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Competitive [3,3] sigmatropic rearrangement of aryl propargyl ether moiety *vs* propargyl vinyl amine part in 6-[N-(4′-aryloxybut-2-ynyl) N-methyl amino]coumarins

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Thermal rearrangement of 6-[*N*-(4′-aryloxybut-2-ynyl)*N*-methylamino]coumarins in refluxing *N*,*N*-DEA has led to Claisen rearrangement at the aryloxypropargyl segment resulting in the formation of *N*-(4′-coumarinylmethyl),*N*-methylcoumarins in excellent yield.

Keywords: 6-Aminocoumarin, Claisen rearrangement, benzopyran, 1,4-dichlorobut-2-yne, sigmatropic rearrangement

Coumarin[1] and its derivatives[2] are interesting due to their physiological activity[1]. The biological activity[3,4] of 4-alkyl and 3-alkyl coumarins has made their synthesis[5] an important target. Recently, the synthesis of a new tricyclic pyrrolocoumarin system has been reported by the amine oxide rearrangement, a [2,3] Meisenheimer rearrangement followed by a [3,3] Claisen rearrangement[6] of the substrate **7**. We have also reported the thermal [3,3] sigmatropic rearrangement of 6-prop-2-ynyloxycoumarins[7] to furnish a number of pyrano [3,3-*f*] chromen-2(*7H*)-ones. Extensive work has been reported on the *aza*-Claisen rearrangement of allyl aryl amines[8] and aryl propargyl amines[9]. There is also report on the sequential Claisen rearrangement of 1,4-(bis)aryloxybut-2-ynes **1**[10] and related systems **2-5**[11] *etc*. However, there is no report on the successful Claisen rearrangement of substrates of the type **6**[12]. When attempted, only decomposition occurred even under nitrogen atmosphere. This prompted the study of the thermal [3,3] sigmatropic rearrangement of the substrates **7**. Herein are reported the results **(Figure 1)**.

Results and Discussion

The starting materials 6-[*N*-(4-aryloxybut-2-ynyl)-*N*-methylamino] coumarins **7a-d** were synthesized in good yields by refluxing 6-(*N*-methylamino) coumarin **8** and 1-aryloxy-4-chlorobut-2-ynes **9a-d** in dry acetone in the presence of anhydrous potassium

