SYNTHESIS OF 7-AZABICYCLO[2.2.1]HEPTANE AND 8-AZABICYCLO[3.2.1]OCTANE SYSTEMS USING RADICAL CYCLIZATION†

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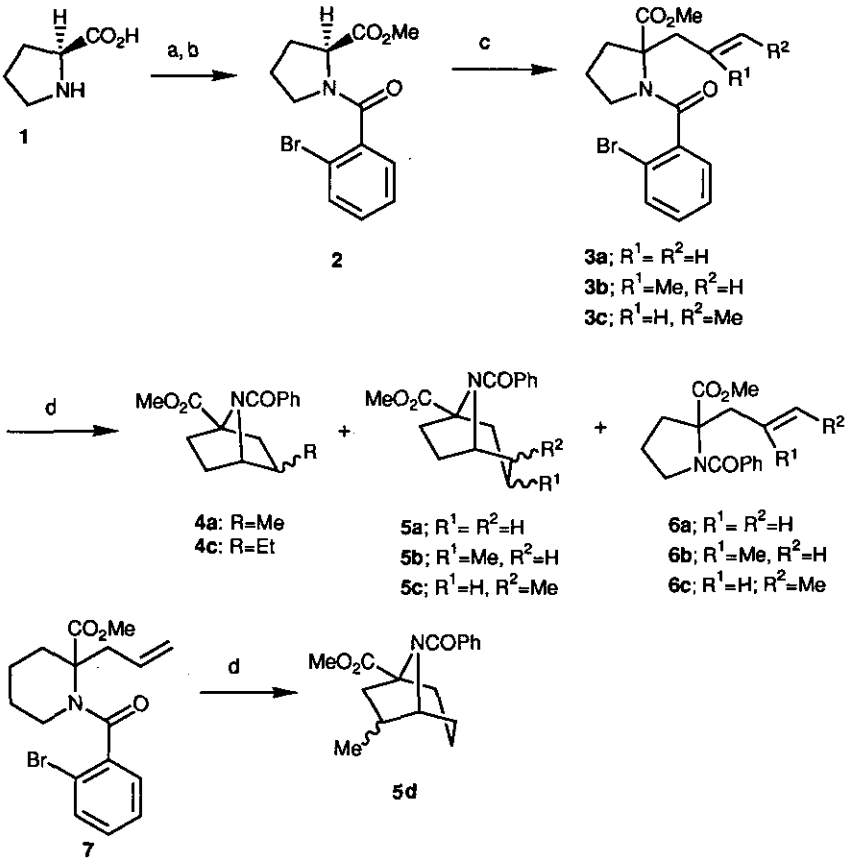
Abstract—A new method for the synthesis of the titled systems using cyclization of the α-acylamino radicals generated from methyl *N*-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine- 2-carboxylates and the piperidine congener by Bu_3SnH-mediated radical translocation reaction is described.

α-Acylamino radical cyclizations have been used for the synthesis of a variety of the nitrogen-containing heterocycles.[1,2] These radicals can be generated mainly by two methods:[3] one is by use of the tin hydride method from functionalized acylamino derivatives[1] and the other is by a 1,5-hydrogen atom transfer from *o*-halobenzamides.[2] We report here a new entry to the 7-azabicyclo[2.2.1]heptane and 8-azabicyclo[3.2.1]octane systems using cyclization of the α-acylamino radicals generated from methyl *N*-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine-2-carboxylates (**3**) and the piperidine congener (**7**) by the latter method.

The radical precursors (**3a-c**) were prepared by alkylation of methyl *N*-(*o*-bromobenzoyl)pyrrolidine-2-carboxylate (**2**), which in turn was prepared from L-proline (**1**) in two steps in quantitative yield, with prop-2-enyl bromide, 2-methylprop-2-enyl chloride, or but-2-enyl bromide in 93, 45, and 96% yields, respectively.

† This paper is dedicated to Professor Alan R. Katritzky, University of Florida, on the occasion of his 65th birthday.

Treatment of **3a** with tributyltin hydride (Bu_3SnH) (2.3 equiv.) in the presence of a catalytic amount of azoisobutyronitrile (AIBN) in boiling toluene gave the 7-azabicyclo[2.2.1]heptane (**4a**) (40% as a diastereomeric mixture in a ratio of 2:1, from which only the major *exo* isomer, mp 88-92°C, was obtained as a pure compound), the 8-azabicyclo[3.2.1]octane (**5a**) (30%), mp 111-114°C, and the reduction product (**6a**) (12%). The structures of the cyclized products were derived from the spectroscopic evidence [**4a**: ν_{max} 1740, 1650 cm^{-1}; δ ($CDCl_3$) 3.91 (d, *J*=4.8 Hz, H-4) for the *exo* isomer and 4.05 (t, *J*=4.5 Hz, H-4) for the *endo* isomer.[4] **5a**: ν_{max} 1740, 1640 cm^{-1}; δ ($CDCl_3$) 4.33 (quintet, *J*=3.2 Hz, H-5)].

