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Synthesis of bioactive heterocycles: tandem reaction of 4-*N*-(4′-aryloxybut-2′-ynyl),*N*-methylaminocoumarin with 3-chloroperoxybenzoic acid

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Abstract—A number of 4-*N*-(4′-aryloxybut-2′-ynyl),*N*-methylaminocoumarins (**4a–e**) on treatment with one equivalent of 3-chloroperoxybenzoic acid at 0–5°C for 10 min and then stirring at rt for 10 h afforded pyrrolo[3,2-*c*]coumarin derivatives in 70–75% yields. The 4-*N*-(4′-aryloxybut-2′-ynyl),*N*-methylaminocoumarins **4a–e** were in turn prepared from 4-tosyloxycoumarin (**2**) and (4-aryloxybut-2-ynyl)-*N*-methylamine (**3a–e**).

Several years ago Majumdar and Thyagarajan reported[1–4] an unusual sulfoxide rearrangement to give benzo(*b*)thiophene derivatives. They extended the reaction to aryl propynyl amine oxides[5–7] to afford indole derivatives in excellent yields. Amine oxide rearrangements have been shown to be excellent methods for C–C bond formation as well as for construction of pyrrole rings in fused heterocycles.[8–10] This is a very mild and simple method affording fused pyrroles[11–13] in almost quantitative yield. We have recently reported[14] the aza-Claisen rearrangement of 4-*N*-(4′-aryloxybut-2′-ynyl),*N*-methylaminocoumarin to give unusual products. The importance of coumarin derivatives for their physiological[15–22] and biological[23–25] activity is well known. This prompted us to undertake a study on the synthesis of pyrrolo[3,2-*c*]coumarin derivatives by the application of suitably substituted amines. Herein we report the results.

The starting materials, 4-*N*-(4′-aryloxybut-2′-ynyl),*N*-methylaminocoumarins **4a–e**, were prepared in 70–80% yields by the reaction of 4-tosyloxycoumarin (**2**) with (4-aryloxybut-2-ynyl)*N*-methylamine (**3**) in refluxing ethanol for 10–12 h (Scheme 1). 4-Tosyloxycoumarin was in turn prepared in 90% yield from the reaction of 4-hydroxycoumarin (**1**) and tosyl chloride in pyridine (Scheme 1). The substrates **4a–e** were characterized from their elemental analysis and spectroscopic data.[26] Substrates **4a–e** contain a propargyl amine moiety. Our aim was to use a sigmatropic rearrangement for the formation of the C–C single bond at the C-3 position of the coumarins **4a–e**. We considered the well known exceedingly mild and simple amine oxide methodology for the construction of the fused pyrrole ring and decided to find out whether the five-membered pyrrole ring with a 3,4-double bond in the coumarin moiety could be constructed via the aforesaid amine oxide rearrangement. Consequently, the tertiary amine **4a** was treated with 1 equiv. of 3-chloroperoxybenzoic acid in chloroform at 0–5°C for 10 min. *N*-Oxide formation was monitored by TLC. The reaction mixture was then stirred at room temperature for 10–12 h to afford pyrrolo[3,2-*c*]coumarin derivative **5a** as the only isolable product (75%, mp 105°C). This was characterized from its elemental analysis and spectroscopic data.[27] All the remaining substrates **4b–e** were similarly treated to provide pyrrolo[3,2-*c*]coumarin derivatives **5b–e** in 70–75% yields (Scheme 1)

The mechanism of this reaction may be explained by formation of the unstable *N*-oxides **6** by the reaction of the tertiary amines (**4a–e**) with 1 equiv. of 3-chloroperoxybenzoic acid. The *N*-oxides (**6**) subsequently undergo a [2,3] sigmatropic rearrangement to give **7** followed by a [3,3] sigmatropic rearrangement and tautomerism leading to enamines **9**. The carbonyl group and the amine moiety are suitably juxtaposed in **9** to give the cyclic allylic alcohols **10**. The water present in *m*-chloroperoxybenzoic acid then acts as a nucleophile and causes SN_2' displacement of the –OH group to give the final products, the pyrrolo[3,2-*c*][1]benzopyran-4-ones **5a–e** (Scheme 2).

