TETRACYCLIC ISOQUINOLONES AND QUINAZOLONES *VIA* ARYL RADICAL CYCLIZATIONS[1]

Bimal K. Banik, Vegesna S. Raju, Maghar S. Manhas, and Ajay K. Bose*

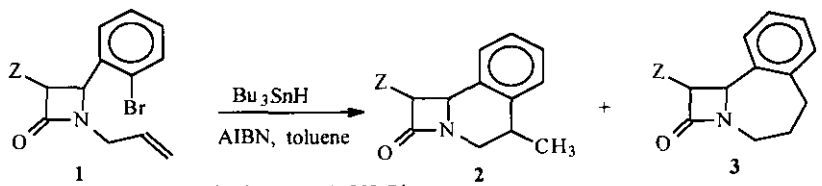
Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, New Jersey 07030, USA

Dedicated to Prof. Koji Nakanishi on the occasion of his 75th birthday

Abstract - The Schiff base from o-bromobenzaldehyde and allylamine was allowed to react with homophthalic anhydride to form an isoquinolone. Reaction of the same Schiff base with isatoic anhydride led to a quinazolone. Generation of a free radical from the bromoaryl moiety under the influence of tributyltin hydride converted the isoquinolone and the quinazolone to tetracyclic systems. This approach can lead to a convenient synthesis of alkaloids of the benzophenanthridine and protoberberine families.

Aryl radical[2,3] cyclizations are receiving increasing attention now. The majority of cases of such cyclization involve the formation of 5-membered ring structures through a 5-exo-trig cyclization with minor amounts of 6-membered compounds formed through a 6-endo-trig cyclization route.[4] Only in a few cases, a comparison has been made between 6- and 7-membered ring formation.[5] Recently, we[2] reported the synthesis of fused bicyclic β-lactams (**2**) and (**3**) *via* tributyltin hydride mediated aryl radical cyclization of several monocyclic β-lactams (**1**). We observed that the yield of the 7-membered ring containing β-lactam (**3**) was low compared to the β-lactam (**2**) (**Scheme 1**).

Scheme 1



1 2 3

Z = O Ph, O Ac, O CH_2Ph

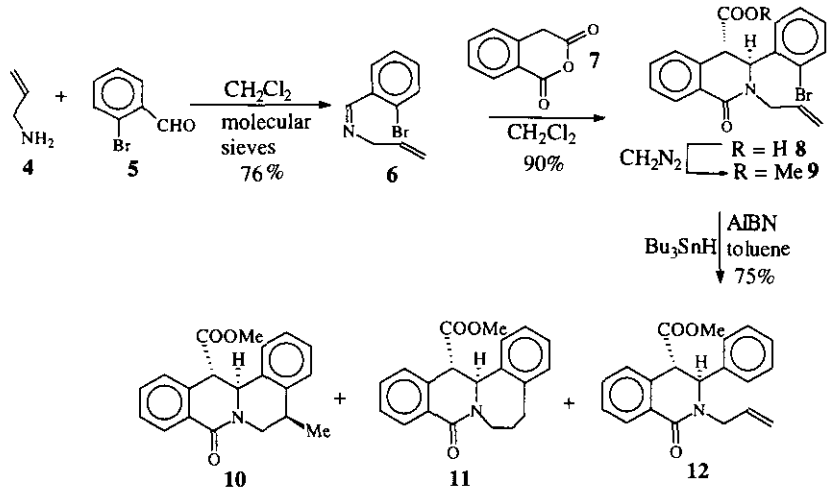
As an extension of our earlier studies[2] on aryl radical induced synthesis of fused β-lactams (**2, 3**) and our research on heterocycles,[6] we wish to report here a simple approach to tetracyclic isoquinoline and quinazole systems. The strategy is to use the Schiff base (**6**) derived from *o*-bromobenzaldehyde (**5**) and allyl amine (**4**) to construct a lactam ring and then generate an aryl free radical to induce the formation of an additional ring.

