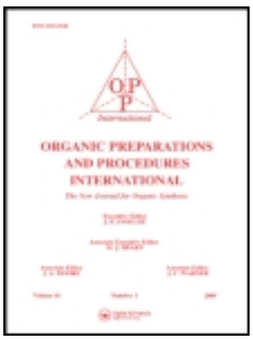

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Benzoxazinone Intermediate for the Synthesis of Deferasirox. Preparation of Deferasirox

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Deferasirox (Exjade, ICL-670A), 4-[3,5-*bis*(2-hydroxyphenyl)-*1H*-1,2,4-triazol-1-yl]benzoic acid (**6**), is an iron chelator developed for the treatment of chronic iron overload in patients who are receiving long-term blood transfusions for conditions such as *beta*-thalassemia and other chronic anemias.[1–7] It is the first orally administered medication approved for this purpose by USFDA in November 2005.[8] Its pharmacokinetic profile shows *deferasirox* to be effective in convenient, once-daily oral administration schedule, as it can provide 24 h chelation coverage in patients with transfusion-dependent anemias. *Deferasirox* (*Figure 1*) contains two phenolic oxygens and triazole nitrogens acting as a tridentate ligand that chelate Fe(III).[9–12] Tridentate chelators require two ligand molecules to bind one iron atom.

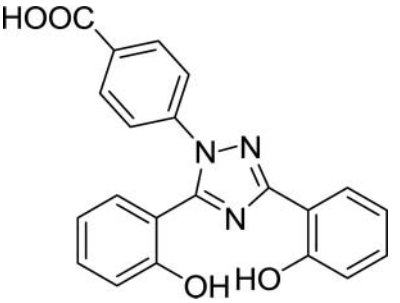

Figure 1 Structure of *Deferasirox* (**6**)

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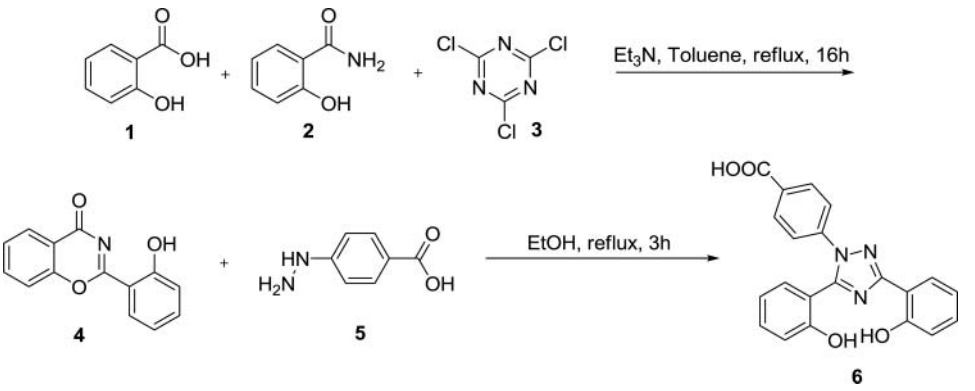
The 1,2,4-triazole ring substituted with three aryl groups is the key structural motif of deferasirox. Although a number of efficient triazole syntheses have been described,[13–18] direct access to appropriately functionalized 1,2,4-triazole rings is a difficult challenge as the nature of the substituents limits the availability of readily accessible starting materials and typically requires multi-step sequences. Staben and Blaquiere reported a four-component condensation of fully substituted 5-aryl-1,2,4-triazoles by carbonylative heterocyclization of aryl halides.[19] This route allows regioselective access to a 5-triazolyl heterobiaryl linkage without the need to use organometallic reagents and through reactive acylamidine intermediates. Paulvannan *et al.* investigated the four-step synthesis of 1,3,5-trisubstituted 1,2,4-triazole *via* a silver carbonate-mediated cyclization of a triazole as the key step. This approach proved to be compatible with a wide range of functional groups and amenable to scale-up as well.[20] Recently, Staben *et.al* developed a highly regioselective one-pot process for the preparation of 1,3,5-trisubstituted 1,2,4-triazoles from the reaction of carboxylic acids, primary amidines, and mono substituted hydrazines in moderate yields.[21]

