Novel formation of spirocyclic oxazolines in the reaction of some (*E*)-3-(4-methoxybenzylidene)flavanones with NaN_3/c.H_2SO_4-HOAc

Asok K. Mallik[a]*, Falguni Chattopadhyay[a] and Amarendra Patra[b]

[a]*Department of Chemistry, Jadavpur University, Kolkata 700 032, India*

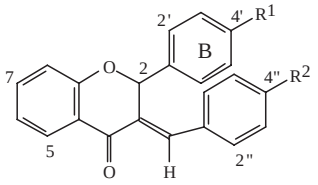
[b]*Department of Chemistry, University College of Science, Calcutta University, Kolkata 700 009, India*

On treatment with NaN_3/c.H_2SO_4-HOAc, some (*E*)-3-(4-methoxybenzylidene)flavanones yield a new type of flavonoid-derived spirocyclic oxazolines in moderate yield. A plausible mechanism for formation of these products is suggested.

Keywords: flavanones, sodium azide, spirocyclic oxazolines

Treatment of ketones with NaN_3/TFA, or with NaN_3/c.H_2SO_4-HOAc are two important methods for effecting their Schmidt reaction.[1] In our recent studies on Schmidt reaction of *E*-3-benzylideneflavanones (**1**) by treatment with NaN_3/ TFA, we observed the novel formation of 3-benzoylchromones.[2] We then undertook a study of the reaction of *E*-3-benzylideneflavanones by treatment with NaN_3/c.H_2SO_4-HOAc. Thus, from a number of substrates different types of results were obtained, which are very much dependent on the substituent pattern in the substrate. Herein, we report the novel formation of flavonoid derived spirocyclic oxazolines from (*E*)-3-(4-methoxybenzylidene) flavanones.

In an earlier report[2] we stated that on treatment with NaN_3/ c.H_2SO_4-HOAc **1a** yielded a product having the structure **2a**.



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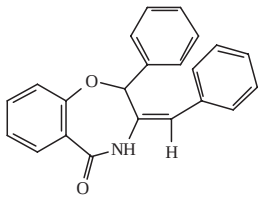
a: $R^1 = R^2 = H$; **b**: R^1 =H, R^2 = OMe
c: $R^1 = R^2$ = OMe; **d**: R^1 = Cl, R^2 = OMe
e: R^1 = OMe, R^2 = H; **f**: R^1 = OMe, R^2 = Cl



2a

Table 1 Products of reaction of benzylideneflavanones **1a–f** with NaN_3 in H_2SO_4/HOAc (see Scheme 1)

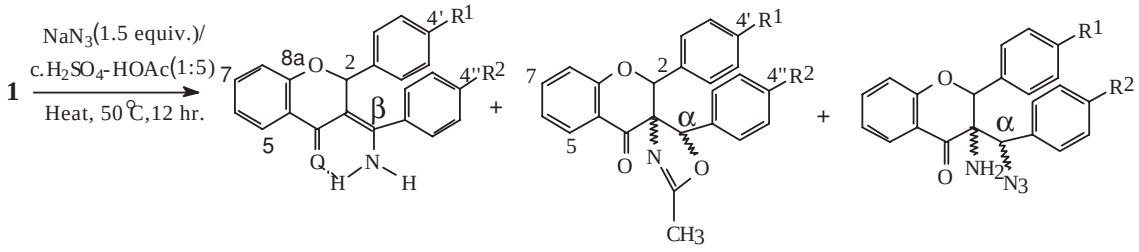
Substrate	Products/yield%
1a	**3a** (35)
1b	**3b** (20) + **4b** (35)
1c	**4c** (39) + **5c** (18)
1d	No reaction
1e[a]	**3b** (22) + **4b** (30)
1f[a]	**1d** (90)

[a]The compounds **1e** and **1f** first underwent skeletal rearrangement producing **1b** and **1d**, respectively, of which only **1b** underwent further reaction.

Thorough spectroscopic studies, however, have established the correct structure of this compound as **3a**. When **1b** was treated in the same way, interestingly, it gave the novel spirocyclic oxazoline **4b** in moderate yield along with **3b**. This observation encouraged us to study the reaction of *E*-3-benzylideneflavanones having methoxy group at the 4" and also at the 4' position under the similar reaction conditions. The results obtained are presented in Scheme 1 and Table 1.

