Reaction of 2-[(*E*)-styryl]quinazolin-4(3*H*)-one with acetylenic esters: formation of unexpected N-3 alkenylation products

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Attempted hetero Diels–Alder reaction with 2-[(*E*)-styryl]quinazolin-4(3*H*)-one (**1**) and dimethyl acetylenedicarboxylate (**2**) resulted in unexpected N-3 alkenylation products, 2-[(*E*)-styryl]-3-[(*Z*)-1,2-bis(methoxycarbonyl)vinyl]quinazolin-4(3*H*)-one (**4a**) and 3-[(*E*)-1,2-bis(methoxycarbonyl) vinyl] 2-[(*E*)-styryl]-quinazolin-4(3*H*)-one (**4b**) in low yield. Treating **1** and 2-methylquinazolin-4(3*H*)-one (**9**) with methyl propiolate (**7**) also furnished N-3 alkenylation products in low yield. The structure of **4b** has been established by X-ray analysis. The molecules of **4b** are linked by intermolecular C-H….N hydrogen bonds into centrosymmetric dimers forming R^2_2 (12) rings.

Keywords: N-3 alkenylation, 2-substituted quinazolin-4(3*H*)-one, X-ray structure determination

The hetero Diels–Alder (HDA) reaction[1] has emerged as an important methodology for the synthesis of six-membered heterocycles containing oxygen,[1c,2] nitrogen[3] and sulfur[4] as hetero atoms. This reaction was also utilised for the synthesis of complex natural products like streptonigrin[5] and lavendamycin.[6] Among the various heterodienes, 1-azabutadiene derivatives have been extensively employed[7] in HDA reactions. The results of reaction of 2-[(*E*)-styryl]quinazolin-4(3*H*)-one (**1**) containing the 1-azabutadiene moiety, with dimethyl acetylenedicarboxylate (**2**) which has been used successfully in HDA reactions[8] are presented here.

Heating equimolar amounts of **1** and **2** in MeCN under refluxing condition yielded two products **4a** and **4b** in low yields (Table 1). ^{1}H NMR spectra of **4a** and **4b** (Table 2) revealed that none of them was the expected cycloaddition product (**3**). Two distinct doublets in the ^{1}H NMR spectra, at δ 6.65, 8.02 (*J* =15Hz) for **4a** and δ 6.93, 8.02 (*J* =15Hz) for **4b**, indicated the presence of (*E*)–styryl chain in both compounds. From the IR bands at 1749, 1743 cm^{-1} for **4a** and 1735, 1690 cm^{-1} for **4b** alongwith two 3H singlets in the ^{1}H NMR signal (δ 3.64, 3.88 in **4a** and δ 3.83, 3.91 in **4b**), it was evident that each product contained two methylester groups. The doublet at δ 8.24 and 8.25(*J* =8Hz) for **4a** and **4b**

Table 1 Physical constants, yield and analytical data of **4a**, **4b**, **8**, **10a** and **10b**

Compound No.	M.p./°C	Yield/%	Mol. formula	Found (Calcd.)/%		
				C	H	N
4a	135-136	8	$C_{22}H_{18}N_2O_5$	67.47(67.68)	4.61(4.65)	7.30(7.17)
4b	189-190	5	$C_{22}H_{18}N_2O_5$	67.85(67.68)	4.71(4.65)	7.18(7.17)
8	154-155	12	$C_{20}H_{16}N_2O_3$	72.08(72.27)	4.82(4.85)	8.45(8.43)
10a	104-105	13	$C_{13}H_{12}N_2O_3$	64.06(63.94)	5.06(4.95)	11.39(11.47)
10b	123	10	$C_{13}H_{12}N_2O_3$	63.86(63.94)	4.76(4.95)	11.36(11.47)

