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Studies of bioactive heterocycles: amino Claisen rearrangement of 4-*N*-(4-aryloxybut-2-ynyl),*N*-methylaminocoumarins

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Abstract—Thermal amino-Claisen rearrangement of 4-*N*-(aryloxybut-2-ynyl),*N*-methyl-aminocoumarins (**8a–e**) in refluxing *o*-dichlorobenzene gave 4-aryloxymethylene-1-methyl-1,2,3-trihydropyrido[3,2-*c*][1]benzopyran-5-ones (**9a–e**) in 56–72% isolated yields. Substrates (**8a–f**) were prepared from 4-chlorocoumarin (**6a**,**b**) and *N*-(4-ary-loxybutynyl),*N*-methylamine (**7a–f**) in 68–77% yields.

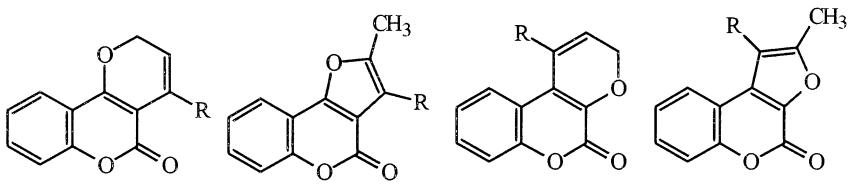
Coumarin and coumarin derivatives are reported to possess various physiological activities.[1] 3-Alkyl and 4-alkylcoumarins are well known[2] for their anthelmintic, hypnotic, insecticidal, antifungal activities and anti-coagulant effect on blood and diuretic properties. Extensive work has been carried on the synthesis[3] of these compounds. Pyrano[3,2-*c*][1]benzopyran-5(2*H*)-one derivatives **1** and furo[3,2-*c*][1]benzopyran-4-one derivatives **2** have been constructed by Claisen rearrangements.[4–6] Similarly, pyrano[2,3-*c*][1]benzopyran-5(3*H*)-one derivatives **3** and furo[2,3-*c*][1]benzopyran-4-one derivatives **4** have also been synthesised by the application of Claisen rearrangements.[4,7,8] Although the oxygen Claisen rearrangement of coumarins has been studied in detail, the amino-Claisen rearrangement has not been studied so far. This prompted us to undertake a study of the amino-Claisen rearrangement of 4-*N*-(4-aryloxybut-2-ynyl),*N*-methylaminocoumarins (**8a–f**).

4-Chlorocoumarin (**6a**) and 8-methyl-4-chlorocoumarin (**6b**) were prepared in 80 and 76% isolated yields by heating the corresponding 4-hydroxycoumarins with $POCl_3$ at 135–140°C for 4 h (Scheme 1). These were characterised from their elemental analyses and spectroscopic data.

The starting materials 4-*N*-(4-aryloxybut-2-ynyl),*N*-methylaminocoumarins **8a–f** were prepared[9] in 68–77% yields by refluxing 4-chlorocoumarins (**6a**,**b**) and the corresponding *N*-4-(aryloxybut-2-ynyl),*N*-methylamine **7a–f** in ethanol for 10–14 h (Scheme 2).

Compounds **8a–f** were characterised from their elemental analyses and spectroscopic data. The IR spectrum of **8a** showed ν_{max} at 1710 cm^{-1} due to the presence of a carbonyl group. The ^1H NMR spectrum of **8a** revealed a three proton singlet at δ 2.99 due to the NCH_3 and two sets of two-proton singlets at δ 4.09 and 4.76 due to the NCH_2 and OCH_2, respectively. A one proton singlet appeared at δ 5.74 due to the C_3-H of the coumarin moiety. The mass spectrum of **8a** showed a molecular ion peak at m/z 319.

The substrates **8a–f** possess two potential sites for Claisen rearrangement. The aryloxypropargyl ether



1 a) R = H
b) R = CH_2OAr

2 R = H

3 a) R = H
b) R = CH_2OAr

4 a) R = CH_2OAr
b) R = H

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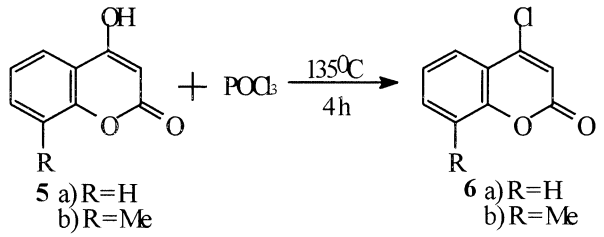


Scheme 1.

moiety may undergo an oxy-Claisen rearrangement, while the vinylpropargyl-*N*-methylamine fragment may undergo an amino-Claisen rearrangement. Hence these substrates provide scope for studying the competition between oxygen Claisen and amino-Claisen rearrangements. It is well known that the amino-Claisen rearrangement[10] requires higher activation energies than the oxygen Claisen rearrangement. However, the activation energy required for the arylpropargyl ether rearrangement[11] is much higher than that of propargylvinyl ether rearrangement.[12]

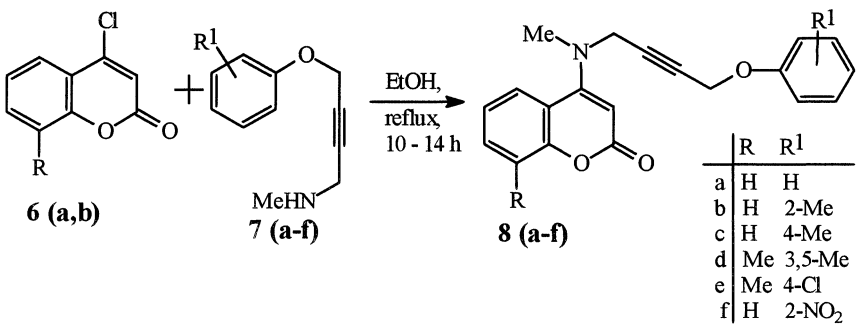
The substrate **8a** was refluxed in *o*-dichlorobenzene for 19 h at 180°C to give 4-aryloxymethylene-1-methyl-1,2,3-trihydropyrido[3,2-*c*][1]benzopyran-5-one **9a**, mp 88°C, in 72% yield (Scheme 3).

