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Synthesis of 3,6-epoxy[1,5]dioxocines from 2-hydroxyaromatic benzaldehydes ☆

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ABSTRACT

Convenient and facile one step synthesis of medicinally relevant new 3,6-epoxy[1,5]dioxocines from 2-hydroxyaromatic benzaldehydes is described. The scope of the method was validated by examining the use of both electron rich and electron-deficient 2-hydroxyaromatic benzaldehydes.

Dioxocines are synthetic intermediates in the preparation of a variety of organic compounds of medicinal interest. The dehydrating dimerization of salicylaldehydes is known to furnish 6*H*,12*H*-6,12-epoxydibenzo[*b*,*f*][1,5]dioxocins[1] which upon further functionalization, could be converted to preussomerin family of natural products, which were first isolated from the coprophilous fungus *Preuussia Isomera*.[2] Furthermore, some 12*H*-dibenzo[*d*,*g*][1,3]dioxocin derivatives have also been investigated for their antidyslipidemic activity. In fact, it is interesting to note that such a structure, is necessarily related to their pharmacological activity and is present in many biologically active natural products. Figure 1 shows the chemical structures of some naturally occurring potent dioxocine derivatives.[3,4]

Due to their interesting biological activities, various diverse synthetic strategies have been developed for the synthesis of these compounds.[5–8] Their synthesis is associated with many drawbacks such as the use of potentially hazardous catalyst, application of costly reagents, sophisticated reaction conditions, unwanted side products, poor yield and some starting materials that are not readily available. On the other hand, recently Getautis co-workers have reported an one-pot method for the synthesis of 3,6-epoxy[1,5]dioxocines, catalysed by the phase transfer catalyst (benzyl triethylammonium chloride) condensation of electron-deficient salicylaldehydes with epichlorohydrin, but this method has limitations like longer reaction times (60 h) and is applicable for electron-deficient salicylaldehydes only.[9] So there is scope to develop a convenient and general approach towards the synthesis of 3,6-epoxy[1,5]dioxocines. Herein, we wish to report a facile and general method for the preparation of new substituted 3,6-epoxy[1,5]dioxocines in good yields by the Et_3N catalysed reaction of epichlorohydrin with both electron rich and electron-deficient salicyl aldehydes.

Et_3N is quite economical, eco-friendly and a mild base that can also avoid the problem of side reactions in base-sensitive substrates. It has been demonstrated that this commercially available base could be used as an efficient catalyst for the synthesis of a wide variety of organic compounds.[10–24]

An initial study was performed by the treatment of 4-hydroxy-5-methylisophthalaldehyde **1a**, with epichlorohydrin in the presence of a catalytic amount of potassium carbonate at ambient temperature. Initially, we observed the formation of two products (TLC monitoring during the course of the reaction) that differed slightly in their polarity. As the reaction time increased, the more polar product gradually got converted (TLC monitoring) in to the less polar one. It is apparent that compound **1aa** undergoes intramolecular cyclization, which results in the formation of the stable 3,6-epoxy[1,5]dioxocines **2a**. Complete conversion and 80% isolated yield were obtained after 8 h. The synthetic approach is depicted in Scheme 1.

Encouraged by these results, we screened several different bases (organic and inorganic) as catalyst for the reaction of 4-hydroxy-5-methylisophthalaldehyde **1a**, with epichlorohydrin. The results are shown in Table 1. Much to our delight, Et_3N was found to be an excellent catalyst to catalyse the reaction. It not only shortens the reaction time but also provides excellent yields. To the best of our knowledge, there are no reports of Et_3N-catalysed synthesis of 3,6-epoxy[1,5]dioxocines.

To optimize the Et_3N requirements, 0.5, 0.75, 1.0 and 1.5 mmol (entries 5–8 in Table 1) were employed, and the best results were

☆ Part VI in the series, 'Studies on Novel Synthetic Methodologies'.

