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A Sustainable and Catalytic Synthesis of Dibenzosuberone

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Dibenzosuberone (DBS) is a key intermediate for the synthesis of relevant active pharmaceutical ingredients (APIs) for the treatment of several diseases related to the central nervous system. Herein, the design and development of a milder and greener approach to improve the well-established methodology for the synthesis of DBS limiting waste production *via* the use of immobilized catalysts are presented.

Introduction

Dibenzosuberone (DBS, **1**; Figure 1) is one of the key intermediates in the synthesis of several APIs[1–5] (e.g., Amitriptyline, Nortriptyline, Noxiptiline or Cyproheptadine) employed in the treatment of nervous system-related diseases and as anti-cancer drugs[6] (e.g., suberenyl chloride). DBS belongs to the family of tricyclic antidepressant drugs, commonly known as tricyclic (or abbreviated TCA) which are extensively used against migraines, tension headaches, anxiety attacks and schizophrenia.[7,8] Moreover, they have shown bioactivity towards the serotonin transporter and the norepinephrine transporter.[9–11]

For all these reasons, DBS represents a target molecule of primary importance and there are several well-established methodologies for its synthesis.[1,12–15]

DBS is generally prepared by intramolecular Friedel-Crafts acylation of 2-(phenethyl) benzoic acid (**2**), but its current synthesis calls for more sustainable methods.[16] Therefore, an innovative method that would make use of **2** would be highly desirable. In fact, its synthesis[1] and supply chain are established and the whole filing would be streamlined. Indeed, due
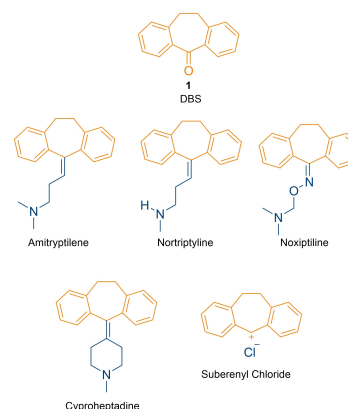

Figure 1. DBS and DBS-derived APIs.

to the inherent low reactivity of carboxylic acids, these often require to be activated by converting them into the corresponding acyl chlorides using at least stoichiometric amounts of Lewis acids[17,18] such as AlCl₃ or SOCl₂. Another interesting approach to access DBS starting from **2** exploiting photocatalysis is reported by Chu *et al.* Although this methodology is novel, it requires 1.5 eq. of triphenylphosphine and 1 eq. of amine base, that would end up in the waste, negatively affecting the greenness of the process.[19] Despite the significant efforts made so far to make the Friedel-Crafts reaction more sustainable and greener without losing efficiency, current industrial processes employ Lewis acids as activating agents in large excess and use chlorinated solvents such as dichloromethane, dichloroethane or chlorobenzenes. Another commonly used method to perform the Friedel-Crafts acylation reaction exploits polyphosphoric acid (PPA) as an activating agent.[1] A significant drawback of this procedure is that its waste is difficult and expensive to dispose of. In fact, PPA is used in more-than-stochiometric amount. Since it is highly viscous and hygroscopic, it requires large amounts of water to recover the desired product. Moreover, an appropriate treatment to neutralize the acidity of the aqueous waste and to eliminate the large amounts of salts generated during the process is needed.

Consequently, it is highly desirable to develop an efficient, economical, and sustainable process, which relies on the use of

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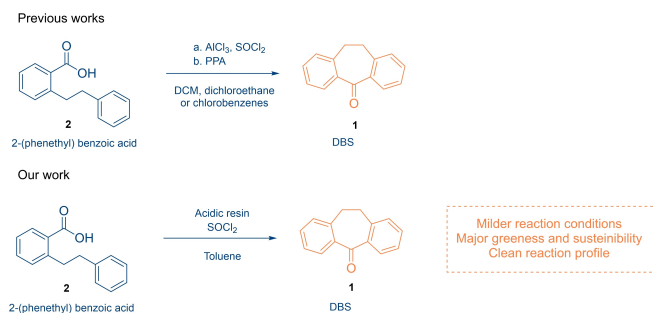E-mail: simone.mantegazza@dipharma.com
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Scheme 1. The presented developed methodology compared to previously reported strategies for the synthesis of DBS **1**.

