Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# The Preparation of 2-Hydroxyethyl-2,3-dihydro-2h-1,4-benzoxazin-3(4h)-one Derivatives

R. F. Frechette [a] & M. J. Beach [a]
[a] The R. W. Johnson Pharmaceutical Research Institute , 1000 Route 202, P.O. Box 300, Raritan, NJ, 08869
Published online: 22 Aug 2006.

To cite this article: R. F. Frechette & M. J. Beach (1998) The Preparation of 2-Hydroxyethyl-2,3-dihydro-2h-1,4-benzoxazin-3(4h)-one Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:18, 3471-3478, DOI: 10.1080/00397919808004455

To link to this article: http://dx.doi.org/10.1080/00397919808004455

SYNTHETIC COMMUNICATIONS, 28(18), 3471-3478 (1998)

# THE PREPARATION OF 2-HYDROXYETHYL-2,3-DIHYDRO-2H-1,4-BENZOXAZIN-3(4H)-ONE DERIVATIVES

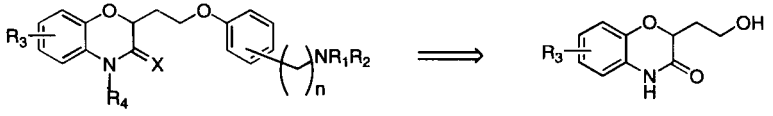
Roger F. Frechette* and Michael J. Beach

*The R.W. Johnson Pharmaceutical Research Institute*
*1000 Route 202, P.O. Box 300, Raritan, NJ 08869*



**Abstract:** An efficient synthesis of 2-hydroxyethyl-2,3-dihydro-2*H*-1,4-benzoxazin-3(4*H*)-one derivatives is described using α-bromo-γ-butyrolactone as a bis-electrophile containing a latent hydroxyethyl functional group.

Bacterial resistance to antiinfective chemotherapy has emerged as a major threat to human health in recent years.[1] In response to this threat, antibacterial investigators have sought to discover agents that inhibit new bacterial targets.[2] We have discovered a class of benzoxazinone antibacterial agents as a result of a research program targeting the two-component regulatory systems found exclusively in bacteria and some lower eukaryotes.[3,4] This series of compounds, represented generically by **1**, was prepared by elaboration of the 2-hydroxyethyl-2,3-dihydro-1,4-benzoxazin-3-one intermediates, **2**. A practical preparation of **2** is described in this communication.

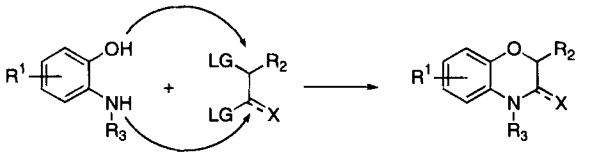



**1** **2**

*To whom correspondence should be addressed

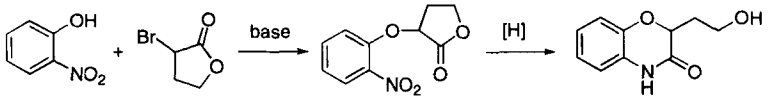
The benzoxazine nucleus has commonly been prepared by the reaction of a bis-electrophile with an aryl ring containing a phenolic oxygen and an o-amino group (Scheme 1).[5] This conceptually simple strategy has been employed widely for the preparation of 2,3-dihydro derivatives. However, examples of substitution at the 2-position with a 2-carbon spacer bearing a reactive handle, such as hydroxyethyl or haloethyl are rare. Although, in a few isolated examples,[5b,6] hydroxyethyl derivatives have been prepared by reduction of analogs at higher oxidation states, no efficient, practical routes have been identified to date.

**Scheme 1**




The generic 2-hydroxyethyl-2,3-dihydro-1,4-benzoxazin-3-one structure is, in principle, derivable by a modification of the strategy described in Scheme 1 whereby a masked hydroxyethyl moiety is contained within the bis-electrophile at $R_2$. α-Bromo-γ-butyrolactone, **3** is an inexpensive, readily available reagent that meets these criteria. A two-step approach to the target structure requires bromide displacement with the anion of an o-nitrophenol, followed by reductive cyclization. In practice (Scheme 2), reaction of 2-nitrophenol **4** with **3** in DMF, in the presence of $K_2CO_3$, at ambient temperature afforded the 2-nitrophenoxydihydrofuranone **5**. Treatment of the crude reaction mixture with glacial