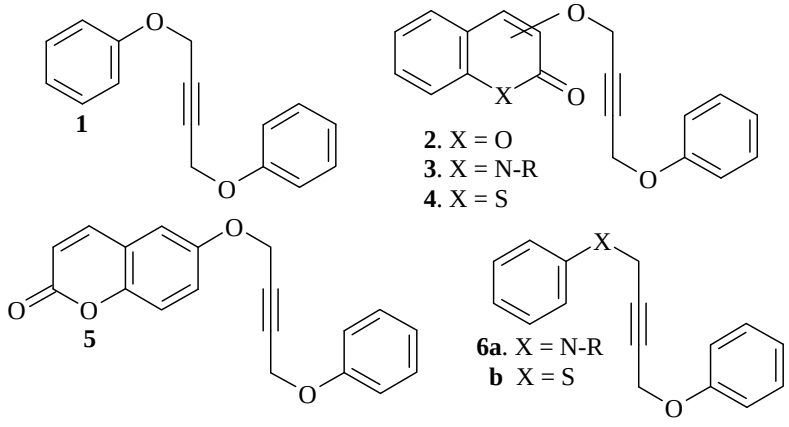


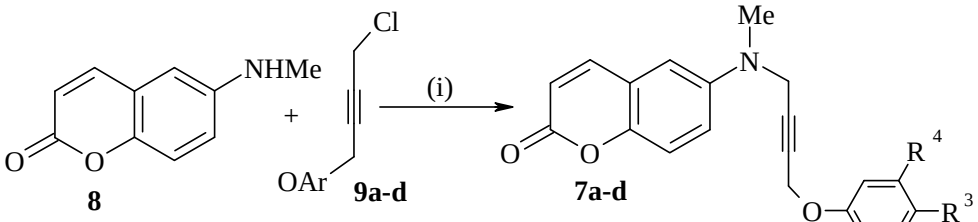
Figure 1

carbonate and a small amount of sodium iodide[13] **(Scheme I)**. Compounds **7a-d** were characterized from their elemental analysis and spectroscopic data. The IR spectrum of **7a** showed ν_{max} at 1721 cm^{-1} due to the presence of a carbonyl group. The ^1H NMR spectrum of **7a** revealed a three proton singlet at δ 2.94 due to the *N*-CH_3 and two sets of two proton singlets at δ 3.74 and 4.07 due to the *N*-CH_2 and O-CH_2 respectively. Another two sets of one proton doublets appeared at δ 6.37 (J = 9.50 Hz) and 7.56 (J = 9.50 Hz) respectively due to the C_3-H and C_4-H proton of the coumarin moiety. The mass spectrum of **7a** showed a molecular ion peak at *m/z* 349 (M^+).

The starting materials are unique as the system is tailored to possess aryloxy propynyl moiety as well as *N*-vinyl and *N*-methylpropynyl amine moiety **(Scheme I)**. Therefore, these substrates provide an excellent scope for studying the competition between oxy Claisen *versus* amino Claisen *i.e.* Claisen rearrangement of substrates aryl propargyl amine *versus* aryl propargyl ether in the same molecule. It is well-known that the oxy Claisen is favoured over amino Claisen due to the higher energy of activation[14] for nitrogen containing substrates. It is also an established phenomenon that the activation energy needed for the propargyl vinyl ether rearrangement[15] is much less than the aryl propargyl ether rearrangement[16]. Apparently three products **10**, **11** and **12** are easily expected from the specially tailored substrates **7a-d**, by a single [3,3] sigmatropic rearrangement **(Scheme II)**.

The formation of products **10a-d** from the substrates **7a-d** may be explained by the occurrence of the thermal [3,3] sigmatropic rearrangement at the aryloxy propynyl moiety of substrates **7a-d** followed by enolisation, [1,5] hydrogen shift and electrocyclic ring closure to give product **10**. The occurrence of the same sequence of reactions at the aryl propargyl amine part of the substrates **7** may have afforded the products **11** and or **12** which were actually not obtained **(Scheme III)**.