The structures of the spirocyclic oxazolines were established from their detailed NMR spectroscopic analysis including homo-decoupling and HETCOR (one-bond as well as long range). The configuration of these compounds, however, remains unsettled as none of **4b** and **4c** gave quality crystals from a number of common solvents.

It is interesting to note that the *E*-3-(4-methoxybenzylidene) flavanone **1d** bearing an electron-withdrawing group in the B-ring, did not undergo any reaction. This suggested a participation of the B-ring during conversion of **1** to **3** and/or **4**. Plausible mechanistic paths for conversion of **1** to **3** and **4**, consistent with the above observation, are given in Schemes 2 and 3, respectively. Scheme 3 also shows the formation of **5c** from **1c**.

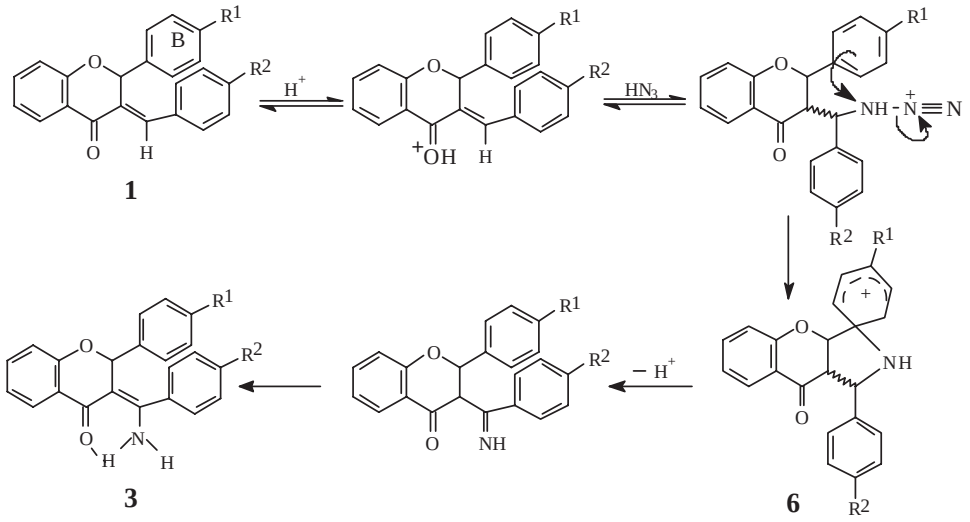


3 **4** **5**

a: $R^1 = R^2 = H$; **b**: R^1 =H, R^2 = OMe; **c** $R^1 = R^2$ = OMe
d: R^1 = Cl, R^2 = OMe; **e**: R^1 = OMe, R^2 = H; **f**: R^1 = OMe, R^2 = Cl

Scheme 1

* Correspondent. E-mail: mallikak52@yahoo.co.in



Scheme 2

The *E*-3-benzylideneflavanones **1e** and **1f** underwent skeletal rearrangement producing the isomers **1b** and **1d** respectively, which is in accordance with our earlier observation.[2] Between **1b** and **1d** so produced, only the former underwent further reaction. Regarding the formation of **3**–**5**, it is noteworthy that protonated chalcones usually undergo attack by HN_3 at the carbonyl carbon, leading ultimately to normal Schmidt reaction products,[3] but here the β-carbon of the protonated *E*-3-benzylideneflavanones is attacked by HN_3. The greater electron deficiency at the β-carbon of *E*-3-benzylideneflavanones compared to that at the same carbon of chalcones due to an unfavourable steric interaction between H-2 and H-2",6" of *E*-3-benzylideneflavanones[4] may be one of the reasons for this difference.

Thus, we report the formation of a new type of flavonoid-derived spirocyclic oxazolines from a very simple reaction.

