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Environmentally Benign Large-Scale Synthesis of a Precursor to Vortioxetine

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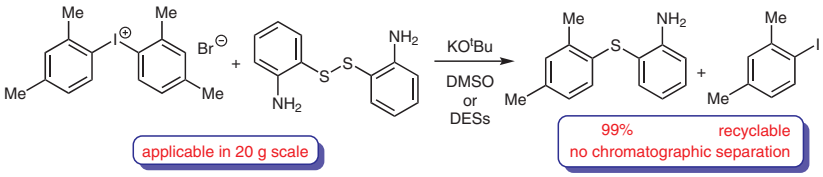

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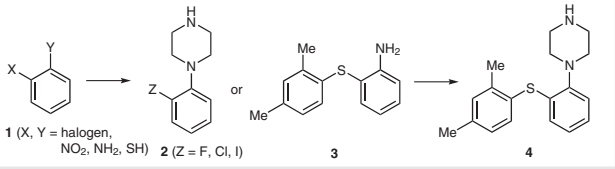
Abstract An eco-friendly, high-yielding, and transition-metal-free synthesis of 2-[(2,4-dimethylphenyl)thio]aniline precursor to vortioxetine is reported. Vortioxetine, a multi-modal acting drug with high affinity for a range of serotonergic targets, is used for the treatment of major depressive disorder (MDD). The synthesis – applicable in multi-gram scale – involves the reaction of bis(2,4-dimethyl)iodonium bromide with commercial 2-aminophenyl disulfide, whereas its reaction with 2-aminothiophenol afforded the same product but in low to moderate yields. This method works equally well in deep eutectic solvents (DESs), based on choline chloride (ChCl).

Key words iodonium salts, vortioxetine, major depressive disorder, green chemistry, deep eutectic solvents, hypervalent iodine

Vortioxetine (**4**), a multi-modal acting drug with high affinity for a range of serotonergic targets, was first prepared in 2007[1] and is now on the market for the treatment of major depressive disorder (MDD). This is a prevalent disease that is considered by the World Health Organization (WHO) to be one of the leading causes of disability worldwide.[2] The emergence of vortioxetine aroused the strong interest of pharmaceutical companies and researchers, and a large number of patents and publications regarding its preparation appeared in the literature,[3] as summarized in Scheme 1.



Scheme 1 General scheme summarizing the existing syntheses of vortioxetine (**4**)

In general, all syntheses start from a 1,2-disubstituted benzene derivative with the generation of aromatic carbon–heteroatom bond, usually through transition-metal-assisted nucleophilic aromatic substitution. This is a major drawback for industrial production of vortioxetine making urgent the development of environmentally more friendly syntheses.

Recently, a number of elegant short preparations of vortioxetine appeared in the literature. In 2015, Greaney et al.[4] prepared this molecule by a tandem S- and N-addition to benzyne, using 2-iodophenyl arylsulfonates as benzyne precursors. However, the synthesis requires quite expensive materials, low temperatures, and the use of CuCl as a catalyst. In 2017, Diness et al.[5] reported a general method for transition-metal-free N-arylation of amines, also applicable for the preparation of vortioxetine. Starting from 1,2-difluorobenzene, the dimethylphenylsulfanyl group was introduced by a direct S_NAr reaction, followed by displacement of the second fluorine atom with piperazine and LiHMDS in refluxing THF. More recently, Biju et al.[6] developed a transition-metal-free thioamination of arynes using sulfonamides. Treatment of the benzyne generated in situ from 2-(trimethylsilyl)phenyl triflate (using excess CsF) with N-Boc-protected 1-[(2,4-dimethylphenyl)thio]piperazine in DME as solvent, followed by deprotection led to the formation of vortioxetine. In 2020, Jafarpour et al.[7] reported an iodine-mediated oxidative cross-coupling reaction of arylhydrazines and thiols for construction of thioethers in the absence of any transition metals or photocatalysts and this method was applied in the synthesis of the key structure of vortioxetine.

From the existing data, it can be concluded that the most difficult step is the formation of aromatic thioether.[8] Looking for an eco-friendly method for large scale synthesis of vortioxetine, our attention was turned to diaryl iodonium salts,[9] which recently gained growth interest as arylating

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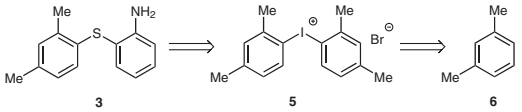
agents. For our purpose, they could be suitable reagents for construction of the unsymmetrical sulfide **3**, which then could be readily converted to vortioxetine by the existing methods.