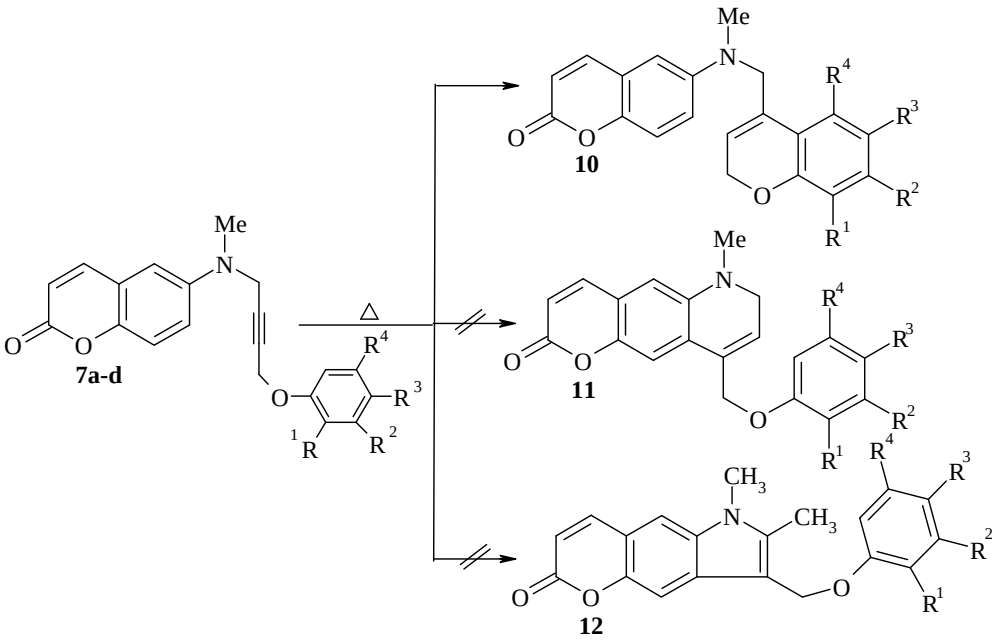
The substrates **7a-d** present a scope for two [3,3] sigmatropic rearrangements and the preference for the first rearrangement in these substrates is not easily predictable at first sight. Hence, the reaction has been carried out in *N*,*N*-DEA and experimentally it has been found that instead of the amino-Claisen products **11** and/or **12**, the oxy-Claisen product **10** is being formed probably due to the high energy of activation for the amino-Claisen rearrangement as compared to the oxy-Claisen rearrangement. Product **10**, a crystalline solid was obtained in 88% yield. From its elemental analysis and spectral data this was characterized as **10a**. The IR spectrum of **10a** gives a band at 1719 cm^{-1} due to the lactone carbonyl group of the coumarin moiety. The ^1H NMR spectrum of **10a** showed a three proton singlet at δ 3.06 and two proton singlets at δ 4.25 due to the presence of N-CH_3 and N-CH_2 group. A one proton multiplet and a two proton doublets appeared at δ 5.59 and 4.70 respectively due to the presence of vinyl proton and O-CH_2 protons of the benzopyran moiety of the compound **10a**. Its molecular ion peak appeared at *m/z* 349 (M^+). ^{13}C NMR spectrum of this compound revealed signals at δ 161.7, 154.5, 148.5, 146.7, 146.5, 144.1, 129.1, 123.2, 119.2, 117.8, 117.2, 117.0,



