Synthesis of 2-Substituted 3,4-Dihydro-2*H*-1,4-benzoxazines in Water Under Phase Transfer Catalysis Conditions

Domenico Albanese,* Dario Landini, Vittoria Lupi, Michele Penso

Dipartimento di Chimica Organica e Industriale and CNR, Via Venezian 21, 20133 Milano, Italy
Fax: (+39)-02-5835-4159, e-mail: domenico.albanese@unimi.it

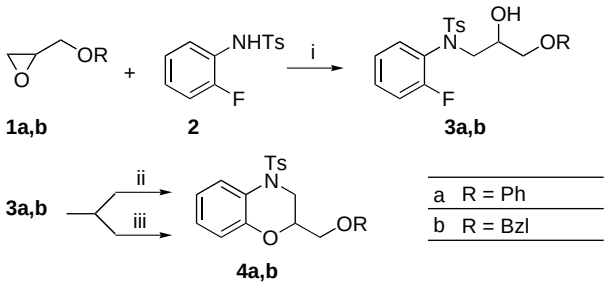
Received: December 12, 2001; Accepted: February 19, 2002

Abstract: 2-Substituted 3,4-dihydro-2*H*-1,4-benzoxazines have been prepared in excellent yields and short reaction times through the cyclization of hydroxysulfonamides in water under PTC conditions.

Keywords: 1,4-benzoxazines; cyclization; green chemistry; phase transfer catalysis; water as solvent

3,4-Dihydro-2*H*-1,4-benzoxazine derivatives have received considerable attention due to their wide range of biological and therapeutic properties.[1] The 1,4-benzoxazine skeleton is usually built up by cyclocondensation of *o*-aminophenols with α,β-dibromo esters[2] or α-haloacyl halides followed by carbonyl reduction with BH_3.[3] These procedures are hampered by the use of toxic lachrimatory bromo derivatives and DMF difficult to be efficiently removed. 2-Vinyl-1,4-benzoxazines have also been prepared with ee's up to 79% by reaction of (*Z*)-1,4-diacetoxybut-2-ene with *N*-protected *o*-aminophenols in the presence of a palladium catalyst associated with phosphine ligands.[4,5]

We recently reported a novel, straightforward synthesis of 2-substituted 3,4-dihydro-2*H*-1,4-benzoxazines **4** through the ring opening of epoxides **1** with *N*-(2-fluorophenyl)-*p*-tolylsulfonamide (**2**) followed by cyclization of the hydroxysulfonamides **3** thus obtained (Scheme 1).[6]



i) K_2CO_{3cat}, $TEBA_{cat}$, 90 °C. ii) *t*BuOK, THF, reflux.
iii) 50% NaOH, $\mathbf{6}_{cat}$, 90 °C.

Scheme 1.

The ring opening step takes place in a completely regioselective fashion under solid-liquid phase transfer catalysis (SL-PTC) conditions in the presence of catalytic amounts of solid anhydrous potassium carbonate and traditional PT catalysts such as $BnEt_3N^+Cl^-$ (TEBA) or $MeBu_3N^+Cl^-$ in the absence of organic solvent. The subsequent cyclization proceeds through the selective formation of the alkoxide anion with a non-nucleophilic strong base such as potassium *tert*-butoxide, in THF at reflux. Although good yields of benzoxazines **4** were obtained, the use of more environmentally friendly reagents would be desirable in order to develop a clean process, amenable to a simple and economic scale-up.

In order to address the question, we decided to investigate whether or not the cyclization could be carried out in water as solvent by using a cheap inorganic base such as NaOH. Should this task be achieved, the solvent-free transformation of epoxides **1** to the corresponding 2-substituted benzoxazines **4** would be available.

Here we report that the ring closing of hydroxysulfonamides **3** to benzoxazines **4** can be performed in high yields and short reaction times by using aqueous NaOH in the presence of a PTC catalyst, without organic solvents.

The cyclization proceeds through intramolecular aromatic nucleophilic substitution (S_NiAr) of fluoride anion promoted by a suitable base. In particular, the base should selectively generate the alkoxide anion without fluoride displacement. Although the leaving group capability of fluoride in aromatic nucleophilic displacements is well known, only isolated examples of S_NiAr reactions of fluoride with thiolate[7] or phenolate[8] anions have been reported.

