



## Convergent synthesis of dendrimers based on 1,3,3-trisubstituted 2-oxindoles

A. Vandendriessche<sup>a</sup>, J. Thomas<sup>a</sup>, C. Van Oosterwijck<sup>a</sup>, J. Huybrechts<sup>b,1</sup>, B. Dervaux<sup>c</sup>, S. D'hollander<sup>c</sup>, F. Du Prez<sup>c</sup>, W. Dehaen<sup>a</sup>, M. Smet<sup>a,\*</sup>

<sup>a</sup> Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

<sup>b</sup> Department of Biology, University of Leuven, Naamsestraat 59, B-3000 Leuven, Belgium

<sup>c</sup> Department of Organic Chemistry, Ghent University, Krijgslaan 281 (S4-bis), B-9000 Ghent, Belgium

### ARTICLE INFO

#### Article history:

Received 14 May 2009

Received in revised form 3 August 2009

Accepted 4 August 2009

Available online 11 August 2009

#### Keywords:

Dendrimers

Convergent synthesis

Isatin

Superelectrophilic substitution

### ABSTRACT

Dendrons and dendrimers were convergently prepared using an isatin as AB<sub>2</sub> monomer by superelectrophilic arylation in trifluoromethanesulfonic acid. This strategy has the advantage that incomplete reactions of the AB<sub>2</sub> monomer are minimized, thus simplifying purification. As the obtained dendrons/dendrimers are analogues of the hyperbranched polymers with a degree of branching of 100% developed earlier in our group, an opportunity is created to compare the latter with their structurally perfect counterparts.

© 2009 Elsevier Ltd. All rights reserved.

### 1. Introduction

Dendrimers have attracted a lot of attention during the last two decades. They have a perfectly controlled, highly branched, monodisperse structure and find applications in numerous fields such as catalysis, biosensors, MRI, as endo- and exoreceptors, drug delivery systems and unimolecular micelles [1–7].

Here we report the first application of the potential superelectrophilicity of isatin (a heterocyclic 1,2-dicarbonyl compound) in the convergent synthesis of dendrimers.

It is well known that in superacidic environment isatin, as a 1,2-diketone, gets doubly protonated and the resulting superelectrophile condenses readily with aromatic hydrocarbons to give exclusively 3,3-diaryloxindoles in high yield. This is a result of the much higher reactivity of the monoarylated intermediate compared to the reactivity of

the starting material and the reversibility of the first arylation (Scheme 1) [8].

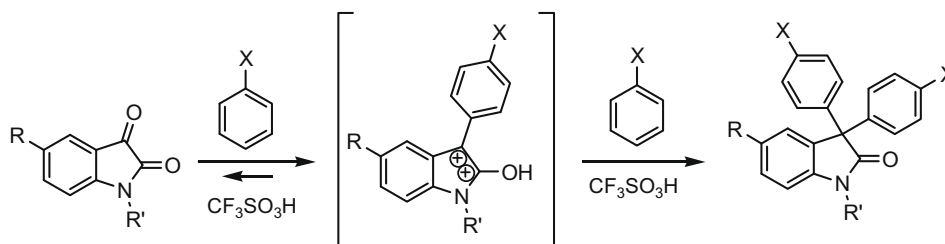
Based on this effect we previously synthesized hyperbranched poly(arylene oxindole)s with a degree of branching of 100% [9,10]. Even though both these hyperbranched polymers and the target analogous dendrimers would have a poly(arylene oxindole) backbone consisting of exclusively dendritic and terminal units, there are some important differences to consider. Dendrimers are monodisperse and have a spherical structure whereas hyperbranched polymers do not have such a perfectly controlled structure, which is apparent on the basis of their relatively high dispersity of molar mass and topology. Given that 100% branched hyperbranched polymers are still poorly studied in literature, having at hand the analogue dendrimers of the fully branched hyperbranched poly(arylene oxindole)s developed in our group could offer the opportunity to study their differences in more detail. This is a first issue that triggered our interest in the dendrimers described below.

On the other hand, the convergent synthesis of dendrimers is often complicated by purification problems caused

\* Corresponding author. Tel.: +32 16 32 7464; fax: +32 16 32 7990.

E-mail address: [Mario.Smet@chem.kuleuven.be](mailto:Mario.Smet@chem.kuleuven.be) (M. Smet).

<sup>1</sup> Fax: +32 16 32 3902.



Scheme 1. Superelectrophilic arylation of isatin.

by the presence of only partly reacted protected  $AB_n$  monomer in the reaction mixture. In convergent dendrimer synthesis, dendrons are prepared first, starting from the periphery, and attached to the core in the final step of the sequence, resulting in a dendrimer. Although this methodology has many advantages as compared to the divergent strategy, the synthesis can be complicated already from relatively low generations on due to incomplete reaction of the  $AB_n$  monomer with the activated dendrons in the propagation step due to steric hindrance. If the presence of the byproduct resulting from this partial reaction could be avoided, this would simplify the purification to a significant extent. Therefore, we reasoned that the superelectrophilic arylation of isatin, used as the  $AB_2$  monomer, could be an attractive strategy for dendrimer growth as in this case complete reaction of both B functionalities is strongly favoured and hence less byproducts should be expected.