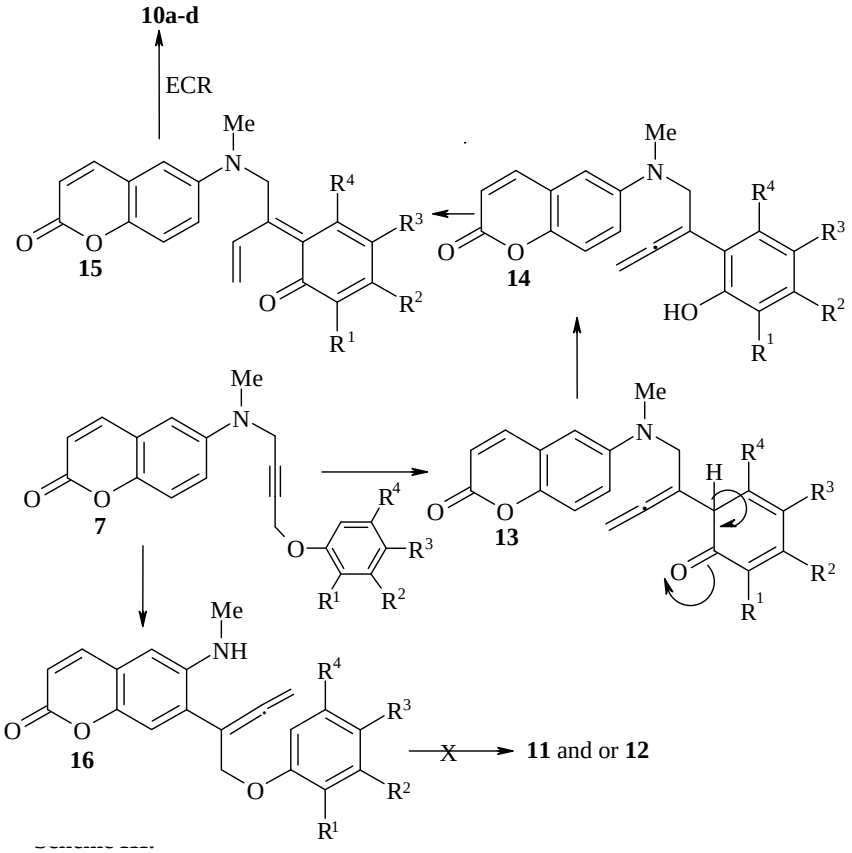
8 **9a-d** **7a-d**

7	R^1	R^2	R^3	R^4	Yield
a	H	H	OMe	H	92%
b	H	Me	H	Me	90%
c	H	Me	H	H	84%
d	Me	H	H	Me	90%

Scheme I—Reagents and reaction condition: (i) dry Me_2CO-K_2CO_3, NaI, reflux, 12-15 hr



Scheme II



Scheme III

116.9, 114.2, 109.0, 108.9, 65.7, 56.1, 54.1, 39.2. Other substrates **7b-d** were similarly treated to give the products **10b-d** in 79-86% yield.

The compounds **10a-d** which have been synthesized by a single Claisen rearrangement, still possess an allyl aryl amine moiety for a second Claisen rearrangement. Therefore, the compounds **10a-d** were allowed to undergo further Claisen rearrangement by treating with boron trifluoride etherate in dry dichloromethane. However, no change of starting material was observed. Attempts to achieve the second Claisen rearrangement of product **10** with anhydrous $AlCl_3$ in dichloromethane, benzene and toluene caused decomposition of the starting material and 6-amino-N-methyl coumarin was isolated from the reaction mixture. Attempt to carry out the reaction in the presence of anhydrous zinc chloride in dry toluene/ethanolic H_2SO_4 gave back the starting material.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. UV-Vis absorption spectra were recorded in ethanol solution on a Shimadzu UV-240 IPC spectrometer (λ_{max} in nm), IR spectra were run on a Perkin-Elmer 120-000A apparatus (ν_{max} in cm^{-1}) for solid samples (KBr discs) and are liquid samples (neat). ^1H and ^{13}C NMR spectra were determined for solutions in $CDCl_3$ with TMS as internal standard on a Brucker DPX-400. Elemental analyses and MS data were collected on a Leco 932 CHNS analyzer and on a JEOL-JMS-600 instrument respectively. Progress of reaction was monitored by TLC run on silica gel-G (E-Merck, India). Silica gel (60-120 mesh) was used for column chromatographic separation. 1-aryloxy-4-chlorobut-2-ynes are prepared according to the earlier published procedure[17].

General procedure for the preparation of 6-[*N*-(4-aryloxybut-2-ynyl)-*N*-methylamino] coumarins, 7a-d

A mixture of 6-(*N*-methylamino) coumarin **8** (0.002 mol) and 1-aryloxy-4-chlorobut-2-yne **9** (0.002 mol) was refluxed in acetone (75 mL) in the presence of anhydrous potassium carbonate (1 g) and sodium iodide (Finkelstein condition) for 18 hr. The reaction mixture was cooled, filtered and the solvent was removed. The residue was extracted with dichloromethane (3×25 mL), the combined extracts were washed with saturated brine and dried (anhyd. Na_2SO_4). The solvent was removed to give the crude product which was purified by column chromatography over silica gel. The pure products were obtained by eluting the column with ethyl acetate: petroleum ether (1:4).

