

Novel synthesis of 10-membered cyclic bis-ethers from 4-(*N*-alkylanilino)but-2-yn-1-ols¹

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A number of symmetrical 10-membered cyclic bis-ethers **5a–f** are synthesized in a single step in good yields from the reaction of 4-(*N*-alkylanilino)but-2-yn-1-ols **3a–f** with *m*-chloroperbenzoic acid in dichloromethane at room temperature during 8 h.

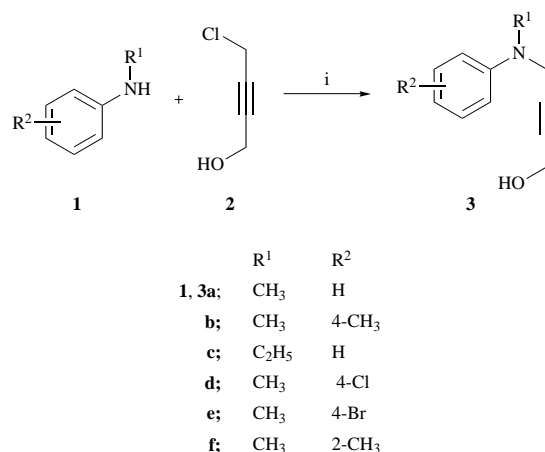
Introduction

The sigmatropic rearrangement of ylides and related anionic species is highly useful in synthetic organic chemistry, as the rearrangement is very easy to carry out.² The Wittig,³ Stevens,^{2b} Sommelet⁴ and Meisenheimer rearrangements⁵ of allylic systems have been categorised as [2,3] sigmatropic processes according to the Woodward–Hoffman rules.⁶ Extensive studies on the Meisenheimer rearrangement of allylic systems suggests an intramolecular, five-membered cyclic, low-energy transition state for the reaction.⁷ The semipolar bonding nature of the N–O bond in tertiary amine oxides⁸ is a characteristic feature of the widespread application of this type of substrate in synthetic methodology. This novel rearrangement was extended to propynylic systems by Thyagarajan and co-workers⁹ and a methodology for the synthesis of indole derivatives in high yield was developed starting from readily available *N*-alkylanilines. This protocol involves two consecutive sigmatropic rearrangements, *viz.* a [2,3] shift and a [3,3] shift, which is unique in the sense that the Claisen rearrangement in the second step takes place through two heteroatoms, and finally ketolisation leads to an intermediate 3-methyleneindoline. This key 3-methyleneindoline intermediate contains a most important allyl alcohol moiety with an exocyclic double bond, as well as a tertiary alcoholic functional group, a potential site for allylic rearrangement. Earlier work revealed that this key intermediate reacts with an 'external' nucleophile¹⁰ such as cyanide, benzoate, thiophenolate or chloride. To our knowledge no example of an 'internal' nucleophile for allylic rearrangement in this system is known. Our continued interest in this area prompted us to undertake a study of the amine oxide rearrangement of a substrate originally designed to contain an internal nucleophilic hydroxy group. Here we report the results of our investigation.

Results and discussion

The required substrates, *e.g.* 4-(*N*-alkyl-substituted anilino)but-2-yn-1-ols **3**, were prepared in good yields (83–90%) as viscous liquids by refluxing an appropriate *N*-alkylaniline **1** with 4-chlorobut-2-yn-1-ol **2** in acetone in the presence of anhydrous potassium carbonate (Scheme 1). Compounds **3a–f** were characterised from their elemental analyses and spectral data.