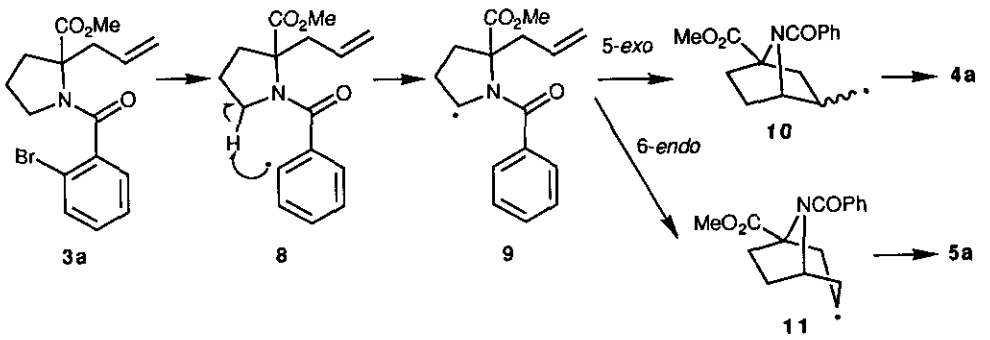


Scheme 1. *Reagents and conditions*: (a) $SOCl_2$, MeOH, reflux; (b) *o*-bromobenzoyl chloride, Et_3N, CH_2Cl_2; (c) (i) $(TMS)_2NLi$, THF, -78°C; (ii) $R^2CH{=}CR^1CH_2X$; (d) Bu_3SnH, AIBN, toluene, reflux

The pyrrolidine (**3b**), when treated with Bu_3SnH and AIBN, gave the 8-azabicyclo[3.2.1]octanes (**5b**) (75% as a diastereomeric mixture in a ratio of 3.5:1) in a regioselective manner along with the corresponding reduction product (**6b**) (15%), whereas **3c** afforded the 7-azabicyclo[2.2.1]heptane (**4c**) [63% as a diastereomeric mixture

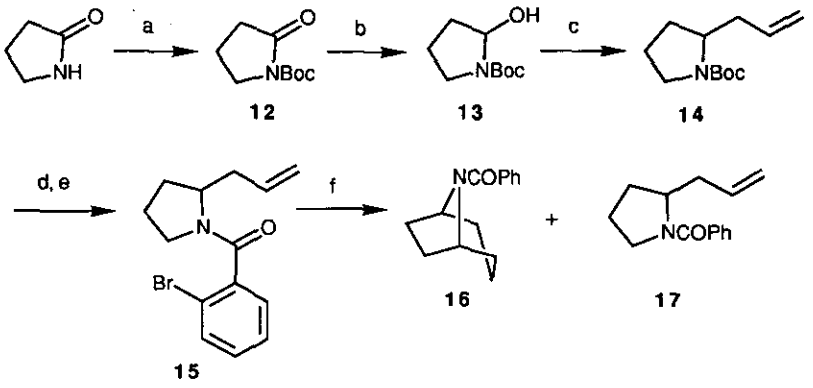
(*exo* and *endo*) in a ratio of 2:1], the 8-azabicyclo[3.2.1]octane (**5c**) (29% as a single isomer), and the reduction product (**6c**) (8%). Similar treatment of the piperidine congener (**7**), prepared from pipecolinic acid, gave regioselectively the 8-azabicyclo[3.2.1]octane (**5d**) in quantitative yield as a diastereomeric mixture (2:1).

A mechanistic rationalization for the formation of the azabicyclic compounds (**4a**) and (**5a**) involves a [1,5] hydrogen transfer of the initially formed aryl radical (**8**) to form the α-acylamino radical (**9**) . This step is followed by either a 5-*exo*-trig or a 6-*endo*-trig cyclization to lead to new radical intermediates (**10**) and (**11**) which are then reduced to **4a** and **5a**, respectively.



Scheme 2

It was of interest to see if the methoxycarbonyl group is essential for this reaction to take place. Therefore, we have synthesized *N*-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidine (**15**) and examined its behavior toward Bu_3SnH. The compound (**15**) was prepared as illustrated in the Scheme 3. Thus, reduction of the *N-tert-*



Scheme 3. *Reagents and conditions*: (a) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; (b) $LiEt_3BH$, THF; (c) CH_2=$CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (d) CF_3CO_2H, CH_2Cl_2; (e) *o*-bromobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2; (f) Bu_3SnH, AIBN, toluene, reflux

butoxycarbonyl-2-pyrrolidone (**12**) with lithium triethylborohydride (1.5 equiv.) in tetrahydrofuran at room temperature gave the 2-hydroxypyrrolidine (**13**) which was treated with allyltrimethylsilane (1.5 equiv.) in the presence of boron trifluoride etherate in dichloromethane to give the 2-(prop-2-enyl)pyrrolidine (**14**) in 49% overall yield. Deprotection of **14** followed by acylation with *o*-bromobenzoyl chloride gave the desired **15** in 96% yield. Unfortunately, when treated with Bu_3SnH (2.6 equiv.) and AIBN in boiling toluene, **15** gave the reduction product (**17**) as the major product (81%) and the expected azabicyclic compound (**16**), mp 94-95°C (lit.,[5] mp 94-95°C), was obtained only in 17% yield. It is interesting to note that the corresponding 5-*exo* product was not isolated.

In summary, we found that the *N*-(*o*-bromobenzoyl)pyrrolidines (**3**) and the piperidine analogue (**7**), on treating with Bu_3SnH and AIBN in boiling toluene, gave the azabicyclic compounds (**4**) and/or (**5**). Further applications of this reaction are under intense investigation..

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