activating systems in catalytic amount, along with more benign solvents (Scheme 1). Towards this aim, a collaboration between academia and industry was established to develop an alternative approach that addresses all these issues by exploiting immobilized catalysts. Immobilization of catalysts gained increasing traction over the last years.[20–27] In fact, many advantages arise from immobilization, including improved stability, reusability, and localization of the catalyst itself. Supported catalysts can be easily separated and removed from the products and the reaction medium. Furthermore, they can be regenerated with an appropriate procedure and reused for several catalytic cycles. Thanks to this strategy the amount of waste produced, along with the costs related to a specific process, can be considerably reduced. Our novel process for the preparation of DBS **1** is carried out in presence of a sulfonated styrene-divinylbenzene copolymer ion exchange resin that is economical, both in direct cost and in the spending associated with the treatment of waste water. Moreover, it is eco-compatible and allows for easy recycling of the catalyst used for the cyclization *via* acidic rinsing. The reaction conditions are mild and provide the target molecule in high yields and purity.

Results and Discussion

Following an evaluation of different routes, Olah's methodology,[12,13] who proposed the use of a cation exchange resin for preparing DBS **1**, was further assessed. According to Olah's group a superacidic resin is needed and less acidic resins catalyze Friedel-Crafts acylations only on highly activated aromatics.[28] Despite these premises, we set out to develop a convenient protocol for preparing **1** *via* cyclization of diphenylethane-2-carboxylic acid (**2**) in presence of a sulfonated styrene-divinylbenzene co-polymer ion exchange resin. In particular, Olah *et al.* employed Nafion-H resin as a catalyst to affect the formation of the desired product with yields of 95% in presence of high-boiling solvents such as 1,2-dichlorobenzene, 1,3-dichlorobenzene or *p*-xylene. Even though this approach paved the way for the DBS synthesis using acidic resins as activating agents, we found that, in our hands, the procedures described by Olah and coworkers are challenging to apply on an industrial scale. In fact, a drawback of the methodology is that, while Olah

reported to prepare their own Nafion-H, commercially available Nafion-H resin is usually supplied in the form of sheets (i.e.: NRE-212) that must be manually cut before being added to the reaction mixture; at least at the time of the development of this process, its beads form (i.e.: RE-50) was less straightforward to access. Furthermore, the recovery of the resin after completion of the reaction is not straightforward, and the resin itself seems to degrade during the reaction. In addition to this, the high-boiling solvents needed for the reported reaction are difficult to deal with.

To overcome the difficulties encountered in the protocol reported in literature, we carried out a screening of ion exchange resins and reaction solvents to obtain **1** in high yield and purity from **2** (Table 1).

Since Olah *et al.* employed resins produced in house, no direct comparison with the commercially available Nafion NRE-212 resin used in the present work could be made. As reported in entry 1, when using commercial perfluorinated polymer resin, no conversion to the desired product was detected by NMR. Furthermore, a higher quantity of undesired impurities was formed by employing the perfluorinated polymer resins. When SOCl₂ was added as activating agent to the reaction mixture with the Nafion NRE-212 resin (entry 3), no conversion to **1** was detected, while it led to the formation of several unwanted products, as already disclosed by Olah and coworkers.[13] Although less commercially accessible, Nafion RE-50 possesses similar acidity and ion exchange capacity with respect to Nafion NRE-212, and comes in form of beads instead of sheets, making its use operationally simpler. As shown in entry 4, employing Nafion RE-50 and SOCl₂ as activating agent showed promising, although not satisfactory results, leading to the formation of the desired product **1** in 55% yield. A further improvement of the methodology was achieved with the use of Amberlyst-15 as acidic resin and SOCl₂ as activating agent, which led to the formation of the desired product in 77% yield (entry 5). Amberlyst-15 has the advantage of being affordable, readily available, more sustainable, and environmentally friendly compared to Nafion which is a perfluorinated sulfonated resin.

