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Assessment of the regioselectivity in the condensation reaction of unsymmetrical *o*-phthaldialdehydes with alanine

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ABSTRACT

One approach for the synthesis of isoindolinones, a privileged bioactive heterocyclic core structure, involves a condensation reaction of *o*-phthaldialdehydes with a suitable nitrogen-containing nucleophile. This fascinating reaction is revisited here in the context of the use of *o*-phthaldialdehydes that contain additional substituents in the aromatic ring leading to a detailed analysis of the regioselectivity of the reaction. Eleven monosubstituted *o*-phthaldialdehydes were synthesised and reacted with alanine. The regioselectivity observed across the eleven substrates led to the design of a disubstituted substrate that reacted with very high control. A gram-scale reaction followed by esterification gave one major regioisomer in high yield. In addition, the regioselectivity observed on reaction of two novel mono-deuterated substrates led to an increased mechanistic understanding.

1. Introduction

The isoindolinones make up an important class of bioactive molecules that includes the known drugs Pazinaclone (**1**),[1a] Indoprofen (**2**)[1b] and Chlorthalidone (**3**)[1c] (Fig. 1a).

Common methods of obtaining isoindolinones that are unsubstituted in the aromatic ring, for example compound **4** (Fig. 1b), include selective reduction of **5**,[2] reductive amination-cyclisation of **6**[3] or **7**[4] with a primary amine (RNH_2) and, of interest here, the condensation reaction of *o*-phthaldialdehyde (**8**) with a primary amine (RNH_2).[5,6a]

To date, the majority of studies performed on this condensation reaction have focused on evaluating the scope of the amine nucleophile that can be tolerated in the reaction[5a,5b,5d,6a,6b] and/or proposing potential reaction mechanisms.[5a,5b,6] In contrast, examples of the use of this condensation reaction with monosubstituted *o*-phthaldialdehydes are rare (SI1 part I). One report describes a regioselectivity of 1:1 for the products **11**:**12** resulting from the condensation of **9** with **10** (Scheme 1a).[7] However, the observed regioselectivity was measured only after filtration or purification by column chromatography. Isolated yields for the formation of a single isomer, **14** in most cases, resulting from the condensation of **13** with various amines have also been reported (Scheme 1b).[8] Other studies have provided only isolated yield(s) after purification (for one or for each isomer), incomplete regioisomeric ratio (rr) data within a series or have claimed to form a single regioisomer (no yield provided) without discussing the other possible isomer (SI1 part I).[7–9]

The work reported here revisits this issue by presenting a detailed study of the regiochemical outcome of the condensation of alanine (**16**) with 3-monosubstituted *o*-phthaldialdehydes **17** (to give **18** and **19**, Scheme 1c) and with 4-monosubstituted *o*-phthaldialdehydes **20** (to give **21** and **22**, Scheme 1d). Based on the initial results, the design of a highly regioselective substrate was achieved consistent with an improved understanding of the reaction. Further mechanistic insights were provided by the use of novel mono-deuterated substrates.

2. Results and discussions

2.1. Synthesis of monosubstituted *o*-phthaldialdehydes

Five 3-substituted *o*-phthaldialdehydes **17a-e** were synthesised using 2–5 step routes involving either a Swern oxidation of the corresponding diol **23** or an acetal deprotection of the corresponding monoacetal **24** or diacetal **25** (Scheme 2 and SI1 part II.1 for more details). It should be noted that the synthesis of pure samples of **17a-e** was particularly challenging (in line with literature reports[10]) with significant decomposition occurring during purification attempts and on storage. In several cases freshly

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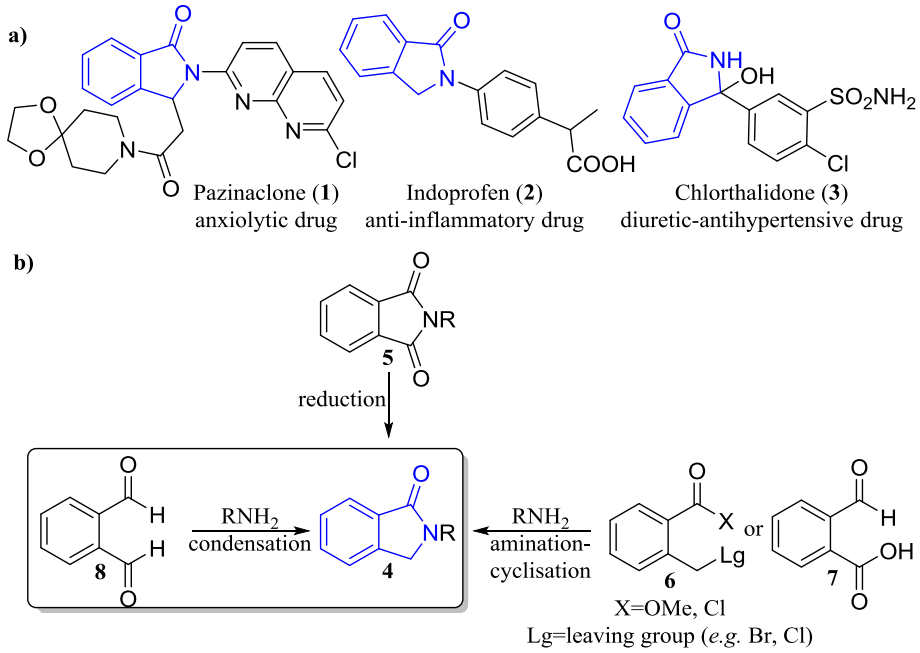

