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Novel concise synthesis of 2-substituted 3,4-dihydro-2*H*-1,4-benzoxazines by ring opening of glycidols under solid-liquid phase transfer catalysis conditions†

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The ring opening of glycidols with *N*-(2-fluorophenyl)toluene-*p*-sulfonamide under SL-PTC conditions, followed by ring closure with Bu^{t}OK, provides a novel high yielding synthesis of 2-substituted 3,4-dihydro-2*H*-1,4-benzoxazines.

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 various dibromo derivatives[2] or α-halogeno acyl bromides.[3] Recently 2-vinyl-1,4-benzoxazines have also been prepared with ees 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 phospine ligands.[4,5]

Following an alternative approach we devised a novel synthesis of 2-substituted 3,4-dihydro-2*H*-1,4-benzoxazines through formation of the C–N bond by ring opening of glycidols with a suitable nitrogen nucleophile. The benzoxazine synthesis could be completed through nucleophilic aromatic substitution of a good leaving group incorporated in the incoming nucleophile. We report herein our preliminary results in this area which reveals that the new approach enables the efficient synthesis of non-racemic chiral 2-substituted benzoxazines.

In previous papers we reported on the ring opening of epoxides with nitrogen nucleophiles under solid/liquid phase transfer catalysis (SL-PTC) conditions affording corresponding β-hydroxyamides in good to excellent yields.[6,7] On the basis of these results and due to the good nucleofugality of fluoride anion in aromatic nucleophilic substitution, *N*-(2-fluorophenyl)toluene-*p*-sulfonamide **1** was chosen as the nitrogen nucleophile incorporating the aromatic moiety of benzoxazine and the leaving group.

Thus, the ring opening was performed by stirring at 90 °C a heterogeneous mixture of 1,2-epoxy-3-phenoxypropane **2a**, sulfonamide **1** (1.1 equiv.), anhydrous K_2CO_3 (0.1 equiv.), $BnEt_3NCl$ (0.1 equiv.) and dioxane, affording *N*-(2-fluorophenyl)-*N*-(2-hydroxy-3-phenoxypropyl)toluene-*p*-sulfonamide **3a** in 95% yield after 17 h (Scheme 1). The optimisation of reaction conditions (Table 1) led us to discover that the best results were obtained without solvent, giving 94% of **3a** after 1 h. The PTC agent is essential in order to give high yields in short reaction times since 56 h were necessary to generate 86% of **3a** in the absence of $BnEt_3NCl$.

Table 1 Synthesis of β-hydroxysulfonamide **3**[a]

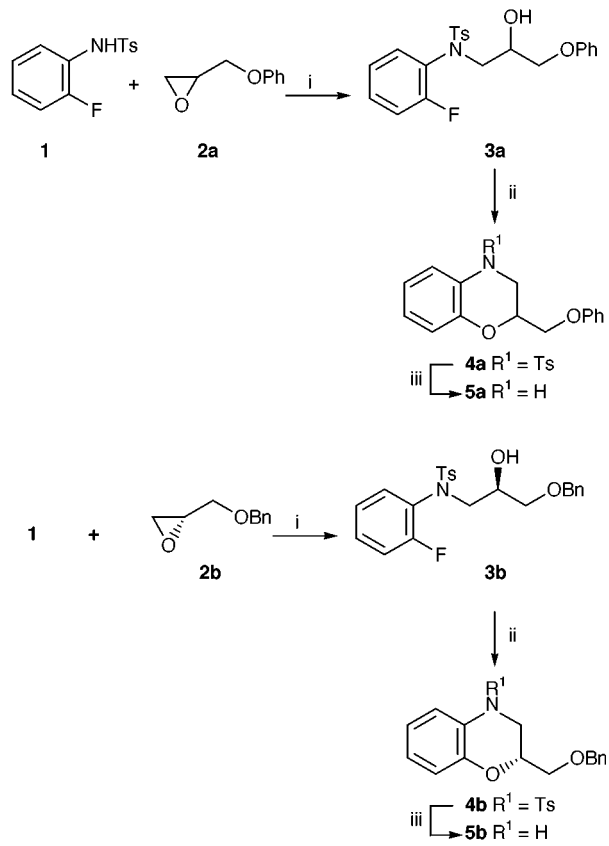
Entry	Epoxide	Dioxane/M	*t*/h	Yield (%)[b]
1	**2a**	2.5	17	95
2	**2a**	10	3	85
3	**2a**	—	1	94
4	**2a**	—	56	86[c]
5	(*S*)-**2b**	—	2	90

[a] All reactions carried out using 1.1 equiv. of sulfonamide **1**, 0.1 equiv. of $BnEt_3NCl$ and 0.1 equiv. of anhydrous K_2CO_3. [b] Isolated yield. [c] Without $BnEt_3NCl$.

