Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 4773–4778

Intramolecular low-temperature 1,3-dipolar cycloadditions of nitrones: synthesis of chromano-heterocycles

Gurpinder Singh,[a] M. P. S. Ishar,[a,*] Vivek Gupta,[b] Gurmit Singh,[a] Mohit Kalyan[b] and Surinderjit Singh Bhella[a]

[a]*Bio-Organic and Photochemistry Laboratory, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar-143 005, Punjab, India*
[b]*Department of Physics, University of Jammu, Jammu Tawi-180 006, India*

Received 28 October 2006; revised 25 February 2007; accepted 15 March 2007
Available online 18 March 2007

Abstract—In contrast to the reported facile intramolecular 1,3-dipolar cycloadditions of in-situ generated nitrone on heterocyclic systems, reactions of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromones with *N*-phenyl-/methylhydroxylamine under comparable conditions, afford fused isoxazolidines only in low to moderate yields; the corresponding amides derived from rearrangement of in situ generated nitrones are formed as major products. However, when reactions were carried by stirring the reactants at an ice-cold temperature in dichloromethane, highly stereoselective intramolecular 1,3-dipolar cycloadditions lead to novel fused isoxazolidines in high yields (80–90%).

1. Introduction

1,3-Dipolar cycloadditions to olefinic and acetylenic dipolarophiles are the most straightforward approach to regio- and stereo-selective synthesis of five-membered heterocycles;[1] these have also been extensively exploited for the synthesis of precursors/ scaffolds[2] for a variety of molecular frameworks.[1,2] In particular, the intramolecular 1,3-dipolar cycloadditions have shown potential in the synthesis of carbo- and heterocyclic frameworks.[1–3] The immediate product of nitrone–olefin cycloaddition i.e., isoxazolidines have now been well established as heterocyclic analogues of the five-membered sugar moiety of nucleosides and a variety of isoxazolidine-based molecules are being investigated for antiviral, and anticancer activities.[4] Recently, intramolecular nitrone–olefin cycloadditions on carbo- and heterocyclic systems have been utilized to obtain fused isoxazolidines of either biological significance or the obtained isoxazolidines have been cleaved to obtain useful synthetic precursors.[2,3,5] However, intramolecular cycloadditions have stereochemical constraints and under forcing conditions the nitrone to amide rearrangement may also intervene.

A variety of biological activities have been attributed to molecules possessing chromone moiety[6] and presently intramolecular 1,3-diploar cycloadditions to obtain chromone-fused isoxazolidines are investigated.

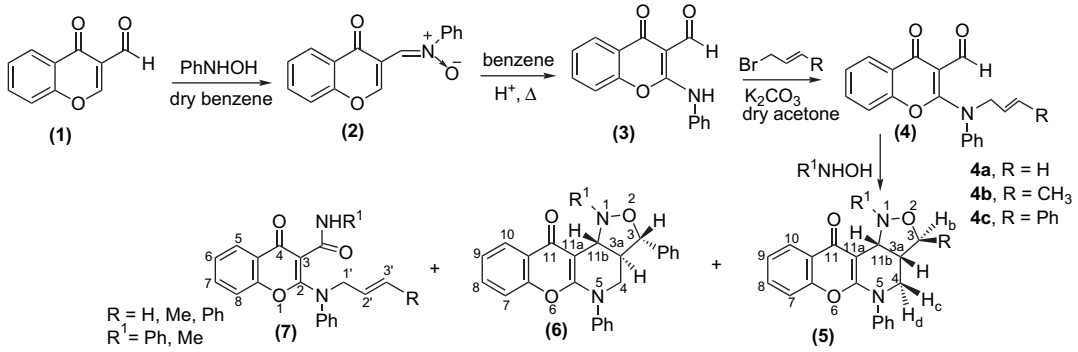
2. Results and discussion

The starting compounds **4a–c** were obtained by a route reported earlier[7] (Scheme 1). Initially, the reactions of **4a–c** were carried with *N*-phenyl-/methylhydroxylamine (R^1= Ph, Me) by stirring their dichloromethane solutions at ambient temperature, which led to the formation of fused isoxazolidines **5a**, **c–f**, and **6c** in low to moderate yield (5–37%) and corresponding amides **7a–f** were obtained as major products (44–90%). Carrying out reactions under more drastic conditions such as refluxing their dry benzene solutions and heating their toluene solutions in sealed tubes led to increased formation of amides and no cycloadducts were isolated; the results are summarized in Scheme 1 and Table 1.

