Amino-Claisen versus Oxy-Claisen Rearrangement: Regioselective Synthesis of Pyrrolocoumarin Derivatives

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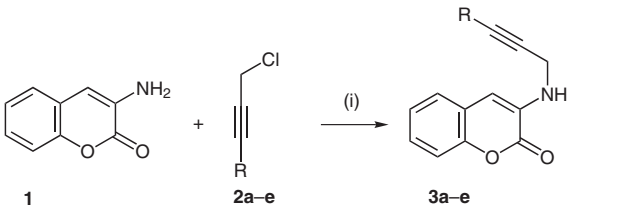
Abstract: Pyrrolocoumarin and its derivatives have been synthesized regioselectively in excellent yields by the amino-Claisen rearrangement of 3-*N*-propargylaminocoumarin and 3-*N*-(aryloxybut-2-ynyl)aminocoumarins.

Key words: amino-Claisen rearrangement, oxy-Claisen rearrangement, [3,3]-sigmatropic rearrangement, 3-aminocoumarin, pyrrolocoumarin, 5-*exo-trig*

Coumarins fused with heterocyclic compounds and aza-analogues of coumarins have received great attention due to their potential biological activities.[1] In particular, those coumarins fused to pyridines have been reported to have antialergic,[2] antidiabetic,[3] and analgesic[4] properties. Besides this, 3-aminocoumarin core is an ubiquitous subunit in many natural products with remarkable biological activities. In medicinal chemistry, members of this family have wide practical applications as antibiotic and antiviral agents.[5,6] For example, novobiocine is a 3-aminocoumarin derived antibiotic, an ATP competitive inhibitor of gyrase subunit blocking the negative super cooling of relaxed DNA.[5,6] Recently, Sames et al. reported[7] that the various pyrrolocoumarins may be used as the fluorogenic probes. We have very recently reported[8] 3-aminocoumarin-annulated pyrido[2,3-*c*]coumarin derivatives by palladium-catalyzed intramolecular Heck reaction. Therefore, in the interest of synthesizing new coumarin ring systems for possible evaluation as biologically active compounds or any other useful compounds such as fluorogenic probes and laser dyes, we have synthesized a variety of pyrrolocoumarin derivatives by the application of the less studied amino-Claisen rearrangement. Additional interest is derived from our longstanding efforts in the synthesis of coumarin-annulated heterocycles.[8,9]

The starting materials 3-*N*-(4-aryloxybut-2-ynyl)aminocoumarins **3a–d** and 3-*N*-propargylaminocoumarin (**3e**) were prepared in 51–63% yields by refluxing 3-aminocoumarin (**1**), with either the corresponding 1-aryloxy-4-chlorobut-2-ynes[10] **2a–d** or propargyl bromide (**2e**) in anhydrous ethyl methyl ketone in the presence of anhydrous potassium carbonate and a small amount of sodium iodide[11] (Scheme 1).



3a, R = $CH_2OC_6H_4$(4-OMe), 63%
3b, R = $CH_2OC_6H_3$(2,4-Cl_2), 51%
3c, R = $CH_2OC_6H_2$(4-Cl-3,5-Me_2), 59%
3d, R = $CH_2OC_6H_3$(3-Me-4-Cl), 55%
3e, R = H, 60%

Scheme 1 *Reagents and conditions*: (i) anhyd ethyl methyl ketone, K_2CO_3, NaI, reflux, 24–30 h.

Compounds **3a–e** were characterized from their elemental analyses and spectroscopic data. The IR spectrum of **3a** showed an absorption at 3221 cm^{-1} due to the presence of a NH group. The ^1H NMR spectrum of **3a** revealed a three-proton singlet at $\delta = 3.78$ due to the OCH_3 and two sets of two-proton singlets at $\delta = 4.06$ and 4.65 due to the NCH_2 and OCH_2 respectively. A one-proton singlet appeared at $\delta = 6.44$ due to the H-4 of coumarin moiety. The mass spectrum of the compound **3a** showed a molecular ion peak at $m/z = 335$ [M^+].