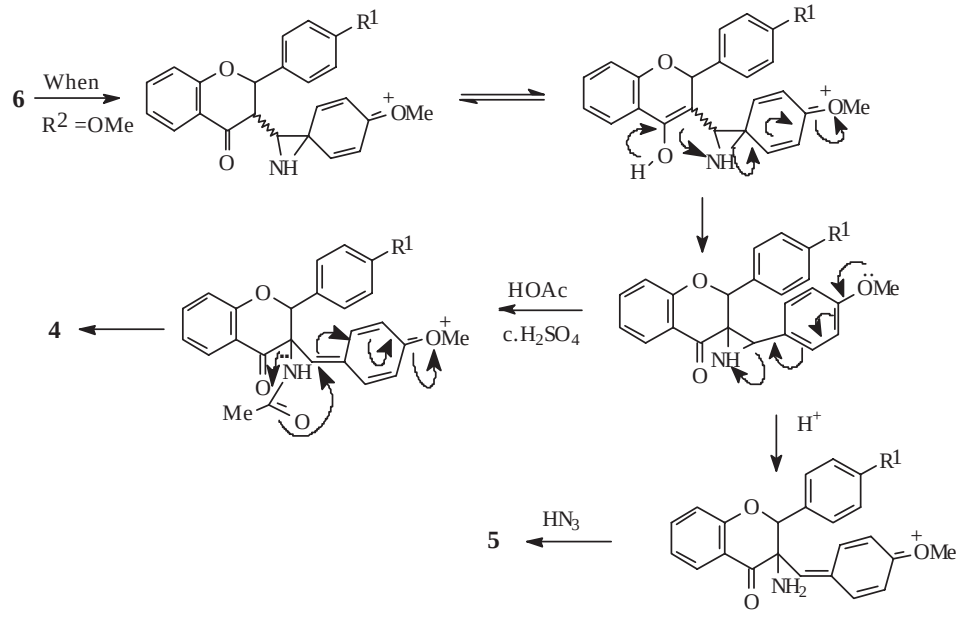
Experimental

Melting points were recorded on a Kofler block. IR spectra were recorded in KBr on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker DPX-300 (300MHz) and Bruker AM-300L (300.13 MHz) spectrometers. ^{13}C NMR spectra were recorded in $CDCl_3$ using the above instruments at 75MHz. EI mass spectra were recorded on JEOL JMS D-300 and Shimadzu QP-1000 spectrometers.

Analytical samples were routinely dried *in vacuo* at room temperature. Column and thin layer chromatography was carried out using silica gel (100–200 mesh, Tara Chemicals, Kolkata) and silica gel G (Qualigens Fine Chemicals, Mumbai), respectively. Petroleum ether had the boiling point range 60–80 °C.

Reaction of (E)-3-benzylideneflavanones with NaN_3/c.H_2SO_4: General procedure: An appropriate (*E*)-3-benzylideneflavanone (1 mmol) was dissolved in c.H_2SO_4-HOAc (1:5, 6 ml) between 0 and 10 °C, and to the cold solution sodium azide (1.5 mmol) was added in three portions at five minute intervals with stirring. The resulting mixture was heated at 50 °C for 12 h and then diluted with water (150 ml) and extracted with chloroform (3 × 30 ml). The chloroform extract was then washed with water (4 × 25 ml) and dried over anhydrous sodium sulfate. The concentrate of the chloroform extract was chromatographed over silica gel using petroleum ether – ethyl acetate mixtures (PE–EA) as eluants in order to get pure products. The melting points and analytical and spectral data of the products were as follows.

Compound **3a**: Eluted by PE-EA (8:2), m.p. 201–202 °C. IR: ν_{max} KBr): 3250 (N-H), 1600 (β-amino-αβ-unsaturated carbonyl)