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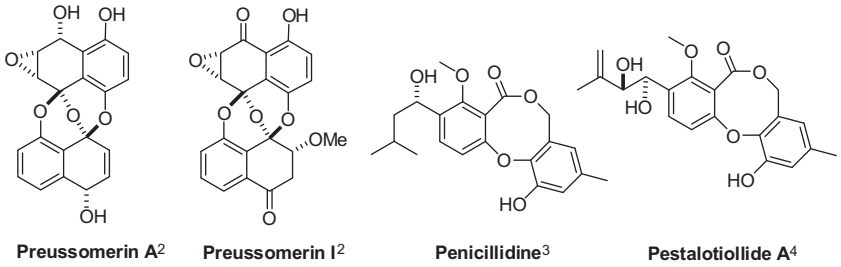
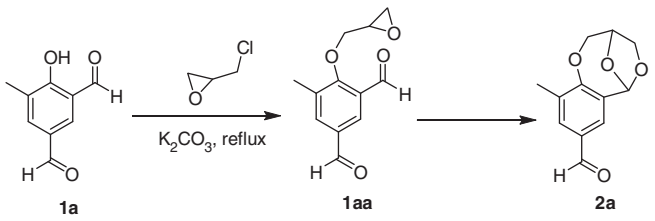
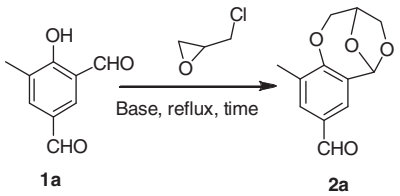


Figure 1. Structures of some naturally occurring potent dioxocine derivatives.



Scheme 1. Synthesis of 3,6-epoxy[1,5]dioxocines **2a**.

Table 1
Optimization of reaction conditions for the synthesis of 3,6-epoxy[1,5]dioxocines **2a**



Entry	Product	Base (mmol)	Time (h)	Yield (%)
1	**2a**	K_2CO_3 (1.0)	8.0	80
2	**2a**	KOH (1.0)	6.0	72
3	**2a**	$NaHCO_3$ (1.0)	30.0	65
4	**2a**	DABCO (1.0)	2.0	84
5	**2a**	Et_3N (1.5)	0.8	84
6	**2a**	Et_3N (1.0)	1.0	88
7	**2a**	Et_3N (0.75)	1.0	93
8	**2a**	Et_3N (0.5)	1.2	86
9	**2a**	*N*-Methylmorpholine (1.0)	1.1	92

obtained with 0.75 mol of Et_3N at reflux in terms of yield and time duration (entry 7 in Table 1). In the absence of Et_3N, the reaction did not proceed. Initially, the reaction was attempted with different solvents (ethanol, DCM, DMF) but the yields were found to be better in the absence of any solvent as shown in Table 2 (entry 4).

With this finding, we examined the applicability of this catalytic system to various substituted 2-hydroxyaromatic benzaldehydes, possessing electron-donating or electron-withdrawing substituents and all afforded the desired products in very satisfactory yields. A variety of new 3,6-epoxy[1,5]dioxocines were synthesized in a one-step process in good to high yields in the presence of Et_3N under reflux to afford the respective products. The representative results are shown in Table 3. Substituents on the salicylaldehydes had little influence both on the yield and the time of the reaction. Interestingly, electron-deficient 2-hydroxyaromatic benzaldehydes underwent faster condensation with epichlorohydrin compared to neutral and electron rich 2-hydroxyaromatic benzaldehydes to afford the respective products.

To demonstrate the generality and the applicability of the optimized reaction conditions to other more complex molecules, that is, electron rich 2-hydroxyaromatic benzaldehydes containing chalcone moiety at *para*-position was utilized for the reaction. These derivatives (**1k**–**p**) readily condensed with epichlorohydrin to form their corresponding 3,6-epoxy[1,5]dioxocines (**2k**–**p**) in good to excellent yields, indicating that this reaction is quite general and has very broad substrate scopes. These chalcones (**1k**–**p**) were obtained from the condensation reaction of respective 2-hydroxyaromatic dicarbaldehydes with acetophenones (Table 3).[25]

This reaction is clean and free from side reactions, such as self-condensation of aldehydes, which are normally observed under basic conditions. It is apparent that the polycyclic compound formed is the result of intramolecular cyclization of the initial adduct formed by the reaction of epichlorohydrin on the phenol. This was also confirmed by the fact that we could isolate the intermediate formed during the early course of the reaction. The structures of the products were established from their spectroscopic (IR, ^1H NMR, ^{13}C NMR, 2D NMR and elemental analysis or HRMS) data.[26]