The tertiary amine **3a** was treated with 1 equiv. of *m*-chloroperbenzoic acid (MCPBA) in chloroform (~0.2 mol dm⁻³) at 0–5 °C. Formation of a highly polar *N*-oxide **4a** was detected by TLC within 20 min. The reaction mixture was stirred for a further 8–10 h at 0–5 °C or at room temperature. However, no new product could be isolated or detected, and we obtained recovery of 50% of the starting amine **3a** even after column chromatography. The reaction was then conducted in both dichloromethane and benzene respectively, but our results were more or less the same. The lower susceptibility of amine oxide **4a** to [2s,3s] sigmatropic rearrangement indicates the decreased



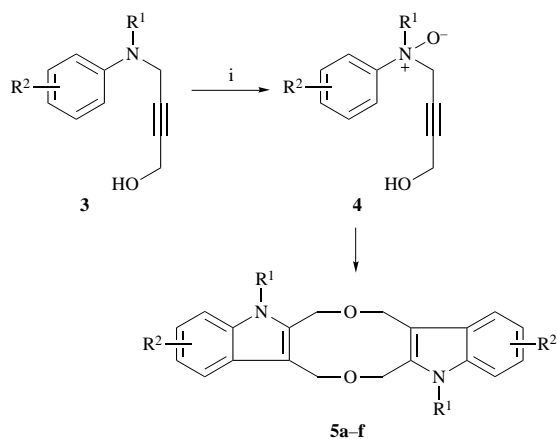
Scheme 1 Reagents and conditions: i, Me₂CO, K₂CO₃, reflux, 10 h

nucleophilicity of the unshared electron pairs of the amine oxide oxygen atom and the decreased dipole moment of the semi-polar N⁺–O⁻ bond of the amine oxide¹ due to hydrogen bonding.¹¹

The susceptibility of amine oxide **4a** to rearrangement was then determined under conditions less favourable to hydrogen bonding. To reduce the extent of hydrogen bonding¹ the reaction was carried out in very dilute solution. Oxidation of amine **3a** with 1 equiv. of MCPBA in chloroform (~0.025 mol dm⁻³) led to a white crystalline solid, mp 208 °C, in 56% yield, the IR spectrum of which showed no peak for either hydroxy or carbonyl functions.

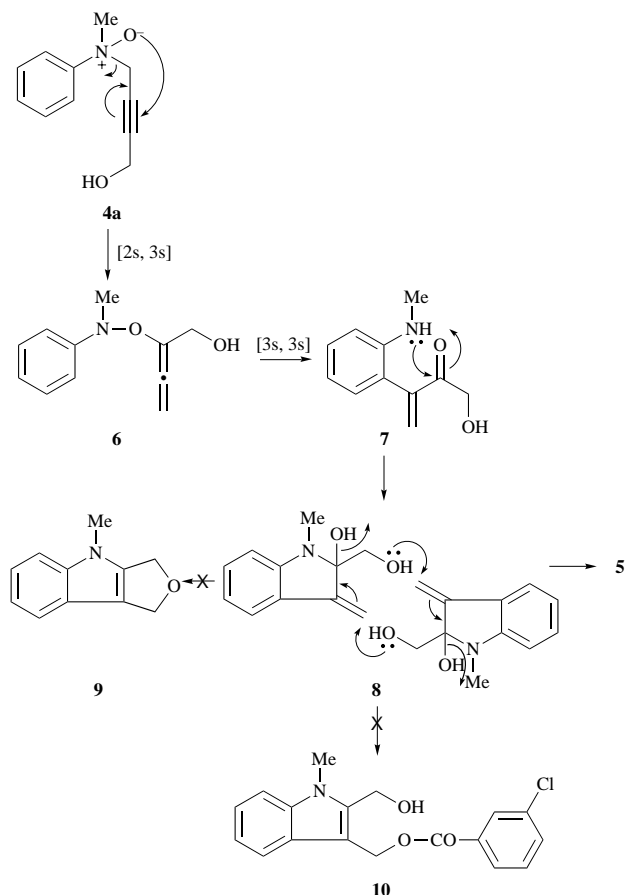
This product was found to remain unaffected when refluxed in dry methanol. The product was characterised as compound **5a** on the basis of its elemental analysis and spectral data. Formation of a single product from the reaction mixtures encouraged us to treat similarly all the remaining substrates **3b–f** with 1 equiv. of MCPBA in chloroform for 8–10 h at room temperature to furnish products **5b–f** in 51–62% yield (Scheme 2).