When hydroxysulfonamide **3a** was mixed with 20% aqueous NaOH (2 molar equivalents) and heated at 90 °C for 36 h, only 41% of the expected benzoxazine **4a** was recovered along with 51% of the starting **3a**. The addition of 0.1 molar equivalent of Aliquat® 336 (**5**) produces a dramatic rate acceleration and benzoxazine **4a** was isolated in 94% yield after 12 h (Table 1, entry 4). Various reaction parameters such as concentration and amount of aqueous NaOH, type and amount of catalyst,

  1615-4150/02/3443+4-299 – 302 $ 17.50+.50/0

Table 1. Cyclization of hydroxysulfonamides **3**.[a]

Entry	Product	NaOH [%]	Catalyst [mol equiv]	*t* [h]	Yield [%]
1	**4a**	20	– –	36	41
2	**4a**	20	Aliquat (0.01)	72	77
3	**4a**	20	Aliquat (0.05)	23	89
4	**4a**	20	Aliquat (0.1)	12	94
5	**4a**	20	Aliquat (0.2)	10	86
6	**4a**	20	Aliquat (0.3)	6	86
7	**4a**	20	Aliquat (0.5)	2	94
8	**4a**	30	Aliquat (0.2)	8	88
9	**4a**	40	Aliquat (0.2)	6	92
10	**4a**	50	Aliquat (0.2)	5	91
11	**4a**	20	**6**[b] (0.2)	8	91
12	**4a**	20	**6**[b] (0.1)	10	85
13	**4a**	50	**6**[b] (0.05)	31	88
14	**4a**	50	**6**[b] (0.025)	31	64
15	**4a**	30	**6**[b] (0.2)	8	85
16	**4a**	40	**6**[b] (0.2)	7	90
17	**4a**	50	**6**[b] (0.2)	6	90
18	**4a**	20	$Bu_4N^+Br^-$ (0.2)	8	83
19	**4a**	20	$MeBu_3N^+Cl^-$ (0.2)	8	70
20	**4a**	20	$Me_4N^+Cl^-$ (0.2)	8	52
21	**4a**	40	SDS[c] (0.2)	8	–
22	**4a**	20	Triton X 100[d] (0.2)	8	18
23	**4a**	20	Triton X 405[e] (0.2)	8	23
24	**4a**	20	PEG 400 (0.2)	8	58
25	**4a**	50	**6**[b] (0.2)	6	97[f]
26	(*S*)-**4b**	50	**6**[b] (0.2)	3	99[f]
27	**4a**	50	–	26	47
28	**4a**	50	**7**[g]	26	35

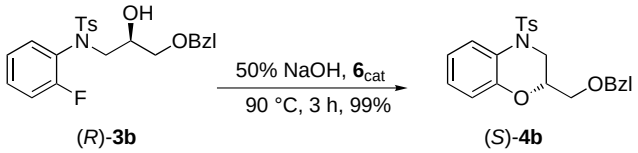
[a] Reaction conditions: **3** (1 mol equiv), aqueous NaOH (2 mol equiv), 90°, method A.
[b] n-$C_{14}H_{29}N^+Me_3Cl^-$.
[c] Sodium dodecyl sulfate.
[d] 4-(C_8H_{17})-C_6H_4-($OCH_2CH_2)_n$, n ~ 10.
[e] 4-(C_8H_{17})-C_6H_4-($OCH_2CH_2)_n$, n ~ 40.
[f] Method B.
[g] Trioctylamine.

are of paramount importance for the outcome of the cyclization (Table 1).

The reaction rate increases with the NaOH concentration (entries 5, 8 – 10, 11, 15 – 17) without affecting yields. In fact benzoxazine **4a** was isolated in 91% yield in 5 hours only when 50% NaOH was used in the presence of **5** (entry 10). This behaviour is in agreement with the well-known higher reactivity of concentrated alkaline solutions, due to the low hydration state of the hydroxide anion.[9]

The best results were obtained with more lipophilic ammonium salts such as Aliquat® **5** and $Bu_4N^+Br^-$, whereas less lipophilic ones, for example $Me_4N^+Cl^-$, are less efficient. As good results were obtained with n-$C_{14}H_{29}N^+Me_3Cl^-$ (**6**), which is a PT catalyst with surfactants properties, it was reasoned that the cyclization may also proceed through a micellar mechanism. However, the cyclization does not proceed at all in the presence of surfactants such as sodium dodecyl sulfate (SDS) (entry 21) and is very sluggish with surfactants of the Triton X series (entries 22 and 23). These results indicate the reaction occurs through a PTC mechanism since the catalytic activity of Triton's X, although low, can be ascribed to their polyethylene glycol unit. In fact, PEGs are known to be PT catalysts[10] and a 58% yield of benzoxazine **4a** was isolated after 8 h when PEG 400 was used as catalyst (entry 24). On the other hand, as expected in the case of a PTC process,[10] the reaction rate gradually increases with the amount of catalyst used (entries 2 – 7, 11 – 14).