The substrates **3a–e** possess two potential reactive sites for the Claisen rearrangement. The aryloxypropargyl ether moiety may undergo an oxy-Claisen rearrangement, while the vinylpropargylamine segment may undergo an amino-Claisen rearrangement. Thus, these substrates provide scope for studying the competition between oxy-Claisen rearrangement and amino-Claisen rearrangements. It is a well-established phenomenon that the amino-Claisen rearrangement[12] requires higher activation energies compared to the oxy-Claisen rearrangement. However, the activation energy required for the arylpropargyl ether rearrangement is much higher than that of the propargylvinyl ether rearrangement.[13]

The Claisen rearrangement of the substrates **3a–e** was attempted in refluxing chlorobenzene and *o*-dichlorobenzene, but without success. However, the substrate **3a**, upon refluxing in *N*,*N*-dimethylaniline for eight hours, gave a solid product **4a** in 91% yield. This was characterized from its elemental analysis and spectroscopic data. Compound **4a** exhibited IR absorption band at 3229 cm^{-1} due to the presence of NH group. The ^1H NMR spectrum of **4a** displayed two three-proton singlets at $\delta = 2.53$ and 3.78 resulting from $=CCH_3$ and OCH_3 respectively; a

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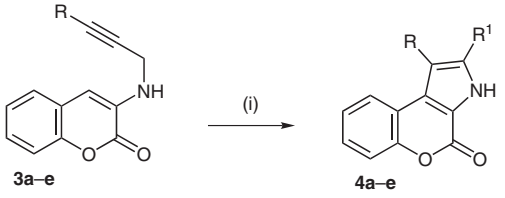
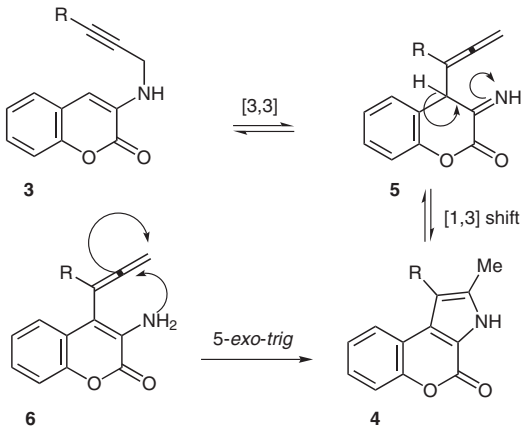


3a–e 4a–e

4a, R = $CH_2OC_6H_4$(4-OMe), R^1 = Me, 91%
4b, R = $CH_2OC_6H_3$(2,4-Cl_2), R^1 = Me,94%
4c, R = $CH_2OC_6H_2$(4-Cl-3,5-Me_2), R^1 = Me, 90%
4d, R = $CH_2OC_6H_3$(3-Me-4-Cl), R^1 = Me, 91%
4e, R = H, R^1 = H, 90%

Scheme 2 *Reagents and conditions*: *N*,*N*-dimethylaniline, reflux, 6–9 h.



3 5 6 4

Scheme 3 Probable mechanism of the amino-Claisen rearrangement

two-proton singlet at δ = 5.13 resulting from OCH_2; a broad singlet at δ = 10.3 due to the NH proton and the remaining protons are aromatic in nature. The mass spectrum of **4a** displayed a molecular ion peak at *m*/*z* 335 [M^+]. To test the generality of the reaction, the thermal rearrangements of four other substrates **3b–e** were studied and all of them were converted under refluxing condition in *N*,*N*-dimethylaniline for about 7–9 hours to give the cyclized product through the amino-Claisen rearrangement instead of the low activation energy needing oxy-Claisen rearrangement (Scheme 2). It is notable here that out of the two possibilities[14] of the formation of two cyclized products, that is, either the five-membered pyrrolocoumarin derivatives or the six-membered pyridocoumarin derivatives we obtained exclusively the pyrrolocoumarin derivatives by the regioselective amino-Claisen rearrangement.

The formation of the products **4** from the substrate **3** may be rationalized by an initial [3,3]-sigmatropic rearrangement of the propargylamine moiety of the substrate **3** to give the allene intermediate **5**, followed by an imine-enamine tautomerism to give the tautomerized intermediate **6** (not isolated). Subsequently, a 5-*exo*-*trig* cyclization occurring in the intermediate **6** gives the corresponding cyclized product pyrrolocoumarin derivatives **4** (Scheme 3).