Table 2 Spectral data of **4a**, **4b**, **8**, **10a** and **10b**

Compound No.	IR(KBr) ν_{max} (cm^{-1})	^{1}H NMR δ(CDCl$_3$)	^{13}C NMR δ(CDCl$_3$)	MS M$^+$(*m/z*)
4a	1749sh, 1743,1692	3.64(s,3H), 3.88(s,3H), 6.65(d,1H,*J*=15Hz),7.37–7.79(m,9H), 8.02(d,1H,*J*=15Hz), 8.25(d,1H,*J*=8Hz),	52.5,53.7,117.9,120.2,126.7,126.9, 127.5,127.9,128.8,129.3,129.9,134.9, 135.0,137.6,141.2,147.6,150.2,161.4, 162.5,162.6	390
4b	1735,1690, 1672	3.83(s,3H), 3.91(s,3H), 6.52(s,1H), 6.93(d,1H,*J*=15Hz),7.38–7.99(m,8H), 8.02(d,1H,*J*=15Hz), 8.24(d,1H,*J*=8Hz),	52.7,53.3,118.4,120.1,126.9,127.4, 128.0,128.9,130.0,131.8,134.8,134.9, 135.1,141.2,147.4,150.6,161.6,162.1, 163.9	390
8	1719,1690	3.85(s,3H), 6.64(d,1H,*J*=14Hz), 7.00(d,1H,*J*=15Hz),7.40–7.81(m,8H), 7.95(d,1H,*J*=15Hz),7.96(d,1H,*J*=14Hz), 8.28(d,1H,*J*=8Hz)	52.0,119.2,119.5,120.2,127.1,127.2, 127.4,127.9,128.9,130.0,134.9,137.2, 141.2,146.5,150.3,161.2,166.1	332
10a	1715,1695	2.68(s,3H), 3.84 (s,3H), 6.90(d,1H,*J*=14Hz),7.48(t,1H,*J*=8Hz), 7.62(d,1H,*J*=8Hz), 7.73–7.81(m,2H), 8.27(d,1H,*J*=8Hz),	24.1,52.0,118.0,120.4,126.9,127.18, 127.21,135.0,136.7,146.0,151.9,161.3, 166.7	244
10b	1729,1670	2.50(s,3H), 3.65 (s,3H), 6.33(d,1H,*J*=9Hz), 6.97(d,1H,*J*=9Hz), 7.45(t,1H,*J*=8Hz), 7.65(d,1H,*J*=8Hz), 7.75(t,1H,*J*=8Hz),8.24(d,1H,*J*=8Hz),	23.2,52.0,120.2,123.0,126.7,126.9, 134.7,136.1,142.4,147.3,161.3,163.5	244

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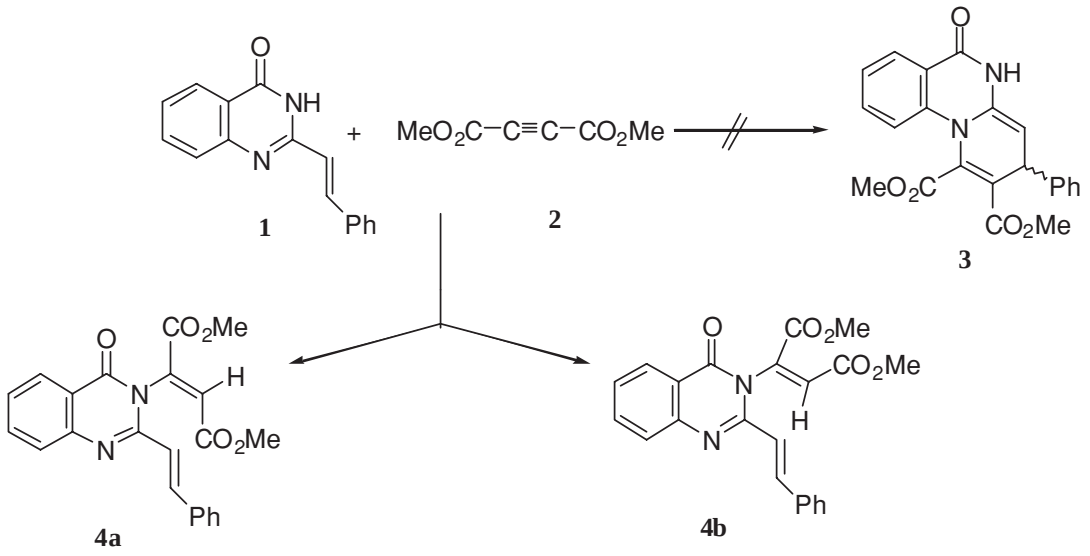

Fig. 1

respectively, was characteristic[9] of the *peri*-proton at C-5 in the quinazolin-4(3*H*)-one system. A marked difference in the ^{1}H NMR spectra of the products was a sharp singlet (1H) at δ 6.52 present in **4b** but absent in **4a**. Furthermore, **4a** showed a 9H multiplet for aromatic protons (δ 7.37–7.79) while in **4b** it was a 8H multiplet (δ 7.38–7.99). From the spectral data, it appears that both **4a** and **4b** are N–alkenylation products rather than the expected HDA cycloaddition adduct (**3**). The ^{13}C NMR spectra of **4a** and **4b** in respect to the C-2, C-4, C-8 and C-8a signals matched better with the corresponding signals in 2,3-dimethylquinazolin-4(3*H*)-one (**5**)[10] than those in the isomeric 1,2-dimethyl compound (**6**) (Table 3). Thus from the ^{13}C NMR data, the compounds were identified as the N-3 alkenylation products, 3-[(*Z*)-bis(methoxycarbonyl) vinyl]2-[(*E*)-styryl]-quinazolin-4(3*H*)-one (**4a**) and 3-[(*E*)-bis (methoxycarbonyl)vinyl]2-[(*E*)-styryl]-quinazolin-4(3*H*)-one (**4b**) as shown in Fig.1. This was subsequently confirmed by the X-ray crystallographic study of **4b**.