Since quaternary ammonium salts are known to be partially decomposed by strongly alkaline solutions,[11] in particular when they are heated, affording the corresponding tertiary amines and 1-alkenes, trioctylamine (**7**) was used as catalyst. However, it shows no catalytic activity as evidenced by comparison with the same reaction carried out without catalyst (entries 27 and 28).



(*R*)-**3b** (*S*)-**4b**

Scheme 2.

The choice of catalyst plays a fundamental role in designing the solvent-free route to benzoxazines **4.** In fact, the use of a partially water-soluble PTC catalyst such as n-$C_{14}H_{29}N^+Me_3Cl^-$ (**6**) enables benzoxazines **4** to be simply recovered in excellent yields 97 – 99% by filtration of the reaction mixture after dilution with water (entries 25 and 26).

It is also worth noting that the ring closing step occurs without racemization of the stereocenter as demonstrated in the case of (*R*)-**3b** (Scheme 2).

In fact, when enantiomerically pure (*R*)-**3b**, generated from the ring opening of (*S*)-benzyl glycidyl ether with **2**, was treated with 50% NaOH in the presence of **6**, enantiopure benzoxazine (*S*)-**4b** was isolated in 99% yield after 3 h (entry 26).

In conclusion, these results showed that the ring closure of hydroxysulfonamides **3** to benzoxazines **4** can be efficiently carried out in water by using cheap reagents under PTC conditions.[12] In view of the availability of a wide variety of enantiopure epoxides, the new PTC methodology provides a straightforward and environmentally safe tool for the synthesis of chiral 2-substituted benzoxazines, valuable intermediates for the synthesis of biologically active compounds.[1]

Experimental Section

N-Tosyl-2-phenoxymethyl-1,4-benzoxazine (4a)

Method A: A mixture of hydroxysulfonamide **3a** (0.2 mmol, 83 mg), 50% NaOH (0.4 mmol, 32 mg), Aliquat ® (0.04 mmol, 16 mg) was magnetically stirred at 90 °C until the starting material was no longer detectable (TLC analysis). After cooling, the reaction mixture was diluted with AcOEt and 5% NH_4Cl. The organic phase was washed with brine, dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (230 – 400 mesh) AcOEt-PE (1:10) to give **4a**; yield: 72 mg (91%); mp 112.4 °C; ^{1}H NMR ($CDCl_3$): $\delta = 2.38$ (s, 3H), 3.38 (dd, 1H, $J = 9.9$ and 14.5 Hz), 3.67 (m, 1H), 3.92 (dd, 1H, $J = 6.3$ and 10.2 Hz), 4.10 (dd, 1H, $J = 4.3$ and 10.2 Hz), 4.48 (dd, 1H, $J = 2.5$ and 14.5 Hz) 6.80 – 7.90 (m, 13H); ^{13}C NMR ($CDCl_3$, selected data): $\delta = 21.5$, 46.2, 67.2, 69.6; IR (nujol): $\nu_{max} = 1342$ (SO_2N), 1161 cm^{-1} (SO_2N); anal. calcd. for $C_{22}H_{21}NO_4S$: C 66.82, H 5.35, N 3.54, S 8.11; found: C 67.05, H 5.25, N 3.65, S 8.30%.

Method B: A mixture of hydroxysulfonamide **3a** (0.2 mmol, 83 mg), 50% NaOH (0.4 mmol, 32 mg), n-$C_{14}H_{29}N^+Me_3Cl^-$ (**6**; 0.04 mmol, 24 mg of 50% aqueous solution) was magnetically stirred at 90 °C for 6 h (TLC analysis). After cooling 3 mL of water were added and the mixture left under stirring for 20 min. The mixture was filtered to give **4a**; yield: 77 mg (97%); mp 112.4 °C.

N-Tosyl-(2*S*)-benzyloxymethyl-1,4-benzoxazine (4b)