In conclusion, the occurrence of a [3,3]-sigmatropic rearrangement at the propargyl vinyl amine moiety in preference to the arylpropargyl ether moiety in the substrates **3a–e** studied so far is noteworthy. In our present study, the amino-Claisen rearrangement leads to the exclusive formation of the pyrrolocoumarins and its derivatives. This result is interesting in view of an earlier report[15] where it has been shown that the oxy-Claisen rearrangement is favored over the amino-Claisen rearrangement in substrates, namely, 5-*N*-(4-aryloxybut-2-ynyl)-*N*-methyl-1,3-dimethylpyrimidine-2,4-diones, during the thermal rearrangement.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer L120-000A spectrometer (cm^{-1}) using KBr disks. NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ (chemical shifts in δ) with TMS as the internal standard. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel G was used for TLC. Petroleum ether refers to the fraction boiling between 60–80 °C.

Compounds 3a–e; General Procedure

A mixture of 3-aminocoumarin (**1**; 0.32 mmol, 500 mg), an appropriate amount of **2** (0.32 mmol, 1.2 equiv) and anhyd K_2CO_3 (2.0 g) in anhyd ethyl methyl ketone (75 mL) was refluxed in the presence of a pinch of NaI for 30–35 h. The mixture was cooled, filtered, and the solvent was removed. The residue was then extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 layer was washed with H_2O (2 × 50 mL), brine (30 mL), and dried (Na_2SO_4). Removal of CH_2Cl_2 gave a crude product, which was then chromatographed over silica gel using 10% EtOAc–petroleum ether to give the compounds **3a–e**.

3a

Yield: 63%; solid; mp 120–121 °C.

IR (KBr): 1725, 3221 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.78 (s, 3 H, OCH_3), 4.02 (s, 2 H, NCH_2), 4.67 (s, 2 H, OCH_2), 6.41 (s, 1 H, H-4 of coumarin moiety), 6.83 (d, *J* = 8.8 Hz, 2 H, ArH), 7.19 (d, *J* = 8.8 Hz, 2 H, ArH), 7.22–7.31 (m, 4 H, ArH), 10.00 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 76.7, 77.0, 77.3, 80.3, 84.6, 114.4, 114.6, 115.8, 115.9, 116.1, 116.3, 119.2, 124.6, 126.8, 128.8, 141.9, 149.8, 151.3, 154.3, 157.3.

MS: *m*/*z* = 335 [M^+].

Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.79; H, 4.99; N, 4.37.

3b

Yield: 51%; solid; mp 165–166 °C.

IR (KBr): 1723, 3227 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.03 (s, 2 H, NCH_2), 4.69 (s, 2 H, OCH_2), 6.43 (s, 1 H, H-4 of coumarin moiety), 6.90 (s, 1 H, ArH), 7.08 (d, *J* = 8.6 Hz, 2 H, ArH), 7.17–7.29 (m, 4 H, ArH), 10.00 (s, 1 H, NH).

MS: *m*/*z* = 373 [M^+].

Anal. Calcd for $C_{19}H_{13}Cl_2NO_3$: C, 60.98; H, 3.50; N, 3.74. Found: C, 61.13; H, 3.61; N, 3.64.

3c

Yield: 59%; solid; mp 127–128 °C.

IR (KBr): 1722, 3230 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.36 (s, 6 H, CH_3), 4.03 (s, 2 H, NCH_2), 4.66 (s, 2 H, OCH_2), 6.42 (s, 1 H, H-4 of coumarin moiety), 6.72 (s, 2 H, ArH), 7.18–7.27 (m, 4 H, ArH), 10.02 (s, 1 H, NH).

MS: *m*/*z* = 367 [M^+].

Anal. Calcd for $C_{21}H_{18}ClNO_3$: C, 68.57; H, 4.93; N, 3.81. Found: C, 68.71; H, 4.91; N, 4.01.

3d
Yield: 55%; solid; mp 139–140 °C.

IR (KBr): 1719, 3227 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (s, 3 H, CH_3), 4.02 (s, 2 H, NCH_2), 4.66 (s, 2 H, OCH_2), 6.41 (s, 1 H, H-4 of coumarin moiety), 6.68 (dd, *J* = 6.8, 1.7 Hz, 2 H, ArH), 6.76 (d, *J* = 1.7 Hz, 1 H, ArH), 7.21–7.31 (m, 4 H, ArH), 9.99 (s, 1 H, NH).

MS: *m*/*z* = 353 [M^+].

Anal. Calcd for $C_{20}H_{16}ClNO_3$: C, 67.90; H, 4.56; N, 3.96. Found: C, 68.14; H, 4.37; N, 4.03.