Table 2
Optimization of reaction solvents

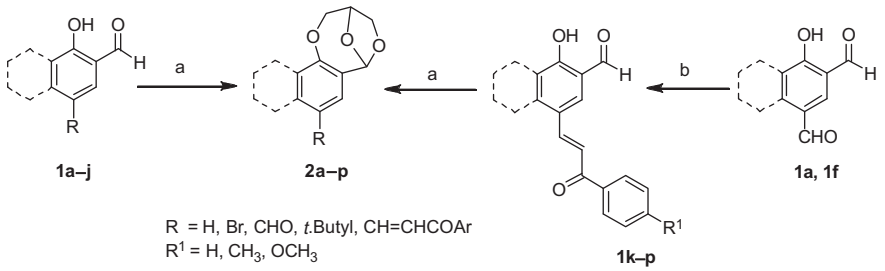
Entry	Product	Solvent	Time (h)	Yield (%)
1	**2a**	Ethanol	3.5	72
2	**2a**	DCM	2.5	76
3	**2a**	DMF	3.0	68
4	**2a**	Neat	1.0	93

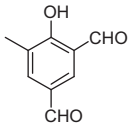
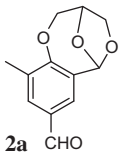
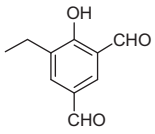
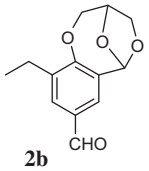
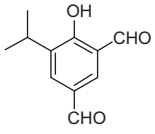
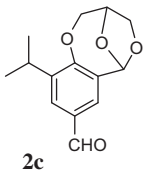
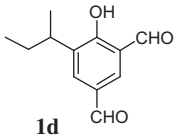
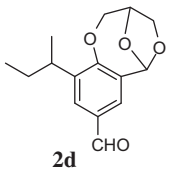
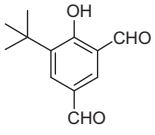
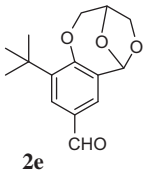
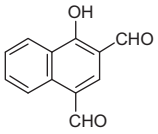
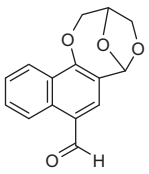
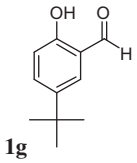
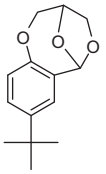
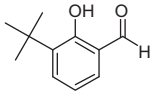
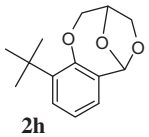
The isolated product was found to be a mixture of two enantiomers, in which the chiral centres have *R*,*S* and *S*,*R* configuration.[9]

To the best of our knowledge, there is only one report of the condensation of salicylaldehydes and epichlorohydrin, using benzyl triethylammonium chloride as PTC to form 3,6-epoxy[1,5]dioxocines.[9] The reaction was conducted in the presence of PTC and required a long time (60 h). Moreover, electron rich salicylaldehydes failed to give the desired product under the reaction conditions employed.

In conclusion, we have demonstrated here a simple, and efficient route for the synthesis of 3,6-epoxy[1,5]dioxocines utilizing Et_3N as a catalyst. This method not only provides an excellent complement to dioxocines synthesis, but also avoids the use of hazardous acids or bases and harsh reaction conditions. The advantages of this method include good substrate generality, the use of inexpensive reagents/catalyst and experimental operational ease. The functional groups such as aldehyde and α–β unsaturated carbonyl

Table 3
Et_3N mediated general synthesis of 3,6-epoxy[1,5]dioxocines



Entry	Reactant	Product	Time (min)	Yield[a] (%)	Mp (°C)
1	 **1a**	 **2a**	60	93	98–100
2	 **1b**	 **2b**	65	91	98–100
3	 **1c**	 **2c**	65	92	80–82
4	 **1d**	 **2d**	70	91	78–80
5	 **1e**	 **2e**	70	92	105–107
6	 **1f**	 **2f**	70	90	182–183
7	 **1g**	 **2g**	85	89	145–147
8	 **1h**	 **2h**	90	88	140–142

(*continued on next page*)

Table 3 (*continued*)

