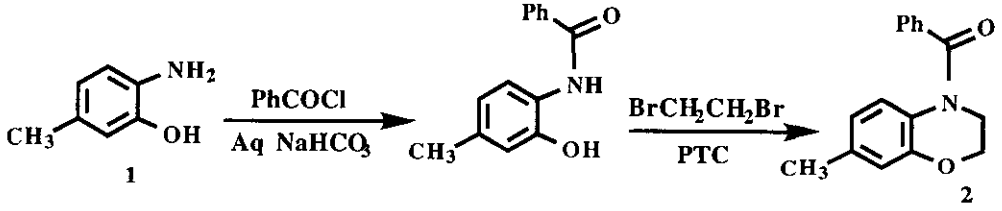
SYNTHESIS AND REACTIONS OF 3,4-DIHYDRO-2*H*-1,4-BENZOXAZINE DERIVATIVES

Sambasivarao Kotha,# * Vandana Bindra, and Atsuo Kuki *
Department of Chemistry, Baker Laboratory, Cornell University
Ithaca, NY 14853, U. S. A.

Abstract - Several 3,4-dihydro-2*H*-1,4-benzoxazine derivatives were prepared from commercially available benzoxazoles by use of an efficient two step sequence. Aryl functionalization reactions allowing access to further benzoxazine derivatives are also described.

1,4-Benzoxazine and its related derivatives possess interesting pharmacological [1] and anti-microbial properties.[2,3] In addition, some dyes related to benzoxazines exhibit intense fluorescence properties both in the solution phase and in the crystalline state.[4]

In connection with another project related to the design of electron-rich aromatic molecules, we need to synthesize large quantities of several derivatives of *N*-alkylated 3,4-dihydro-2*H*-1,4-benzoxazines. Toward this goal, we initially attempted to prepare these compounds from commercially available *o*-aminophenols *via* a four step sequence which involves protection and deprotection steps. Although, we were able to prepare **2** easily under phase transfer conditions



