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A metal catalyst-free and one-pot synthesis of (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol derivatives in water†

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A robust and metal catalyst-free method has been developed for the general and green synthesis of racemic (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol derivatives. This simple, mild and practical method involves the reaction of 2-aminophenols with (±)-epichlorohydrin in the presence of NaOH in water at room temperature. The reaction features high regioselectivity and a good substrate scope to produce both *N*-substituted and *N*-unsubstituted products.

The (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol framework (**A**, Fig. 1) has attracted particular attention as compounds containing this framework either show interesting biological activities or are precursors of several bioactive molecules. For example, compounds represented by **B** containing the framework **A** have been reported to possess both thrombin inhibitory and fibrinogen receptor antagonistic activities.[1] On the other hand benzoxazine derivatives **C** and **D** (Fig. 1) possessing dual selective serotonin reuptake inhibitory properties and 5-HT_{1A} receptor activities are prepared from starting materials based on **A**.[2]

The construction of 1,4-benzoxazine skeleton is usually performed by cyclocondensation of 2-aminophenols with various (i) dibromo derivatives[3] *e.g.* 2,3-dibromopropionic acid esters[2,4,5] or (ii) α-halogeno acyl bromides.[6] A Pd-mediated coupling of (*Z*)-1,4-diacetoxybut-2-ene with *N*-protected 2-aminophenols has also been used to prepare 1,4-benzoxazines (with ee's up to 79%) having a vinyl group at C-2.[7,8] The compound **A** or its analogs in turn are prepared *via* the reduction of 3,4-dihydro-2*H*-benzo[1,4]-oxazine-2-carboxylate derivatives[2,4,5] (obtained through the reaction of 2-aminophenol with 2,3-dibromopropanoate esters) or 3-oxo-benzoxazine derivatives[2] (Method a & b, Scheme 1). In 1999, the synthesis of OPh/

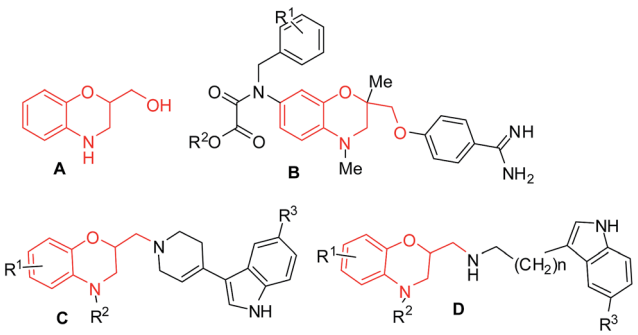
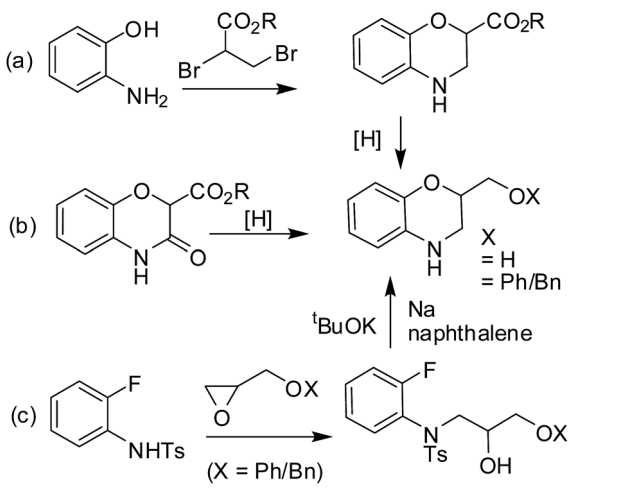


Fig. 1 (3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol framework (**A**) and its bioactive derivatives (**B**–**D**).