Our explanation for the formation of products **5** from alcohols **3**, and the involvement of the amine oxide **4**, in this conversion has decisively been confirmed. The formation of pentacycles **5** from amine oxides **4** is explicable by a [2s,3s] sigmatropic rearrangement of the amine oxide **4a** to give intermediate **6** which then undergoes a [3s,3s] shift to enone **7** followed by ketolisation to give the intermediate 3-methyleneindoline **8**. Acid-catalysed allylic rearrangement then occurs with intermolecular nucleophilic attack of the hydroxy-group's oxygen lone pair on the exomethylene moiety of another molecule of the indoline **8** to give the dimeric 10-membered cyclic bis-ethers **5** (Scheme 3). It is logical to expect the formation of a cyclic product **9** from the intermediate **8** (Scheme 3) by an intramolecular nucleophilic attack of the hydroxy-group's oxygen



	R ¹	R ²
5a;	CH ₃	H
b;	CH ₃	4-CH ₃
c;	C ₂ H ₅	H
d;	CH ₃	4-Cl
e;	CH ₃	4-Br
f;	CH ₃	2-CH ₃

Scheme 2 Reagents and conditions: i, MCPBA, CHCl₃, 0–5 °C, 8 h



Scheme 3

lone pair on the exomethylene with concomitant allylic rearrangement, but this did not occur. Additionally there is no indication of the formation of ester **10** from reaction of **8** with an external nucleophilic benzoate anion which is already present in the reaction mixture. Although there remained the possibility of the formation of compound(s) **9** and/or **10**, only product **5** was obtained even when the reaction was carried out

in very dilute solution. From the present observations it may be concluded that $-\text{CH}_2\ddot{\text{O}}\text{H}$ is a stronger nucleophile than the *m*-chlorobenzoate anion in chloroform and that intermolecular nucleophilic attack is favoured over intramolecular nucleophilic attack.

Experimental

Mps were determined in capillaries submerged in a sulfuric acid bath with an ordinary thermometer and are uncorrected. UV Absorption spectra were recorded on an Hitachi 200-20 spectrometer for solutions in absolute ethanol. IR Spectra were run for KBr discs (solid) or thin films (liquid) on a Perkin-Elmer 1330 apparatus. ¹H NMR Spectra were determined for solutions in deuteriochloroform with tetramethylsilane as internal standard on a JEOL FX-100 spectrometer at IICB, Calcutta. *J* Values are given in Hz. Elemental analysis and recording of mass spectra were carried out by RSIC (CDRI), Lucknow. Silica gel (60–120 mesh) was obtained from Qualigen (India). Light petroleum refers to the fraction with distillation range 40–60 °C.

General procedure for the synthesis of 4-(*N*-alkyl-substituted anilino)but-2-yn-1-ols 3a–f

A mixture of 4-chlorobut-2-yn-1-ol **2** (1.04 g, 0.01 mol), an *N*-alkylaniline **1a–f** (0.01 mol) and anhydrous potassium carbonate (3 g) in dry acetone (100 cm³) was refluxed for 8 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residue was extracted with chloroform (3 × 20 cm³) and the extract was dried over sodium sulfate. The solvent was removed and the product was purified by column chromatography over silica gel. The pure products were obtained as viscous liquids by elution of the column with benzene.

Compound 3a. Yield 91%, viscous liquid; $\lambda_{\text{max}}/\text{nm}$ 253 (log ϵ 2.81) and 296 (1.85); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3400, 2905, 1600, 1350 and 1200; $\delta_{\text{H}}(100 \text{ MHz})$ 1.70 (s, 1 H), 2.98 (s, 3 H), 4.04 (s, 2 H), 4.16 (s, 2 H), 6.72–7.00 (m, 2 H) and 7.12–7.40 (m, 3 H); m/z 175 (M^+) (Found: C, 75.0; H, 7.7; N, 7.6. C₁₁H₁₃NO requires C, 75.43; H, 7.43; N, 8.00%).

