Synthesis of 4-acetylaminobenzo[15]crown-5

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The synthesis of 4-acetylaminobenzo[15]crown-5 is reported by the reaction of benzo[15]crown-5, glacial acetic acid and hydroxylamine hydrochloride, where C-acylation, oximation, and Beckmann rearrangement are conducted in a one–pot reaction with polyphosphoric acid as catalyst.

Keywords: 4-acetylaminobenzo[15]crown-5; polyphosphoric acid; Beckmann rearrangement

4-Acetylaminobenzo[15]crown-5 is an important intermediate in the synthesis of crown ether cyanine dyes;[1] in addition, the acetylamino group can easily be hydrolysed to give an amine,[2] which also is a useful intermediate.[3,4] The classical procedure for the synthesis of 4-acetylaminobenzo[15]crown-5 involves several steps,[2,5] typically nitration of the benzo[15]crown-5, followed by reduction of the introduced nitro group to give the amine and finally, acylation of the amine to afford the amide. In this procedure, the reduction of the nitro group is usually under a nitrogen atmosphere and catalysts such as palladium or Raney nickel are employed, which are often an inconvenience.

We now report a facile one-pot reaction which can be conducted under mild conditions and avoids the time-consuming nitration step and the inconvenient reduction step.

The reaction starts with *para*-selective C-acylation of the benzo[15]crown-5, which is followed by oxime formation and Beckmann rearrangement *in situ*. The reaction is initiated by stirring at a moderate temperature, a mixture of polyphosphoric acid (PPA), benzo[15]crown-5, glacial acetic acid and hydroxylamine hydrochloride (Scheme 1).

At the beginning of the reaction, the temperature should be slowly increased to 60°C, then stirred at this temperature, because heating quickly and at much higher temperatures easily leads to decomposition of the benzocrown ether. Furthermore, the moderate temperature mainly results in *para*-attack in the C-acylation step; this has been confirmed by previous work on the synthesis of 4- acetylbenzo[15]crown-5.[6]

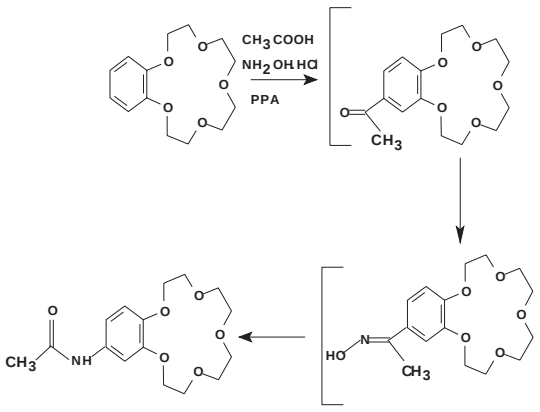
In the reaction, polyphosphoric acid is chosen as catalyst with advantages of mild acid characteristics combined with versatility in facilitating Friedel–Crafts reactions and Beckmann rearrangements.[7,8] Further, after the polyphosphoric acid is hydrolysed, the solution is washed with sodium carbonate to readily remove acidic by-products. No organic solvents need be used during the course of the reaction, with a resulting environmental benefit, *i.e.* no atmospheric pollution by escaping solvents.

In conclusion, we have found a facile and convenient method for the synthesis of 4- acetylaminobenzo[15]crown-5 with the advantage of mild conditions, simple operation, short reaction time and less pollution compared with the classical procedure. It is a novel procedure for the synthesis of 4-acetylaminobenzo[15]crown-5.

Experimental

Melting point was determined in open capillaries and is uncorrected. IR spectra was recorded in KBr on a Brucker IFS66V/S spectrophotometer and ^{1}H NMR spectra on an INOVA-400MHz instrument using $CDCl_3$ as solvent and TMS as internal reference. Elemental analysis was determined on PE-2400 CHN instrument.

The synthesis of 4-acetylaminobenzo[15]crown-5 was carried out by adding benzo[15]crown-5 (6mmol; 1.61g), glacial acetic acid (7.5mmol; 0.45g) and hydroxylamine hydrochloride (6mmol; 0.42g) to



Scheme 1

a round-bottomed flask containing 10g PPA and a magnetic stirring bar with stirring at 60°C. After 10h the mixture was cooled to room temperature, ice-water (50ml) was added to hydrolyse the PPA, then neutralized with aqueous Na_2CO_3 under ice-water conditions. The aqueous solution was extracted with ethyl acetate, and the extracts were dried over Na_2SO_4. After evaporation of ethyl acetate a white solid was obtained which, upon recrystallisation from ethanol, yielded the amide (48%), m.p. 144–146°C (Lit. 144°C). Elemental analysis, Found: C 59.06, H 7.22, N 4.17; Calc: C 59.07, H 7.13, N 4.3%. IR: 3286 (N–H), 2918 (CH_3), 1656 (C–O), 1607, 1458 (Ar), 1295 (C–N), 1256 (Ar–O–CH_2), 1132(CH_2–O–CH_2), cm^{-1}. ^{1}H NMR, ?: 2.15 (s, 3H, CH_3O), 3.73–4.14 (m, 16H, 4xOCH_2CH_2O), 6.79–7.31 (m, 3H, Ar-H), 7.22 (s, 1H, NH).

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