Scheme 1 Reported synthesis of **A** and its derivatives.[2,4,5,9]

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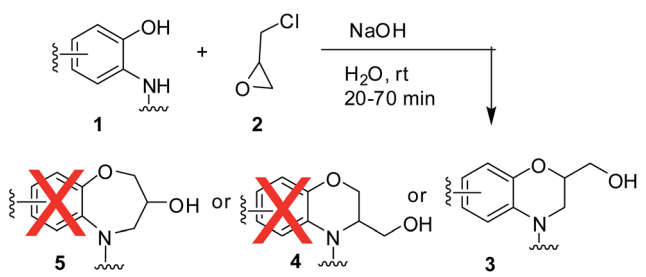
† Electronic supplementary information (ESI) available: Experimental procedures, copies of the ^{1}H and ^{13}C NMR spectra and HRMS. See DOI: 10.1039/c5ra14478g

OBn analogue of **A** has been reported *via* the ring opening of glycidols with *N*-(2-fluorophenyl)toluene-*p*-sulfonamide under solid–liquid phase transfer catalysis followed by ring closure with ^{t}BuOK (Method c, Scheme 1).[9] While these methods have found applications in the synthesis of related bioactive molecules, all of them involved multi-step processes, expensive catalysts or reagents and conditions that are not at all environmental friendly. Due to our ongoing research on evaluation of benzo[*b*][1,4]oxazine derivatives[10] for their potential activities against various pharmacological targets we required access to a library of compounds based on **A**.

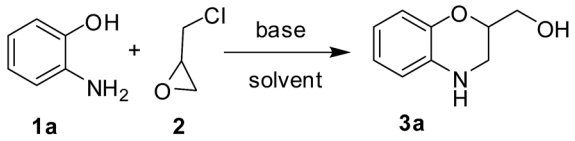
This prompted us to devise an alternative approach to access our target compounds following a synthetic strategy based on that reported by Albanese *et al.*[9] (Method c, Scheme 1). Herein we report a one-pot procedure that allows faster and efficient access to racemic **A** and its derivatives (**3**) *via* the reaction of 2-aminophenols (**1**) with (±)-epichlorohydrin (**2**) in the presence of NaOH in water (Scheme 2). Though one example of synthesizing (4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)-methanol in 67% yield using a similar strategy has been reported,[11] the methodology involved the sequential use of $LiClO_4$ in toluene for 14–48 h and then NaOMe in MeOH for 14–72 h both at 50 °C. Moreover, in addition to the use of more than one reagent, toxic solvents, longer reaction time and relatively higher reaction temperature, the scope of this particular reaction was not investigated. Thus, development of a more convenient and general method for the synthesis of **3** was necessary. Notably, though the formation of some unidentified minor impurities was observed during our reaction (Scheme 2) no isomeric product (*e.g.* **4** or **5**) formation was observed in these cases (*vide infra* for product characterization).

Epichlorohydrin is a versatile precursor in the synthesis of many organic compounds[12] and known to be moderately soluble in water. Likewise, 2-aminophenols are soluble in water especially in the presence of alkali. Water on the other hand being a green, cheap and easily available solvent is a preferred medium for conducting many organic reactions[13] wherever feasible. Thus, we anticipated that the reaction of 2-aminophenols with epichlorohydrin may proceed either in an aqueous medium or in pure water under an appropriate reaction condition. Accordingly, the reaction of **1a** (1 mmol) with **2** (1.2 mmol) was performed initially in the presence of Na_2CO_3 in pure water at room temperature (25 °C) for 20 min when trace of desired product **3a** was isolated (entry 1, Table 1) with the



Scheme 2 Synthesis of *N*-unsubstituted/substituted (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol derivatives in water.