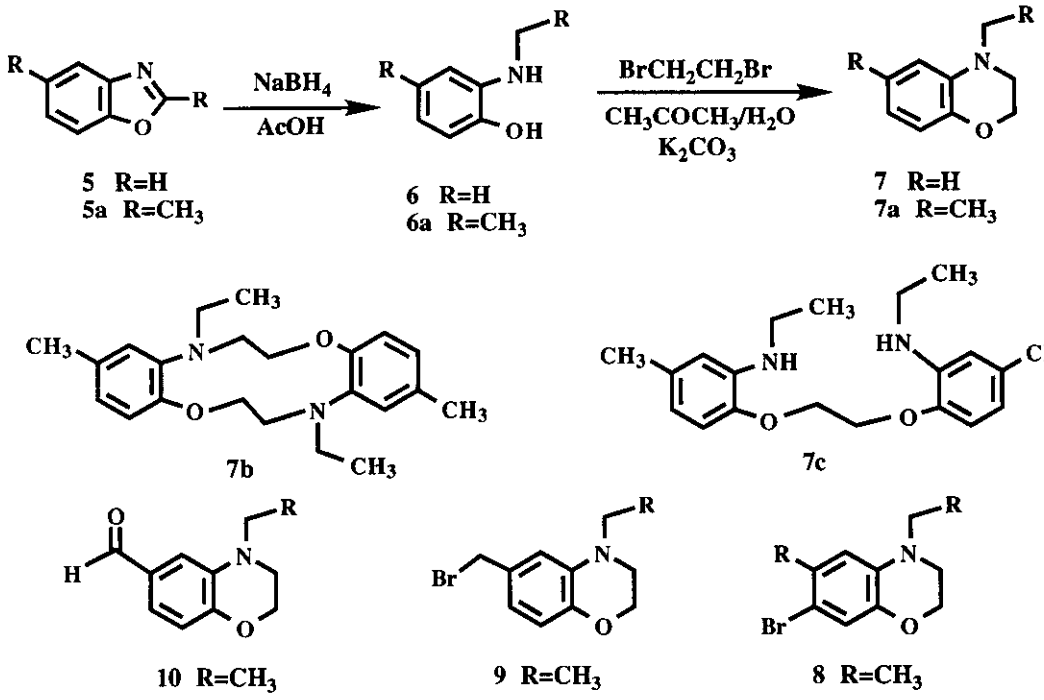
Scheme 1

(PTC)[5] using **1** as starting material, *N*-Alkylation of **3** with methyl iodide in presence of a base such as sodium hydride to provide **4** proved to be inefficient (Scheme 1). At this juncture, an alternative route which involves the ring closure reaction of *N*-alkylated *o*-aminophenol derivatives to the corresponding dihydro 1,4-benzoxazines was pursued. Partial *N*-alkylation of *o*-aminophenol is not a trivial exercise without involvement of protective groups.[6] An indirect and more efficient method to prepare such mono-*N*-alkylated *o*-aminophenols was identified. This can be achieved

---

Present address: Hoechst Celanese Corporation, 1901 Clarkwood Road, Corpus Christi Technical Center, Corpus Christi, TX, 78469, U. S. A.

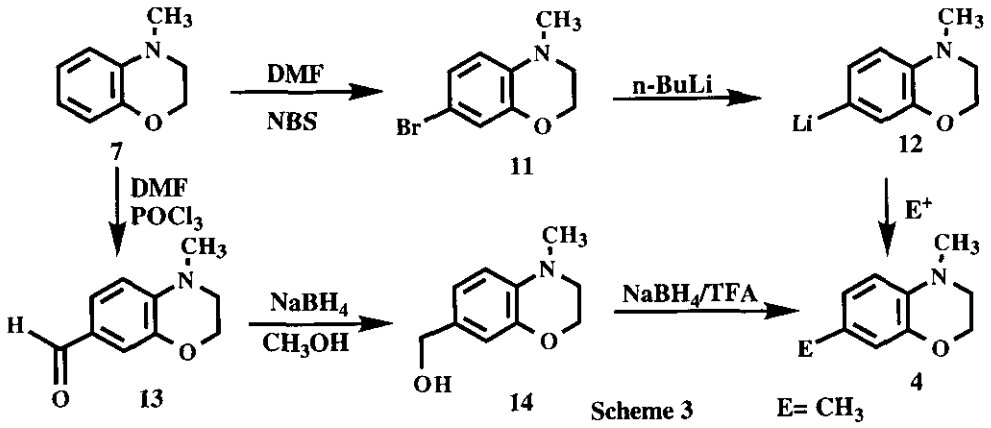
by the reduction of the commercially available benzoxazoles using sodium borohydride in presence of catalytic quantities of acetic acid (Scheme 2).[7] Thus, **5** gave, in quantitative yield, **6**. Ring closure of **6a** using 1,2-dibromoethane under phase transfer conditions which involves the usage of the aliquat 336 gave the required compound (**7a**) as a minor product. Separation of the required ring closure product (**7a**)[10] from the unwanted dimers (**7b**) and (**7c**) proved to be cumbersome and inefficient. After considerable experimentation, a more rewarding result was obtained under milder reaction conditions (1,2-dibromoethane-acetone/water mixture and potassium carbonate). This ring closure conditions provided the alkylated benzoxazine (**7**)[10] which requires no column chromatography in 74% overall yield. This result is crucial for the preparation of large quantities of these electron rich aromatic molecules[8] of diverse applications. Having established this two step sequence, we next turned our attention to functionalize these benzoxazine derivatives.



