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Synthesis of 25X-BOMes and 25X-NBOHs (X = H, I, Br) for pharmacological studies and as reference standards for forensic purposes ☆

Wellington Alves de Barros [a], Marcelo Pereira Queiroz [a], Leonardo da Silva Neto [a], Graziele Martins Borges [a], Felipe Terra Martins [b], Ângelo de Fátima [a,*]

[a] Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Minas Gerais, Belo Horizonte, MG 31270-901, Brazil
[b] Instituto de Química, Universidade Federal de Goiás, CP 131, 74001-970 Goiâni-GO, Brazil

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ABSTRACT

An expeditious method is reported for the synthesis of three NBOHs (25H-, 25I- and 25B-NBOH; 9–38% overall yield) and three NBOMes (25H-, 25I- and 25B-NBOMe; 7–33% overall yield) from salicylaldehyde and 2-methoxyaldehyde, respectively. The X-ray structures of 25H-, 25I- and 25B-NBOH.HCl were also determined. Our approach should provide a general entry for preparing such a class of substances for pharmacological and forensic purposes.

Introduction

The consumption of New Psychoactive Substances (NPS) has increased and become a severe health problem in many countries. Indeed, from 2009 to 2017, 802 NPS were reported to the United Nations Office on Drugs and Crimes (UNODC) in 111 countries; among these NPS were 136 phenethylamines, which included NBOMes and NBOHs [1,2]. These substances are substituted phenethylamines bearing methoxy groups in positions 2 and 5, and a halogen in position 4 (i.e. chlorine, bromine, or iodine) of the A ring, and a methoxy (for NBOMes) or hydroxyl (for NBOHs) group in position 2′ of the B ring (Fig. 1) [3]. The first synthesis of NBOMes was described in 2003 by Heim [4], who also disclosed that these substances are 5HT agonists, and that the presence of an *ortho*-methoxy or -hydroxy group to the *N*-benzyl moiety increased the 5HT receptor affinity of such substituted phenethylamines. From 2010, reports on NBOMes began to appear due to their powerful stimulating properties [5]. Due to adverse effects such as hypertension, tachycardia, visual and auditory hallucinations, acute kidney injury, among others, the number of deaths associated with their intake has also increased since then [6–11]. Within a short time, accounts of toxicity and lethal overdoses from such classes of NPS appeared, resulting in the scheduling of these substances by the United States Drug Enforcement Administration (USA) in 2013. In Brazil, the first NBOMes and NBOHs were listed as illicit substances by Brazilian authorities in 2014 and 2016, respectively [12].

However, despite being recognized as illegal substances, only a few studies on their adverse/toxic effects are available. In addition, the identification and quantification of NBOMes and NBOHs is hampered by the lack of readily available analytical standards and the requirement of methods such as gas chromatography for analyzing and comparing seizure samples with reference standards. Even when analytical standards are available, the delivery times can be long and the costs can be high due to the need to import these substances. Lastly, in numerous cases - as is the case for NBOMes and NBOHs - reference standards are not marketed by brands that serve globally, which makes accessing them difficult [13].

Results and discussion

The majority of synthetic approaches for preparing NBOMes and NBOHs start from phenethylamines (2C-X; X = H, I, Br or Cl), obtained from commercial sources [14–16]; however, it should

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* Corresponding author.
E-mail address: adefatima@qui.ufmg.br (Â. de Fátima).

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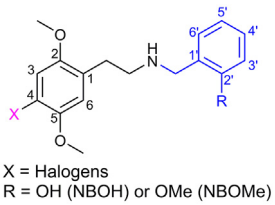

Fig. 1. Representative structure of NBOMes and NBOHs.

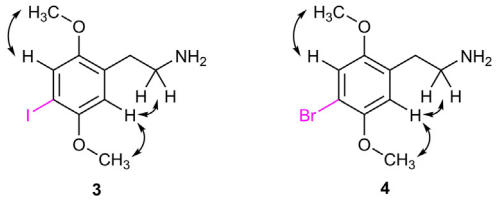

Fig. 2. Significant correlations observed in the NOESY spectra of **3** and **4**.

be noted that these phenethylamines are very expensive (1.0 mg costs up to 57.5 US dollars, Sigma-Aldrich, CAS Number: 56281-37-9). In addition, the few procedures available starting from simple materials have multiple steps and low yields. Nichols and co-workers reported the synthesis of 25I-NBOMe in 10 steps and 5.1% overall yield [17]. Karlsen and co-workers synthesized intermediates **3** and **4** in 6 steps and 30% and 35% overall yield, respectively [18]. Therefore, we proposed that NBOMes and NBOHs could be synthesized from 2-(2,5-dimethoxyphenyl)ethan-1-amine **2** and its halogenated derivatives as intermediates (Scheme 1).