Table 1 Effect of reaction conditions on the reaction of **1a** with **2**[a]



Entry	Base	Solvent	Time (min)	%Yield[b]
1	Na_2CO_3	H_2O	20	5
2	Na_2CO_3	H_2O	60	11
3	Na_2CO_3	H_2O	60	19[c]
4	$NaHCO_3$	H_2O	60	0
5	K_2CO_3	H_2O	20	10
6	NaOH	H_2O	20	70
7	NaOH	H_2O	20	67[c]
8	NaOH	H_2O	60	75
9	NaOH	MeOH	60	60
10	NaOH	Ethylene glycol	60	61
11	NaOH	1,4-Dioxane	60	0
12	Et_3N	H_2O	60	10
13	DABCO	H_2O	60	Trace

[a] Reactions were performed using **1a** (1 mmol) and (±)-epichlorohydrin **2** (1.2 mmol) in the presence of a base (1.4 mmol) in a solvent (5 mL) at 25 °C. [b] Isolated yield. [c] Reaction was performed at 50 °C.

recovery of most of **1a**. An increase in reaction time or temperature did not improve the product yield significantly (entries 2 and 3, Table 1) whereas no product was formed when a weaker base *e.g.* $NaHCO_3$ was used (entry 4, Table 1). The use of K_2CO_3 was also found to be inefficient (entry 5, Table 1). Notably, the use of a stronger base *e.g.* NaOH showed complete disappearance of **1a** (by TLC) after 20 min and afforded **3a** in 70% yield (entry 6, Table 1). The compound **3a** was characterized by spectral (NMR and MS) and analytical (HRMS) data.[14a] Indeed, the reaction of **1a** with **2** could possibly afford three different products *e.g.* the 6-membered ring product **3a** or its regioisomer **4a** or the 7-membered ring product **5a** (Fig. 2). However, compound **4a** was ruled out by 2D NMR study *i.e.* heteronuclear multiple-bond correlation spectroscopy (HMBC) (see Fig. S-1 in ESI†). The HMBC study (Fig. 2) performed by using compound **3a** indicated three 3-bond correlations, one for the ring junction carbon A [with H^c (3.96–3.94 δ, m)] and another two for the other ring junction carbon B [with $H^{a\prime}$(3.35–3.34 δ, m) and H^a (3.04–3.01 δ, m) separately]. An opposite HMBC result was expected for the regioisomer **4a** [*i.e.* two 3-bond correlations for carbon A with H^a & $H^{a\prime}$ separately and one for carbon B with H^c]. Moreover, literature survey revealed that

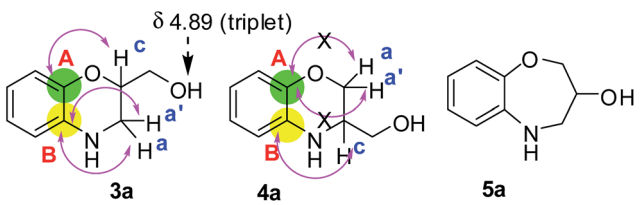
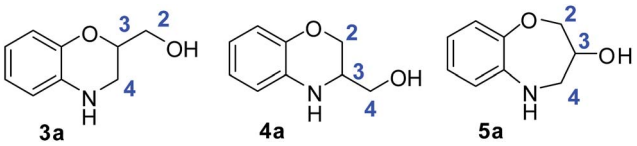


Fig. 2 Compound **3a** and its isomeric structures **4a** and **5a**.

Table 2 Reported ^{1}H NMR signals for compounds **3a**, **4a** and **5a**

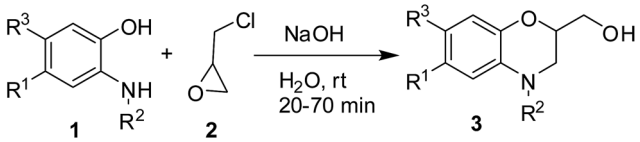


Compd	H-2[a]	H-2[b]	H-3	H-4[a]	H-4[b]
3a (ref. 5)	3.83 (dd) J = 4.4, 11.8	3.77 (dd) J = 5.9, 11.8	4.17–4.25 (m)	3.35 (dd) J = 2.9, 11.8	3.28 J = 7.3, 11.8
4a (ref. 14*b*)	4.18 (dd) J = 10.8, 2.9	4.06 (dd) J = 10.8, 5.9	3.55 (m)	3.72 (dd) J = 10.7, 4.9	3.64 (dd) J = 10.7, 7.1
5a (ref. 14*b*)	4.25 (ddd) J = 12.3, 3.8, 1.4	3.86 (dd) J = 12.3, 2.0	3.93 (m)	3.36 (ddd) J = 12.9, 4.9, 1.4	3.17 (dd) J = 12.9, 2.4