An ORTEP[11] view of the molecule of **4b** with atom numbering scheme is shown in Fig. 2. The *E*- configuration of the vinyl chain at N(3) is established by the torsion angle N(3)–C(17)–C(20)–C(21) of 174.2(4)°. The styryl quinazolinone part of the molecule is essentially planar with an RMS deviation 0.045 Å. The coplanarity of the heterocyclic ring atoms with the styryl moiety strongly suggests a resonance interaction extending to the adjacent atoms. This is reflected in the C(2)–C(9) [1.459(5) Å] and C(10)–C(11) [1.457(5) Å] distances which lie in between single and double bond lengths, confirming a high degree of delocalisation. In the crystal packing of **4b**, the styryl quinazolinone moieties are arranged in layers approximately parallel to the ac plane with the carbon atoms of the vinylmethoxy carbonyl groups [C(19), C(20), C(22)] linking the layers via hydrogen bonds. Intermolecular C–H···N hydrogen bonds [C(20)···N(1) 3.272(6) Å, C(20)–H(20)···N(1) 166.2°] link the molecules in to centrosymmetric dimers forming $R_2^2(12)$rings. Additional intermolecular C-H···O hydrogen bonds [C(22)···O(1) 3.219(7), C(19)···O(4) 3.303(6) Å, C(22)–H(22A)···O(1) 1491.1, C(19)–H(19B)···O(4) 137.5°] between the layers stabilise the molecular structure of **4b**.

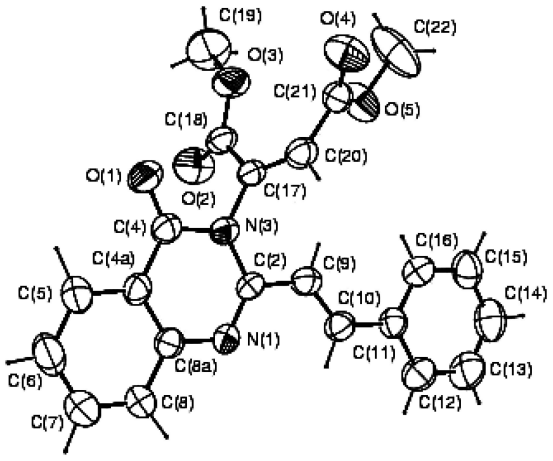

Fig. 2

To investigate any possible HDA reaction involving other conjugated esters, **1** was reacted with methyl propiolate (**7**). In this case also, N-alkenylation occurred in preference to the HDA reaction, yielding 3-[(*E*)-2-(methoxycarbonyl)vinyl] 2-[(*E*)-styryl]-quinazolin-4(3*H*)-one (**8**) (Fig.3.) as the only product.

Although the alkylation of quinazolin-4(3*H*)-ones at N-3 with alkyl halides under neutral or basic condition is well known,[12] N-3 alkenylation of quinazolin-4(3*H*)-one derivatives is yet to be reported. It seemed interesting to react 2-methylquinazolin-4(3*H*)-one (**9**) with methyl propiolate (**7**). As expected, two isomeric N-3 alkenylation products, viz, 3-[(*E*)-2-(methoxycarbonyl)vinyl]2-methyl-quinazolin-4(3*H*)-one (**10a**) and 3-[(*Z*)2-(methoxycarbonyl) vinyl]2-methyl-quinazolin-4(3*H*)-one (**10b**) were isolated in low yields. From the analytical and spectral data (Table 1, 2), the structures of **8**, **10a** and **10b** were assigned (Fig. 4.). The present work, to the best of our knowledge, is the first ever report of N-3 alkenylation of 2-substituted quinazolin-4(3*H*)-ones under neutral condition.