Amine **2** was easily obtained from 2,5-dimethoxybenzaldehyde using the Henry reaction, followed by dehydration of the Henry adduct, providing **1** in 79% yield [19]. The reduction of **1** with $LiAlH_4$ provided **2** in 74% yield (Scheme 1) [20]. In order to obtain halogenated (X = I or Br) substituted phenethylamines, it was necessary to introduce such halogens at position 4 of 2-(2,5-dimethoxyphenyl)ethan-1-amine (**2**, Scheme 1). Due to the higher prevalence of 25I-, 25B-NBOMe and 25I-, 25B-NBOH in Brazil [21–24], this series of halogens was prepared. 2-(4-Iodo-2,5-dimethoxyphenyl)ethan-1-amine (**3**) was synthesized using I_2 under Ag_2SO_4 catalysis in ethanol. Amine **3** was obtained in 40% yield after 48 h (Scheme 1) and the regioselectivity of the iodide substitution was established based on the NOE correlations between the aromatic hydrogens and the methoxy groups (Figs. 2 and S7) [18].

Various bromination methodologies were evaluated for the synthesis of 2-(4-bromo-2,5-dimethoxyphenyl)ethan-1-amine **4** (Table 1). We attempted to use Br_2 in AcOH [17], *N*-bromosuccinimide (NBS) in acetonitrile [25–28], and Br_2 in THF under pyridine catalysis (Entries 1–3, respectively; Table 1), however, a low conversion of **2** to **4** (<10%) was observed. The purification of such amines was also challenging, since both compounds had similar polarity and were consequently difficult to separate by column chromatography. The 1,4-dioxane-Br complex is a mild brominating agent, which has been used for the bromination of activated aromatic systems [29,30]. Gratifyingly, the use of Br_2 in a mixture of AcOH/1,4-dioxane (1:1) gave amine **4** in 53% yield after 72 h (Entry 5; Table 1) [31]. In addition, the workup procedures used in this reaction (see ESI) provided the pure desired amine **4** as a crystalline material. The regioselectivity of bromine substitution was also established based on the NOE correlations between the aromatic hydrogens and the methoxy groups (Figs. 2 and S10).

Having amines **2**, **3** and **4** in hand, our efforts were then directed to the preparation of the corresponding Schiff bases followed by reduction using $NaBH_4$. The reactions were carried out in a single pot under microwave irradiation (30 min, 70 °C; MWI) [32]. Salicylaldehyde and 2-methoxybenzaldehyde were used to obtain NBOHs (25H-, 25I- and 25B-NBOH) and NBOMes (25H-, 25I- and 25B-NBOMe), respectively (Scheme 2).

Seeking to assess the robustness of the proposed route, 25H-NBOH and 25H-NBOMe were synthesized on a 1.2 g scale. For all synthesized NBOH compounds, we performed a single crystal X-ray diffraction on their hydrochloride derivatives (Scheme 2).

Conclusion

The synthesis of three NBOHs (25H-, 25I- and 25B-NBOH; 9–38% overall yield) and three NBOMes (25H-, 25I- and 25B-NBOMe; 7–33% overall yield) from inexpensive and commercially available aldehydes is reported. The X-ray structures of 25H-, 25I- and 25B-NBOH.HCl are also reported. Furthermore, our approach should provide a general entry for preparing such substances for pharmacological and forensic purposes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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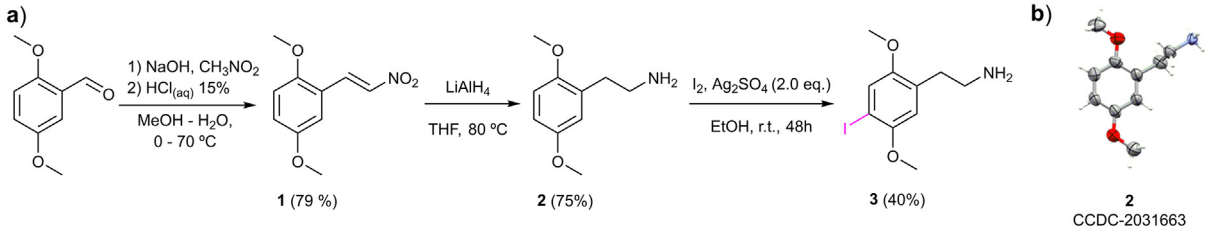
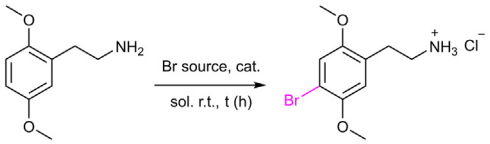


Scheme 1. a) Preparation of amines **2** and **3**. b) 50% probability ellipsoid plot for the non-hydrogen atoms of amine **2** as the acetate salt (hydrogen atoms are arbitrary radius spheres, counterion not shown in the ellipsoid diagram).