all these compounds *i.e.* **3a**, **4a** and **5a** are known and have been characterized earlier (Table 2).[5,14b] Accordingly, the ^{1}H NMR data (recorded in $CDCl_3$)[14c] of the obtained alcohol was found to correlate clearly with that reported[5] for **3a** but not with **4a** and **5a**.[14b] Thus, **3a** appeared to be the chemical structure of the isolated product. We were delighted with the regioselective formation of compound **3a** and decided to continue the optimization study further. However, no further or marginal improvement of yield of **3a** was observed when the reaction was performed at higher temperature and for a longer duration (entries 7 and 8, Table 1). The use of other solvent *e.g.* MeOH, ethylene glycol, and 1,4-dioxane (entries 9–11, Table 1) and organic bases *e.g.* Et_3N and DABCO (entries 12 and 13, Table 1) were also examined and found to be either less effective or ineffective. Overall, considering both reaction time and product yield, the condition of entry 6 of Table 1 was identified as optimal and used for further study.

Having established the optimal reaction conditions for the regioselective synthesis of **3a** the generality and scope of this single-step methodology was examined. A variety of 2-amino phenols (**1**) including ring substituted as well as *N*-substituted derivatives were employed in this one-pot reaction (Table 3) and the reaction proceeded well in all of these cases. Groups like NO_2, Cl, Br, and Me on the benzene ring of **1** (entries 2–5 and 10–12, Table 3) or its various *N*-benzyl substituents carrying F, Cl or OMe groups (7–9 and 13–14, Table 3) were well tolerated. Thus a range of *N*-unsubstituted/substituted (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol derivatives were synthesized in good to acceptable yields. Yields were generally good (>75%) when *N*-benzyl substituted 2-amino phenols (**1f–n**) were used

Table 3 Synthesis of (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol derivatives (**3**) *via* the reaction of 2-aminophenols (**1**) with (±)-epichlorohydrin (**2**) in water[a]

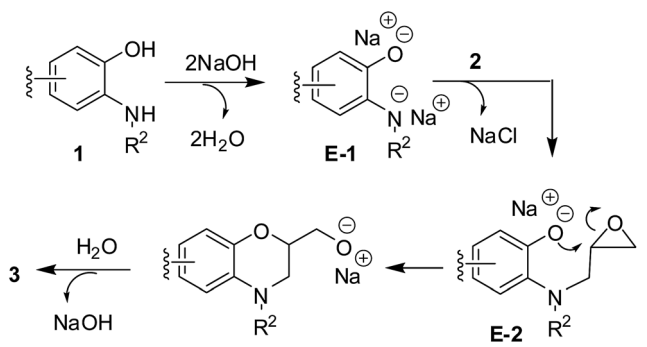


Entry	2-Aminophenol (**1**); R^1, R^2, R^3	Product (**3**)	Time (min)	Yield[b] (%)
1	**1a**; H, H, H	**3a**	20	70
2	**1b**; H, H, NO_2	**3b**	25	65
3	**1c**; Cl, H, H	**3c**	20	70
4	**1d**; Br, H, H	**3d**	20	68
5	**1e**; H, H, Me	**3e**	20	68
6	**1f**; H, Bn, H	**3f**	60	78
7	**1g**; H, $CH_2C_6H_4Cl$-*p*, H	**3g**	60	76
8	**1h**; H, $CH_2C_6H_4Cl$-*o*, H	**3h**	70	78
9	**1i**; H, $CH_2C_6H_3(OMe)_2$-*m*,*p*, H	**3i**	60	75
10	**1j**; Cl, Bn, H	**3j**	60	78
11	**1k**; H, $CH_2C_6H_4Cl$-*p*, Me	**3k**	70	75
12	**1l**; H, Bn, Me	**3l**	60	77
13	**1m**; H, $CH_2C_6H_4F$-*o*, H	**3m**	60	78
14	**1n**; H, $CH_2C_6H_4OMe$-*p*, H	**3n**	60	75