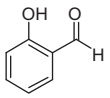
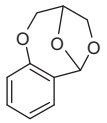
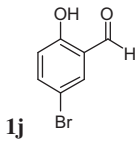
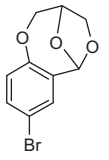
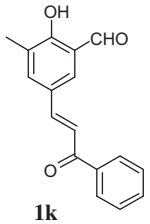
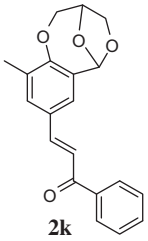
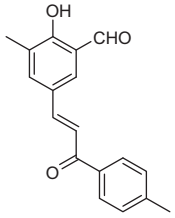
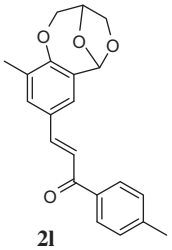
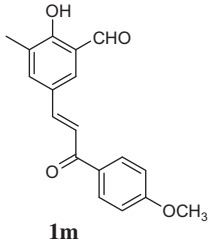
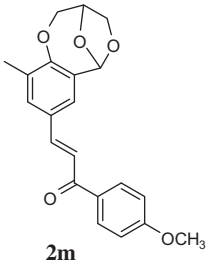
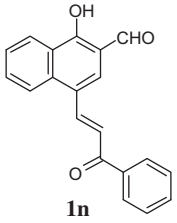
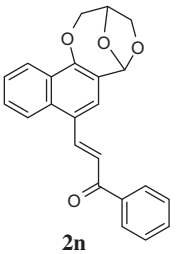
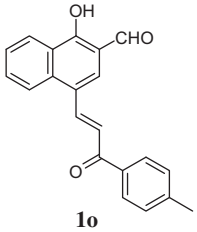
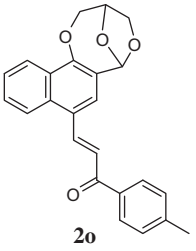
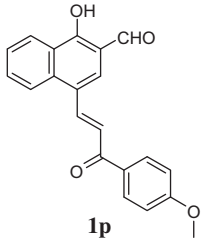
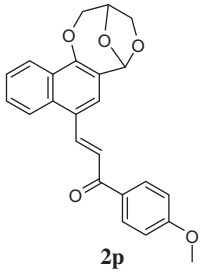
Entry	Reactant	Product	Time (min)	Yield[a] (%)	Mp (°C)
9	 **1i**	 **2i**	75	90	Oily
10	 **1j**	 **2j**	45	93	Oily
11	 **1k**	 **2k**	65	92	120–122
12	 **1l**	 **2l**	65	90	142–143
13	 **1m**	 **2m**	65	91	140–142
14	 **1n**	 **2n**	70	89	132–134
15	 **1o**	 **2o**	70	90	137–138

Table 3 (*continued*)

Entry	Reactant	Product	Time (min)	Yield[a] (%)	Mp (°C)
16	 **1p**	 **2p**	70	87	174–175

Reagents and conditions: (a) Epichlorohydrin, Et_3N, reflux, 45–90 min; (b) concd HCl, *p*-$R^1C_6H_4COCH_3$, dioxane, 80–90 °C, 2.5–3.5 h.
[a] Isolated yields.

groups are tolerated under the reaction conditions to provide structurally interesting 3,6-epoxy[1,5]dioxocines in high yields.

Acknowledgments

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Supplementary data

Supplementary data (spectral data of all the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.095.

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26. *General procedure for the synthesis of 3,6-epoxy[1,5]dioxocines* (**2a**–**p**): A solution of 2-hydroxyaromatic benzaldehydes (3.0 mmol) was dissolved in excess of epichlorohydrin to which Et_3N (2.3 mmol) was added and the reaction mixture was then refluxed for 45–90 min. After completion of the reaction, excess of epichlorohydrin was removed under reduced pressure. The solid residue was poured in water and extracted threefold with 20 mL of $CHCl_3$. The combined organic layers were dried on Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The crude products were purified over column chromatography (60–120 mesh) to afford final compounds. The representaive spectral data of the compound (**2a**) is given: white solid; mp 98–100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.88 (s, 1H), 7.67 (s, 1H), 7.60 (s, 1H), 6.10 (s, 1H), 4.72–4.69 (m, 1H), 4.47–4.42 (m, 1H), 4.31 (d, J = 6.8 Hz, 1H), 4.04–3.96 (m, 2H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.0, 160.1 133.2, 133.1, 131.6, 130.8, 128.4, 105.8, 75.4, 74.1, 66.0, 16.6; IR (KBr): 3015, 1690, 1597, 1068 cm^{-1}; ESI-MS (*m/z*): 221 $(M+H)^+$. HRMS calcd for $C_{12}H_{12}O_4$ $(M+H)^+$ 221.0814. Found: 221.0815.