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Synthesis of benzoic acids and polybenzamides containing tertiary alkylamino functionality

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ABSTRACT

The high-yielding and easily scalable synthesis of a number of benzoic acids bearing a tertiary alkylamino functionality has been achieved. The flexible synthesis began from readily available aminobenzoic acids or terephthaloyl chloride and requires almost no chromatography. Coupling of the synthesised amino acids to a range of substituted anilines was achieved when utilizing a specific combination of DIC, HOBt and DMAP.

1. Introduction

Tertiary alkylamines are a common functional group found in, and added to, a number of polymeric materials, pharmaceutical compounds and natural products. Tertiary amines are commonly added to increase the aqueous solubility and, in the case of medicinal compounds, to increase interactions with the pharmacological target.[1] Benzoic acid and benzamide moieties containing a tertiary alkylamine have been incorporated into peptidomimetic proteasome inhibitors[2] (e.g., **1**, Fig. 1), anti-inflammatory agents[3] (e.g., **2**), kinase inhibitors[3] and antitumour agents.[4,5] They are also frequently found in synthetic DNA minor groove binding compounds[6] (MGBs), such as compound **3**, where the aminobenzamide fragments often mimic a heterocycle attached to a guanidine group. In our current investigation of polybenzamide DNA MGBs we wished to develop a robust synthesis amenable to a range of polybenzamides containing a variety of tertiary amines.

2. Results and discussion

We decided to prepare the benzoic amino acids of type **4** and **5** (Fig. 2) using a benzyl ester to protect the carboxylic acid functionality as we initially found that use of the methyl or ethyl esters was problematic due to the polarity and water solubility of the intermediates. The desired procedures would also require little or no chromatographic purification, which would reduce the possibility of compound loss due to their inherent polarity. This would hopefully allow a scalable synthesis of a range of benzoic amino acids of type **4** and **5**, which are useful building blocks in the synthesis of bioactive compounds.

Our initial investigation was into the synthesis of *N*,*N*-dialkylgylcine amides of *meta*- and *para*-aminobenzoic acids (e.g., **4**),

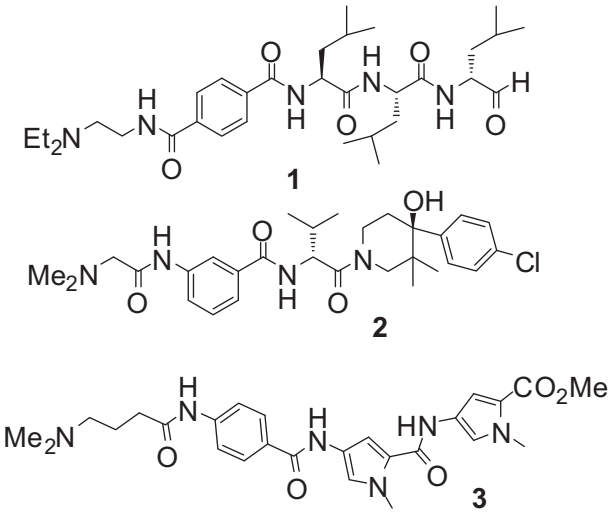

Fig. 1. Examples of compounds with benzamide tertiary amide functionality.

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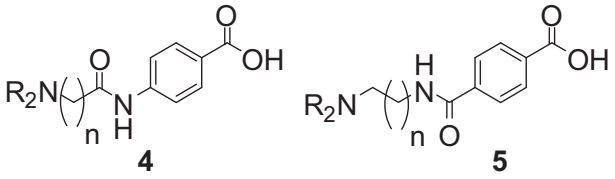
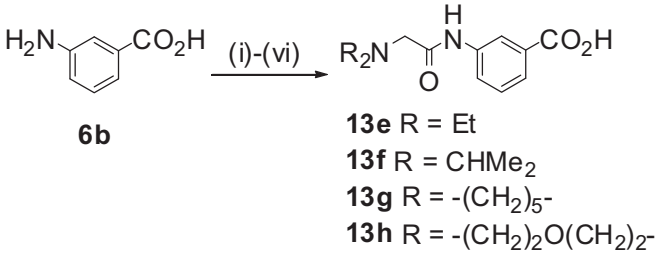


Fig. 2. Benzoic acids containing tertiary alkylamino moieties.



Scheme 2. Reagents, conditions and yields: (i) $(Boc)_2O$, NaOH, 1:1 dioxane/water, 0 °C to rt, 98%; (ii) Cs_2CO_3, BnBr, DMF, 0 °C to rt, 2.5 h, 91%; (iii) 3:1 DCM/TFA, rt, 1 h, 98%; (iv) 1.1 equiv bromoacetyl bromide, DCM, 0 °C to rt, 20 h, quant.; (v) 2 equiv amine, DCM, reflux, 18 h, for **12e**, $HNEt_2$, 91%.; for **12f**, HN^iPr_2, quant; for **12g**, piperidine, quant.; for **12h**, morpholine, quant.; (vi) 10% w/w of 10% Pd/C, H_2 (1 atm), MeOH, rt, 3 h, **13e**–**h**, quant.

