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Fused Tricyclic β-Lactams *via* Intramolecular Aryl Radical Cyclization[1#]

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 # Dedicated to Dr. William H. McLean

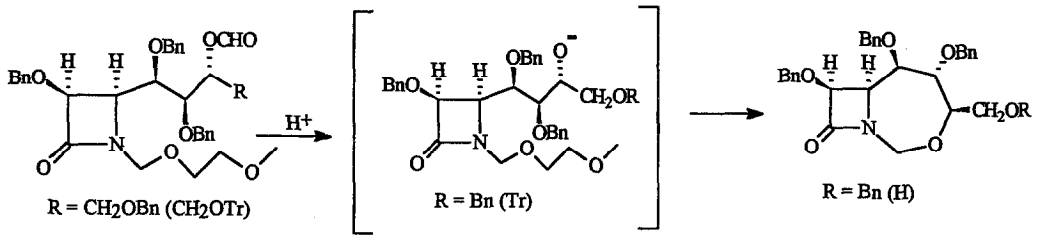
Abstract: *Easy access to fused tricyclic β-lactams starting with o-bromobenzaldehyde and allyl amine has been devised using intramolecular aryl radical cyclization under the influence of tributyltin hydride. The major product resulted from exo cyclization leading to the formation of a 6-membered ring and thus a tricyclic β-lactam . In some cases, a minor product was a 7-membered ring-containing tricyclic β-lactam formed by endo cyclization.*

More than five decades after the discovery of penicillin, the chemistry and biological activity of β-lactams continue to attract widespread attention from research workers. There is growing interest in the design and synthesis of new antibiotics because of the rising incidence of bacterial resistance to antibacterial agents in current clinical use. Monocyclic, bicyclic and tricyclic β-lactams are receiving scrutiny from medicinal and synthetic chemists[2a]. A recent publication[2b] indicates that the ease of attack on the β-lactam carbonyl of a fused β-lactam by a nucleophile (such as hydroxyl groups from water, alcohols and enzymes) depends on both steric and stereoelectronic factors. Therefore, the size and shape of the ring fused to the 4-membered ring could have an important influence on the chemical and biological activity of fused β-lactams, such as penicillins and analogs.

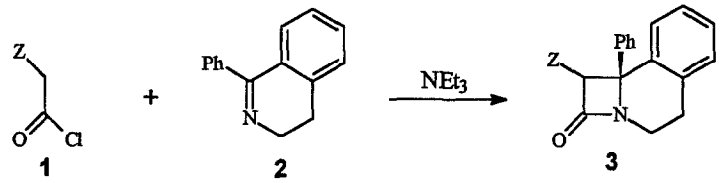
With our long standing interest in the synthesis of diversely substituted β-lactams, we[3] developed recently a novel method for the preparation of β-lactams fused to a 7-membered ring (**Scheme 1**). Earlier, we[4] had reported the synthesis of tricyclic fused β-lactams **(3)** by the annelation of 3,4-dihydroisoquinoline **(2)** with a variety of acid chlorides **(1)** and triethylamine (**Scheme 2**). We wish to describe here, a convenient route to fused tricyclic β-lactams some of which contain a 7-membered ring.

Our strategy is to prepare a monocyclic β-lactam of the appropriate stereochemistry and with suitable appendages on the β-lactam nitrogen and the adjacent carbon to permit the formation of a ring using free radical reaction.

Scheme 1



Scheme 2

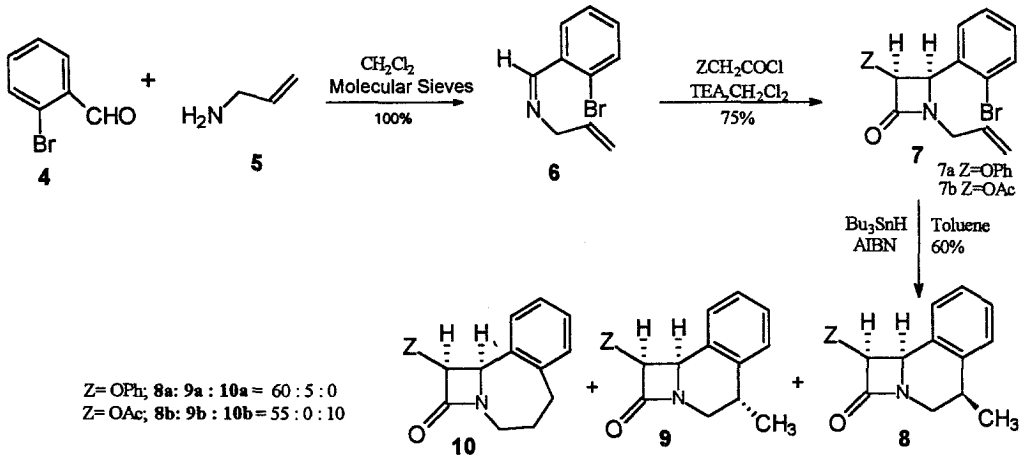


The use of tributyltin hydride for the reductive cyclization of a variety of substrates has been explored in several laboratories[5] for the preparation of polycyclic compounds. Bachi[6] has reported the preparation of fused β-lactams using free radicals generated by tributyltin hydride treatment. The preparation of 6- and 7-membered ring structures from the reaction of aryl radicals with unsaturated amides (non-β-lactam) have been described[7]. We have combined these approaches to devise an easy access to tricyclic β-lactams starting with readily available chemicals.