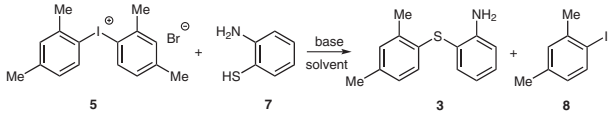
According to our retrosynthetic analysis, compound **3** could be prepared from the symmetrical iodonium salt **5** (Scheme 2). We reasonably supposed that reaction of **5** with commercial 2-aminothiophenol (**7**) could afford the desired target along with iodoxylene by-product **8**, which could be recycled to **5** by known procedures[10] diminishing thus mass wastage. Diaryl iodonium salts have been reported in the literature[11] to react with thiols and thioethers in metal-free conditions to afford aryl sulfides.



Scheme 2 Retrosynthesis of **3**, the precursor to vortioxetine

To this end, we decided to use the iodonium bromide **5** (Table 1), as an easily accessible compound from inexpensive starting materials.[12] It was prepared according to the literature, by reaction of *m*-xylene with $NaIO_4$ in a glacial AcOH/concd H_2SO_4 mixture and subsequent addition of KBr, a process applicable in multi-gram scales. Then, we investigated the reaction of iodonium bromide **5** with 2-aminothiophenol (**7**; 2 equiv) and a base (2 equiv) at room temperature in a solvent given in Table 1.

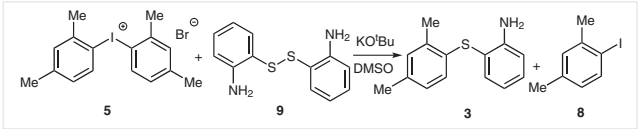
Table 1 Reaction of Iodonium Bromide **3** with 2-Aminothiophenol (**7**)



Entry	Solvent	Base	Time (h)	**3** Yield (%)	**8** Yield (%)
1	THF	NaH	0.5	57	99
2	toluene	NaH	2	45	99
3	DMSO	NaH	2	50	86
4	THF	NaOMe	2	28	73
5	toluene	NaOMe	4	47	92
6	DMSO	NaOMe	2	30	93
7	MeOH	NaOMe	12	32	95
8	DMSO	NaOH	2	30	93
9	toluene	Et_3N	12	20	99

The reaction progress was monitored by TLC and, as expected, the desired compound **3** and iodoxylene **8** were formed and separated chromatographically from 2-aminophenyl disulfide side-product **9**. Alternatively, the products were extracted with ethyl acetate and the organic layer was washed with aqueous 1.4 M HCl to remove the 2-aminophenyl disulfide side-product **9** as a hydrochloric salt and then extracted with aqueous 9 N HCl. 1-Iodo-2,4-dimethylbenzene remained in the organic layer and the desired product 2-[(2,4-dimethylphenyl)thio]aniline (**3**) was isolated from the aqueous phase by adjusting its pH to 7. However, the yields of sulfide **3** were low to moderate, the best of them being obtained under the conditions of Table 1 entry 1, making the method unsuitable for industrial production.

Searching in the literature,[13] we found that unsymmetrical diaryl sulfides can be prepared by a potassium *tert*-butoxide-mediated reaction of aryl disulfides[14] with aryl bromides. This finding prompted us to try the reaction of iodonium bromide **5** with the commercial disulfide **9** (Scheme 3). Since, as reported,[13] the reaction of aryl bromides proceeds via a benzyne formation by the action of potassium *tert*-butoxide to the aryl bromides, leading to the formation of regioisomers, we excluded from the beginning the use of iodide **8** or the respective bromide as starting materials, hoping that such an undesirable pathway would be avoided in the case of much more reactive iodonium bromide **5**.

