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Research Article

Microwave-assisted cyclocondensation of 1,2-diaminobenzene with [4-^{18}F]fluorobenzoic acid: microwave synthesis of 2-([4-^{18}F]fluorophenyl) benzimidazole

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Summary

The synthesis of 2-([4-^{18}F]fluorophenyl)benzimidazole, which has potential to be used as a building block for many endogenous and pharmaceutical compounds, is reported. A range of solvents and catalysts as well as conventional and microwave heating have been investigated to optimise the reaction conditions. The cyclocondensation of 1,2-diaminobenzene with radiolabelled [4-^{18}F]fluorobenzoic acid in neat methanesulphonic and polyphosphoric acids under microwave heating led rapidly to the cyclised phenylbenzimidazole. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: fluorine-18; microwave; benzimidazole; cyclocondensation

Introduction

The use of microwaves to enhance synthetic chemical reactions has become increasingly popular over the last decade. The first reported applications of microwaves in synthetic chemistry were in 1986.[1,2] While the uptake of microwaves as a synthetic tool was initially slow, there has been an exponential increase in its reported use in recent years. There are many areas

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in which microwaves have been found to be useful. In radiochemistry these have been summarised in several review articles.[3–5]

Benzimidazoles are found in many natural compounds (e.g. histidine and pyrimidines) and are important building blocks for pharmaceuticals.[6] If reactions forming this ring system could be rapidly performed, a wide range of compounds labelled with short lived positron emitters (^{11}C $t_{1/2}$ 20 min, ^{18}F $t_{1/2}$ 110 min) might be synthesised. When cyclization of the aromatic diamine with an aliphatic acid was performed with microwave heating the reaction proceeded rapidly.[7] However aromatic and sterically hindered alkyl acids generally require more vigorous conditions with respect to heat, pressure and reaction time. The synthesis of 2-phenylbenzimidazole in $\approx$ 10 min using a microwave oven has been recently reported.[8] Here we present the results of experiments in which the cyclocondensation of 1,2-diaminobenzene with [4-^{18}F]fluorobenzoic acid (Figure 1) is rapidly achieved using microwave heating, as briefly reported previously.[9]

Results and discussion

Initial cyclization experiments with [4-^{18}F]fluorobenzoic acid were conducted in ethanol with acid catalysis (HNO_3). These conditions had given excellent conversion to benzimidazole when performing the cyclocondensation with formic acid under microwave-enhancement,[7] a reaction which also highlighted the gains that can be made when employing microwave heating rather than conventional heating. Here when the formic acid was replaced by [4-^{18}F]fluorobenzoic acid under otherwise identical conditions (1 min at 100 W) there was no reaction. Cyclization did not occur, even when power settings were doubled (200 W) or reaction times extended (5 min at 60 W and 2 min at 100 W).

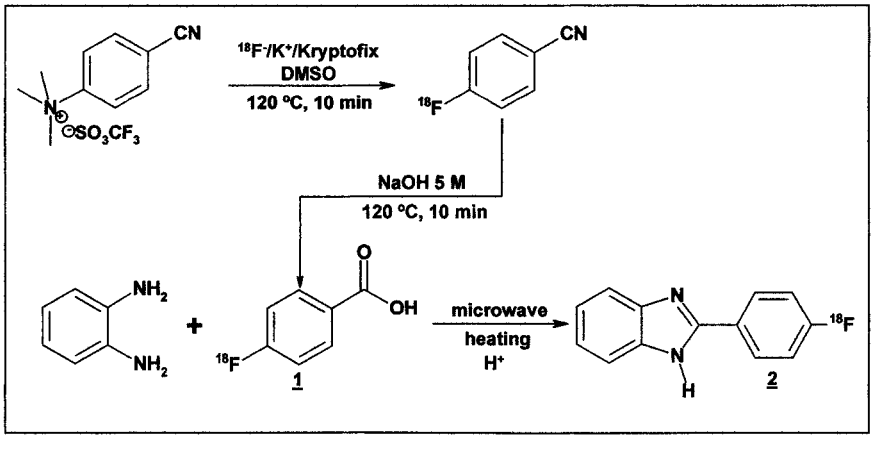

Figure 1. Synthesis of [4-^{18}F]fluorobenzoic acid (1) and its subsequent cyclocondensation with the diamine to form 2-([4-^{18}F]fluorophenyl)benzimidazole (2)

Similarly, with all other conditions the same, no products were observed using the unlabelled 4-fluorobenzoic acid at higher concentrations after 72 h of conventional heating at 100°C.