3e
Yield: 60%; solid; mp 85–86 °C.

IR (KBr): 1724, 3225 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.02 (s, 1 H, ≡CH), 4.01 (s, 2 H, NCH_2), 6.40 (s, 1 H, H-4 of coumarin moiety), 7.17–7.26 (m, 4 H, ArH), 10.00 (s, 1 H, NH).

MS: *m*/*z* = 199 [M^+].

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.35; H, 4.55; N, 7.03.

Compounds 4a–e; General Procedure
The respective compound **3a**–**e** (0.2 g) was refluxed in *N*,*N*-dimethylaniline (5 mL) for 6–8 h. The mixture was cooled, poured into ice-cold aq HCl solution (1:1) and kept aside for overnight. The mixture was then extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with dil. HCl (3 × 20 mL), brine (20 mL), and dried (Na_2SO_4). EtOAc was distilled off and the residual mass was chromatographed over silica gel using 15% EtOAc–petroleum ether to give products **4a**–**e**.

4a
Yield: 91%; solid; mp 141–142 °C.

IR (KBr): 1717, 3229 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.53 (s, 3 H, $=CCH_3$), 3.78 (s, 3 H, OCH_3), 5.13 (s, 2 H, OCH_2), 6.85 (d, *J* = 7.6 Hz, 2 H, ArH), 6.93 (d, *J* = 7.6 Hz, 2 H, ArH), 7.28–7.30 (m, 1 H, ArH), 7.45–7.48 (m, 2 H, ArH), 7.87 (d, *J* = 7.6 Hz, 1 H, ArH), 10.31 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.5, 55.7, 61.3, 113.9, 114.9, 116.3, 116.4, 117.5, 124.7, 124.9, 129.6, 133.1, 136.5, 151.9, 152.4, 152.5, 154.7, 160.2.

MS: *m*/*z* = 335 [M^+].

Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.81; H, 5.07; N, 3.99.

4b
Yield: 94%; solid; mp 215–216 °C.

IR (KBr): 1726, 3227 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.55 (s, 3 H, $=CCH_3$), 5.24 (s, 2 H, OCH_2), 6.96 (d, *J* = 8.7 Hz, 1 H, ArH), 7.22 (s, 1 H, ArH), 7.26–7.33 (t, *J* = 7.5 Hz, 1 H, ArH), 7.40 (d, *J* = 1.7 Hz, 1 H, ArH), 7.44–7.51 (m, 2 H, ArH), 7.89 (d, *J* = 7.8 Hz, 1 H, ArH), 10.30 (s, 1 H, NH).

MS: *m*/*z* = 373 [M^+].

Anal. Calcd for $C_{19}H_{13}Cl_2NO_3$: C, 60.98; H, 3.50; N, 3.74. Found: C, 61.07; H, 3.33; N, 3.89.

4c
Yield: 90%; solid; mp 138–139 °C.

IR (KBr): 1719, 3230 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.36 (s, 3 H, CH_3), 2.57 (s, 3 H, $=CCH_3$), 5.22 (s, 2 H, OCH_2), 6.73 (s, 2 H, ArH), 7.28 (d, *J* = 7.8 Hz, 1 H, ArH), 7.43–7.48 (m, 2 H, ArH), 7.78 (d, *J* = 7.8 Hz, 1 H, ArH), 10.30 (s, 1 H, NH).

MS: *m*/*z* = 367 [M^+].

Anal. Calcd for $C_{21}H_{18}ClNO_3$: C, 68.57; H, 4.93; N, 3.81. Found: C, 68.77; H, 5.15; N, 3.98.

4d
Yield: 91%; solid; mp 152–153 °C.

IR (KBr): 1721, 3228 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (s, 3 H, CH_3), 2.53 (s, 3 H, $=CCH_3$), 5.23 (s, 2 H, OCH_2), 6.77 (dd, *J* = 7.2, 1.7 Hz, 1 H, ArH), 6.84 (d, *J* = 1.7 Hz, 1 H, ArH), 7.18 (d, *J* = 7.6 Hz, 1 H, ArH), 7.21–7.32 (m, 4 H, ArH), 10.31 (s, 1 H, NH).

MS: *m*/*z* = 353 [M^+].