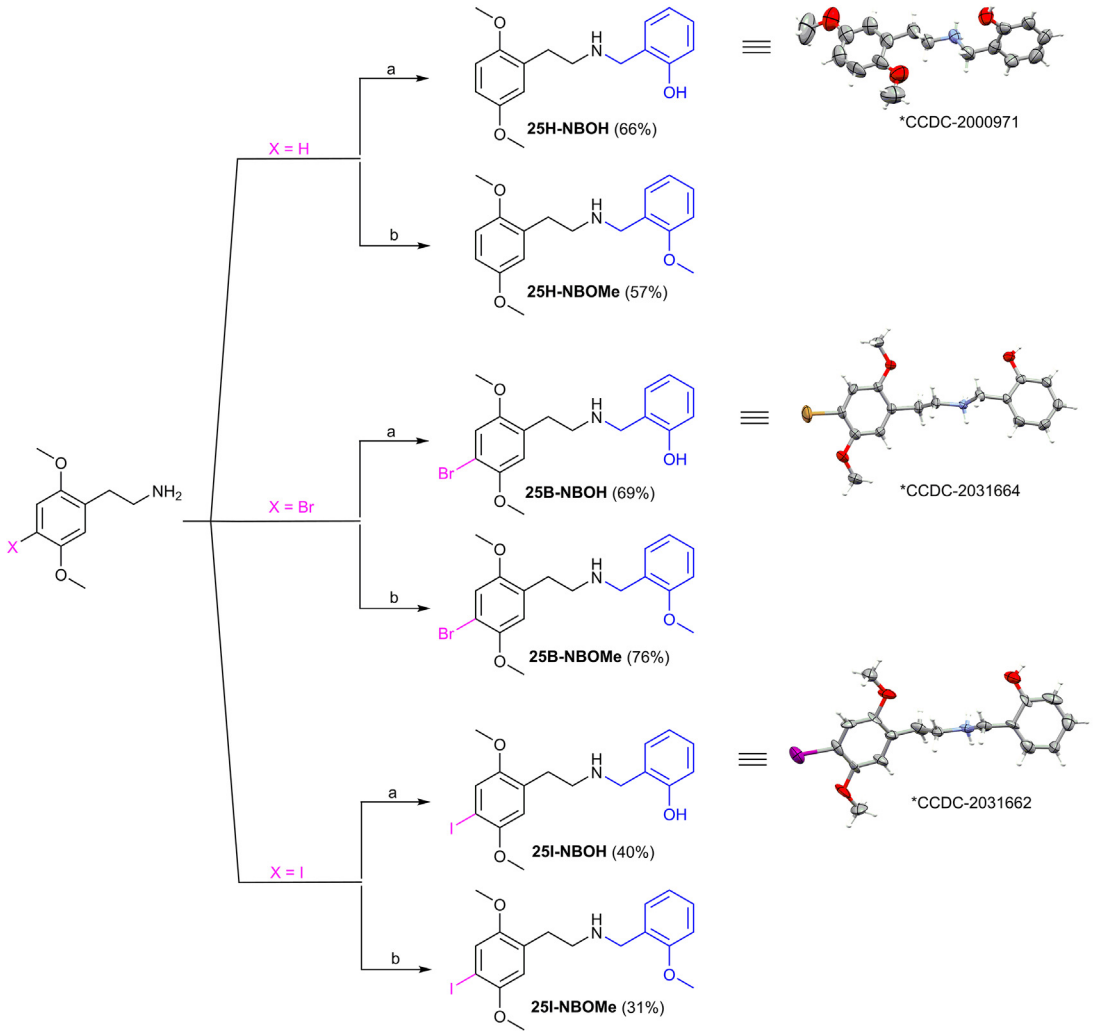
Table 1
Bromination of amine **4** using different brominating agents and conditions.



2 **4**

Entry	Solvent	Br source	t (h)	cat.[a]	Yield **4** (%)
1	AcOH	Br_2	24	–	–[b]
2	CH_3CN	NBS	2	–	–[b]
3	THF	Br_2	5	Py	–[b]
4	AcOH/1,4-dioxane (1:1)	Br_2	24	–	24%
5	AcOH/1,4-dioxane (1:1)	Br_2	72	–	53%

[a] Catalyst.
[b] Low conversion, not isolated.



Reagents and conditions: (a) i. salicylaldehyde, EtOH, 70 ºC, MWI, 30 min; ii. $NaBH_4$, r.t., 2 h; (b) 2-methoxybenzaldehyde, EtOH, 70 ºC, MWI, 30 min; ii. $NaBH_4$, r.t., 2 h. *Hydrochlorides were obtained by treating the corresponding NBOHs with an EtOH solution containing 1.0 mol L^{-1} of HCl.

Scheme 2. Reductive amination of amines **2**, **3** and **4** to give NBOHs (25H-, 25I- and 25B-NBOH) and NBOMes (25H-, 25I- and 25B-NBOMe). 50% probability ellipsoid plots for the non-hydrogen atoms of 25H-NBOH, 25B-NBOH and 25I-NBOH (hydrogen atoms are arbitrary radius spheres) are also presented.

Appendix A. Supplementary data

Supplementary data (experimental and characterization details) to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152804.

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