Studies of amine oxide rearrangement: an unusual product from the reaction of 4-[*N*-alkylanilino]but-2-yn-1-ol with *m*-chloroperoxybenzoic acid

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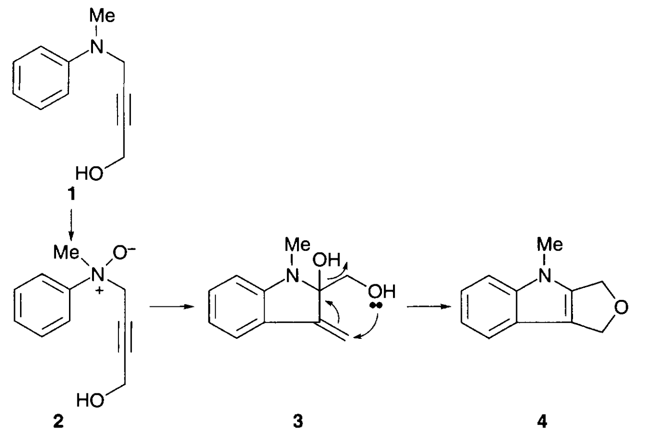
Treatment of a dilute solution of 4-[*N*-methylanilino]but-2-yn-1-ol 1 with MCPBA in chloroform/dichloromethane/benzene gives a symmetrical ten-membered cyclic bisether 5 containing two indole moieties in 56% yield.

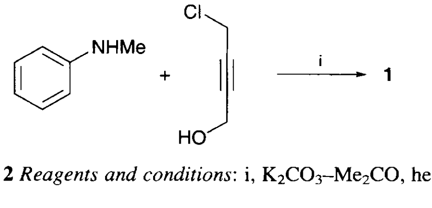
Thyagarajan and coworkers have demonstrated [1–3] the construction of the five-membered nitrogen heterocyclic ring of indole by rearrangement of aryl propynyl amine oxides. This was found to be an excellent, high yielding and one-step process. The rearrangement of the amine oxides readily occurs and the nitrogen heterocycles are obtained by simply stirring a solution of *N*-aryl propynylamine with 1 equiv. of MCPBA at room temperature. This methodology was later successfully used to form fused five-membered nitrogen heterocycles.[4–6]

From the mechanistic aspect of the reaction an initial [2,3]-sigmatropic rearrangement is followed by a [3,3]-shift and intra-molecular ketol formation to give intermediate **3** which may then react with a nucleophile like cyanide, thiophenate or benzoate. With this in mind we undertook a study of the amine oxide rearrangement of **1**. It is logical to expect the formation of a cyclic product **4** (Scheme 1) by utilising the internal nucleophile hydroxy group of **1** in the rearrangement. Here we report the results of this investigation.

The starting material 4-[*N*-methylanilino]but-2-yn-1-ol **1** was prepared by treating *N*-methylaniline with 4-chloro-but-2-yn-1-ol in acetone under reflux in the presence of anhydrous potassium carbonate. Compound **1** was obtained in 91% yield as a viscous liquid (Scheme 2).



Scheme 1

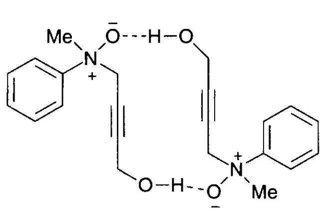


Scheme 2 *Reagents and conditions*: i, K_2CO_3–Me_2CO, heat

Treatment of **1** (0.2 mol dm^{-3}) with 1 equiv. of MCPBA (0.2 mol dm^{-3}) in CH_2Cl_2, $CHCl_3$ or C_6H_6 gave the *N*-oxide within 20 min. The reaction was monitored by TLC. However, on standing at 0–5 °C or at room temperature for 8–10 h only the starting material **1** (50%) could be isolated/detected even after column chromatography. A search of the literature revealed that a similar observation was made by Cope *et al.*[7] With the Meisenheimer rearrangement of allyl dialkyl amine oxides where the nucleophilicity of the lone pair of the amine oxide oxygen atom was reduced due to the greater tendency for hydration of the aliphatic amine oxides. Though there was no water for hydration present in our experiment it was realised that the propynylic hydroxy group in substrate **1** may be capable of reducing the reactivity of the lone pair of the oxygen atom of the amine oxide forming species **A** or **B** through inter- or intramolecular hydrogen bonding. Perhaps the [2,3]-sigmatropic rearrangement is not favoured over H-bond formation. Consequently the unstable amine oxide **2** decomposes to give the amine **1**.

