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3-Mercaptopropionic acid as a new reagent for the industrially applicable synthesis of highly pure O-desmethylvenlafaxine from venlafaxine

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3-Mercaptopropionic acid as a new reagent for the industrially applicable synthesis of highly pure *O*-desmethylvenlafaxine from venlafaxine

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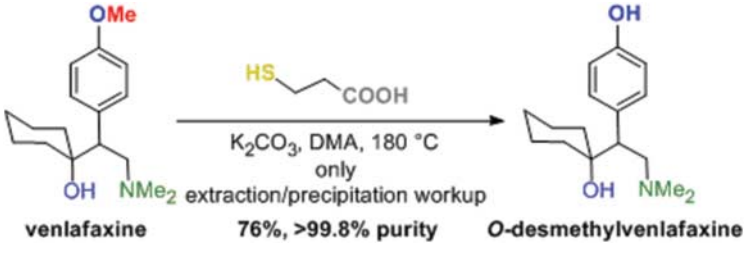
3-Mercaptopropionic acid was introduced as a cheap new *O*-demethylating agent as exemplified by its application in the synthesis of antidepressant *O*-desmethylvenlafaxine from venlafaxine. The application of 3-mercaptopropionic acid allowed high conversion of venlafaxine to *O*-desmethylvenlafaxine and a facile workup, which enabled the isolation of the desired *O*-desmethylvenlafaxine with a high $> 99.8\%$ chromatographic purity and 76% yield by a simple extractive workup followed by the precipitation.



Keywords: aryl alkyl ethers; demethylation; mercapto alkyl carboxylic acid; *O*-desmethylvenlafaxine; drugs

1. Introduction

Venlafaxine **1** was the first serotonin and norepinephrine reuptake inhibitor and exhibited particular efficacy in the treatment of major depression.[1] To further improve the efficacy and safety profile of this agent, *O*-desmethylvenlafaxine (also known as desvenlafaxine) **2** was identified to be its major active metabolite, which displayed the highest preclinical antidepressant activity and tolerability.[2] *O*-desmethylvenlafaxine succinate is nowadays an active pharmaceutical ingredient itself and is used for the treatment of major depressive disorders.[3] From its approval in the USA and Canada in 2008 under a brand name Prestiq® (Wyeth), it has become an important drug with ca. US$ 600 million sales in 2012 on the territory of North America.

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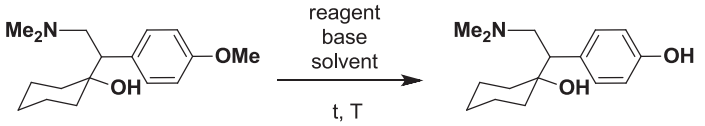
This therapeutic and commercial potential renders *O*-desmethylvenlafaxine an attractive synthetic target. Since there are many already known efficient total syntheses of venlafaxine,[4–9] the most appealing preparation of **2** seems to be through the *O*-demethylation of **1** and not via a protecting-group-free new total synthesis. Generally, the *O*-dealkylation of ethers or ether cleavage is an important functional group transformation.[10–16] Very frequently employed reagents for the *O*-dealkylation of aryl alkyl ethers are boron tribromide [17–19] and variously substituted alkyl and aryl thiols/thiolates [20–27] due to their selectivity and high attained yields. Other well-known *O*-dealkylating agents are, for example, diorganophosphides ($LiPPh_2$),[28] magnesium iodide,[29] iodocyclohexane,[30] aluminum chloride,[31,32] cerium chloride,[33] methyl magnesium iodide,[34] L-Selectride® or SuperHydride®,[35] methionine and methanesulfonic acid,[36–39] silicon tetrachloride/lithium iodide with catalytic boron trifluoride [40] and HBr.[41,42] Some of the above mentioned reagents were as well applied in the synthesis of **2** from **1**.[43–58] For example, $LiPPh_2$ (derived *in situ* from diphenylphosphine and hazardous as well as expensive *n*BuLi) gave only ca. 30% yield of **2** from **1** after the chromatographic purification.[43] The use of toxic and dangerous BBr_3 at cryogenic conditions (–40°C) provided 71% of the crude pharmaceutically unacceptable **2**.[44] The use of the moisture sensitive and pyrophoric L-Selectride® in a complicated multistep unit operation procedure provided **2** in ca. 90% yield.[45] Application of the foul-smelling and industrially unacceptable EtSH/NaH gave crude **2** in 79% yield after extractive workup, which had to be purified further via fumarate salt to provide the analytical pure material in 60% yield.[44] The application of inconvenient to use Na_2S (optionally in the presence of Se) in *O*-demethylation of **1** at 145°C in 1-methylpyrrolidone provided **2** in 60–77% yield after the extractive workup without a defined purity.[49] The malodorous sodium salt of PhSH gave only 19% yield of **2** in PEG 400 at 160°C, while the higher molecular weight dodecanethiol in the presence of NaOMe at 150–190°C afforded ca. 80% of **2** from **1** with an undefined purity.[46] Nevertheless, attractive bi-functional reagents such as 2-(diethylamino)ethanethiol/NaO*t*Bu/DMF were recently developed.[25] The key advantage in the design of the $Et_2NCH_2CH_2SH$ for the *O*-dealkylation of aryl alkyl ethers lies in the fact that the excess of $Et_2NCH_2CH_2SH$ and its by-product 2-(diethylamino)ethyl methyl sulfide are soluble in the acidic aqueous media, which enables an easy and essentially odorless workup. However, the drawback of this reagent in respect to its use in the *O*-demethylation of **1** was already indicated in the original report.[25] Namely, the $Et_2NCH_2CH_2SH$ performed well only on the substrates containing electron withdrawing groups (EWG), which are not present in **1** and must be used in dry solvent under inert atmosphere. Moreover, the $Et_2NCH_2CH_2SH$ contains a fully substituted amino group as in **1** and **2**, which would render an efficient purification based on extraction, via pH adjustment, difficult. Although $Et_2NCH_2CH_2SH$ was recently also applied in the preparation of **2** from **1**, this patent literature report asserted the reactivity drawbacks of $Et_2NCH_2CH_2SH$. Indeed, reaction of **1** with $Et_2NCH_2CH_2SH$ in the presence of NaOMe in PEG 400 at 195°C allowed only 45% yield of **2** after the extractive workup with the HPLC purity of only 96.8 area%, which is way below the required level for the pharmaceutical application.[50]