To the best of our knowledge, the most commonly employed route for the production of *deferasirox* is the two-step procedure that has been reported by several research groups.[9,22–24] The first step involves the condensation of inexpensive substrates, namely salicylic acid (**1**) with salicylamide (**2**) using thionyl chloride in the presence of pyridine at reflux in xylene to give 2-(2-hydroxyphenyl)benz[e][1,3]oxazin-4-one (**4**) as a solid in yield (50–55%). In a second step, compound **4** is treated with 4-hydrazinobenzoic acid (**5**) in boiling ethanol to afford *deferasirox* in high yield (80%). Although this method seems to be the most efficient procedure in terms of readily available and inexpensive starting materials and its suitability to scale-up, the major problem for the larger-scale production lies in the fact that the preparation of intermediate **4** utilizes highly corrosive thionyl chloride at high temperatures making this process extremely dangerous and difficult to use on an industrial scale.

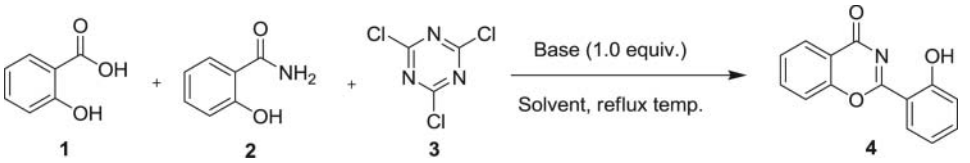
The great demand for pure benzoxazinone **4** has prompted us to investigate other effective chlorinating agents. In addition of thionyl chloride, there are a number of chlorinating agents that could be applied for this process, such as $AlCl_3$+$SOCl_2$, PCl_3, PCl_5, oxalyl chloride and DMF, Ph_3P and CCl_4, phosgene and triphosgene.[25–27] However, those reagents are also toxic and the purification of the crude products is often problematic, time-consuming, tedious and inconvenient.

Recently, cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, **3**) has been used extensively as a highly efficient chlorinating agent in a number of reactions.[28–38] It is a relatively inexpensive and easily handled solid compared to all of the chlorinating reagents



Scheme 1 Synthetic Route to *deferasirox* (**6**) Using Cyanuric Chloride.

Table 1
Optimization Reaction Conditions for the Synthesis of 2-(2-Hydroxyphenyl)benz[e][1,3] oxazin-4-one



1 2 3 4

Entry	**1** (equiv.)	**2** (equiv.)	**3** (equiv.)	Time (hr.)	Solvent	Base	Isolated yield (%)
1	1.0	1.0	1.0	3	Xylene	Et_3N	15
2	1.0	1.0	1.0	16	CH_2Cl_2	Et_3N	<10
3	1.0	1.0	1.0	3	Toluene	Et_3N	22
4	1.0	0.85	1.0	3	Toluene	Et_3N	23
5	0.85	1.0	1.0	3	Toluene	Et_3N	20
6	1.0	0.85	0.33	3	Toluene	Et_3N	<10
7	1.0	0.85	0.4	3	Toluene	Et_3N	11
8	1.0	0.85	0.5	3	Toluene	Et_3N	27
9	1.0	0.85	0.6	3	Toluene	Et_3N	30
10	1.0	0.85	0.67	3	Toluene	Et_3N	36
11	1.0	0.85	0.7	3	Toluene	Et_3N	35
12	1.0	0.85	0.8	3	Toluene	Et_3N	30
13	1.0	0.85	0.9	3	Toluene	Et_3N	26
14	1.0	0.85	0.67	3	Toluene[a)]	Et_3N	38
15	1.0	0.85	0.67	6	Toluene[a)]	Et_3N	42
16	1.0	0.85	0.67	16	Toluene[a)]	Et_3N	54
17	1.0	0.85	0.67	16	Toluene[a)]	DIPEA	21
18	1.0	1.0	1.0	16	Toluene[a)]	DIPEA	13
19	1.0	0.85	0.67	16	Toluene[a)]	DBU	41
20	1.0	1.0	1.0	16	Toluene[a)]	DBU	37