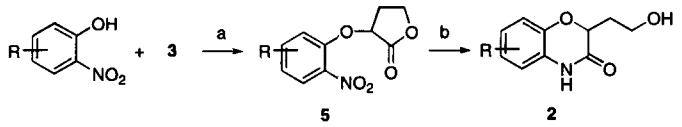
**Scheme 2**




acetic acid prior to aqueous work-up provides **5** in sufficient purity to carry on and avoids an unproductive lactone ring hydrolytic cleavage that must be reversed[7a,b] before proceeding

to the next step. The reductive cyclization step could then be executed with palladium catalyzed heterogeneous hydrogenation of the nitrophenoxyfuranone to afford 2-hydroxyethylbenzoxazin-3-one **2**. Both steps were accomplished in greater than 60% overall crude yield, with no significant loss of efficiency noted in reactions carried out up to 200 mmol scale. Additional examples are shown in Table 1.[8]

**Table 1: Cyclization Results Using the Procedure Outlined in Scheme 2**



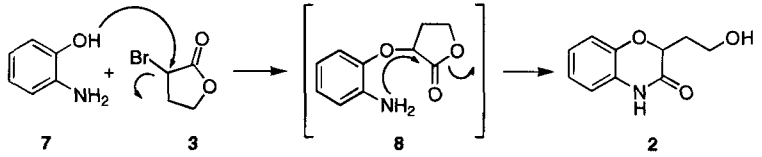

5 2

| compound | R* | yield 5[9](%) | yield 2[10](%) |
|---|---|---|---|
| a | H | 70 | 86 |
| b | 6-$OCH_3$ | 52 | 76 |
| c | 6-$CH_3$ | 33 | 70 |
| d | 6-$CF_3$ | 51 | 54 |

[a] $K_2CO_3$/DMF [b] EtOH/10%Pd/C, $H_2$ (3 atm) * Product numbering

Having established a conservative route to the desired products, a more direct approach was considered. The two steps were combined into a one pot process starting with **3** and an o-aminophenol **7** (Scheme 3). The success of this reaction sequence relied upon initial

**Scheme 3**

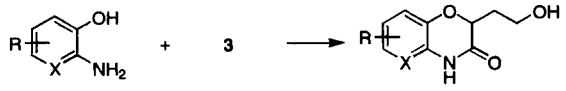



7 3 8 2

nucleophilic displacement of bromide by the phenolate of **7**, to afford the furanone intermediate **8**, followed by intramolecular ring closure to simultaneously form the bicyclic heterocycle and liberate the hydroxyethyl group. In a polar, aprotic solvent (e.g., DMF or THF) and in the presence of either excess $K_2CO_3$ or 2 equivalents of NaH, this reaction proceeded smoothly to afford the 2-substituted benzoxazin-3-ones. In all cases, the basic

reaction conditions afforded exclusively the product of phenolate displacement of the bromide in the first step. Although the reaction could be carried out at ambient temperature, elevated temperatures resulted in somewhat shorter reaction times with comparable product yields. Table 2 indicates the yields for the best two sets of reaction conditions for each of the aminophenol substrates examined. The yields are unoptimized but adequate for a rapid, inexpensive entry into this structural type.

**Table 2: Cyclization Results Using the Procedure Outlined in Scheme 3[11]**




2

| Compound | R[b] | X | rxn[a] | yield (%) |
|---|---|---|---|---|
| 2a | H | CH | A | 65 |
| 2a | H | CH | B | 59 |
| 2e | 7-$NO_2$ | CH | A | 66 |
| 2e | 7-$NO_2$ | CH | B | 51 |
| 2f | 7-$CH_3$ | CH | C | 41 |
| 2f | 7-$CH_3$ | CH | B | 30 |
| 2g | 6-Cl | CH | A | 58 |
| 2g | 6-Cl | CH | B | 51 |
| 2h | 6,7-fused phenyl | CH | A | 67 |
| 2h | 6,7-fused phenyl | CH | B | 47 |
| 2i | H | N | C | 64 |
| 2i | H | N | B | 57 |

[a] (A) $K_2CO_3$/THF; (B) NaH/THF; (C) NaH/DMF [b] Product numbering.

In summary, reaction of an o-aminophenol with α-bromo-γ-butyrolactone, in the presence of base, is an effective strategy for the preparation of 2-hydroxyethyl-2,3-dihydro-1,4-benzoxazin-3-ones, important intermediates in the synthesis of a series of novel antibacterial agents.[9] The process can be carried out in two separate operations, proceeding by reduction of an intermediate nitrophenoxydihydrofuranone, or in a single operation using o-aminophenols as the initial bis-nucleophilic species. The reactions described here are amenable to large scale preparations of these potentially versatile intermediates. Additional investigations are underway to increase the efficiency of the coupling and ring closure reactions, to expand the scope of the reaction and to explore the reactivity of the products.