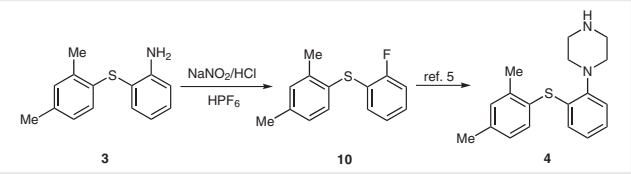


Scheme 3 Synthesis of the unsymmetrical sulfide **3** from iodonium salt **5** and disulfide **9**

To our satisfaction, when potassium *tert*-butoxide (1.25 equiv) was added portionwise to a DMSO solution of iodonium bromide **5** (in a 10 g scale) and **9** (0.5 equiv; molar ratio **5**:**9** = 2:1) and the resulting mixture was initially stirred at 40–45 °C for 15 minutes and then heated at 80 °C for 3 hours, the desired product **3** was isolated in quantitative yield (99%) (Scheme 3). Exactly the same were the results in a 20 g scale. The iodoxylene by-product **8** formed can be recycled to **5** by a known procedure.[10]

Interestingly, after experimentation, we found that compound **3** can be isolated from the reaction mixture without using any chromatographic method, as follows: the mixture was poured into ethyl acetate and then extracted with aqueous 9 N HCl. Iodoxylene **8** was obtained from the organic layer, whereas 2-[(2,4-dimethylphenyl)thio]aniline (**3**) was taken from the aqueous phase by adjusting its pH to 7, with addition of solid $NaHCO_3$ and further extraction with ethyl acetate (99%).

In addition to the known methods of preparing vortioxetine (**4**) from **3**, we tried another approach, involving conversion of **3** to the fluoro analogue **10** (Scheme 4). Indeed, conventional diazotization of the amino group in **3**, followed by treatment with HPF_6 afforded the known fluoro compound **10**, which is known to give vortioxetine,[5] upon reaction with piperazine and LiHMDS in refluxing THF.



Scheme 4 Alternative approach to vortioxetine (**4**)

The synthesis of 2-[(2,4-dimethylphenyl)thio]aniline (**3**) was also successful when the reaction was carried out in deep eutectic solvents (DESs). Over the past decades an ongoing effort focuses in the replacement of hazardous volatile organic solvents by alternatives, which do not emit flammable or toxic vapors at a wide range of temperatures. In 2001, Abbott et al.[15] introduced DESs based on choline chloride (ChCl), low cost mixtures with similar physical properties and behavior to ionic liquids, as an alternative medium. Type III eutectics employed for our purpose are formed from choline chloride and hydrogen bond donors, such as urea and glycerol. These liquids are simple to prepare and unreactive with water and they appear to have great interest due to the fact that they are considered more eco-friendly and pose useful characteristics such as low vapor pressure and the possibility of recycling.[16] For our purpose we used DES-urea, that is, the ionic compound of choline chloride/urea (1:2), and DES-glycerol, that is, the ionic compound of choline chloride/glycerol (1:2), both being prepared according to the procedures disclosed in the literature.[17]

The reactions between disulfide **9** and bis(2,4-dimethylphenyl)iodonium bromide (**5**) in DESs was carried out in a sealed tube by adding KO*t*-Bu portionwise at 40–45 °C and then the mixture was heated at 80 °C for 3 hours. Products **3** and **8** were obtained upon addition of the resulting mixture to water and extraction with ethyl acetate and separated as above.

In conclusion, we have developed an eco-friendly high yielding and transition-metal-free synthesis of 2-[(2,4-dimethylphenyl)thio]aniline precursor to vortioxetine, a multi-modal acting drug with high affinity for a range of serotonergic targets, which is now on the market for the treatment of major depressive disorder. The synthesis – applicable in multi-gram scale – involves the reaction of bis(2,4-dimethyl)iodonium bromide, which is accessible from *m*-xylene, with commercial 2-aminophenyl disulfide, whereas its reaction with 2-aminothiophenol afforded the same product but in low to moderate yields. This method works equally well in deep eutectic solvents, based on choline chloride.

All reagents are commercially available and were used without further purification. Solvents were dried by standard methods. The progress of reactions was checked by TLC on Merck silica gel 60F254 glass plates (0.25 mm). The spots were visualized by heat staining with anisaldehyde in EtOH/H_2SO_4. Column chromatography was performed with Merck silica gel 60 (0.063–0.200 mm). Melting points were determined with a Kofler hot-stage microscope. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz, respectively. Chemical shift values are referenced against residual protons in the deuterated solvents, and multiplicity (standard abbreviations). *J*-values are reported in hertz (Hz).