Compound **9a** was characterised from its elemental analysis and spectroscopic data. The IR spectrum of **9a** showed ν_{max} at 2910 cm^{-1} due to aromatic CH stretching and at 1680 cm^{-1} due to the carbonyl group. The ^1H NMR spectrum revealed a two-proton triplet at δ 2.82 ($J=5.4$ Hz) due to C**H**$_2$-CH$_2$-N, another two-proton triplet at δ 3.34 ($J=5.4$ Hz) due to N-C**H**$_2$-CH$_2$ and a one proton singlet at δ 8.23 due to C**H**=OAr. The mass spectrum of **9a** showed a molecular ion peak at m/z 319.

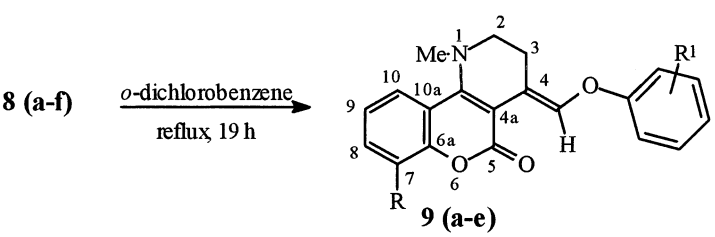
To test the generality of the reaction, the thermal rearrangements of five other aryloxybutynylamines **8b–f** were studied. In the cases of **8b–e** the products **9b–e** were obtained in 56–64% yields. However, substrate **9f** remained unchanged even after 20 h of heating.

The formation of products **9** from **8** may be explained by an initial [3,3] sigmatropic rearrangement of the propargylamine moiety of the substrate **8** to give the allene intermediate **10**, followed by imine–enamine tautomerism, [1,5]H shift and electrocyclic ring closure to give the unstable endocyclic intermediate **13** (not isolated). A [1,3] prototropic shift in **13** may give the final product **9** ('pathway a'). This 'pathway a' derives support from our recent observation[13] that in the case of the thermal rearrangement of 4-[*N*-(4-aryloxybut-2-ynyl],*N*-methylamino-6-methyl-2-pyrone both endocyclic and exocyclic products are formed and the endocyclic products are converted to exocyclic products under the same reaction conditions. However, in the present study, despite strenuous efforts, we could not isolate product of the type **13** at all. One more pathway may be considered. Another [1,5]H shift or tautomerism may convert **12** to butadienyl derivative **14**, which may then undergo a '6-endo'cyclization to give **9** ('pathway b') (Scheme 4).

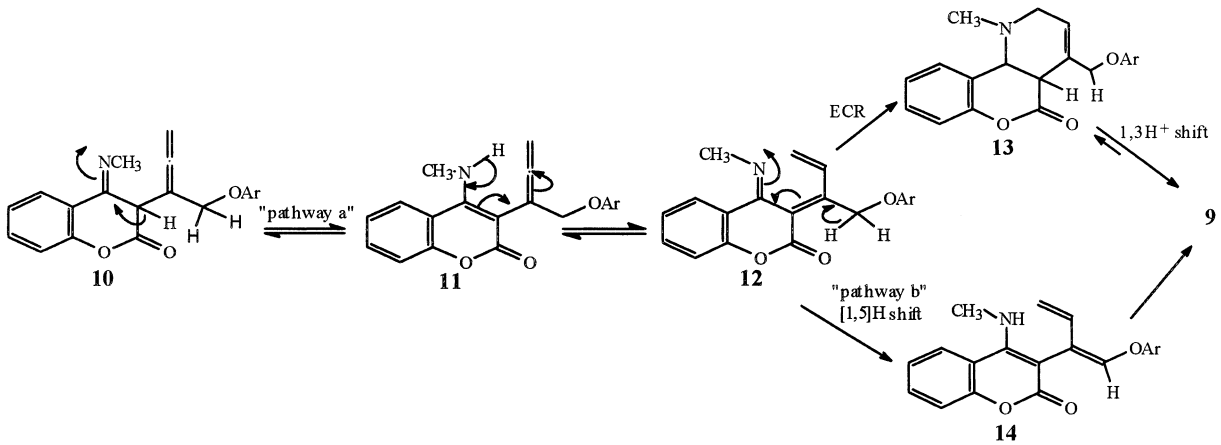
The occurrence of a [3,3] sigmatropic rearrangement at the propargyl vinyl amine moiety in preference to the arylpropargyl ether moiety in all the substrates (**4a–e**) studied so far is noteworthy. In the present examples



Scheme 2.



Scheme 3.



Scheme 4.

the amino-Claisen rearrangement leads to the exclusive formation of unusual products containing exocyclic double bonds (**9a**–**e**), instead of the normal products containing a endocyclic double bond (**13**). It is interesting to note that the occurrence of an oxygen Claisen rearrangement at an aryloxy propargyl ether moiety has recently been reported in preference to rearrangement of the vinyl propargylamine moiety of 5-*N*-(4-aryloxy-but-2ynyl),*N*-methyl-1,3-dimethylpyrimidine-2,4-dione during a thermal rearrangement.[14]

Acknowledgements

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