Tetracyclic Isoquinolones. We tested this approach on isoquinolones prepared readily from Schiff bases. Following the method of Cushman and Madaj[7] we allowed the known Schiff base[2] (**6**) to react

with homophthalic anhydride (**7**) in refluxing dichloromethane solution for 1 h and obtained an isoquinolone (**8**) as a single isomer in excellent yield. The ^{1}H-NMR spectrum of **9** , the methyl ester of **8** prepared with diazomethane, showed the stereochemistry to be *trans* as evident by the coupling constant between the adjacent protons on the isoquinolone ring.[8]

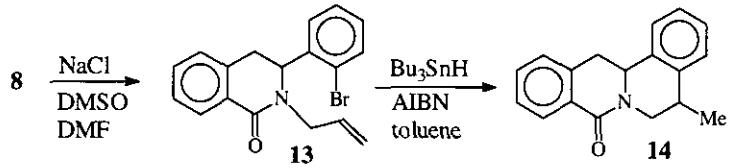
Cyclization of **9** induced by refluxing it with tributyltin hydride in toluene solution in the presence of azobisisobutyronitrile (AIBN) and purification by chromatography gave three products (**10**, **11** and **12**) in the ratio of 7 : 2 : 1, respectively (**Scheme 2**). The major product (**10**) showed a doublet at δ 1.38 in its NMR spectrum indicating the formation of a 6-membered ring. We have depicted the stereochemistry of the methyl group arising from *exo*-cyclization on the basis of our earlier results.[2,9] The other minor products (**11** and **12**) were formed through an endocyclization pathway and a debromination route, respectively. The structure of **11** and **12** was confirmed by spectroscopic and analytical data.

Scheme 2



Decarboxylation of **8** following the method developed by Krapcho[10] gave an unsaturated amide (**13**). Radical cyclization of **13** as described for **9** afforded essentially a single 6-membered cyclic compound (**14**) (**Scheme 3**) as evident from its ^{1}H NMR spectrum. These results indicated that the ester substituent in **9** played an important role in controlling the regiospecificity of the cyclization reaction.

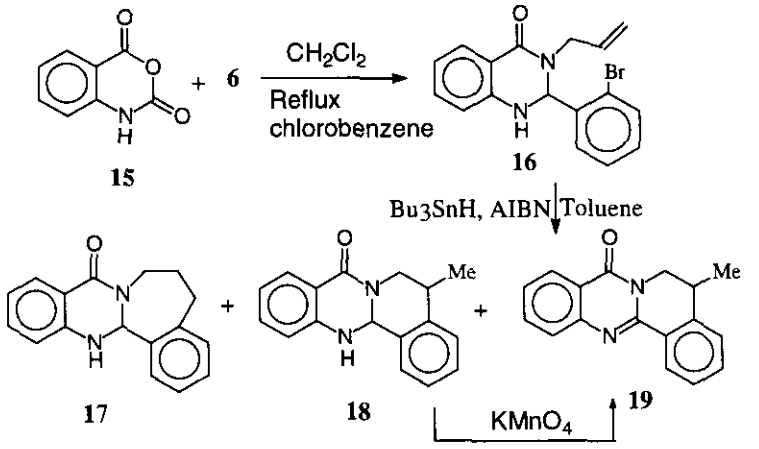
Scheme 3



Tetracyclic Quinazolones. The quinazolone (**16**) is readily prepared from our starting material, the Schiff base (**6**), by following literature methods.[7] Reaction of isatoic anhydride (**15**) with **6** in refluxing chlorobenzene solution for 3 h gave **16** in 53% yield after chromatographic purification.

Treatment of **16** with tributyltin hydride and AIBN in refluxing toluene solution for about 12 h led to three products, (**17**, **18** and **19**) in the ratio 1 : 8 :1, which were separated by column chromatography. The major product (**18**) could be assigned its structure on the basis of its ^{1}H-NMR spectrum. Its ^{13}C NMR spectrum showed close similarity with the spectrum of the tricyclic β-lactam (**2**) that we had prepared earlier. While **18** had been formed *via exo*-cyclization, the product (**17**), lacking a methyl signal, was obviously the result of *endo*-cyclization. The stereochemistry of the methyl group was not obvious from the NMR spectra of **18**. A study of single crystal X-Ray diffraction of **18** has been planned.