Compound 7a: Yield 92%, gummy mass; UV-Vis (EtOH): nm 387, 254; IR (neat): 1721 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.94 (s, 3H), 3.74 (s, 3H), 4.07 (s, 2H), 4.59 (t, 2H, *J*=1.69 Hz), 6.37 (d, 1H, *J*=9.50 Hz), 6.72-6.82 (m, 5H), 7.00-7.03 (dd, 1H, *J*=2.93 Hz, *J*=2.93 Hz), 7.20-7.22 (d, 1H, *J*=9.08 Hz), 7.56 (d, 1H, *J*=9.50 Hz); ^{13}C NMR ($CDCl_3$): δ 161.6, 154.7, 151.9, 147.5, 146.3, 144.1, 119.5, 119.4, 117.6, 117.1, 116.4, 114.8, 111.9, 82.6, 80.2, 57.1, 56.0, 43.6, 39.5; MS: *m/z* 349 (M^+). Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.20; H, 5.44; N, 4.01. Found: C, 72.29; H, 5.40; N, 3.97%.

Compound 7b: Yield 90%, gummy mass; UV-Vis (EtOH): nm 381, 254, IR (neat): 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.21 (s, 6H), 2.95 (s, 3H), 4.07 (s, 2H), 4.60 (t, 2H, *J*=1.51 Hz), 6.35 (d, 1H, *J*=9.50 Hz), 6.49 (s, 2H), 6.57 (s, 1H), 6.74-6.75 (d, 1H, *J*=2.91 Hz), 7.00-7.03 (dd, 1H, *J*=2.94 Hz, *J*=2.94 Hz), 7.18-7.20 (d, 1H, *J*=9.07 Hz), 7.53-7.55 (d, 1H, *J*=9.50 Hz); MS: *m/z* 347 (M^+); Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.08; H, 6.05; N, 4.03. Found: C, 76.01; H, 6.15; N, 4.17%.

Compound 7c: Yield 84%, gummy mass; UV-Vis (EtOH): nm 377, 254; IR (neat): 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H), 2.95 (s, 3H), 4.08 (d, 2H, *J*=1.42 Hz), 4.62-4.63 (t, 2H, *J*=1.68 Hz), 6.36-6.38 (d, 1H, *J*=9.50 Hz), 6.66-6.76 (m, 4H), 7.01-7.03 (dd, 1H, *J*=2.95 Hz, *J*=2.95 Hz), 7.07-7.10 (m, 1H), 7.19-7.21 (m, 1H), 7.54-7.56 (d, 1H, *J*=9.50 Hz); MS: *m/z* 333 (M^+); Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.67; H, 5.70; N, 4.20. Found: C, 75.49; H, 5.61; N, 4.03%.

Compound 7d: Yield 90%, gummy mass; UV-Vis (EtOH): nm 378, 254; IR (neat): 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.14 (s, 3H), 2.23 (s, 3H), 2.94 (s, 3H), 4.06 (s, 2H), 4.62 (t, 2H, *J*=1.70 Hz), 6.36-6.38 (d, 1H, *J*=9.50 Hz), 6.68-6.70 (m, 1H), 6.75 (d, 1H, *J*=2.84 Hz), 6.79-6.81 (m, 1H), 6.91 (s, 1H), 7.00-7.03 (dd, 1H, *J*=2.89 Hz, *J*=2.91 Hz), 7.19-7.21 (m, 1H), 7.53-7.56 (d, 1H, *J*=9.50 Hz); MS: *m/z* 347 (M^+); Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.08; H, 6.05; N, 4.03. Found: C, 76.13; H, 5.99; N, 3.94%.

General procedure for the synthesis of the compounds, 10a-d

Compounds **7a-d** (0.2 g) was refluxed in *N*,*N*-diethylaniline (3 mL) for 15 hr. The reaction mixture

was cooled, poured into ice cold (1:1) aqueous HCl solution and kept aside overnight. The mixture was then extracted with dichloromethane (3×25 mL). The dichloromethane extract was washed with dil. HCl (3×20 mL) and brine, dried (anhyd. Na_2SO_4). Dichloromethane was distilled off and the residual mass was chromatographed over silica-gel (60-120 mesh). Compounds **10a-d** were eluted with ethyl acetate:petroleum ether (1:4).