[a)]Using a Dean-Stark trap to remove water.

mentioned above. Thus, an alternative process utilizing mild reaction conditions using cyanuric chloride was devised for this purpose as shown in *Scheme 1*. Compound **4** was characterized using infrared spectroscopy (FT-IR), nuclear magnetic resonance (NMR), mass spectroscopy (MS) and the purity of the product was confirmed using high performance liquid chromatography (HPLC).

Table 1 (*Entries 1–13*) shows the results of our initial investigation of reaction conditions for the preparation of compound **4**. The proper selection of non-polar solvents was one of the most important factors since it could help in the isolation of the product **4** from the relatively less toxic, bio-degradable by-product, *i. e.* cyanuric acid derivatives in the purification step after the completion of the reaction. Toluene was found to be the solvent of choice. Exactly 0.67 equiv. of cyanuric chloride (with respect to the acid) was required to obtain the highest yield (36%) of **4** (*Entry 10*). The yield was not significantly improved either by increasing or decreasing the amount of cyanuric chloride. However, the yield was improved to 54% by carrying out the reaction at higher temperatures for

16 h with the use of a Dean-Stark trap for the removal of water formed (*Table 1, Entries 14–20*). Other hindered bases (*N,N*-diisopropylethylamine, DIPEA and 1,8-diazabicycloundec-7-ene, DBU) were tested but the best results were obtained with triethylamine as the base (*Table 1*).

The purification of the products can often be problematic in organic chemistry. The most efficient method for the purification of solids is by recrystallization from a suitable solvent system. In our case, the product **4** was isolated as a pale-yellow solid with precipitation occurring after a short period of time. The crude product may be recrystallized from ethanol, with the optimal crystallization depending on the amount of ethanol used.[39]

The resulting pure compound **4** was then treated with 4-hydrazinobenzoic acid in ethanol at reflux for 3 h. using a procedure modified and improved from that reported in the literature.[24] The reaction mixture was then cooled to room temperature, and the precipitated material was collected and dried under vacuum overnight. The resulting compound was recrystallized from ethanol and decolorized using charcoal to give **6** in 86% yields as a white solid.

The likely role of cyanuric chloride is to convert salicylic acid to its acid chloride which then reacted with salicylamide to give the bis-salicylimide **7** (*Figure 2*); the reaction does not proceed without triethylamine. In this case, there are two competitive reactions generating both the anhydride of salicylic acid and the acid-amide coupling product **7** that could initially be detected during the progress of the reaction. The condensation between salicyloyl chloride and salicylamide has also been carried out at higher temperature (170°C) in xylene with the higher yield of **4**.[22] However, salicyloyl choride is a highly unstable and difficult to handle and makes this method less attractive on a commercial scale. The use of the reaction conditions reported here minimizes the formation of **7** and thus leads to increased purity of final product (*deferasirox*) compared to the original procedure reported in the patent.[24]

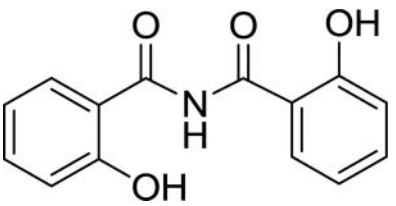


Figure 2 Structure of Uncyclized Product **7**

In summary, we have developed a milder process for preparation of 2-(2-hydroxyphenyl)benz[e][1,3]oxazin-4-one (**4**) using cyanuric chloride as chlorinating agent to give the desired product with high purity in satisfactory yield (54%). There is no requirement for chromatography in the purification steps, *i. e.* the product can be easily isolated by simple filtration. We anticipate that our approach should help facilitate the large scale synthesis of *deferasirox*. The industrial-scale production is currently being evaluated and optimized at The Government Pharmaceutical Organization in Thailand. The operational simplicity and ease of manipulation makes our method a less dangerous and more attractive protocol and amenable for scale-up for the chemical industry.