Scheme 4



15 16 17 18 19

The third product (**19**) (mp 146-148 °C) displayed a methyl doublet signal at δ 1.35. Its IR spectrum showed no peak at 3500 cm^{-1} (i.e., absence of the N-H group) seen in **17** and **18**; a sharp peak at 1660 cm^{-1} was observed which is indicative of the type of amide bond present in **18**. On the basis of elemental analysis, CIMS, and NMR spectral data, this compound was deduced to be **19**, the *oxidation* product of **18**. Oxidation under reductive conditions has been reported in the literature.[11] The structure assigned was further confirmed by the oxidation of **18** to **19** with aqueous potassium permanganate solution (**Scheme 4**).

Concluding Remarks.

We have prepared a variety of tetracyclic heterocyclic compunds[12] *via* aryl radical mediated cyclizations of simple substrates. The information reported in this paper should be useful for the synthesis of benzophenanthridine and protoberberine group of alkaloids.

ACKNOWLEDGEMENT

This research was supported by Stevens Institute of Technology and the Howard Hughes Medical Institute (through a grant to our Chemical Biology Education Enhancement Program). We thank Ms. Edith Borges, an undergraduate research participant, for technical assistance.

REFERENCES AND NOTES

1. Presented in part at the 208th American Chemical Society National Meeting, Washington, D.C. Aug, 1994; ORGN 32. For a related publication see Ref. 2.
2. B. K. Banik, G. V. Subbaraju, M. S. Manhas, and A. K. Bose, *Tetrahedron Lett.*, 1996, **37**, 1363.
3. (a) B. Giese, "Radicals in Organic Synthesis : Formation of Carbon-Carbon Bonds" , Pergamon Press , Oxford, 1986. (b) M. Ramaiah, *Tetrahedron*, 1987, **43**, 3541. (c) D. P. Curran, *Synthesis* 1988, **417**, 489. (d) D. P. Curran, *Synlett*,1991, **63**. (e) W. B. Motherwell and D. Crich, "Free Radical Chain Reactions in Organic Synthesis", Academic Press , San Diego,1992.
4. A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073.; T. V. Rajan Babu, *Acc. Chem. Res.*, 1991, **24**, 139.
5. (a) A. G. Schultz, M. A. Holoboski, and M. S. Smyth, *J. Am. Chem. Soc.*, 1993, **115**, 7904. (b) J. H. Rigby and M. N. Qabar, *J. Org. Chem.*, 1993, **58**, 4473. (c) A. K. Ghosh, K. Ghosh, S. Pal, and U. R. Ghatak, *J. Chem. Soc., Chem. Commun.*, 1993, 809. (d) A. J. Clark, K. Jones, C. McCarthy, and J. M. D. Storey, *Tetrahedron Lett.*, 1991, **32**, 2829. (e) N. S. Narasimhan and I. S. Aidhen, *Tetrahedron Lett.*, 1988, **29**, 2987. (f) T. Ghosh and H. Hart, *J. Org. Chem.*, 1988, **53**, 2398. (g) A. Gopalasamy and K. K. Balasubramanian, *J. Chem. Soc., Chem. Commun.*, 1988, 28.
6. M. S. Manhas, D. R. Wagle, J. Chiang, and A. K. Bose, *Heterocycles*, 1988, **27**, 1755.
7. M. Cushman and E. J. Madaj, *J. Org. Chem.*, 1987, **52**, 907.
8. According to ref. 7, the reaction at rt between various Schiff bases and **7** gave a mixture of *cis* and *trans*-products depending upon the solvent. But, only the formation at rt of *cis*- isomers was reported with Schiff bases having larger substituents on the nitrogen. In contrast, we isolated a single *trans*-compound using refluxing dichloromethane as the reaction medium.
9. From ^{13}C NMR spectra of fused tricyclic β-lactams (such as **2**), we found that the methyl group and the ring junction proton are in the same relative position[2] in **10** and **2**.
10. A. P. Krapcho, *Synthesis*, 1982, 805.
11. R. W. Bowman, H. Heaney, and B. M. Jordan, *Tetrahedron*, 1991, **47**, 10119.
12. All new compounds gave satisfactory spectral and elemental analysis.

Received, 1st May, 1997