Scheme 2

Reaction of **7a** with *N*-bromosuccinimide (NBS) in presence of radical initiator such as benzoyl peroxide gave no product corresponding to **9**. Under forcing reaction conditions ring brominated product (**8**) was observed in low yields. Similiarly, usual benzylic oxidation reactions gave no aldehyde product (e.g.,**10**). Ring bromination of **7** with NBS in *N,N*-dimethylformamide (DMF) gave **11**[10] in 89% yield. Lithiation of **11** with *n*-butyllithium gave the reactive species (**12**), which can be quenched with various electrophiles (E= H^+, D^+, CH_3^+, Br^+) to give the corresponding benzoxazine derivatives. Under Vilsmeier formylation conditions, aldehyde (**13**)[10] was obtained from **7** in 78% isolated yield. The regiochemistry of the brominated product (**11**) was established unequivocally

by simple chemical reactions as shown in Scheme 3. When **12** was reacted with methyl iodide, **4** was obtained in 82% yield. Proton magnetic resonance spectra and tlc comparison of **4** prepared by two independent routes (Scheme 1 and Scheme 3 *via* **12**) clearly established its structure. Similarly, aldehyde (**13**) was converted *via* **14** to compound (**4**) by step-wise reduction reactions *using sodium borohydride as the reducing reagent.*[9]



Scheme 3

In conclusion, we have demonstrated a two step synthesis of 3,4-dihydro-2*H*-1,4-benzoxazine derivatives starting from benzoxazoles. [11]

A typical procedure for sodium borohydride-acetic acid reduction of benzoxazole followed by ring closure is described as follows: To a solution of **5** (11.6 g, 0.097 mol) in dry tetrahydrofuran was added sodium borohydride (11.6 g, 0.3 mol) in small portions under nitrogen atmosphere. Acetic acid (10 ml) in tetrahydrofuran (40 ml) was added slowly.[12] At the conclusion of the reaction (18 h, tlc, 3:1 EtOAc/Hexane), the solvent was removed at reduced pressure and the reaction mixture was poured into saturated ammonium chloride (250 ml) and the aqueous layer was extracted with ethyl acetate (3 x 150 ml). The organic layer was washed with brine (150 ml) and dried ($MgSO_4$). Removal of solvent gave a quantitative yield of **6**, which was directly used in the next step.

To a mixture of **6** (9 g, 0.07 mol) in acetone was added dibromoethane (28.4 g, 0.127 mol). To this solution was added potassium carbonate (18 g, 0.13 mol) in water (170 ml). The resulting dark blue colored solution was refluxed for 3 days. After the acetone was removed under reduced pressure, the residue was poured into water and extracted with ethyl acetate (4 x 125 ml). The organic layer was washed with brine (200 ml) and dried ($MgSO_4$). Removal of solvent gave a dark oily product (10.7 g) *which is essentially one major* compound. The minor impurity (< 5%) was removed *via* silica gel chromatography. Compound (**7**) was further purified by distillation at 160-62^{0}C/1mm Hg.

ACKNOWLEDGEMENTS

Financial support from NIH (NIHGMS R29-GM39576), and the Camille and Henry Dreyfus Foundation (TS-89-12) is gratefully acknowledged. We would like to thank Dr. S. Krishnamurthy, (Eastman Kodak Company, Rochester, New York) for bringing the reference 6b to our attention.