† Experimental and spectral data for **3a**,**b**, **4a**,**b** and **5a**,**b** are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/2095/

The ring opening takes place in a completely regioselective fashion, affording β-hydroxysulfonamides derived from the nucleophilic attack on the less substituted carbon atom of the oxirane ring. In accordance with the observed regiochemistry, non-racemic chiral glycidols generate enantiopure β-hydroxysulfonamides, as revealed in the case of (2*S*)-[(benzyloxy)methyl]oxirane (*S*)-**2b** which generates (2*R*)-*N*-(2-fluorophenyl)-*N*-(2-hydroxy-3-benzyloxypropyl)toluene-*p*-sulfonamide-(*R*)-**3b** in 90% yield after 2 h.‡

With a viable route to β-hydroxysulfonamides **3** in hand, it remained to perform the ring closing step to demonstrate the utility of this strategy. The 1,4-benzoxazine ring can be formed by intramolecular nucleophilic substitution (S_Ni Ar) of fluoride anion promoted by a suitable base. In particular the base should selectively generate the alkoxide anion without direct substitution of fluoride. Only isolated examples of S_Ni Ar of fluoride anion by thiolate[8] or phenolate anion[9] have been reported along with a single example of bromide substitution by phenolate.[10] The task was achieved with a cheap non-nucleophilic strong base such as Bu^{t}OK. In fact *N*-tosyl-2-phenoxymethyl-



Scheme 1 *Reagents and conditions*: i, K_2CO_3–$BnEt_3NCl$, 90 °C; ii, Bu^{t}OK, THF, reflux; iii, Na, naphthalene, DME, −78 °C.

1,4-benzoxazine **4a** was isolated in 85% yield when reacted with Bu^{t}OK in THF for 30 min at reflux. Moreover the yield could be increased up to 92% by portionwise addition of Bu^{t}OK. Similarly (*R*)-**3b** was converted into the corresponding 1,4-benzoxazine (*R*)-**4b** in 86% yield after 1 h.

It is likely that the ring closure proceeds through a pure S_Ni Ar mechanism due to the activation exerted by the *p*-tolylsulfonyl group even though an $S_{RN}1$ or benzyne pathway cannot at the moment be ruled out.

In order to probe the scope and limitations of the process, *N*-(2-chlorophenyl)-*N*-(2-hydroxy-3-phenoxypropyl)toluene-*p*-sulfonamide **7** was prepared in 94% yield by ring opening of **2a** with *N*-(2-chlorophenyl)toluene-*p*-sulfonamide **6** as previously described. However **7** did not generate the corresponding benzoxazine when treated with Bu^{t}OK.

Removal of the *N*-tosyl group with Na/naphthalene[11] gave the unprotected 1,4-benzoxazines **5a,** (*R*)-**5b** in 77–84% yield. Conversion of (*R*)-**5b** into the corresponding Mosher amide confirmed that the ring closure occurs without racemisation.§

In view of the availability of a wide variety of enantiopure epoxides[12] this method provides a straightforward and new approach towards the synthesis of chiral 2-substituted 3,4-dihydro-2*H*-1,4-benzoxazines since the stereocenter of the epoxide is not affected during the ring opening and the next cyclisation occurs without racemisation.

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Notes and references

‡ ^{19}F NMR analysis of the Mosher's ester (ref. 13) prepared from (*R*)-**3b** and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride showed a single signal for the aromatic fluorine at δ −118.607, whereas the diastereomeric esters obtained from racemic **3b** showed two separated signals at δ −118.319 and −118.607.

§ ^{1}H NMR analysis of the Mosher's amide prepared from (*R*)-**5b** and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride showed a single signal for the methoxy group at δ 3.82m, whereas the diastereomeric amides obtained from racemic **5b** showed two separated signals at δ 3.76 and 3.82.

1 D. W. Combs, M. S. Rampulla, S. C. Bell, D. H. Klaubert, A. J. Tobia, R. Falotico, B. Haertlein, C. Lakah-Weiss and J. B. Moor, *J. Med. Chem.*, 1990, **33**, 380; 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 and T. G. Daley, *J. Med. Chem.*, 1992, **35**, 124; M. Largeron, H. Dupuy and M. B. Fleury, *Tetrahedron*, 1995, **51**, 4953.

2 T. Kuroita, M. Sakamori and T. Kawakita, *Chem. Pharm. Bull.*, 1996, **44**, 756.

3 Y. Matsumoto, R. Tsuzuki, A. Matsuhisa, K. Takayama, T. Yoden, W. Uchida, M. Asano, S. Fujita, I. Yanagisawa and T. Fujikura, *Chem. Pharm. Bull.*, 1966, **44**, 103.

4 A. Yamazaki, I. Achiwa and K. Achiwa, *Tetrahedron: Asymmetry*, 1996, **7**, 403.

5 P. Lhoste, M. Massacret and D. Sinou, *Bull. Soc. Chim. Fr.*, 1997, **134**, 343.

6 D. Albanese, D. Landini and M. Penso, *Tetrahedron*, 1997, **53**, 4787.

7 D. Albanese, D. Landini, M. Penso and S. Petricci, *Tetrahedron*, 1999, **55**, 6387.

8 G. Campiani, A. Garofalo, I. Fiorini, M. Botta, V. Nacci, A. Tafi, A. Chiarini, R. Budriesi, G. Bruni and M. Romeo, *J. Med. Chem.*, 1995, **38**, 4393.

9 S. Carrington, A. H. Fairlamb and I. S. Blagbrough, *Chem. Commun.*, 1998, 2335.

10 G. E. Bonvicino, L. H. Yogodzinski and R. A. Hardy Jr., *J. Org. Chem.*, 1962, **27**, 4272.

11 J. J. Folmer, C. Acero, D. L. Thai and H. Rapoport *J. Org. Chem.*, 1998, **63**, 8170.

12 E. N. Jacobsen, *Comprehensive Organometallic Chemistry II*, ed. E.W. Abel, F. G. A. Stone, G. Wilkinson and L. H. Hegedus, Pergamon, Oxford, 1995, vol. 12, ch.11.1; R. A. Johnson and K. B. Sharpless, *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, ch. 4.1.

13 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2453.

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