Bis(2,4-dimethyl)iodonium Bromide (5)

m-Xylene (128 mL, 1.04 mol) was dissolved in a mixture of concd H_2SO_4 (133 mL) and glacial AcOH (933 mL) and the resulting mixture was warmed up, with stirring, to 50–55 °C. While keeping the same temperature, $NaIO_4$ (85.6 g, 0.4 mol) was slowly added portionwise over 1.5 h. The stirred mixture was kept at the same temperature 50–55 °C for another 1.5 h, then cooled to r.t. and finally poured into stirred ice/H_2O (2 L). The resulting solid was filtered off, the cold filtrates were extracted with Et_2O (4 × 800 mL) and the ethereal extracts were discarded. A solution of KBr (80 g, 0.67 mol) in H_2O (400 mL) was added to the vigorously stirred aqueous solution and after 1 day, the precipitated iodonium bromide **5** was collected by filtration and repeatedly washed with cold H_2O until the filtrates were neutral, and dried in a vacuum desiccator to give the crude product (85.7 g) in 64% yield (based on $NaIO_4$) with spectral and physical data in agreement to those reported in the literature;[12] mp 167–169 °C (Lit.[12] mp 167–169 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.2 Hz, 2 H), 7.09 (s, 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 2.58 (s, 6 H), 2.26 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.16, 140.08, 136.43, 132.22, 129.53, 121.69, 25.49, 21.15.

Reaction of Bis(2,4-dimethyl)iodonium Bromide (5) with 2-Aminothiophenol (7)

A suspension of diarylodonium salt **5** (0.150 g, 0.36 mmol), NaH (0.028 g, 0.72 mmol), and 2-aminothiophenol (**7**; 0.077 mL, 0.72 mmol) in anhyd THF (2.5 mL) was carefully flashed with argon and stirred at r.t. for 0.5 h. Upon completion of the reaction (checked by TLC), the mixture was poured into brine (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were extracted with aq 1.4 M HCl (2 × 10 mL) to remove the 2-aminophenyl disulfide side-product as a hydrochloric salt and then with aq 9 N HCl (2 × 10 mL). 1-Iodo-2,4-dimethylbenzene (**8**) was obtained from the organic layer as a pure product (0.083 g, 99%) after drying (Na_2SO_4) and evaporation of the solvent. The pH of the aqueous phase was subsequently adjusted to 7 with the addition of $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated off to give 2-[(2,4-dimethylphenyl)thio]aniline (**3**; 0.047 g, 57%) in satisfactory purity. Alternatively, the solvent of the initial EtOAc extractions was evaporated off and the residue was chromatographed on a silica gel column using hexane/EtOAc as the eluent to give first 1-iodo-2,4-dimethylbenzene (**8**), followed by 2-aminophenyl disulfide (**9**), and lastly the desired 2-[(2,4-dimethylphenyl)thio]aniline (**3**).

Reaction of Bis(2,4-dimethyl)iodonium Bromide (5) with 2-Aminophenyl Disulfide (9)

KO*t*-Bu (3.37 g, 30 mmol) was added portionwise to a solution of 2-aminophenyl disulfide (**9**; 2.98 g, 12 mmol) and bis(2,4-dimethylphenyl)iodonium bromide (**5**; 10 g, 23.9 mmol) in DMSO (50 mL), and the mixture was stirred at 40–45 °C for 15 min and then heated at 80 °C. The progress of the reaction was monitored by TLC. Upon completion of the reaction (3 h), the mixture was cooled to r.t. and poured into

EtOAc (200 mL). The organic layer was washed with brine (2 × 150 mL) and extracted with aq 9 N HCl (2 × 100 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated to give 1-iodo-2,4-dimethylbenzene (**8**) as a pure product (3.4 g, 62%). The pH of the aqueous phase containing hydrochloric salt of 2-[(2,4-dimethylphenyl)thio]aniline was adjusted to 7 with the addition of solid $NaHCO_3$ and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give 2-[(2,4-dimethylphenyl)thio]aniline (**3**) as a pure product (5.4 g, 99%) with spectral and physical data in agreement to those reported in the literature;[18] mp 34–36 °C (Lit.[18] mp 34–36 °C).

1-Iodo-2,4-dimethylbenzene (8)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.0 Hz, 1 H), 7.06 (s, 1 H), 6.70 (d, *J* = 7.9 Hz, 1 H), 2.39 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 141.00, 138.64, 138.07, 130.76, 128.34, 97.01, 27.92, 20.85.