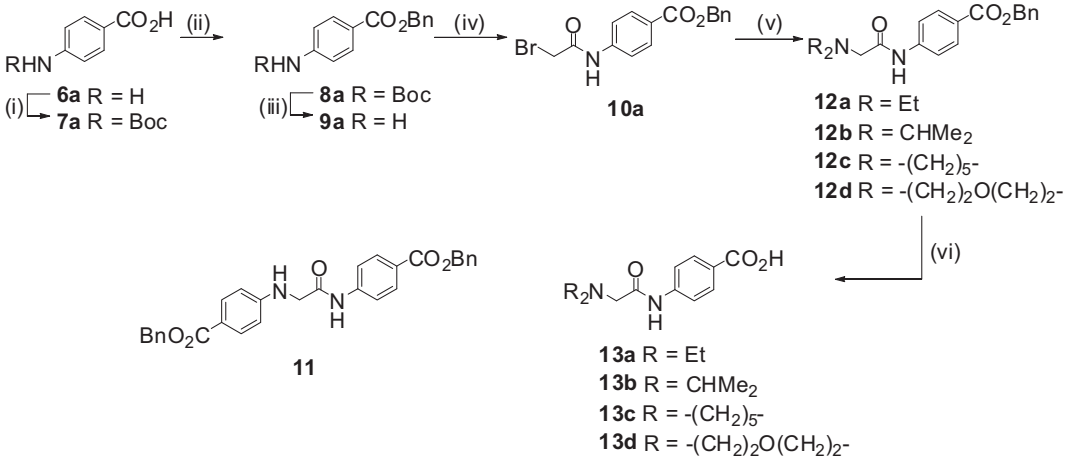
a commonly added functionality found in a number of synthetic materials.[3,7] Whilst there are a number of methods that are non general, in that a dialkylglycine component, most commonly commercially available *N*,*N*-dimethylglycine, is added complete to an alkyl ester of an aminobenzoic acid, we desired a flexible approach, where the variable amine component could be easily modified. The use of a benzyl ester, which would be removed by hydrogenolysis, would also reduce the difficulty in the isolation of the free amino acid as the hydrolysis of the small alkyl ester is reported with highly variable yields.[1,3,4]

Our synthesis began from *p*-aminobenzoic acid **6a**, which was Boc protected using di-*tert*-butyl dicarbonate in dioxane/water[8] giving acid **7a** in 87% yield (Scheme 1). Acid **7a** was then converted into benzyl ester **8a**, using benzyl bromide and Cs_2CO_3 in DMF, before Boc deprotection with trifluoroacetic acid gave benzyl 4-aminobenzoate **9a** in 81% yield over two steps. Purification for both steps involved simple workup procedures and gave solids pure enough for use but, which could be recrystallized if required. Aniline **9a** was then reacted with bromoacetyl bromide in DCM at 0 °C to give bromide **10a** in quantitative yield. It should be noted that if bromoacetyl bromide was added at room temperature exclusive formation of the double addition product **11** occurred. Bromide **10a** was then heated at reflux with either diethylamine, diisopropylamine, piperidine or morpholine to give tertiary amines **12a**–**d** in 97–100% yields. With the tertiary amino functionality introduced, the final step was the hydrogenolysis of the benzyl ester. This was achieved using catalytic 10% Pd/C (1 atm H_2) in methanol giving, after filtration, the desired acids **13a**–**d** in quantitative yields.

For the synthesis of acids of type **4** with a longer spacer unit between the amide and tertiary amine moieties we initially investigated the coupling aniline **9a** with 4-bromobutanoic acid in an effort for form amide **14** (Scheme 3). However whilst a number of conditions were trialled, this proved unsuccessful giving only a complex mixture of products, including lactam **15** in low yields. We therefore decided to install the complete γ-amino acid in an effort to alleviate these problems.[9] Thus, ethyl 4-bromobutanoate **16** was reacted with equimolar amounts of either dimethylamine or morpholine and when heated at reflux in toluene, gave amino esters **17a** and **17b** in 92% and 97% yields, respectively.[10,11]

Hydrolysis of esters **17a**–**b** using concd hydrochloric acid gave amino acid salts **18a**–**b** in quantitative yield. Coupling of acids **18a**–**b** with aniline **9a** or **9b** gave amides **19a**–**d** in 65–74% yields. The coupling reaction was best performed using the water soluble carbodiimide, EDC, the byproducts of which were easily separable from the benzyl esters **19a**–**d**. Hydrogenolysis of esters **19a**–**d** gave the desired acids **20a**–**d** in quantitative yields (Scheme 3).

For the synthesis of acids **5**, with reversed amide connectivity, we began by preparing benzyl 4-(chlorocarbonyl)benzoate **21** adapting methods from the patent literature.[11] Conversion of ter-



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When *meta*-aminobenzoic acid **6b** was used in place of acid **6a**, following the same procedures resulted in *meta*-substituted benzoic acids **13e**–**h** in 75–83% yields over the six steps (Scheme 2). None of the steps required chromatographic purification and each step was performed between 5 and 100 mmol scale with no appreciable change in yields.

ephthaloyl chloride **22** to the dibenzyl ester **23** was achieved using benzyl alcohol in the presence of NEt_3 and gave dibenzyl terephthalate **23** in 88% yield (Scheme 4). Mono-hydrolysis of diester **23** using lithium hydroxide in acetone/water gave acid **24**, in 93% yield, which was converted, using oxalyl chloride, into acid chloride **21** in quantitative yield. Reaction of acid chloride **21** with amines