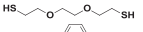
2. Results and discussion

We first decided to verify the performance of some benchmark reagents mentioned above such as PhSH and $Et_2NCH_2CH_2SH$. In our hands, the thiophenol/K_2CO_3/NMP [24] system provided a low $< 5\%$ conversion. Similarly, $Et_2NCH_2CH_2SH$-based method [25,50] afforded in our hands only 30–80% conversions depending on the reaction conditions (mild to harsh). All this indicated that the desired transformation of **1** to **2** might be indeed a capricious one (see Scheme in Table 1). Therefore, the aim of this work was to find another *O*-demethylation approach towards **2**, which would bypass the drawbacks of the known methods. Main shortcomings of

Table 1. Screening of various agents for the *O*-demethylation of venlafaxine **1** to give *O*-desmethylvenlafaxine **2**.[a]



1 **2**

Entry	Reagent	Base	Solvent[b]	*T* (°C)	Time (h)	**1**/**2**[c]
1	62% $_{aq.}$ HBr [41,42]	–	–	20	24	7/38
2	$SiCl_4$/LiI (cat. BF_3) [40]	–	PhMe	70	20	28/1
3	Methionine [36–39]	–	$MeSO_3H$	40	20	0/5
4	Deloxan® MP	K_2CO_3	DMF	80	18	92/0
5		EtONa	EtOH	150[d]	48	57/40
6		K_2CO_3	DMF	153[e]	72	72/17
7		K_2CO_3	DMA	165[e]	72	59/20
8		K_2CO_3	DMPU	246[e]	72	35/6
9		K_2CO_3	NMP	204[e]	72	41/17
10		K_2CO_3	DMA	180[d]	96	27/69
11		K_2CO_3	DMA	165[e]	72	96/3
12		K_2CO_3	DMA	180[d]	144	6/92

[a]All reactions were performed on a 10 mmol scale.
[b]DMA = dimethylacetamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; NMP = *N*-methyl-2-pyrrolidone.
[c]Reaction outcomes by HPLC analysis of the crude reaction mixtures in area% between **1** and **2**. The sum of **1** and **2** is lower than 100% owing to the presence of unidentified side products.
[d]Reaction performed in a stainless steel autoclave.
[e]Reaction performed at the reflux temperature.

these methods are associated with the high toxicity and safety issues of some reagents (*e.g.* BBr_3), reactivity and an unfavorable impurity profile (*e.g.* $LiPPh_2$ and $Et_2NCH_2CH_2SH$) as well as often tedious to remove thioether by-products, which are formed when aryl or alkyl thiols are used as *O*-dealkylating reagents.