Experimental Section

All reagents were purchased from commercial available sources such as Aldrich or Fisher and used without further purification. ^{1}H and ^{13}C magnetic resonance spectra were recorded on a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts are reported in δ (ppm) from tetramethylsilane with the solvent resonance as an internal standard. Data are listed as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz). FT-IR spectra were obtained on a Perkin Elmer RXI spectrometer. High resolution ESIMS data were recorded on a Bruker MicrO-TOF mass spectrometer. Melting points were determined on a Mettler Toledo MP 90.

Synthesis of 2-(2-hydroxyphenyl)-benz[e][1,3]oxazin-4-one (4)

In a round bottom flask fitted a reflux condenser and a Dean-Stark trap, a suspension of salicylic acid (27.6 g, 0.2 mol), salicylamide (23.3 g, 0.17 mol) and 2,4,6-trichloro-1,3,5-triazine (24.8 g, 0.134 mol) in 600 mL toluene was heated under a nitrogen atmosphere for 30 minutes at 80°C. Then triethylamine (28.08 mL, 0.2 mol) was added slowly to the solution and the resulting mixture was heat to reflux for 16 h. Precipitation of some solid began to occur during the reaction; the reaction mixture was cooled to about 80°C and then filtered hot (by suction) as quickly as possible to remove the solid mixture of triethylamine hydrochloride, cyanuric acid and other solids. The filtrate was then evaporated and the resulting crude solid was recrystallized[39] from ethanol (600 mL) to give 21.9 g (54% yield) of benzoxazinone **4** in better than 98% purity as a very pale yellow solid. All spectroscopic data of product **4** matched those of an authentic sample.

Compound **4**, mp 202.5–204.2°C, (*lit.*[22] mp. 203–204°C); FTIR (KBr): 1704, 1614, 1540, 1355, 1245, 765, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.96 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.48–7.52 (m, 3H), 7.75–7.79 (m, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.17 (t, J = 7.0 Hz, 1H), 12.68 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 113.9, 119.7, 120.9, 121.5, 122.2, 129.9, 130.5, 131.4, 138.4, 139.5, 156.8, 165.8, 166.6, 167.8; HRMS: Calcd for $C_{14}H_9NO_3Na$ ($M+Na^+$) 262.0475. Found: 262.0476.

Synthesis of Deferasirox (6)

A solution of compound **4** (2.39 g, 10 mmol) and 4-hydrazinobenzoic acid (1.67g, 11 mmol) was heated with stirring in 30 mL ethanol for 3 h at reflux. The reaction mixture was then cooled to room temperature; the precipitated solid was collected and dried under vacuum overnight. Recrystallization and decolorization with activated charcoal in ethanol afforded 3.21 g (86% yield) of deferasirox (**6**) as a white solid. All spectroscopic data of product **6** matched those of an authentic sample.

Compound **6**, mp. 261–263°C, (*lit.*[40] mp. 259–261°C);^{1}H NMR (DMSO-d_6): δ 6.81 (d, J = 8.0 Hz, 1H), 6.91–6.98 (m, 3H), 7.30–7.35 (m, 2H), 7.50 (d, J = 8.5 Hz, 3H), 7.94 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 6.5 Hz, 1H), 9.99 (s, 1H), 10.75 (s, 1H), 13.15 (s, 1H); HRMS: Calcd. for $C_{21}H_{16}N_3O_4$ ($M+H^+$): 374.1135. Found: 374.1132.

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39. While the purification of **4** may be performed by the normal procedure to determine the "ideal" volume of solvent, we have determined that the ideal volume of ethanol to be used for crystallization of **4** should be based on the amount of the starting salicylamide used. In our present reported procedure, it is 0.28 M of salicylamide (600 mL of ethanol). A concentration higher than 0.28 M leads to less pure material while lower number gives lower yields.

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