REFERENCES

1. C. Banzatti, A. D. Torre, P. Melloni, D. Pieraccioli, and P. Salvadori, *J. Heterocycl. Chem.*, 1983, **20**, 139, S. Cabiddu, C. Floris, S. Melis, F. Sotgiu, and G. Cerioni., *J. Heterocycl. Chem.*, 1986, **23**, 1815, ; R. C. M. Butler, C. B. Chapleo, P. L. Meyers, and A. P. Welbourn, *J. Heterocycl. Chem.*, 1985, **22**, 177.
2. Recently some novel antibiotics containing the 1,4-Benzoxazine ring system, and with interesting biological activities were isolated. For details see, K. Yoshida, Y. Minami, R. Azuma, M. Saeki, and T. Otani, *Tetrahedron Lett.*, 1993, **34**, 2633 and 2637.
3. G. Thuillier, J. Laforest, P. Bessin, J. Bonnet, and J. Thuillier, *Eur. J. Med. Chem. Chim. Ther.*,1975, 10, 37; K. W. Wheeler, *J. Med. Pharm. Chem.*, 1962, 1378; D. R. Shridhar, S. S. Gandhi, and K. Srinivasa Rao, *Synthesis*, 1982, 986; D. R. Shridhar, M. Jogibhukta, and V. S. H. Krishnan, *Org. Prep. Proceed. Int.*, 1982, **14**, 195 ; K. Yordanova, V. Shevedov, and D. Dantchev, *Arch. Pharm.* (Weinheim), 1990, **323**, 43 ; E. Rekka, S. Retsas, V. J. Dempoulos, and P. N. Kouounakis, *Arch. Pharm.* (Weinheim), 1989,**323**, 53.
4. M. T. Le Bris, *J. Heterocycl. Chem.*, 1985, **22**, 1275.
5. G. Coudert, G. Guillaumet, and B. Loubinoux, *Synthesis*, 1979, 541.
6. (a) T. W. Green and P. G. M. Wuts, "Protective Groups in Organic Synthesis," John Wiley, New York, 1991; (b) After completion of this work we learned that primary amines can be *N*-monomethylated *via* formylation, borane-methyl sulfide reduction; S. Krishnamurthy, *Tetrahedron Lett.*, 1982, **23**, 3315. (c) For synthesis of monomethylated functionalized aromatic amines see: K. Dietliker and H. Heimgartner, *Helv. Chim. Acta*, 1983, **66**, 262, .
7. G. W. Gribble and C. F. Nutaitis, *Org. Prep. Proceed. Int.*, 1985, **17**, 317, ; B. Yadagiri and J. W. Lown, *Synth. Commun.*, 1990, **20**, 175.
8. $E_{1/2}$ for the oxidation of **4** was determined by cylic voltammetry to be 0.61 V vs. SCE in MeCN (0.l mol cm^{-3} tetrabutylammonium perchlorate); S. Kotha and A. Kuki, *J. Chem. Soc. Chem. Commun.* 1992, 404.
9. C. F. Nutaitis and J. E. Bernardo, *Synth. Commun.*, 1990, **20**, 487.
10. ^{13}C Nmr data for selected compounds: compound (**7**) ($CDCl_3$, 100 MHz): 144.2 (s), 136.5 (s),121.3 (d), 118.0 (d), 115.8 (d), 112.4 (d), 64.7 (t), 49.0 (t), 38.6 (q). compound (**7a**) ($CDCl_3$, 100 MHz): 141.9 (s), 134.4 (s), 130.8 (s), 117.6 (d), 115. 9 (d), 112.8(d), 64.5 (t), 46.0 (t), 44.8 (t), 21.2 (t), 10.5 (q). compound (**11**) ($CDCl_3$, 100 MHz): 144.9, 135.3, 123.8, 118.5, 113.5, 109.3, 64. 7, 48.6, 38.6. compound (**13**) ($CDCl_3$, 100 MHz): 190.2 (s), 143.3 (s), 141.9 (s), 126.4 (d), 115. 4 (d), 110.3 (2C) (d), 63.7 (t), 48.5 (t), 38.1 (q).
11. For the preparation of benzoxazoles see : G. V. Boyd, "Comprehensive Heterocyclic Chemistry," Vol. 6, ed. by A. R. Katritzky and C. B. Rees, Pergamon Press, London, 1984; Y. H. R. Jois and H. W. Gibson, *J. Heterocycl. Chem.*, 1992, **29**, 1365 and references cited there in.
12. It is important to add the acetic acid slowly to avoid foaming. A bath for cooling the flask is readied in advance for use in case of vigorous reaction.

Received, 26th July, 1993