[a] Reactions were performed using **1** (1 mmol), and (±)-epichlorohydrin **2** (1.2 mmol) in the presence of NaOH (1.4 mmol) in H_2O (5 mL). [b] Isolated yield.

though the duration of the reaction was longer in these cases. Notably, the reported promising intracellular calcium activity of a *N*-benzyl analogue *e.g.* 4-benzyl-3,4-dihydro-2-[3-[[2-(3,4-dimethoxyphenyl)ethyl] amino]propyl]-2*H*-1,4-benzoxazine[15] prompted us to focus on preparing a range of *N*-benzyl derivatives **3f–n** (Table 3) for further pharmacological study. It is worthy to mention that products **3a–e** were found to be miscible with water and hence usual work-up (*e.g.* extraction with EtOAc) was necessary for their isolation after completion of the reaction. However, the work-up procedure can be avoided for compounds **3f–n** as these products were separated as oil from the reaction mixture. The oil separated can be collected and purified directly by using column chromatography. An attempt to avoid chromatographic purification was not successful as most of these products were isolated either as a liquid or gummy mass. Nevertheless, to test the scalabe potential of this process the reaction of **1a** (0.045 mmol) with **2** (1.2 equiv.) was performed in a bigger scale under the condition of entry 6 of Table 1.[16a] To our satisfaction the product **3a** was seperated as an oil in this case[16b] and isolated in 79% yield after usual purification highlighting the possible practical application of this process.

Based on results presented in Table 1 that the reaction did not proceed well in the absence of a strong base like NaOH a plausible reaction mechanism for the present one-pot synthesis of **3** has been proposed in Scheme 3. The reaction proceeds *via* conversion of aminophenol into a dianion **E-1** in the initial step aided by the strong base NaOH.[17] It is a known fact that this type of dianion undergoes selective *N*-alkylation when reacted with an alkyl halide (indeed, selective *N*-alkylation of the aminophenols has been carried out either by using softer electrophiles or by conversion of the aminophenol into a dianion).[18a] Thus **E-1** reacts with (±)-epichlorohydrin (**2**) to generate the epoxide intermediate **E-2** that undergoes cyclization involving the attack of the oxide anion ($-O^{\ominus}$) at the inner position of the epoxide ring to give the product **3**.[18b] The ring closure thus occurs in a 6-*exo-tet* fashion. Notably, the reaction of **E-1** through its oxide moiety with **2** would lead to the generation of regioisomeric 6-membered ring product *e.g.* **4a** or 7-membered ring product *e.g.* **5a** *via* a 7-*endo-tet* pathway. However, formation of these products were not observed in the present case perhaps due to the better nucleophilicity of $-NR^{\ominus}$ moiety over $-O^{\ominus}$ under the condition employed and 6-*exo-tet* ring closure was preferred over 7-*endo-tet* pathway. Nevertheless, generation of harmless NaCl as the only byproduct clearly indicated greenness of this process.[19]



Scheme 3 The proposed reaction mechanism.

In conclusion, a single-step metal catalyst-free method has been developed for the general synthesis of racemic *N*-unsubstituted/substituted (3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol derivatives in good yields. This simple, mild and practical method involves the reaction of 2-aminophenols with (±)-epichlorohydrin in the presence of NaOH in water at room temperature. The methodology showed high regioselectivity and wider sustrate scope to afford *N*-unsubstituted/substituted derivatives and expected to find applications in accessing related bioactive small organic molecules or intermediates.