Therefore, our goal was to first test various reagents, which were not previously applied for the *O*-demethylation of **1** (Table 1) in order to identify an efficient and easy to remove one suitable for the use in the pharmaceutical industry. First we screened some well-known *O*-demethylating reagents. Agents that lack the thiol group performed very poorly in our case. For example, very well-known *O*-demethylating reagent such as HBr [41,42] gave poor conversion of **1** to **2** with a huge amount of formed impurities as evidenced by almost full conversion of **1** and only 38% of formed **2** (Table 1, Entry 1). The $SiCl_4$/LiI (cat. BF_3) [40] couple performed even worse giving hardly detectable amounts of **2** (1%) and significant amounts of side products (Table 1, Entry 2). Surprisingly, one of the most frequently used *O*-demethylating reagent methionine/methanesulfonic acid [36–39] yielded only 5% of **2** at full conversion of **1** (Table 1, Entry 3). These results redirected our focus to the new thiol group containing reagents that could provide adequate reactivity, selectivity and would enable a facile isolation of the product via a simple filtration (in the case of polymeric mercaptans) or pH-dependent extractive workup. Deloxan® MP, which is a thio-functionalized polysiloxane, gave practically complete recovery of a starting material (Table 1, Entry 4). On the other hand, 3,6-dioxa-1,8-octanedithiol provided only a modest outcome of the desired product after 48 h giving 40% of **2**, albeit with low level of impurities formed as evidenced by the presence of 57% of **1** in the mixture (Table 1, Entry 5). Next, we supposed that mercaptocarboxylic acids could provide an appealing alternative, since

they possess the thiol functional group, which could serve for the efficient demethylation, together with the carboxylic functional group, which would enable a facile removal of the excess of *O*-demethylating reagent and thioether by-product through extraction upon pH adjustment of aqueous suspension of the crude product. We first screened all three isomers of the mercaptobenzoic acid (Table 1, Entries 6–11). The 4-mercaptobenzoic acid gave 6–20% of **2** in temperature range between 153°C and 246°C (Table 1, Entries 6–9). At temperatures above 200°C, higher conversions of **1** were observed; however, the yield of **2** did not increase, which indicates that higher amounts of side products were formed. Interestingly, 3-mercaptobenzoic acid gave **2** in a fair yield of 69% at 180°C after 96 h (Table 1, Entry 10). In contrast, 2-mercaptobenzoic acid was the least active giving rise only to 2% of **2** at 165°C (Table 1, Entry 11). The observed behavior of the mercaptobenzoic acids can be rationalized with a resonance contribution of the carboylic functionality to the benzene ring. The observed low reactivity of the 2-and 4-mercaptobenzoic acids can be ascribed to the EWG property of the CO_2H group, which as a consequence leads to the decreased electron density on ortho and para positions and lowers the nucleophilicity of the attached sulfur atom. In the case of 2-mercaptobenzoic acid, steric factors or intramolecular hydrogen bonding may play an additional role. Since some promising results were obtained with the mercaptobenzoic acids, we were stimulated to continue our investigation along this line. Thus, we reasoned that the mercaptoalkanoic acids could have an improved reactivity. Therefore, we next considered the 3-mercaptopropionic acid as a low molecular weight alternative (which would have an impact on reagent costs as well as lower waste generation) and thus an interesting candidate for the desired transformation. When **1** was reacted with 3-mercaptopropionic acid in the presence of K_2CO_3 at 180°C in dimethylacetamide, we gained the most promising result. Indeed, up to 92% of the desired product **2** was formed along with a low level of side products (ca. 2%) and 6% of the unreacted **1** (Table 1, Entry 12).

Because of the much lower cost of the 3-mercaptopropionic acid (hundreds of times cheaper than the 3-mercaptobenzoic acid and also ca. 10 times cheaper than the $Et_2NCH_2CH_2SH$ as a similar bi-functional although less efficient reagent for the *O*-demethylation of **1**) and lower molecular weight, we next tried to establish its use on a preparative scale (20 mmol) and find out the optimal isolation conditions for the extractive workup. Indeed, we found out that when **1** was treated in the presence of K_2CO_3 (7 equiv) with 3-mercaptopropionic acid (4 equiv) in dimethylacetamide at 180°C, after 144 h the desired *O*-desmethylvenlafaxine **2** was isolated in excellent purity of $>$ 99.8 area% (by HPLC) with 76% yield by simple pH adjustment of aqueous suspension of the crude product and extraction/precipitation workup.[59]