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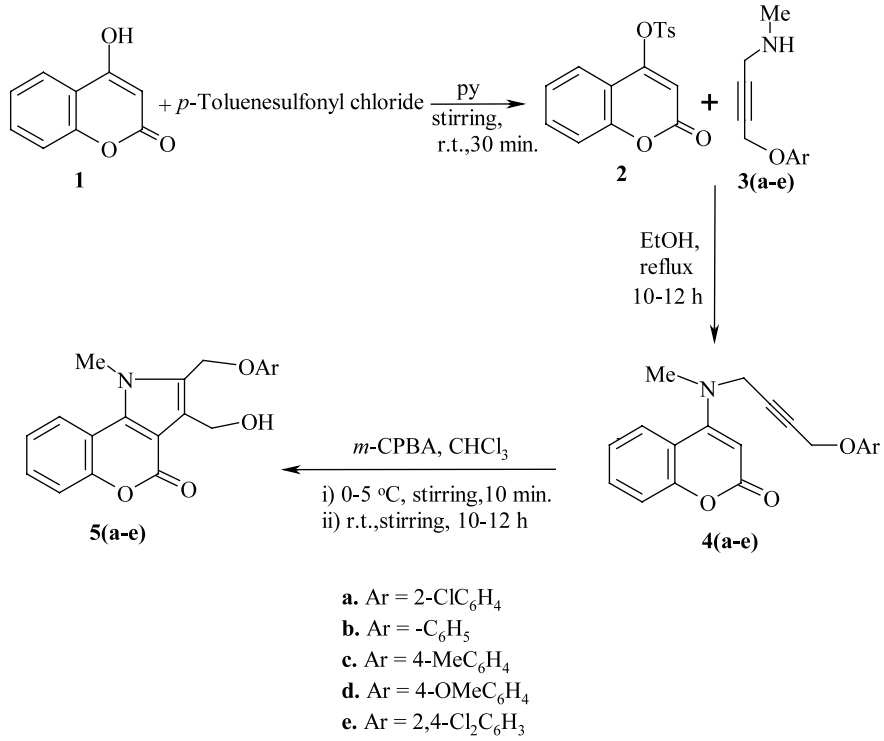
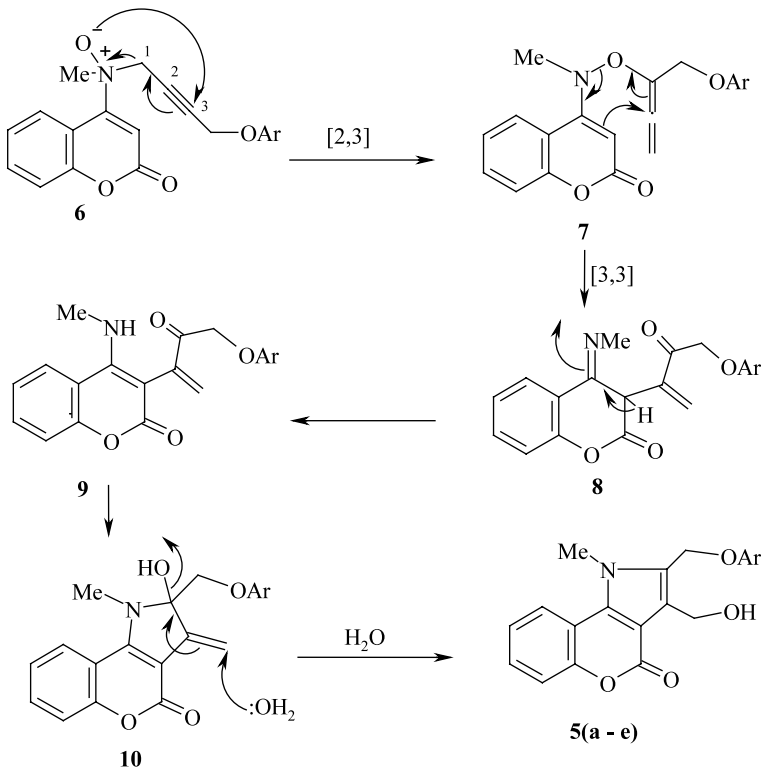


a. Ar = 2-ClC_6H_4
b. Ar = -C_6H_5
c. Ar = 4-MeC_6H_4
d. Ar = 4-$OMeC_6H_4$
e. Ar = 2,4-$Cl_2C_6H_3$

Scheme 1.



Scheme 2.

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26. Compound **4a**: Yield 80%, mp 98°C; λ_{max}: 216, 303 nm; ν_{max}: 1100, 1490, 1710, 2970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 3.02 (s, 3H, N-CH_3), 4.02–4.03 (t, $J=1.6$ Hz, 2H, NCH_2), 4.74–4.75 (t, $J=1.6$ Hz, 2H, CH_2OAr), 5.75 (s, 1H, C_3-H), 6.94–7.06 (m, 3H), 7.27–7.67 (m, 5H); m/z 353, 355 (M^+). Anal. calcd for $C_{20}H_{16}ClNO_3$: C, 67.98; H, 4.53; N, 3.96%. Found: C, 67.81; H, 4.36; N, 3.75%.
27. Compound **5a**: Yield 75%; mp 105°C; λ_{max}: 217, 321 nm; ν_{max}: 1120, 1500, 1690, 2960, 3340 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 3.03 (s, 3H, NCH_3), 4.05 (brs, 2H, CH_2OH), 4.83 (brs, 2H, CH_2OAr), 6.94–7.06 (m, 3H, ArH), 7.27–7.67 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_c 40.53, 44.75, 57.50, 79.10, 84.66, 114.82, 117.18, 122.65, 124.51, 123.66, 124.75, 125.09, 127.18, 129.10, 130.82, 132.9, 135.85, 149.06, 153.54, 162.16 (C-lactone carbonyl) MS: m/z 369, 371 (M^+). Anal. calcd for $C_{20}H_{16}ClNO_4$: C, 65.04; H, 4.33; N, 3.79%. Found: C, 65.15; H, 4.28; N, 3.67%.