Compound 10a: Yield 88%, solid, m.p. 139°C. UV-Vis (EtOH): nm 398, 257; IR (KBr): 1719 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.06 (s, 3H), 3.74 (s, 3H), 4.25 (s, 2H), 4.70 (s, 2H), 5.59 (s, 1H), 6.35 (d, 1H, *J*=9.50 Hz), 6.64-6.73 (m, 3H), 6.79-6.92 (m, 2H), 7.19 (m, 1H), 7.60 (d, 1H, *J*=9.50 Hz); ^{13}C NMR ($CDCl_3$): δ 161.7, 154.5, 148.5, 146.7, 146.5, 144.1, 129.1, 123.2, 119.2, 117.8, 117.2, 117.0, 116.9, 114.2, 109.0, 108.9, 65.7, 56.1, 54.1, 39.2; MS: *m/z* 349 (M^+); Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.20; H, 5.44; N, 4.01. Found: C, 72.03; H, 5.29; N, 4.18%.

Compound 10b: Yield 84%, solid, m.p. 120°C. UV-Vis (EtOH): nm 398, 257; IR (KBr): 1717 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.21 (s, 3H), 2.44 (s, 3H), 3.04 (s, 3H), 4.38 (d, 2H, *J*=1.6 Hz), 4.44 (m, 2H), 5.67-5.68 (m, 1H), 6.35 (d, 1H, *J*=9.50 Hz), 6.60 (t, 2H, *J*=3.22 Hz), 6.65 (s, 1H), 6.85-6.88 (dd, 1H, *J*=2.9 Hz, *J*=2.9 Hz), 7.18 (d, 1H, *J*=9.10 Hz), 7.60 (d, 1H, *J*=9.50 Hz); MS: *m/z* 347 (M^+); Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.08; H, 6.05; N, 4.03. Found: C, 76.00; H, 6.25; N, 4.08%.

Compound 10c: Yield 82%, solid, m.p. 151°C. UV-Vis (EtOH): nm 398, 257; IR (KBr): 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H), 3.06 (s, 3H), 4.25 (d, 2H, *J*=1.87 Hz), 4.74 (t, 2H, *J*=1.73 Hz), 5.74-5.76 (m, 1H), 6.36 (d, 1H, *J*=9.50 Hz), 6.63 (d, 1H, *J*=2.94 Hz), 6.69-6.83 (m, 2H), 6.91 (d, 1H, *J*=2.98 Hz), 6.99 (d, 1H, *J*=7.73 Hz), 7.17 (d, 1H, *J*=8.74 Hz), 7.60 (d, 1H, *J*=9.50 Hz); MS: *m/z* 333 (M^+); Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.67; H, 5.70; N, 4.20. Found: C, 75.89; H, 5.83; N, 4.40%.

Compound 10d: Yield 85%, gummy mass. UV-Vis (EtOH): nm 398, 257; IR (neat): 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H), 2.45 (s, 3H), 3.04 (s, 3H), 4.39 (d, 2H, *J*=1.28 Hz), 4.46 (t, 2H, *J*=2.25 Hz), 5.73-5.75 (m, 1H), 6.36 (d, 1H, *J*=9.50 Hz), 6.60 (d, 1H, *J*=2.84 Hz), 6.68 (d, 1H, *J*=7.65 Hz), 6.86-6.89 (dd, 1H, *J*=2.90 Hz, *J*=2.90 Hz), 6.95-6.97 (d, 1H, *J*=7.62 Hz), 7.19-7.21 (d, 1H, *J*=9.09 Hz), 7.60 (d, 1H, *J*=9.50 Hz); MS: *m/z* 347 (M^+); Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.08; H, 6.05; N, 4.03. Found: C, 75.97; H, 6.19; N, 4.11%.

Conclusion

In conclusion, the successful Claisen rearrangement of the substrates containing both the aryloxy propargyl ether moiety and aryl propargyl amine moiety has been achieved. The rearrangement occurred only at the propargyl ether part of the substrate to afford benzopyran derivatives.

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