As will be discussed in more detail, the commercially available 5-bromoisatin was used as  $AB_2$  monomer to construct the dendrons.

## 2. Experimental part

All chemicals were purchased from ACROS Organics or Sigma–Aldrich and used as received without further purification. NMR spectra were recorded on a Bruker Avance 300 (300 and 75 MHz) or a Bruker Avance 400 (400 and 100 MHz). Gel permeation chromatography (GPC) was performed with a Shimadzu apparatus (UV and RI detection) with a PLgel D column (Polymer Laboratories) and tetrahydrofuran as the eluent at 30 °C and 1 ml/min calibrated with linear polystyrene standards.

The MALDI-TOF MS spectra for compounds **10**, **12**, **21**, **22**, **24** and **25** were recorded on a Reflex IV instrument (Bruker Daltonic, Bremen, Germany), equipped with a nitrogen laser (337 nm) and pulsed ion extraction accessory. The instrument was operated in the positive ion, reflectron mode and calibrated using a standard peptide mixture containing angiotensin II (1045.54 Da), angiotensin I (1295.68 Da), substance P (1346.73 Da), bombesin (1618.82 Da), ACTH clip 1–17 (2092.08 Da) and ACTH clip 18–39 (2464.19 Da) (Bruker Daltonic). The samples were dissolved in tetrahydrofuran. 1  $\mu$ l of this sample solution was transferred to a ground steel target plate, mixed with 0.5  $\mu$ l of a saturated solution of  $\alpha$ -cyano-4-hydroxycinnamic acid (in tetrahydrofuran) and air-dried.

The MALDI-TOF MS for compounds **7**, **8**, **9**, **11**, **23**, **26** were recorded on an Applied Biosystems Voyager DE STR

MALDI-TOF spectrometer equipped with 2-m linear and 3-m reflector flight tubes and a 337-nm nitrogen laser (3-ns pulse). All mass spectra were obtained with an accelerating potential of 20 kV in positive ion mode and in linear and/or reflector mode. *Trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (BMPM) (20 mg/mL in THF) was used as a matrix, sodium iodide (1 mg/mL in THF) was used as a cationating agent, and polymer samples were dissolved in THF (1–2 mg/mL). The ratio of these three solutions on the sample plate was 2/1/1. A poly(ethylene oxide) standard ( $M_n = 10000$  g/mol) was used for calibration. All data were processed using the Data Explorer (Applied Biosystems).

### 2.1. Synthesis of 3,3-bis(4-chlorophenyl)-5-bromo-2-indolone (= B-terminated non-activated dendron of the 1st generation) (**3**)

A mixture of 5-bromoisatin (**1**) (12.0 g, 53.1 mmol) and chlorobenzene (**2**) (39.8 g, 0.354 mol) in trifluoromethanesulfonic acid (triflic acid) (16 ml) was stirred for 24 h at room temperature. After pouring into ice, the mixture was extracted with  $CH_2Cl_2$  (3  $\times$  50 ml), washed with a saturated solution of  $NaHCO_3$ , dried over  $MgSO_4$  and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel and  $CH_2Cl_2$ /EtOAc (95/5) as eluent) to obtain the B-terminated non-activated dendron of the 1st generation **3** (15.4 g, 68%).

MS (CI):  $m/z = 434$  ( $MH^+$ ).  $M_p$ : 125 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta = 9.55$  (s, 1H, NH), 7.36 (dd, 1H,  $^3J = 8.4$  Hz,  $^4J = 2.0$  Hz, 6-H isatin), 7.28 (d, 4H,  $^3J = 8.4$  Hz, *m*-H to Cl), 7.25 (d, 1H,  $^4J = 2.0$  Hz, 4-H isatin), 7.16 (d, 4H,  $^3J = 8.4$  Hz, *o*-H to Cl), 6.82 (d, 1H,  $^3J = 8.2$  Hz, 4-H isatin).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta = 179.0$ , 139.1, 139.0, 134.7, 134.1, 131.8, 129.6, 129.0, 126.4, 115.8, 112.2, 62.2.

### 2.2. Synthesis of 4-methyl-4'-phenoxybenzophenone (**4**)

*p*-Toluoyl chloride (17.8 ml; 135 mmol) was added to a suspension of diphenyl ether (22.0 g; 135 mmol) and aluminium trichloride (20.8 g; 156 mmol) in dichloromethane (25 ml). After heating at reflux temperature for 10 min the mixture was poured onto a mixture of ice (200 ml) and concentrated HCl (20 ml) and was extracted with dichloromethane (3  $\times$  200 ml). The combined organic phases were washed with a saturated solution of  $NaHCO_3$ , dried over magnesium sulfate and concentrated under reduced pressure. The pure compound was obtained by washing with

Download English Version:

<https://daneshyari.com/en/article/1402686>

Download Persian Version:

<https://daneshyari.com/article/1402686>

[Daneshyari.com](https://daneshyari.com)