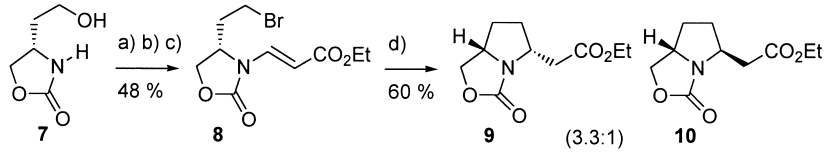


Scheme 1. (a) $(COCl)_2$, DCM; CH_2N_2, ether; Ag_2O, MeOH, 55°C, 90 min; (b) LAH, ether, 0°C, 40 min; (c) CBr_4, Ph_3P, TEA, DCM, rt, 4 h; (d) KF, AcOH, MeOH, 0°C, 10 min; (e) 2.0 equiv. $HCCCO_2Et$, 1.0 equiv. Bu_3P, DCM, 0°C to rt, 90 min; (f) 1.1 equiv. Bu_3SnH, 0.1 equiv. AIBN, benzene (0.025 M), reflux, 5 h (syringe pump, 4 h)

amount of ZnI_2,[1a] and *cis*- and *trans*-2-(phenylseleno)methyl-5-(ethoxycarbonylmethyl)-pyrrolidine thus produced were separated by flash column chromatography. The benzylic methylene protons of the *N*-benzyl derivatives exhibit an AB quartet at δ 3.71 and 3.77 ($J = 14.2$ Hz) for the *cis* isomer and an AB quartet at δ 3.66 and 3.91 ($J = 14.4$ Hz) for the *trans* isomer.



Scheme 2. (a) *p*-TsCl, pyridine, DCM; (b) $HCCCO_2Et$, NMM, DCM, reflux; (c) LiBr, acetone, reflux; (d) 1.3 equiv. Bu_3SnH, 0.15 equiv. AIBN, benzene (0.025 M), reflux, 5 h (syringe pump, 4 h)

It is apparent from these studies that *cis*-2,5-disubstituted pyrrolidine derivatives may be prepared with useful stereoselectivity when azetidinone and oxazolidinone templates are used in the radical cyclization reactions of β-aminoacrylates, and they complement the results of earlier studies in which *trans*-2,5-disubstituted pyrrolidine derivatives were obtained as major products.

Acknowledgements

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