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14 (*a*) Spectral data of compound **3a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.65–6.62 (m, 2H), 6.56–6.54 (m, 1H), 6.47–6.43 (m, 1H), 5.67 (s, 1H), 4.91 (t, J = 6.0 Hz, 1H), 3.96–3.94 (m, 1H), 3.60–3.56 (m, 1H), 3.51–3.48 (m, 1H), 3.35–3.34 (m, 1H), 3.04–3.01 (m, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 142.8, 134.4, 120.7, 116.7, 115.8, 114.5, 74.2, 61.5, 41.6. IR ($CHCl_3$): 3419, 3019, 2928, 2400, 1609, 1502, 1215, 928 cm^{-1}; mass: m/z (ES): 166.08 (M + H, 100%); HRMS: m/z (M + H) calcd for $C_9H_{12}NO_2$: 166.0868; found: 166.0866; (*b*) M. E. Garcia-Rubino, M. C. Nunez, M. A. Gallo and J. M. Canpos, *RSC Adv.*, 2012, **2**, 12631; (*c*) compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, J = 8.1 Hz, 1H), 6.75 (t, J = 8.1 Hz, 1H), 6.66 (t, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 4.17–4.25 (m, 1H), 3.83 (dd, J = 11.8, 4.4 Hz, 1H), 3.77 (dd, J = 11.8, 5.9 Hz, 1H), 3.35 (dd, J = 11.8, 2.9 Hz, 1H), 3.28 (dd, J = 11.8, 7.3 Hz, 1H); see ESI for the copy of the spectra.

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16 (*a*) Scale-up procedure: to a mixture of 2-aminophenol **1a** (5 g, 0.045 mol) in water (40 mL, 8 vol) was added sodium hydroxide (2.56 g, 1.4 equiv.) and the mixture was stirred for 15 min to get a clear solution. To this was added (±)-epichlorohydrin **2** (5.08 g, 1.2 equiv.) and stirring continued at room temperature for another 20 min. After completion of the reaction (indicated by TLC) the mixture was allowed to settle for 10 minutes. The upper aqueous layer was decanted out from the oil separated and the crude product was directly taken for chromatographic purification to give the desired compound; (*b*) It appeared that the products **3a–e** were not separated from the aqueous layer after completion of the reaction when the reaction was performed at lower scale (*e.g.* 1 mmol of **1**) and therefore usual work-up procedure was necessary in these cases. However, this step can be avoided when the reaction is performed at higher scale.

17 Formation of dianion from *N*-substituted 2-aminophenol under equilibrium conditions has been described earlier, see: (*a*) K. S. Min, T. Weyhermuller and K. Wieghardt, *Dalton Trans.*, 2004, 178; (*b*) A. Mukherjee and R. Mukherjee, *Indian J. Chem.*, 2011, **50**, 484.

18 (*a*) F. Z. Dörwald, *Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design*, WILEY-VCH Verlag GmbH & Co, KGaA, Weinheim, 2005, ch. 6, pp. 237–238; (*b*) The earlier method (see ref. 11) involved a Lewis acid assisted addition of amino group of 2-(benzylamino)phenol to the epichlorohydrin to give the corresponding chloro alcohol which initially on base-induced cyclization afforded an epoxide derivative and then on intramolecular ring closure involving the phenolic hydroxy group afforded the desired product.

19 (*a*) We also examined the recovery and reuse of solvent water used in the present reaction. Accordingly, the aqueous part was recovered from the reaction of entry 6 of Table 1 (after neutralizing with dil HCl and extracting the reaction mixture with EtOAc) and reused without removal of dissolved NaCl. After the first recycle of aqueous part it was recovered once again and reused. The desired product **3a** was isolated in 67% and 64% yield after the first and second recycles of the aqueous part, respectively compared to 70% yield after its first use, entry 6 of Table 1; (*b*) Removal of dissolved NaCl from water can be performed by using a number methods, see for example: A. D. Khawaji, I. K. Kutubkhanah and J. M. Wie, *Desalination*, 2008, **221**, 47.