**Table 3: Analytical Data for New Compounds**

| Product | C, H, N analysis (%calc'd/%found) | IR (KBr) υ ($cm^{-1}$) | NMR ($CDCl_3$/TMS), δ, J (Hz) |
|---|---|---|---|
| **5a** | 53.82, 4.06, 6.28/ 53.65, 3.84, 6.05 | 1771 | 7.84 (dd, *J* = 8.1, 1.6, 1H), 7.62-7.48 (m, 2H), 7.16 (m, 1H), 5.02 (apparent t, *J* = 7.4, 1H), 4.62-4.52 (m, 1H), 4.45-4.35 (m, 1H), 2.83-2.55 (m, 2H) |
| **5b** | 52.18, 4.38, 5.53/ 52.19, 4.50, 5.43 | 1765 | 7.52 (d, *J* = 9.1, 1H), 7.39, (d, *J* = 3.1, 1H), 7.31 (dd, *J* = 9.1, 3.0, 1H), 4.87 (apparent t, *J* = 7.5, 1H), 4.55 (m, 1H), 4.36 (m, 1H), 3.87 (s, 3H), 2.82-2.69 (m, 1H), 2.68-2.53 (m, 1H) |
| **5c** | 55.70, 4.67, 5.90/ 55.62, 4.66, 5.82 | 1770 | 7.66 (s, 1H), 7.38 (m, 2H), 4.93 (apparent t, *J* = 7.4, 1H), 4.59 (m, 1H), 4.39 (apparent q, *J* = 7.3, 1H), 2.78-2.61 (m, 2H), 2.38 (s, 3H) |
| **5d** | 45.22, 3.10; 4.79/ 45.37; 2.77; 4.81 | 1782 | 8.14 (d, *J* = 1.9, 1H), 7.83 (dd, *J* = 8.8, 1.9 Hz1H), 7.63 (d, *J* = 8.8, 1H), 5.14 (t, *J* = 7.4, 1H), 4.58-4.65 (m, 1H), 4.40-4.48 (m, 1H), 2.63-2.86 (m, 2H) |
| **2a** | 62.17, 5.74, 7.25/ 62.01, 5.48, 6.95 | 1677 | 8.29 (br s, 1H), 7.01-6.95 (m, 3H), 6.82 (m, 1H), 4.76 (dd, *J* = 7.6, 5.5, 1H), 3.91 (m, 2H), 2.35-2.13 (m, 3H) |
| **2b**[a] | | 1684 | 7.99 (br s, 1H), 6.91 (d, *J* = 8.8, 1H), 6.52 (dd, *J* = 8.8, 2.8, 1H), 6.37 (d, *J* = 2.8, 1H), 4.70 (dd, *J* = 7.5, 5.4, 1H), 3.90 (m, 2H), 3.77 (s, 3H), 2.21 (m, 2H) |
| **2c** | 63.76, 6.32, 6.76/ 63.54, 6.20, 6.76 | 1681 | 7.96 (br s, 1H), 6.90 (d, *J* = 9.1, 1H), 6.80 (d, *J* = 9.1, 1H), 6.61 (s, 1H), 4.72 (apparent t, *J* = 7.3, 1H), 3.90 (apparent q, *J* = 5.4, 2H), 2.32-2.15 (m, 3H), 2.30 (s, 3H) |
| **2d** | 50.58, 3.86, 5.36/ 50.52, 3.86, 5.28 | 1696 | 8.01 (br s, 1H), 7.28 (m, 1H), 7.09 (d, *J* = 8.4, 1H), 7.05 (s, 1H), 4.86 (dd, *J* = 8.2, 5.2, 1H), 3.92 (apparent dd, *J* = 12.7, 5.6, 2H), 2.38-2.17 (m, 1H), 1.92 (t, *J* = 5.6, 1H) |
| **2e** | 50.42, 4.23, 11.76/ 50.37, 4.20, 11.43 | 1699 | 11.32 (br s, 1H), 7.91 (dd, *J* = 2.4, 8.7, 1H), 7.79 (s, 1H), 7.05 (d, *J* = 8.7,1H), 4.82 (dd, *J* = 3.8, 9.0, 1H), 4.70 (br s, 1H), 3.59 (m, 2H), 1.98 (m, 1H), 1.90 (m, 1H) |
| **2f** | 63.76; 6.32; 6.76/ 63.73; 6.30; 6.67 | 1664 | 1.72-1.86 (m, 1H), 1.87-2.00 (m,1H), 2.21 (s, 3H), 3.54-3.60 (m, 2H), 4.59 (dd, *J* = 9.4, 3.9, 1H), 4.65 (t, *J* = 5.3, 1H), 6.72-6.78 (m, 3H), 10.58 (s, 1H) |
| **2g** | 52.76; 4.43; 6.15/ 53.15; 4.50; 6.16 | 1690 | 10.5 (br s, 1H), 6.92 (s, 1H), 6.87 (s, 2H), 4.69 (dd, *J* = 8.9, 4.4, 1H), 3.77-3.82 (m, 2H), 3.33 (br s, 1H), 2.12-2.23 (m, 1H), 1.95-2.08 (m, 1H) |
| **2h**[b] | | | 11.06 (s, 1H), 7.75-7.79 (m, 2H), 7.44 (s, 1H), 7.35-7.38 (m, 2H), 7.28 (s, 1H), 4.77 (dd, *J* = 9.4, 3.8, 1H), 4.69 (t, *J* = 4.8, 1H), 3.56-3.70 (m, 2H), 1.94-2.04 (m, 1H), 1.79-191 (m, 1H |
| **2i**[b] | | | 11.22 (br. s., 1H), 7.92 (d, *J* =3.9, 1H), 7.37 (d, *J* =7.6, 1H), 6.98 (dd, *J* = 7.0, 4.8, 1H), 4.74 (dd, *J* = 8.9, 4.2, 1H), 4.69 (t, *J* = 5.2, 1H), 3.57-3.63 (m, 2H), 1.94-2.06 (m, 1H), 1.78-1.90 (m, 1H) |