Scheme 3

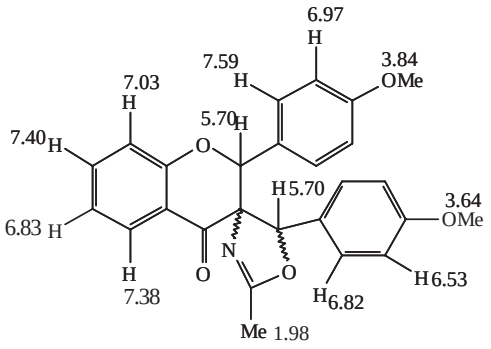


Fig. 1

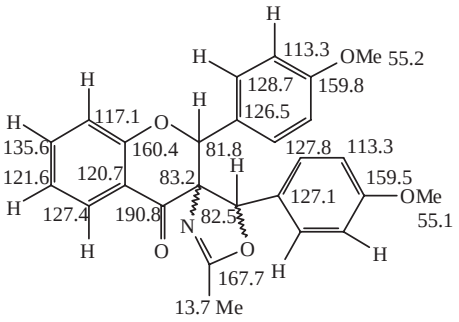


Fig. 2

cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.20 (1H, br. s, exchangeable with D_2O, free NH), 5.94 (1H, s, H-2), 6.83 (1H, d, *J* = 8.1 Hz, H-8), 6.92 (1H, t, *J* = 7.5 Hz, H-6), 7.13–7.45 (11H, m, Ar-H), 7.89 (1H dd, *J* = 7.8 and 1.5 Hz, H-5), and 10.58 (1H, br. s, exchangeable with D_2O, chelated NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.0 (C-2), 100.0 (C-3), 117.8 (C-8), 121.1 (C-6), 124.3 (C- 4a), 126.7 (C-5), 127.5 (C-2",6"), 127.7 (C-2', 6', 4"), 128.1 (C-3",5"), 128.9 (C-3',5'), 129.9 (C-4'),134.0 (C-7), 135.9 (C -1"), 141.8 (C-1"), 159.0 (C-β), 160.8 (C-8a), 184.0 (C-4). EIMS: *m/z* 327 (M^+). Calc. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.2. Found: C, 80.68; H, 4.97; N, 3.98 %.

Compound **3b:** Eluted by PE-EA (8:2), m.p. 196–197 °C. IR: ν_{max} (KBr): 3300 (N-H),1600 (β-amino-αβ-unsaturated carbonyl) cm^{-1} ^{1}H NMR ($CDCl_3$): δ 3.80 (3H, s, OCH_3), 5.22 (1H, br.s, exchangeable with D_2O, free N-H), 6.00 (1H, s, H-2), 6.81–6.93 (4H, m, H-3",5",H-6 and H-8), 7.15–7.34 (8H, Ar-H), 7.88 (1H,dd, *J* = 7.8 and 1.5 Hz, H-5), and 10.61 (1H, exchangeable with D_2O, chelated N-H). ^{13}C NMR ($CDCl_3$): δ 55.37 (OCH_3), 77.87 (C-2), 99.56 (C-3), 114.29 (C-3",5"), 117.84 (C-8), 121.17 (C-6), 124.38 (C-4a), 126.63 (C-5), 127.43 (C-1"), 127.64 (C-4'), 127.70 (C-2',6'), 128.13 (C-3',5'), 128.98 (C-2",6"), 134.01 (C-7), 141.83 (C-1'), 157.43 (C-β), 160.88 (C-8a), 161.1 (C-4"), 182.98 (C-4). Calc. for $C_{23}H_{19}NO_3$: C,77.29; H, 5.36; N, 3.92. Found: C, 77.19; H, 5.27; N, 3.28 %.

Compound **4b**: Eluted by PE-EA (65:35), m.p. 180–182 °C. IR: ν_{max} (KBr): 1690 (C=O), 1670 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.97 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 5.74 (1H,s, H-2)[a], 5.76 (1H, s, H-α)[a], 6.55 (2H, d, *J* = 8.7Hz, H-3",5"), 6.83 (2H, d, *J* = 8.4 Hz, H-2",6"), 6.86 (1H, br. t, *J* = 7.6 Hz, H-6), 7.07 (1H, d, *J* = 8.1 Hz, H-8), 7.39–7.47 (5H, m, Ar-H), and 7.69 (2H, d, *J* = 7.2 Hz, H-2',6').^{13}C NMR (75 MHz, $CDCl_3$), δ 13.7 (CH_3), 55.1 (OCH_3). 81.6 (C-2)[a] 82.8 (C-α)[a], 83.1 (C-3), 113.4 (C-3",5"), 117.1 (C-8), 120.7 (C-4a), 121.9 (C-6), 127.1 (C-1"), 127.5 (C-4'), 127.6 (C-3',5'), 127.8 (C-2',6'), 127.8 (C-2",6"), 128.5 (C-5), 134.5 (C-1'), 125.5 (C-7), 159.6 (C-4"), 160.3 (C-8a), 167.8 (-O-C=N-), and 190.7 (C-4). Calc. for $C_{25}H_{21}NO_3$ C, 78.31; H, 5.52; N, 3.21. Found: C, 78.25; H, 5.27; N, 2.95 %.