Table 1. Optimisation of the reaction conditions for the cyclization of diphenylethane-2-carboxylic acid.[a]

Entry	Resin	Additive	Solvent	Temp (°C)	Conv. (%)[b]
1	Nafion NRE-212	–	*p*-Xylene	120	–
2	Amberlyst-15	–	*p*-Xylene	120	8
3	Nafion NRE-212	SOCl₂	*p*-Xylene	120	–
4	Nafion RE-50	SOCl₂	*p*-Xylene	120	55
5	Amberlyst-15	SOCl₂	*p*-Xylene	120	77
6	Amberlyst-15	SOCl₂	Heptane	100	>95
7	Amberlyst-15	SOCl₂	Toluene	100	>95
8	Graphite/p-TSA	SOCl₂	Toluene	100	–

[a] The reactions were performed with **2** (56 mg, 0.25 mmol, 1 eq.), acidic resin (0.09 mmol, 0.35 eq.), SOCl₂ (60 μL, 0.82 mmol, 3.3 eq.), and solvent (1 mL, 0.25 M) for 24 hours. [b] Measured by ¹H NMR spectroscopy.

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In fact, perfluoroalkyl substances will be banned in the next few years because they are pollutants and some of them are toxic to humans.[29] Having identified a commercially and cost-effective resin to perform the transformation, a further screening was pursued; among the screened solvents and conditions, heptane and toluene converted **2** to **1** in quantitative conversion (entries 6–7). Inspired by previously reported protocols,[30] graphite and p-TSA were tested without any success (entry 8). Although decreasing the amount of thionyl chloride, and ideally avoiding the need of using it at all, is highly desirable, 3.3 equivalents were evaluated as an amount that would allow the reaction to perform smoothly. In fact, Amberlyst-15 is a hygroscopic resin and, consequently, we need an excess to counteract both the water contained in the resin itself and the one released during the intramolecular Friedel-Crafts reaction.[31,32] To evaluate the progress of the reaction over time, with a view to transfer it to larger scale, the cyclization was monitored at different timepoints over 24 hours. The reaction shows basically full conversion after 8 hours at 100 °C and shortly after at 80 °C, indicating that a range of milder temperatures could be used on scale (Figure 2).

With a view to move to a plug-flow or continuous stirred tank reactor, the reaction was tested and monitored in a batch reactor on 5–10 g scale with varying catalyst loadings and temperatures, monitoring the conversion over time (Figures 3–4).

On a larger scale, the reaction seemed to stall at about 60 % conversion with 0.35 eq. of Amberlyst-15. This may be attributed to either a different batch of Amberlyst-15 used or, most probably, to the difference in scale. In fact, no engineering of the vessel and the mixing needed had been carried out at this stage, and this is particularly important for a heterogeneous reaction. However, the reaction reached full conversion in few hours when the catalyst was increased to 0.50, 0.75 and 1 eq. This indicates that, quite likely, a CSTR or a closed-loop reactor may be the best choice to run the process efficiently, while recycling the catalyst.
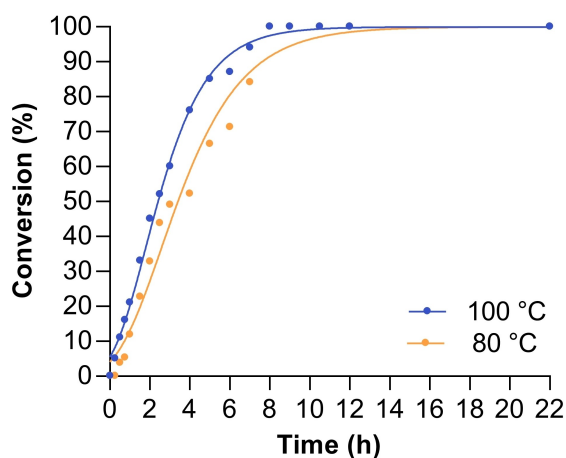

Figure 3. The reactions were performed with **2** (10 g, 44.19 mmol, 1 eq.), Amberlyst-15 (0.35–1 eq.), $SOCl_2$ (17.3 g, 145.82 mmol, 3.3 eq), in toluene (180 mL) at 105 °C.
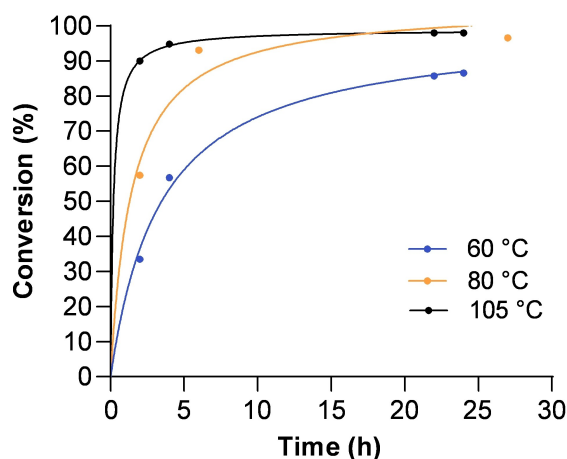
Figure 4. The reactions were performed with **2** (5 g, 22.09 mmol, 1 eq.), Amberlyst-15 (5 eq.), $SOCl_2$ (8.68 g, 72.91 mmol, 3.3 eq.), in toluene (90 mL) at 60–105 °C.