[a] HRMS Calc'd for $C_{11}H_{13}NO_4$ ($MH^+$): 224.0922. Found: 224.0974. [b] Sample could not be purified further by simple trituration or crystallization. NMR of crude product indicates trace impurities (<5%).

## Experimental (Structural data shown in Table 3)

### Two-Step Procedure

**Phenoxydihydrofuranone 5**: The nitrophenol (1eq) was dissolved in DMF (0.6 M) and treated with $K_2CO_3$ (1.3 eq), followed by addition of α-bromo-γ-butyrolactone (1.2 eq) at

RT. After stirring 18 h, an additional amount of $K_2CO_3$ (0.25 eq) was added. After a total reaction time of 48 h, the reaction mixture was cooled in an ice bath and acetic acid (1.65 eq) was added. The crude reaction mixture was poured into water and extracted with 3 portions of EtOAc. The combined extract was concentrated under vacuum and crystallized from ethanol/water. A single crop was collected to afford the analytically pure product.

**Benzoxazinone 2**: The phenoxydihydrofuranone **5** was reacted with $H_2$ at 50 psi in a Parr shaker bottle containing 10% Pd/C (15% w/w) in EtOH (0.5 M) for 13 h. The catalyst was removed by filtration and the filtrate concentrated under vacuum. The crude product was triturated with hot $Et_2O$ and filtered to afford the pure benzoxazinone.

**One-Pot Procedure:**

**Method A:** The aminophenol (1 eq) and $K_2CO_3$ (1.5 eq) were combined in THF (0.1M) at rt for 15 - 30 min. α-Bromo-γ-butyrolactone (1.2 eq) was added in one portion and the resulting mixture was heated to reflux for 5 h. After cooling to rt, the reaction was diluted with water and the solvent removed under vacuum. The aqueous portion was chilled in ice and the resulting solid was filtered and dried under vacuum.

**Method B:** NaH (60% dispersion in mineral oil, 2 eq.) was washed with 3 portions of hexane and then slurried with THF at 0°C, under nitrogen. A solution of the aminophenol in THF (0.1M, 1 eq) was added slowly to the NaH slurry. After gas evolution had ceased, the reaction was warmed to rt and α-bromo-γ-butyrolactone (1.2 eq) in THF (0.3M) was added in one portion. After stirring for 5 min, the reaction mixture was heated to reflux for 4 h. The mixture was diluted with water, the THF evaporated under vacuum, and the remaining aqueous portion was extracted with three portions of EtOAc. The combined extracts were were washed with 1N HCl, and brine, then dried over $MgSO_4$ and concentrated under vacuum, to yield the product.