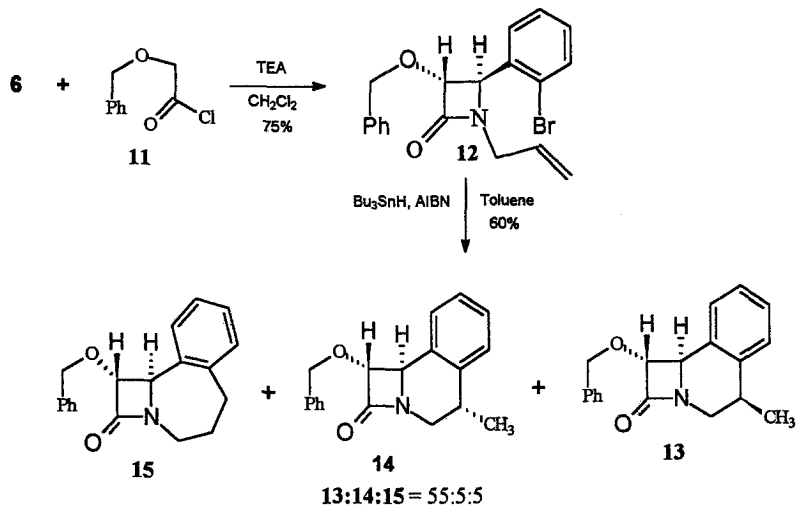
The key intermediate for our projected synthesis was a 3-substituted-4-(*o*-bromophenyl)-2-azetidinone (such as, **7**). Compounds of this type are readily prepared in good yield by the reaction of acid chlorides and triethylamine with Schiff bases from *o*-bromobenzaldehyde (**Scheme 3**). These β-lactams are usually of cis stereochemistry when formed at room temperature (or at lower temperatures). We[1] have found recently that when the cycloaddition reaction is conducted under high power microwave irradiation in a domestic microwave oven[8], the trans β-lactam is formed nearly exclusively in the case of 3-acetoxy-1,4-diaryl-2-azetidinones.

For our preliminary work, we condensed *o*-bromobenzaldehyde **(4)** with allyl amine **(5).** Nearly quantitative yield of the Schiff base **6** was obtained when the reaction was conducted in methylene chloride solution in presence of molecular sieves (**Scheme 3**). The cis β-lactams **7a** and **7b** were formed in high yield when **6** was allowed to react with phenoxy- or acetoxyacetyl chloride in the presence of triethylamine (TEA). Unexpectedly, when the cycloaddition was conducted with benzyloxyacetyl chloride **(11)**, the *trans*-β-lactam **12** was obtained exclusively (**Scheme 4**).

Scheme 3



Scheme 4



We heated the β-lactam **7a** with 1.5 equivalents of Bu_3SnH and azoisobutyronitrile (AIBN), in refluxing toluene under nitrogen for 12 h (**Scheme 3**). The ^{1}H-NMR spectrum of the crude reaction product showed the presence of two compounds. The major product (**8a**, 60% yield) was isolated by column chromatography and purified; the minor product (**9a**, 5% yield) was not completely pure. Both products indicated a doublet (at 1.20-1.40 ppm) corresponding to a secondary methyl group; the ^{13}C-NMR spectra of these compounds [9] displayed methyl peaks at 17.25 and 24.29 ppm, respectively. Therefore, a fused 6-membered ring had been formed in both cases resulting from exo cyclization.

Similar free radical induced cyclization of cis 3-acetoxy-4-(*o*-bromophenyl)-2-azetidinone (**7b**) proceeded via both exo- and endo- pathways. The major product (60%) was **8b**, the analog of **8a**. The minor

product showed no methyl doublet in its NMR spectrum and the spectrum corresponded to a 7-membered ring **10b** formed through endo cyclization.

We have studied radical-induced cyclization of the trans β-lactam **12** under the same conditions (**Scheme 4**). In this case also, the formation of a 6-membered ring (in **13** and **14**), was favored over endo cyclization to a 7-membered ring (in **15**).

A comparison of the ^{13}C-NMR spectra of tricyclic β-lactams proved instructive. The newly formed methyl group in **13** and **14** resonated at 18.42 and 23.62 ppm, respectively. Therefore, it appears that the methyl group and the ring junction proton are in the same relative position in **8a** and **13** even though **8** is derived from a cis β-lactam and **13** from a trans β-lactam. The stereostructures **8a**, **8b** and **13** have been tentatively assigned to the major products of ring closure; definitive structure determination by single crystal X-ray diffraction studies has been planned. Further work is in progress on the use of Schiff bases with additional functional groups besides those in **6**.

In summary, *o*-bromobenzaldehyde derived Schiff bases have been shown to be easily available intermediates for intramolecular radical cyclization to various fused tricyclic β -lactams.

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9. All new compounds were characterized by satisfactory analytical and spectral data.

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