Anal. Calcd for $C_{20}H_{16}ClNO_3$: C, 67.90; H, 4.56; N, 3.96. Found: C, 68.11; H, 4.66; N, 3.86.

4e
Yield: 90%; solid; mp 101–102 °C.

IR (KBr): 1718, 3231 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.52 (s, 3 H, $=CCH_3$), 6.47 (s, 1 H, =CH), 7.28 (t, *J* = 7.0 Hz, 1 H, ArH), 7.35–7.43 (m, 2 H, ArH), 7.74 (d, *J* = 6.9 Hz, 1 H, ArH), 10.10 (s, 1 H, NH).

MS: *m*/*z* = 199 [M^+].

Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.10; H, 4.72; N, 6.91.

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References

(1) (a) Murray, D. H.; Mendez, J.; Broun, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; Wiley: New York, **1982**. (b) O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*; Wiley: Chichester, **1997**. (c) Fylaktakidou, K. C.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des.* **2004**, *10*, 3813. (d) Zhang, W.; Pugh, G. *Tetrahedron Lett.* **2001**, *42*, 5613.
(2) Ukawa, K.; Ishiguro, T.; Wada, Y.; Nohara, A. *Heterocycles* **1986**, *24*, 1931.
(3) Heber, D. *Arch. Pharm.* **1987**, *320*, 402.
(4) Heber, D.; Berghaus, T. *J. Heterocycl. Chem.* **1994**, *31*, 1353.

(5) (a) Santana, L.; Uriarte, E.; Gonzalez-Diaz, H.; Zagotto, G.; Soto-Otero, R.; Mendez-Alvarez, E. *J. Med. Chem.* **2006**, *49*, 1149. (b) Rivkin, A.; Adams, B. *Tetrahedron Lett.* **2006**, *47*, 2395. (c) Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755; and references cited therein. (d) Burlison, J. A.; Neckers, L.; Smith, A. B.; Maxwell, A.; Blagg, B. S. J. *J. Am. Soc. Chem.* **2006**, *128*, 15529.

(6) (a) Gellert, M.; O'Dea, M. H.; Itoh, T.; Tomizawa, Z. I. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4474. (b) Levine, C.; Hiasa, H.; Marians, K. J. *Biochim. Biophys. Acta.* **1998**, *1400*, 29.

(7) Chen, G.; Yee, D. J.; Gubernator, N. G.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4544.

(8) Majumdar, K. C.; Chattopadhyay, B.; Taher, A. *Synthesis* **2007**, 3647.

(9) (a) Majumdar, K. C.; Muhuri, S.; Rahaman, H.; Islam, R.; Roy, B. *Chem. Lett.* **2006**, *35*, 1430. (b) Majumdar, K. C.; Rahaman, H.; Roy, B. *Lett. Org. Chem.* **2006**, *3*, 526. (c) Majumdar, K. C.; Chattopadhyay, B. *Synth. Commun.* **2006**, *36*, 3125. (d) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Synth. Commun.* **2005**, *35*, 1291. (e) Majumdar, K. C.; Chattopadhyay, S. K. *Tetrahedron Lett.* **2004**, *45*, 6871. (f) Majumdar, K. C.; Bhattacharyya, T. *Tetrahedron Lett.* **2001**, *42*, 4231.

(10) (a) Majumdar, K. C.; Thyagrajan, B. S. *Int. J. Sulfur Chem.* **1972**, *2A*, 93. (b) Thyagrajan, B. S.; Majumdar, K. C. *J. Heterocyl. Chem.* **1973**, *12*, 43.

(11) (a) Gazith, M.; Noys, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 6091. (b) Gardner, I. J.; Noyes, R. M. *J. Am. Chem. Soc.* **1961**, *83*, 2409.

(12) Marcinkiewcz, S.; Green, J.; Mamalis, P. *Tetrahedron* **1961**, *14*, 208.

(13) (a) Zsindely, J.; Schmidt, H. *Helv. Chim. Acta* **1968**, *51*, 1510. (b) Majumdar, K. C.; Thyagrajan, B. S.; Balasubramanian, K. K. *J. Heterocyl. Chem.* **1973**, *10*, 159.

(14) Scheurer, V. H.; Zsindely, J.; Schmidt, H. *Helv. Chim. Acta.* **1973**, *56*, 478.

(15) Majumdar, K. C.; Jana, N. K. *Synth. Commun.* **2001**, *30*, 4183.