**Method C:** Same as Method B but substituting DMF as the solvent.

**References and Notes:**


1. Cormican, M. G.; Jones, R. N. *Drugs* **1996**, *51*, (Suppl. 1), 6.

2. (a) Chu, D. T. W.; Plattner, J. J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853. (b) Eliopoulos, G. M.; Wennersten, C. B.; Gold, H. S.; Moellering, R. C. Jr. *Antimicrob. Agents Chemother.* **1996**, *40*, 1745. (c) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673. (d) Tally, F. T.; Ellestad, G. A.; Testa, R. T. *J. Antimicrob. Chemother* **1995**, *35*, 449. (e) Sum, P.-E.; Lee, V. J.; Testa, R. T.; Hlavka, J. J.; Ellestad, G. A.; Bloom, J. D.; Gluzman, Y.; Tally, F. P. *J. Med. Chem.* **1994**, *37*, 184. (f) Onishi, H. R.; Pelak, B. A.; Gerckens, L. S.; Silver, L. L.; Kahan, F. M.; Chen, M. -H.; Patchett, A. A.; Galloway, S. M.; Hyland, S. A.; Anderson, M. S.; Raetz, C. R. H. *Science*, **1996**, *274*, 980.

3. (a) Russo, F. D,; Silhavy, T. J. *Trends Microbiol.* **1993**, *1*, 306. (b) Parkinson, J. S.; Kofoid, E. C. *Ann. Rev. Genetics* **1992**, *26*, 71. (c) Stock, J. B.; Ninfa, A. J.; Stock, A. M. *Microbiological Reviews* **1989**, *53*, 450.

4. (a) Frechette, R. F.; Beach, M. J.; Bernstein, J.; Dow, T.; Foleno, B.; Johnson, C. E.; Loeloff, M.; Weidner-Wells, M. A.; Werblood, H.; Barrett, J. F. Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11 (1997), Publisher: American Chemical Society, Washington, D. C. (b) Frechette, R.; Weidner-Wells, M. A. PCT Int. Appl., 165 pp. CODEN: PIXXD2. WO 9717333 A1 970515. (c) Frechette, R.; Beach, M. PCT Int. Appl., 41 pp.CODEN: PIXXD2 WO 9728167 A1 970807.

5. (a) Shridhar, D. R.; Jogibhukta, M.; Krishnan, V. S. H. *Organic Preparations and Procedures Int.* **1982**, *14*, 195. (b) Masuoka, Y.; Asako, T.; Goto, G.; Noguchi, S. *Chem. Pharm. Bull.* **1986**, *34*, 130. (c) Kajino, M.; Shibouta, Y.; Nishikawa, K.; Meguro, K. *Chem. Pharm. Bull.* **1991**, *39*, 2896. (d) Shridhar, D. R.; Ram, B.; Rao, K. S.; Jain, M. L. *Indian J. Chem., Sect. B* **1985**, *24B*, 992. (e) Combs, D. W. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1663. (f) Hogale, M. B.; Tarapure, V. T.; Shelar, A. R.; Jagdale, M. H. *J. Indian Chem. Soc.* **1985**, *62*, 471. (g) Shridhar, D. R.; Rao, K. S.; Singh, A. N.; Rastogi, K.; Jain, M. L.; Gandhi, S. S.; Krishnan, V. S. H.; Jogibhukta, M.; Lovekar, C. D.; Tripathi, H. N.; Sai, G. S. T. *Indian J. Chem., Sect. B* **1985**, *24B*, 1263. (h) Hogale, M. B.; Nikam, B. P.; Dhore, N. P. *Orient. J. Chem.* **1985**, *1*, 103. (I) Sicker, D.; Hartenstein, H.; Hazard, R.; Tallec, A. *J. Heterocycl. Chem.* **1994**, *31*, 809.

6. Hydroxy substitution at the 2-position of the 1,4-benzoxazinone nucleus with 0, 1 and 3-carbon spacers have been reported: (a) Sicker, D.; Hartenstein, H. *Synthesis* **1993**, 771. (b) Quiroz, A.; Niemeyer, H. M. *Heterocycles* **1991**, *32*, 1681. (c) Bartsch, H.; Schwarz, O. *J. Heterocycl. Chem.* **1982**, *19*, 1189.

7. (a) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (b) The nmr spectrum of the intermediate hydroxy acid was consistent with the structure. The structure was not rigorously proved, except by reconversion to the phenoxyfuranone derivative.

8. In all cases, the products obtained after the crude workup were sufficiently pure to carry on as synthetic intermediates. Analytically pure material could be isolated after a single crystallization or trituration step. Yields shown reflect product obtained after purification at each step with, typically, only one crop collected following a crystallization or trituration procedure. Also, with the exception of the parent system ring (ie., **2a**), product yields were the result of a single trial.

9. Details of the structure activity relationships will be available in a manuscript which is in preparation.

(RECEIVED IN THE U.S.A. 06 APRIL 1998)