A mixture of hydroxysulfonamide (2*R*)-**3b** (0.3 mmol, 129 mg), 50% NaOH (0.6 mmol, 48 mg), n-$C_{14}H_{29}N^+Me_3Cl^-$ (**6**; 0.06 mmol, 36 mg of 50% aqueous solution) was magnetically stirred at 90 °C for 3 h (TLC analysis). After cooling 3 mL of water were added and the mixture left under stirring for 20 min. The mixture was filtered to give (2*S*)-**4b**; yield: 122 mg (99%); mp 107 °C; $[a]_D^{20}$: – 47.1 (*c* 1, $CHCl_3$); R_t: 6.87 min (CHIRALPAK® AD™, *i*-PrOH/hexane, 40:60, 210 nm, flow rate 1 mL/min); R_t of **(±)-4b**: 6.8, 7.6 min; ^{1}H NMR ($CDCl_3$): $\delta = 2.37$ (s, 3H), 3.28 (m, 1H), 3.51 (m, 3H), 4.34 (dd, 1H, $J = 2.0$ and 14.2 Hz), 4.52 (dd, 2H, $J = 12.4$ and 14.6 Hz), 6.80 – 7.85 (m, 13H); ^{13}C NMR ($CDCl_3$, selected data): $\delta = 21.5$, 46.3, 69.6, 70.7, 73.5; IR (nujol): $\nu_{max} = 1350$ (SO_2N), 1164 cm^{-1} (SO_2N); anal. calcd. for $C_{23}H_{23}NO_4S$: C 67.46, H 5.66, N 3.42, S 7.83; found: C 67.28, H 5.70, N 3.48, S 7.71%.

Acknowledgements

Financial support from CNR and MURST (Project "Stereoselezione in sintesi organica: metodologie e applicazioni") is gratefully acknowledged.

References

[1] a) A.-S. Bourlot, I. Sánchez, G. Dureng, G. Guillaumet, R. Massingham, A. Monteil, E. Winslow, M. D. Pujol J.-Y-Mérour, *J. Med. Chem.* **1998**, *41*, 3142 – 3158; b) D. W. Combs, M. S. Rampulla, S. C. Bell, D. H. Klaubert, A. J. Tobia, R. Falotico, B. Haertlein, C. Lakas-Weiss, J. B. Moor, *J. Med. Chem.* **1990**, *33*, 380 – 386; c) E. T. D'Ambra, G. K. Estep, R. M. Bell, A. M. Eissenstat, A. K. Josef, J. S. Ward, A. D. Haycock, R. E. Baizman, M. F. Casiano, C. N. Beblin, M. S. Chippari, D. J. Greo, K. R. Kullnig, T. G. Daley, *J. Med. Chem.* **1992**, *35*, 124 – 135; d) M. Largeron, H. Dupuy, M. B. Fleury, *Tetrahedron* **1995**, *51*, 4953 – 4968.

[2] R. C. M. Butler, C. B. Chapleo, P. L: Myers, A. P. Welbourn, *J. Heterocyclic Chem.* **1985**, 177 – 181.

[3] a) T. Kuroita, N. Marabuyashi, M. Sano, K. Kanzaki, K. Inaba, T. Kawaita, *Chem. Pharm. Bull.* **1996**, *44*, 2051 – 2060; b) Y. Matsumoto, R. Tsuzuki, A. Matsuhisa, K. Takayama, T. Yoden, W. Uchida, M. Asano, S. Fujita, I. Yanagisawa, T. Fujikura, *Chem. Pharm. Bull.* **1996**, *44*, 103 – 114.

[4] A. Yamazaki, I. Achiwa, K. Achiwa, *Tetrahedron Asymmetry* **1996**, *7*, 403 – 406.

[5] P. Lhoste, M. Massacret, D. Sinou, *Bull. Soc. Chim. Fr.* **1997**, *134*, 343 – 347.

[6] D. Albanese, D. Landini, M. Penso, *Chem. Commun.* **1999**, 2095 – 2096.

[7] G. Campiani, A. Garofalo, I. Fiorini, M. Botta, V. Nacci, A. Tafi, A. Chiarini, R. Budriesi, G. Bruni, M. R. Romeo, *J. Med. Chem.* **1995**, *38*, 4393 – 4410.
[8] S. Carrington, A. H. Fairlamb, I. Blagbrough, *Chem. Commun*. **1998**, 2335 – 2336.
[9] D. Albanese, D. Landini, M. Penso, A. Maia, *Ind. & Eng. Chem. Res.* **2001**, *40*, 2396 – 2401.
[10] a) C. M. Starks, C. L. Liotta, M. Halpern, *Phase-Transfer Catalysis. Fundamentals, Applications, and Industrial Perspectives*, Chapman & Hall, New York, **1994**; b) E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed., Verlag Chemie, Weinheim, **1993**.
[11] a) D. Landini, A. Maia, *Chem. Commun.* **1984**, 1041 – 1042. b) D. Landini, A. Maia, A. Rampoldi *J. Org. Chem.* **1986**, *51*, 3187 – 3191.
[12] D. Albanese, M. Zenoni, (to ACS Dobfar), *Brev. It.* A27053, **2001**.