[a]Assignments for H-2 and H-α may be interchanged, and also those for C-2 and C-α.

[b]For this compound the full set of ^{1}H and ^{13}C NMR spectral data of C-2 and the attached *p*-methoxyphenyl moiety may be interchangeable with the same of C-α and the corresponding *p*-methoxyphenyl moiety.

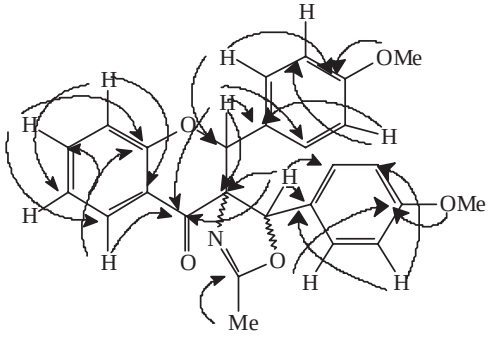


Fig. 3

Compound **4c**: Eluted by PE-EA (65:35), m.p. 178–180 °C. IR: ν_{max} (KBr): 1700 (C=O), 1655 (C=N) cm^{-1}. ^{1}H and ^{13}C NMR ($CDCl_3$) are shown in Figs 1 and 2.[b] HETCOR (one bond and long range [optimised for *J* ≡ 7 Hz]) showed the correlations indicated in Fig. 3. EI MS: *m/z* 429 (M^+). Calc. for $C_{26}H_{23}NO_5$: C, 72.71; H, 5.40; N, 3.2. Found: C, 72.66; H, 5.19; N, 2.98 %.

Compound **5c**: Eluted by PE-EA (65:35), m.p. 158–160 °C. IR: ν_{max} (KBr): 3380 (N-H), 2100 (N_3), 1690 (C=O) cm$^{-1.}$ ^{1}H NMR ($CDCl_3$): δ 1.99 (2H, br.s, exchangeable with D_2O, NH_2), 3.75 (3H, s, OCH_3), 3.83 (3H,s OCH_3), 5.14 (1H, s, H-α), 5.27 (1H, s, H-2), 6.70 (2H, *quasi*-dt – pattern resembles a pair of triplets[5,6], *J* = 9 and 3.1 or 2.1 Hz, H-3",5"), 6.75 (2H, *quasi*-dt, *J* = 9 and 3.1 or 2.1Hz, H-2",6"), 6.99 (2H, *quasi*-dt, *J* = 8.7 and 3.1 or 2.1 Hz, H-3',5'), 7.07 (1H, br .t, *J* = 8.1 Hz, H-6), 7.17 (1H, br. d, *J* = 8.5 Hz, H-8), 7.57 (1H, dt, *J* = 8.1 and 1.5 Hz, H-7),7.59 (1H, dd, *J* = 8.1 and 1.5 Hz, H-5) and 7.67 (2H, *quasi*-dt, *J* = 8.7 and 2.1 or 3.1 Hz, H-2',6'). ^{13}C NMR ($CDCl_3$): δ 55.17 (OCH_3), 55.35 (OCH_3), 64.02 (C-α), 64.79 (C-3), 85.58 (C-2), 113.45 (C-3",5"), 113.74 (C-3',5'), 117.88 (C-8), 120.50 (C-4a), 122.12 (C-6), 127.62 (C-5), 128.09 (C-1"), 128.39 (C-2",6"), 128.72 (C-2',6'), 132.19 (C-1'), 136.09 (C-7), 157.5 (C-8a), 159.99 (C-4"), 160.63 (C-4') and 191.70 (C-4). CI MS: *m/z* 431 (M + H^+) and 388 (*m/z* 431-HN_3)$^+$. Calc. for $C_{24}H_{22}N_4O_4$: C,66.97; H, 5.15; N, 13.02. Found: C,66.92; H, 5.37; N, 12.91 %.

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