Table 3 ^{13}C NMR data of C-2, C-4, C-8 and C-8a of **4a**, **4b**, **5** and **6**

Compound No.	δ_c (ppm)			
	C–2	C–4	C–8	C–8a
4a	150.2	161.4	126.7	147.6
4b	150.6	161.6	126.9	147.4
5*	155.7	161.4	126.2	147.2
6*	162.3	168.5	114.0	141.6

*Reported[10] data for **5** and **6**

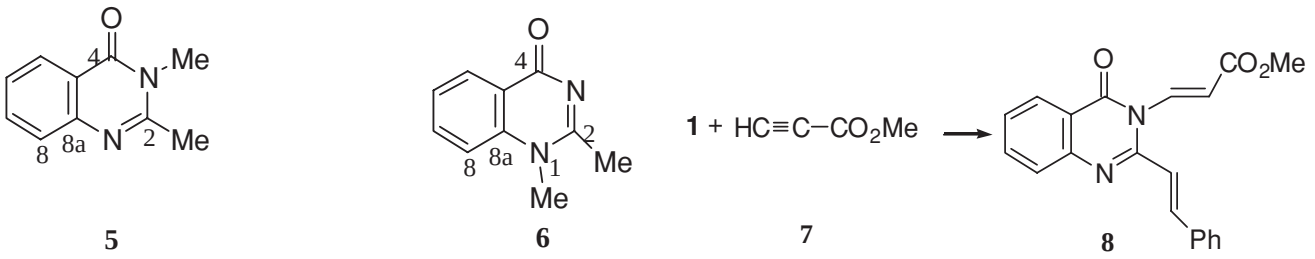

Fig. 3

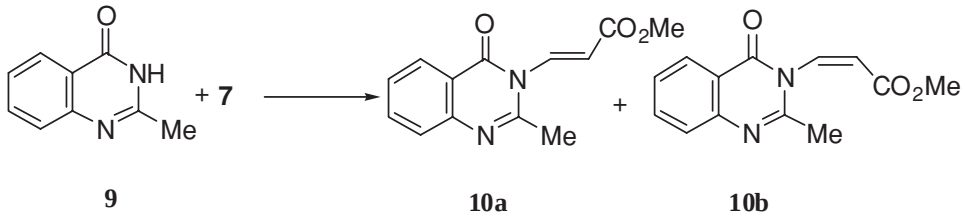

Fig. 4

Experimental

Melting points were determined in open capillaries and are uncorrected. All solvents used for reactions and chromatography were distilled before use. Progress of reactions were monitored by TLC. IR Spectra were recorded on KBr discs on a Perkin- Elmer 297 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 L spectrometer using TMS as reference. Mass spectra (EI) were recorded using a JEOL AX 500 spectrometer. **1**[13] and **9**[14] were prepared following literature procedure.

General procedure of reaction of **1** *with* **2** *and* **7**
Equimolar (3mmol) amount of the reactants in MeCN (120ml) were heated to reflux for 3h. A highly insoluble material having very high m.p. (> 290°C) separated during each reaction (~ 150–200mg) was removed and discarded. Removal of solvent afforded a crude sticky material which was chromatographed over silica gel column. Elution with various proportions of EtOAc–Pet.ether mixture gave a solid which was subjected to repeated crystallisations from EtOAc–Pet. ether and finally from EtOAc to afford the products (**4a, 4b, 8**) in low yield (see Table 1).

General procedure of reaction of **9** *with* **7**
A mixture of the reactants (3 mmol) in MeCN (40 ml) was refluxed for 3h. Concentrating the solution caused separation of unreacted **9** which was removed. The mother liquor was chromatographed over silica gel column using EtOAc–Hexane (1:4) as eluent to afford a solid which was repeatedly crystallised from EtOAc to afford **10a** and **10b** in low yield.

Crystal data **4b**: $C_{22}H_{18}N_2O_5$, M_r = 390.38, monoclinic, $P2_{1/n}$, a = 11.449 (1), b =14.098 (2), c = 12.694 (1) Å, β =105.94 (1)°, V = 1970.1(4) Å^3, D_x = 1.316 g cm^{-3}, Z = 4, μ = 0.095 mm^{-1}, T = 293 K. A colourless prism prepared by slow evaporation from EtOAc was used for data collection in an Enraf-Nonius CAD-4 diffractometer with graphite monochromated MoKα radiation (λ = 0.7107 Å).Cell parameters were determined from a least-squares refinement of the setting angles of 25 reflections (15.0<θ<18.5°). A total of 3372 reflections were collected. The intensities of 3 standard reflections were measured after every 100 reflections and showed no significant intensity variation during data collection. No decay correction was applied. The data were corrected for Lorentz and polarisation effects. Absorption correction based on ψ scan (T_{min} = 0.974, T_{max} = 0.986) was applied. The structure was solved by direct methods and refined on F^2 using SHELXS 97 and SHELXL 97[15]. Hydrogen atoms were included but not refined. The final full-matrix least-squares refinement based on 1720 observed reflections [I>2σ (I)] converged to R=0.067, WR = 0.147. Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (CCDC No. 266215).

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