Therefore, looking at running the process this way, the reaction was tested using a much larger amount of the catalyst (5 eq.) at lower temperatures. The process shows satisfactory conversion after few hours at 80 °C, proving that more sustainable conditions can be used on scale.

These results showed that the process is amenable to be conducted in continuous, as depicted in Scheme 2.

At first, the flow chemistry was tested as segregated steps to identify potential issues. Therefore, at first **2** in toluene was reacted with $SOCl_2$; potential clogging of the tubings proved to be an issue as **2** is prone to precipitation, and this had to be dealt with. The following step, i.e.: the Friedel-Crafts reaction when the acyl chloride cyclised in presence of the resin, showed that preferential routes of the reaction mixture in the packed column could lead to inconsistent conversions. Furthermore, the system had to be run below boiling temperature of the solvent to prevent pressure build-up. Hence, while a continuous

Figure 2. Conversion of **2** to **1** vs time at 100 °C and 80 °C. The reactions were performed with **2** (56 mg, 0.25 mmol, 1 eq.), Amberlyst-15 (0.09 mmol, 0.35 eq.), $SOCl_2$ (60 μL, 0.82 mmol, 3.3 eq.), in toluene (1 mL).
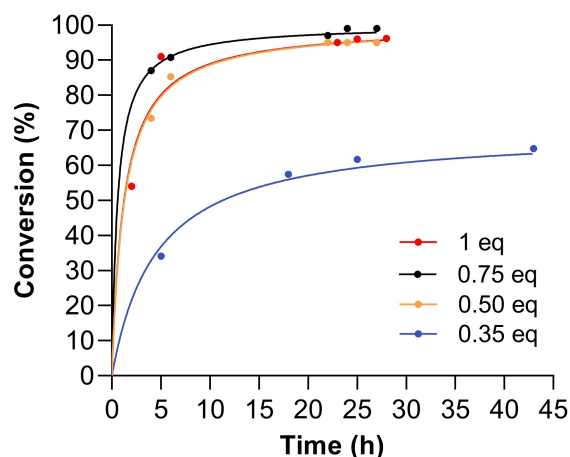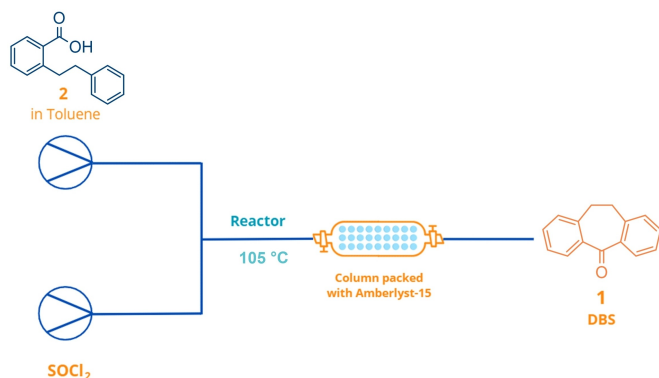
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Scheme 2. Hypothesized strategy to conduct the reaction in flow.
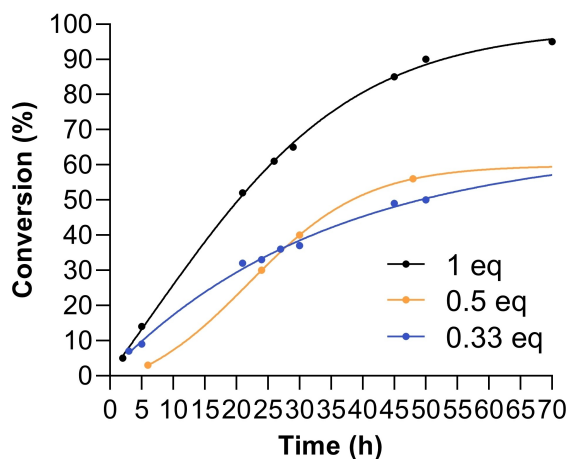

Figure 5. Reactions performed with **2** (10 g, 44.19 mmol, 1 eq.), Amberlyst-15 (0.33–1 eq.), in toluene (180 mL) at reflux temperature of 135 °C in a Dean-Stark apparatus.