Even using microwave heating, the temperatures reached for reactions performed in ethanol do not exceed 100°C by many degrees,[10] unless the vessels are pressurized. To try and increase conversions to the phenylbenzimidazole an obvious step was to attempt the reactions in a range of different solvents that could offer higher temperatures. The solvents investigated can be placed into four groups depending on the conversions observed (Table 1).

All the samples were initially heated at 50 W, typically in 1 min steps, but, if the solvent was amenable, the power was increased to 75 or 100 W and heating time was extended to as much as 5 min. The catalyst used was also varied. Common mineral acids (nitric, phosphoric, hydrochloric, sulphuric) were employed as was *para*-toluene sulphonic acid. None of these solvent/acid catalyst combinations gave appreciable amounts of cyclization (Table 1, Groups A–C).

The most encouraging results were obtained using neat methanesulphonic acid and polyphosphoric acid (Table 1, Group D). To our knowledge there have been only a few reported[8,11] uses of these reagents under microwave conditions. This is surprising as both heat well in a microwave field: methanesulphonic acid reaches 244°C after just 1 minute at 75 W (77°C above its normal boiling point) in the equipment used here. We have, however, found that they heat unpredictably in the presence of other solvents. So the solvent in which the labelled acid was eluted from the solid phase extraction column had to be evaporated prior to performing the cyclocondensation.

The experiments performed with polyphosphoric acid may have had a slight 'head-start' as the solvent (highly viscous) had to be heated to 70°C so it could be transferred into the narrow necked reaction vessel. However, regular analysis showed no sign of product formation at t_0.

In the reaction with polyphosphoric acid the labelled acid was completely consumed after just 3 min (in three, 1 min intervals) heating at 75 W (Figure 2). With methanesulphonic acid, conversion of ^{18}F labelled acid to phenylbenzimidazole was 53% after 2 min (two, 1 min intervals) heating at 75 W (Figure 3). When these reactions were performed with conventional heating,

Table 1. Conversions observed in a range of solvents.

Group	Solvent	Yields
A	Water, DMSO, *N*-methyl piperidine	No reaction
B	Acetonitrile, DMF, diethylene glycol, iso-propanol	$<5\%$
C	Propylene carbonate	$\approx 10\%$
D	Polyphosphoric acid, methanesulphonic acid	$>50\%$

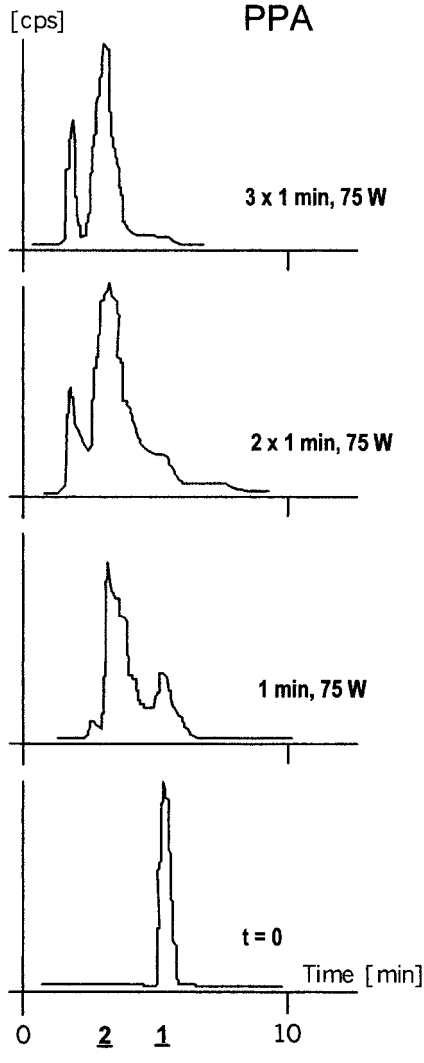

Figure 2. Radio HPLC trace of reaction conducted in polyphosphoric acid (PPA)

no product was detected after 24 h at 100°C. Comparable yields > 65% were obtained after 3–4 h at 180°C.