2-[(2,4-Dimethylphenyl)thio]aniline (3)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 7.7 Hz, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.01 (s, 1 H), 6.86 (d, *J* = 7.9 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.76 (t, *J* = 7.5 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 2.39 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.38, 136.60, 135.79, 135.36, 131.74, 131.20, 130.48, 127.33, 126.60, 118.86, 115.34, 115.13, 20.82, 20.07.

(2,4-Dimethylphenyl)(2-fluorophenyl)sulfane (10)

To a cooled (5 °C), vigorously stirred solution of 2-[(2,4-dimethylphenyl)thio]aniline (**3**; 0.1 g, 0.44 mmol) in H_2O (1,3 mL) and concd HCl (0.6 mL) was added a solution of $NaNO_2$ (0.049 g, 0.572 mmol) in H_2O (1.2 mL) dropwise during 15 min. The mixture was stirred for another 30 min at the same temperature, then HPF_6 (60% solution in H_2O, 0.61 mL) was added and the mixture was heated to 100 °C for 12 h. Upon completion of the reaction, the precipitated solid was filtered off, washed with EtOAc and the organic layer was washed with brine (3 mL) and aq $NaHCO_3$ (3 mL). The organic solution was dried (Na_2SO_4) and the solvent evaporated to dryness to get a sticky residue, which was purified by column chromatography on silica gel using hexane/EtOAc (20:1) as the eluent to afford **10** (0.067 g, 65%) as an oil, with NMR spectra identical to those reported in the literature.[5]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 7.8 Hz, 1 H), 7.17–7.12 (m, 1 H), 7.11 (d, *J* = 1.7 Hz, 1 H), 7.05 (ddd, *J* = 9.9, 8.2, 1.6 Hz, 1 H), 6.98 (ddd, *J* = 8.9, 7.8, 2.0 Hz, 2 H), 6.85 (td, *J* = 7.7, 1.9 Hz, 1 H), 2.35 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.0 (d, *J* = 245.1 Hz), 141.0, 138.9, 134.4, 131.7, 130.2 (d, *J* = 1.9 Hz), 127.7, 127.6, 127.5 (d, *J* = 7.6 Hz), 124.5 (d, *J* = 3.7 Hz), 124.4, 115.5 (d, *J* = 21.7 Hz) 21.1, 20.4.

Choline Chloride-Urea (1:2) Based DES

A mixture of choline chloride (13.96 g, 100 mmol) and urea (12.01 g, 200 mmol) was heated up to 80 °C for 60 min until a clear solution was formed. The obtained DES was used without further purification.

Reaction of Bis(2,4-dimethyl)iodonium Bromide (5) with 2-Aminophenyl Disulfide (9) in DES-Urea

KO*t*-Bu (33.65 mg, 299 mmol) was added portionwise under stirring at 40–45 °C to a mixture of DES-urea (0.7 mL), 2-aminophenyl disulfide (**9**; 29.8 mg, 119 mmol), and bis(2,4-dimethylphenyl)iodonium bromide (**5**; 100 mg, 239 mmol). The tube was sealed and the mixture was heated at 80 °C. The progress of the reaction was monitored by TLC. Upon completion of the reaction (3 h), the mixture was cooled to r.t., poured into brine and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with aq 9 N HCl (2 × 10 mL), dried (Na_2SO_4) and the solvent was distilled off to afford 1-iodo-2,4-dimethylbenzene (**8**; 26 mg) as a crude oily by-product. The pH of the aqueous phase containing the hydrochloride salt of 2-[(2,4-dimethylphenyl)thio]aniline was adjusted to 7 by the addition of solid $NaHCO_3$ and extracted with EtOAc (2 × 10 mL).The combined organic layers were dried (Na_2SO_4) and the solvent evaporated off to give 2-[(2,4-dimethylphenyl)thio]aniline (**3**) as a pure product (48 mg, 88%).

Choline Chloride-Glycerol (1:2) Based DES

A mixture of choline chloride (6.98 g, 50 mmol) and urea (9.21 g, 100 mmol) was heated up to 80 °C for 60 min until a clear solution was formed. The obtained DES was used without further purification.

Reaction of Bis(2,4-dimethyl)iodonium Bromide (5) with 2-Aminophenyl Disulfide (9) in DES-Glycerol

By using the same as above procedure, 1-iodo-2,4-dimethylbenzene (**8**; 27 mg) and 2-[(2,4-dimethylphenyl)thio]aniline (**3**; 46 mg; 85%) were obtained as pure products.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1702823.

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