Figure 6. Reactions performed with **2** (10 g, 44.19 mmol, 1 eq.), Amberlyst-15 (0.33–1 eq.), in toluene (180 mL) at reflux temperature of 13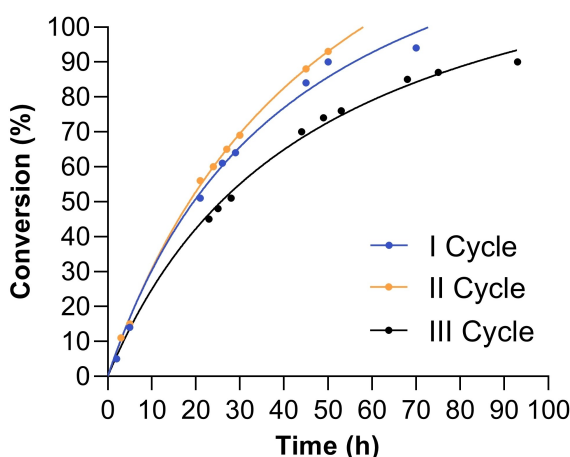5 °C in a Dean-Stark apparatus. The resin was filtered, and washed with toluene, before being used in the subsequent catalytic cycle (see ESI).

chemistry system was desirable, few issues had to be addressed from our engineers.

During the development of the continuous chemistry, given the water present and produced in the reaction, it was surmised that, if water could be removed, the desired product could be afforded without the need of using thionyl chloride. Indeed, we were pleased to observe that running the reaction in a Dean-Stark apparatus, *via* azeotropic distillation of water and toluene, the reaction produced the desired product smoothly in the absence of thionyl chloride. We tested the reaction in these conditions with different equivalents of Amberlyst-15; in the absence of thionyl chloride, 1 eq. of Amberlyst-15 is needed to reach full conversion in a reasonable timeframe (Figure 5).[12,13]

Amberlyst-15 can be easily recycled, and its reuse was proven in three subsequent catalytic cycles; at the end of the reaction, the resin was simply rinsed with toluene to remove any reaction product, prior to reuse (Figure 6).

The optimised methodology proved to be a novel sustainable strategy to access DBS (**1**) with an E-factor as low as 19.5, without incorporating recycling, compared to E-factors 2.3,[1] 19.9,[12] 38.9,[13] 34.6,[14] 15.0,[18] for previous reported procedures that, however, make use of reactants and catalysts that are not fully suitable for industry.

Conclusions

Looking at improving an existing process by abating the large and unsustainable waste produced, an efficient, affordable, and mild process to dibenzosuberone was developed. It makes use of an acidic and cost-efficient resin to activate the carboxylic acid both in presence and in absence of thionyl chloride. Furthermore, a solvent more benign than previously reported ones, such as toluene, has been identified. This work represents a step forward to the synthesis of DBS in terms of sustainability and industrial applicability.

Experimental Section

Synthesis of DBS (1). 60 μL of thionyl chloride (97.3 mg, 0.82 mmol) are added to a solution of 56 mg of 2-(phenethyl)benzoic acid (**2**) (0.25 mmol) in 1 mL of toluene at room temperature. After 30 minutes, 20 mg of Amberlyst-15 resin (0.09 mmol) are added and the mixture is heated to a temperature of 100 °C. After about 24 hours, the mixture is cooled down to room temperature and the resin is filtered off. The organic phase is washed with 1 mL of a 2 M aqueous solution of potassium carbonate and concentrated to residue providing the desired product (**1**). ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.04 (dd, $J = 7.8$, 1.4 Hz, 2H), 7.46 (td, $J = 7.4$, 1.5 Hz, 2 H), 7.35 (td, $J = 7.7$, 1.3 Hz, 2 H), 7.31 – 7.19 (m, 2H), 3.23 (s, 4 H).

Supporting Information

Additional references cited within the Supporting Information.[33–34]

Acknowledgements

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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