Compound 3b. Yield 86%, viscous liquid; $\lambda_{\text{max}}/\text{nm}$ 250 (log ϵ 2.81) and 295 (1.62); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3380, 2905, 1615, 1350 and 1200; $\delta_{\text{H}}(90 \text{ MHz})$ 2.20 (s, 1 H), 2.30 (s, 3 H), 2.95 (s, 3 H), 4.10 (s, 2 H), 4.20 (s, 2 H), 6.80 (d, *J* 8, 2 H) and 7.15 (d, *J* 8, 2 H); m/z 189 (M^+) (Found: C, 76.6; H, 8.4; N, 7.7. C₁₂H₁₅NO requires C, 76.19; H, 7.94; N, 7.41%).

Compound 3c. Yield 84%, viscous liquid; $\lambda_{\text{max}}/\text{nm}$ 253 (log ϵ 2.51) and 296 (1.92); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3385, 2980, 1600, 1350 and 1200; $\delta_{\text{H}}(90 \text{ MHz})$ 1.25 (t, *J* 6, 3 H), 2.20 (s, 1 H), 3.50 (q, *J* 6, 2 H), 4.10 (s, 2 H), 4.25 (s, 2 H), 6.80–7.00 (m, 3 H) and 7.20–7.40 (m, 2 H); m/z 189 (M^+) (Found: C, 75.8; H, 7.8; N, 7.7. C₁₂H₁₅NO requires C, 76.19; H, 7.94; N, 7.41%).

Compound 3d. Yield 90%, viscous liquid; $\lambda_{\text{max}}/\text{nm}$ 258 (log ϵ 2.93) and 304 (2.20); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3420, 2900, 1600, 1500 and 1200; $\delta_{\text{H}}(90 \text{ MHz})$ 2.35 (s, 1 H), 2.95 (s, 3 H), 4.05 (s, 2 H), 4.20 (s, 2 H), 6.75 (d, *J* 8, 2 H) and 7.25 (d, *J* 8, 2 H); m/z 209 and 211 (M^+) (Found: C, 62.77; H, 6.0; N, 7.0. C₁₁H₁₂ClNO requires C, 63.16; H, 5.74; N, 6.70%).

Compound 3e. Yield 83%, viscous liquid; $\lambda_{\text{max}}/\text{nm}$ 258 (log ϵ 2.62) and 303 (1.72); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3420, 2900, 1600, 1500 and 1335; $\delta_{\text{H}}(60 \text{ MHz})$ 2.30 (s, 1 H), 2.90 (s, 3 H), 4.10 (s, 2 H), 4.20 (s, 2 H), 6.70 (d, *J* 8, 2 H) and 7.20 (d, *J* 8, 2 H); m/z 253 and 255 (M^+) (Found: C, 52.0; H, 4.3; N, 5.3. C₁₁H₁₂BrNO requires C, 51.97; H, 4.72; N, 5.51%).

Compound 3f. Yield 78%, viscous liquid; $\lambda_{\text{max}}/\text{nm}$ 250 (log ϵ 2.93) and 295 (1.97); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3400, 2905, 1610, 1500 and 1350; $\delta_{\text{H}}(60 \text{ MHz})$ 2.20 (s, 1 H), 2.25 (s, 3 H), 3.00 (s, 3 H), 4.00 (s, 2 H), 4.20 (s, 2 H) and 6.80–7.20 (m, 4 H); m/z 189 (M^+) (Found: C, 76.62; H, 8.4; N, 7.7. C₁₂H₁₅NO requires C, 76.19; H, 7.94; N, 7.41%).

General procedure for the oxidation and subsequent rearrangement of 4-(N-alkyl-substituted anilino)but-2-yn-1-ols 3a-f

A solution of MCPBA [5 mmol, 1.91 g (45%)] in chloroform (100 cm³) was slowly added to a well stirred solution of the tertiary amine **3a-f** (5 mmol) in chloroform (100 cm³) at 0–5 °C over a period of 20 min. The reaction mixture was stirred at room temperature for an additional 10 h before being washed with 10% aq. potassium carbonate (3 × 25 cm³) and dried (Na₂SO₄). Removal of the solvent gave a crude mass, which was purified by recrystallisation from methanol (**5a,f**) or chloroform–light petroleum (**5b-e**).