Fig. 1. a) Structure of known bioactive isoindolinone containing drugs;[1] **b)** Overview of some of the different routes used to prepare the isoindolinone core **4**.[2-6a]

prepared crude samples of the dialdehydes were used (Table 1, footnote c). Additionally, six 4-monosubstituted *o*-phthaldialdehydes **20a-f** were synthesised using 2–3 step routes either involving a Swern oxidation of the corresponding diol **26** or an acetal deprotection of the corresponding monoacetal **24** (Scheme 2 and SI1 part II.2 for more details).

2.2. Regioselectivity of the condensation reaction of mono-substituted o-phthaldialdehydes

The mono-substituted *o*-phthaldialdehydes **17a-e** and **20a-f** were refluxed for 4 h with alanine (**16**, 1.2 equivalents) in anhydrous acetonitrile before the reaction was concentrated *in vacuo*. The crude reaction mixtures (except when specified, Table 1) were then analysed using a quantitative ^{1}H NMR experiment. A baseline correction was applied using MestReNova-9 software and integrations were calculated relative to one proton on deconvoluted peaks (see Fig. 2 for an example of the analysis applied to the formation of **18a/19a** and SI1 part III.1 for the rest of the NMR analysis; also see the experimental section below for a detailed explanation of the analytical protocol used).

In two of the condensation reactions the structure of the major regioisomer was identified by comparison with the ^{1}H NMR spectrum of a pure sample of one of the regioisomers (for **18a**/**19a**, **21a**/**22a**, for the synthesis of authentic isomers see SI1 part III.2). In the rest of the cases, advanced NMR techniques (HSQC, HMBC, COSY) applied to the crude reaction mixture were used to assign the structure of the major regioisomer. Considering the analysis of the regioisomeric mixture of **18b/19b** as an example (Fig. 3), the proximity of a carbonyl was observed to shift the signal corresponding to the aromatic H7 proton in **18b** and the methyl H1′ protons in **19b** downfield (Fig. 3a and b). Identification of H7 in **18b** was further validated by its correlation with C1 in the HMBC analysis of the regioisomeric mixture (Fig. 3a). In contrast, H4 in **19b** showed a correlation with C3 in this HMBC analysis (Fig. 3c). Using the correlations observed in the COSY spectrum (Fig. 3d), the signals corresponding to H5 and H6 for **18b** and **19b** were finally assigned. The value of the integrals in the 1D quantitative ^{1}H NMR spectra enabled the identification of **18b** as major isomer.

Having assigned the signals corresponding to the two regioisomeric products in each case, and using as many peaks as possible, an average percentage of the major isomer with its 95% confidence interval was then calculated for each reaction (SI1 part III.3). The reaction and its analysis were also carried out in duplicate for each substrate demonstrating high reproducibility (SI1 part III.3).

In both the 3- and 4-substituted series, the regioselectivity of the condensation reaction was dependent on the substituent employed, as expected. In the 3-substituted series, the presence of either an electron-donating or an electron-withdrawing substituent favoured the formation of regioisomer **18** although a decrease in the electron-donating strength led to a clear decrease in the regioselectivity. In the 4-substituted series it was observed that as the electron-donating properties of the substituent decreased (OMe > F/Br/Me > CF_3 > NO_2), the regioselectivity decreased and then switched from **21** being the major isomer to its regioisomer **22** being the dominant product. In both series, the methoxy substituent gave the highest regioselectivity leading to the proposal that a dimethoxysubstituted *o*-phthaldialdehyde **27** (Scheme 3) should react with very high regioselectivity.

2.3. Dimethoxysubstituted o-phthaldialdehyde

As the monomethoxysubstituted substrates **17a** and **20a** led to the major regioisomers **18a** and **21a** respectively, it was proposed that a 3,5-dimethoxysubstituted dialdehyde **27** would react to give **28** with an increased regioselectivity compared to **17a** and **20a** (Scheme 3). A 6-step route was developed to obtain **27** (SI1 part IV.1) and pleasingly, its subsequent reaction with alanine (**16**) gave **28** as the major regioisomer in an **88**:**12** ratio of **28**:**29** (Scheme 3 and SI1 part IV.2).

On scaling up the condensation reaction of **27** (0.97 g instead of 30 mg initially used), the quantitative ^{1}H NMR analysis of the crude reaction mixture was not carried out in this case due to the low solubility of the isoindolinone products requiring a large amount of deuterated solvent for their complete dissolution (Scheme 3). Purification by column chromatography led to the pure and