Experimental

All compounds and solvents were of analytical grade and used as supplied without further purification. All were obtained from Aldrich except DMF (Fluka) and HNO_3 (Merck). 4-Trimethylammonium-benzonitrile trifluoromethanesulphonate was produced from 4-(dimethylamino)benzonitrile according to literature methods.[12,13]

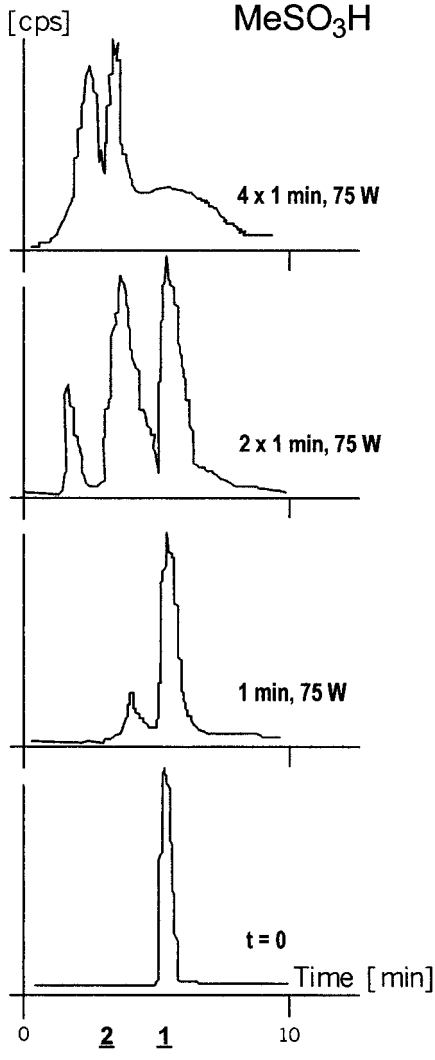

Figure 3. Radio HPLC trace of reaction conducted in methanesulphonic acid

The reference 2-(4-fluorophenyl)benzimidazole was synthesized according to literature methods[14,15] and was characterized using NMR and IR spectroscopy. ^{1}HNMR, Bruker Avance 300 WB, (CD_3OD) δ [ppm]: 7.25-7.35 (m, 4H), 7.60-7.65 (m, 2H), 8.05-8.15 (m, 2H). NH proton indistinguishable from background noise. IR spectroscopy, Perkin Elmer FT-IR Spectrum RX1, gave absorption at 1604 cm^{-1} which is indicative of the N–H stretch in a benzimidazole.

[4-^{18}F]Fluorobenzoic acid was synthesized as described previously.[16] Briefly, no-carrier-added [^{18}F]F^- was produced by the ^{18}O(p,n)^{18}F reaction using the GE Medical Systems' PETtrace cyclotron at the Karolinska Hospital/

Institute. Nucleophilic radiofluorination of 4-trimethylammonium-benzonitrile trifluoromethanesulfonate, followed by alkaline hydrolysis and solid phase extraction (C_{18} eluted with acetonitrile) afforded the radiochemically pure (> 99% according to radio-HPLC) [4-^{18}F]fluorobenzoic acid. The decay corrected yield was 82 ± 10% and the synthesis time was ca. 50–55 min, both counted from resolubilised [^{18}F]F^-.

Typical trials involved 1,2-diaminobenzene (3 ± 0.2 mg), an aliquot of the [4-^{18}F]fluorobenzoic acid and a total reaction volume of 1 ml. Some reactions involved addition of an acid catalyst (3 µl). When it was necessary to remove solvent after elution of the labelled acid, tetrabutylammonium hydroxide (25% in MeOH, 10 µl) was added to prevent loss of the acid during evaporation.

Heating was performed using a Microwell 10 (Personal Chemistry AB, Uppsala). The power applied varied between 50 and 200 W with the time of application varying from 1–5 min depending on the solvents used in the reaction. The reactions were conducted in 10 ml Pyrex reaction vessels[17] sealed with a screw cap and Teflon coated silicon septa.

Radioanalytical HPLC was performed on a system consisting of a Shimadzu LC 6A pump, a Shimadzu SPD-6A UV-spectrophotometer and a Beckman model 170 radioisotope detector to monitor the UV-absorption (λ = 228 nm) and the radioactivity, respectively. Data analysis was performed using a Shimadzu C-R4A. A µBondapak C_{18} column (Waters, 300 × 3.9 mm, 10 µm) was used with a mobile phase composed of 25% MeCN and 75% H_3PO_4 (0.001 M, aq) at a flow rate of 2.5 ml/min. Samples were co-eluted with references of 4-fluorobenzoic acid and 2-(4-fluorophenyl)benzimidazole.

Conclusions

Cyclocondensation of 1,2-diaminobenzene with a ^{18}F-labelled benzoic acid was rapidly achieved using methanesulphonic acid or polyphosphoric acid with monomodal microwave heating. With these short reaction times it should be feasible to perform cyclocondensations with ^{11}C as well as ^{18}F-labelled acids to form 2-aryl benzimidazoles. The results are promising and deserve further development. Due to the handling difficulties with polyphosphoric acid, a system based around methanesulphonic acid would be preferred even though yields with polyphosphoric acid were slightly higher.

Acknowledgements

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