3. Conclusion

In conclusion, 3-mercaptopropionic acid was introduced as a new *O*-demethylating agent, which was successfully used in the preparation of highly pure *O*-desmethylvenlafaxine from venlafaxine hydrochloride. One of the main advantages of 3-mercaptopropionic acid is facile removal of its thioether by-product as well as its own removal from the reaction mixture by simple extraction, which provides high purity of the desired active pharmaceutical ingredient as required by pharmaceutical industry guidelines. Furthermore, the low molecular weight of 3-mercaptopropionic acid in combination with K_2CO_3 as a base minimizes the amount of generated waste streams, which is critical for industrial application. As well, the developed process allows a direct one-pot use of venlafaxine hydrochloride, without necessity of prior preparation of venlafaxine free base. Therefore, we believe that due to its alluring cost advantage and interesting technical properties related to the easy removal of excess reagent and related by-product, 3-mercaptopropionic acid might be an interesting reagent for the *O*-dealkylation of other aryl alkyl ethers containing basic functional groups.

4. Experimental

4.1. *General*

Reagents and solvents were acquired from the commercial sources and were used without further purification. HPLC analysis were performed with MeCN–H_2O as the mobile phase (MeCN gradient 5–90%) on the Waters 2695 instrument with the photodiode array detector and a Waters X Bridge (150 × 4.6 mm, 3.5 µm) column. The NMR spectra were recorded with the Bruker Avance III 500 MHz spectrometer at 25°C. ^{1}H NMR spectra were obtained at 500 MHz, ^{13}C NMR spectra were obtained at 125 MHz. Chemical shifts are reported in ppm relative to Me_4Si (0.0 ppm). The coupling constants (J) are given in hertz. Melting points were determined with the Mettler Toledo DSC822e apparatus (heating rate 10°C/min) and are referred to as onset values and peak values. IR spectra were recorded on the Thermo Nicolet Nexus FTIR spectrometer; only noteworthy absorptions are listed. High-resolution mass spectra were obtained with the VG-Analytical AutospecQ instrument and a Q-TOF Premier instrument.

4.2. *Procedure for the preparation of O-desmethylvenlafaxine 2*

Venlafaxine hydrochloride (**1**·HCl) (6.28 g, 20 mmol), K_2CO_3 (19.37 g, 140 mmol) and dimethylacetamide (40 mL) were charged into a 75 mL stainless steel autoclave. 3-Mercaptopropionic acid (8.48 g, 80 mmol) was slowly added to the reaction mixture. The obtained reaction mixture was gently stirred until the CO_2 evolution stopped and the majority of starting material was dissolved (about 10–30 min). The autoclave was closed and the reaction mixture was heated to 180°C and stirred for six days. Then it was cooled to room temperature and poured into 200 mL of water. The resulting mixture was stirred for at least 2 h until most of the solid (K_2CO_3) was dissolved. The insoluble residue (the mixture of unreacted **1** and product **2**) was filtered off and washed with water (2 × 100 mL). The crude material was transferred into 2 M NaOH (100 mL) where it was stirred for additional 2 h to convert the product **2** into its sodium salt. The undissolved residue **1** was filtered off and discarded, while the filtrate was washed with MTBE (2 × 50 mL) and the organic phase discarded as well. The water phase was acidified with the concentrated acetic acid to pH = 7.6. The precipitate was filtered off and washed with water (2 × 50 mL). The filtrate was basified with 1 M NaOH to pH = 9. Some additional precipitate was formed, which was also filtered off, washed with water (2 × 50 mL) and combined with the first precipitate. The product was dried in vacuum at 50°C to give 4.02 g (76% yield) of *O*-desmethylvenlafaxine **2** with the HPLC purity of > 99.8%. mp 221.9°C (onset) and 223.9°C (peak); ^{1}H NMR (500 MHz, methanol-d_4): δ 0.97 (m, 1H), 1.14 (m, 1H), 1.33 (m, 1H), 1.41 (m, 1H), 1.45–1.68 (m, 6H), 2.25 (s, 6H), 2.53 (dd, 1H, J = 6.6 Hz, J = 12.7 Hz), 2.81 (dd, 1H, J = 6.6 Hz, J = 8.3 Hz), 3.15 (dd, 1H, J = 8.3 Hz, J = 12.7 Hz), 6.71 (m, 2H), 7.03 (m, 2H); ^{13}C NMR (125 MHz, methanol-d_4): δ 22.8, 27.2, 33.4, 38.4, 45.9, 53.8, 61.9, 75.8, 116.0, 131.6, 132.2, 132.7, 157.5; IR (KBr): 3432, 3126, 2939, 2862, 2831, 2786, 1619, 1517, 1447, 1272, 1147, 842 cm^{-1}; HRMS–ESI: m/z $[M + H]^+$ calculated for $C_{16}H_{26}NO_2$: 264.1958; found: 264.1957.

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