Compound 5a. Yield 56%, *crystals* with mp 208 °C; λ_{\max}/nm 225 (3.56) and 272 (2.70); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2920, 1460 and 1190; $\delta_{\text{H}}(100 \text{ MHz})$ 3.90 (s, 6 H), 4.52 (s, 4 H), 4.60 (s, 4 H), 7.40–7.52 (m, 6 H) and 7.80–8.00 (m, 2 H); m/z 346 (M⁺) (Found: C, 76.6; H, 6.1; N, 8.3. C₂₂H₂₂N₂O₂ requires C, 76.30; H, 6.36; N, 8.09%).

Compound 5b. Yield 52%, *crystals* with mp 218 °C; λ_{\max}/nm 231 (3.65) and 275 (2.55); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2940, 1500 and 1400; $\delta_{\text{H}}(200 \text{ MHz})$ 2.55 (s, 6 H), 3.90 (s, 6 H), 4.50 (s, 4 H), 4.55 (s, 4 H), 7.15 (d, *J* 8, 2 H), 7.30 (d, *J* 8, 2 H) and 7.60 (s, 2 H); m/z 374 (M⁺) (Found: C, 77.3; H, 6.7; N, 7.6. C₂₄H₂₆N₂O₂ requires C, 77.00; H, 6.95; N, 7.49%).

Compound 5c. Yield 62%, *crystals* with mp 216 °C; λ_{\max}/nm 229 (3.61) and 277 (2.72); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2920, 1460 and 1400; $\delta_{\text{H}}(200 \text{ MHz})$ 1.50 (t, *J* 6, 6 H), 4.40 (q, *J* 6, 4 H), 4.40 (s, 4 H), 4.54 (s, 4 H), 7.10–7.50 (m, 6 H) and 7.84 (d, *J* 8, 2 H); m/z 374 (M⁺) (Found: C, 77.2; H, 7.2; N, 7.8. C₂₄H₂₆N₂O₂ requires C, 77.00; H, 6.95; N, 7.49%).

Compound 5d. Yield 58%, *crystals* with mp 226 °C; λ_{\max}/nm 223 (3.81) and 299 (2.91); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2940, 1480 and 1400; $\delta_{\text{H}}(200 \text{ MHz})$ 3.90 (s, 6 H), 4.45 (s, 4 H), 4.55 (s, 4 H), 7.20–7.30 (m, 4 H) and 7.75 (s, 2 H); m/z 414, 416 and 418 (M⁺) (Found: C, 63.9; H, 5.1; N, 6.4. C₂₂H₂₀Cl₂N₂O₂ requires C, 63.61; H, 4.82; N, 6.75%).

Compound 5e. Yield 51%, *crystals* with mp 238 °C; λ_{\max}/nm 223 (3.69) and 300 (2.81); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2920, 1485 and 1400; $\delta_{\text{H}}(250 \text{ MHz})$ 3.90 (s, 6 H), 4.50 (s, 4 H), 4.58 (s, 4 H), 7.20–7.40 (m, 4 H) and 7.80 (m, 2 H); m/z 502, 504 and 506 (M⁺) (Found: C, 52.7; H, 3.8; N, 6.0. C₂₂H₂₀Br₂N₂O₂ requires C, 52.38; H, 3.97; N, 5.56%).

Compound 5f. Yield 56%, *crystals* with mp 226 °C; λ_{\max}/nm 230 (3.51) and 275 (2.71); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2950, 1490 and

1440; $\delta_{\text{H}}(60 \text{ MHz})$ 2.50 (s, 6 H), 3.80 (s, 6 H), 4.40 (s, 4 H), 4.55 (s, 4 H) and 7.20–7.60 (m, 6 H); m/z 374 (M⁺) (Found: C, 77.4; H, 6.7; N, 7.7. C₂₄H₂₆N₂O₂ requires C, 77.00; H, 6.95; N, 7.49%).

Acknowledgements

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