To overcome this problem we carried out the reaction in a very dilute solution to reduce the extent of hydrogen bonding so as to permit [2,3]-sigmatropic rearrangement. The same experiment was repeated with **1** in a 0.025 mol dm^{-3} solution in $CHCl_3$. A white crystalline solid **5**, mp 208 °C was obtained in 56% yield ($C_{22}H_{22}N_2O_2$ from elemental analysis and mass spectroscopy). It showed λ_{max} (EtOH)/nm 225 and 272; IR ν/cm^{-1} 2920, 1460 and 1190 and ^1H NMR ($CDCl_3$, 100 MHz) δ 3.90 (6 H, s), 4.52 (4 H, s), 4.60 (4 H, s), 7.40–7.52 (6 H, m, ArH) and 7.80–8.00 (2 H, m, ArH). This data indicates structure **5** rather than **4** (Scheme 3).

The formation of **5** from **1** is easily explained by [2,3]-sigmatropic rearrangement of **2** to give intermediate **6** which then undergoes a [3,3]-shift to **7** followed by ketol formation to give intermediate **8**. Acid catalysed allylic rearrangement then occurs with the intermolecular nucleophilic attack of the hydroxy oxygen lone pair on the exomethylene of another molecule of indolenine **8** to give the dimeric product **5** (Scheme 4). There was no indication for the formation of **9** in the reaction



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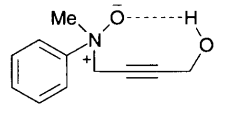

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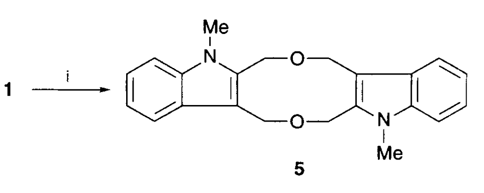
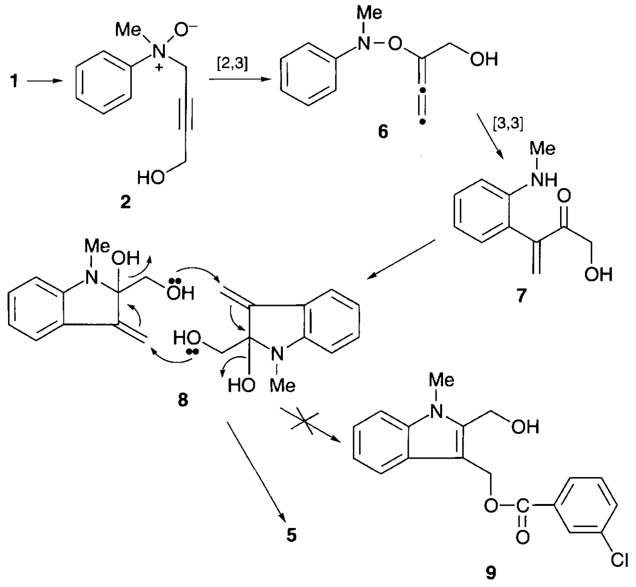


Scheme 3 *Reagents and conditions*: i, MCPBA, 0–5 °C

mixture as evidenced by TLC although MCPBA was present. It is interesting to note that when acetate derivative of **1** (0.10 and 0.25 mol dm^{-3}) in $CHCl_3$ was treated with MCPBA only **5** was obtained in 52% yield. To avoid intermolecular nucleophlic attack and encourage the intramolecular nucleophlic attack by the oxygen lone pair of the CH_2OH group, the reaction mixture was further diluted three to four times. Only product **5** was obtained, and there was no indication for the formation of **4** or **9**. In the present case the inter-molecular nucleophilic attack is favoured over intramolecular nucleophilic attack.



Scheme 4

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