However, when aldehydes, **4a–c**, were mixed with *N*-methylhydroxylamine in dichloromethane at an ice-cold temperature and the stirred solution was slowly brought to the room temperature, regio- and stereo-selective intramolecular 1,3-dipolar cycloadditions of the in situ generated nitrones led to chromano–piperidine-fused isoxazolidines **5d–f** in very high yields (80–90%, Scheme 2) and the corresponding amides **7d–f** were isolated as minor products; no such improvement of yields was observed under similar conditions with *N*-phenylhydroxylamine.

Keywords: Chromone; Nitrone; Isoxazolidine; 1,3-Dipolarcycloadditions; Stereoselectivity; π-Facial selectivity.
* Corresponding author. Tel.: +91 183 2258802 09x3321; fax: +91 183 2258820; e-mail: mpsishar@yahoo.com

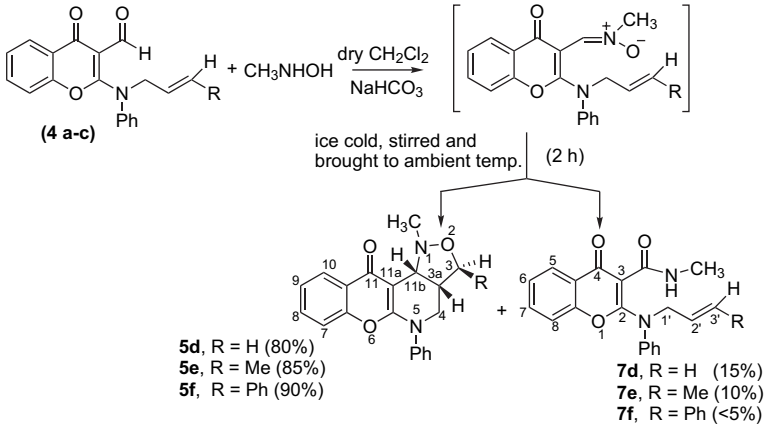
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.086



Scheme 1.

Table 1. Reaction time, reaction conditions, and % yield of various reaction products

Entry	R	R^1	Solvent	Reaction conditions (reaction time, h)	Product (% yield)		
					5	**6**	**7**
1	H	Ph	CH_2Cl_2	Stir, rt (72)	**5a** (37)	**6a** (Nil)	**7a** (44)
2	CH_3	Ph	CH_2Cl_2	Stir, rt (72)	**5b** (Nil)	**6b** (Nil)	**7b** (90)
3	Ph	Ph	CH_2Cl_2	Stir, rt (72)	**5c** (8)	**6c** (5)	**7c** (80)
4	H	Ph	Benzene	Reflux (24)	**5a** (5)	**6a** (Nil)	**7a** (70)
5	CH_3	Ph	Benzene	Reflux (24)	**5b** (Nil)	**6b** (Nil)	**7b** (95)
6	Ph	Ph	Benzene	Reflux (24)	**5c** (10)	**6c** (Nil)	**7c** (80)
7	H	Ph	Toluene	Sealed tube, 140 °C (5)	**5a** (5)	**6a** (Nil)	**7a** (90)
8	CH_3	Ph	Toluene	Sealed tube, 140 °C (5)	**5b** (Nil)	**6b** (Nil)	**7b** (80)
9	Ph	Ph	Toluene	Sealed tube, 140 °C (5)	**5c** (10)	**6c** (Nil)	**7c** (80)
10	H	CH_3	CH_2Cl_2	Stir, rt (48)	**5d** (30)	**6d** (Nil)	**7d** (60)
11	CH_3	CH_3	CH_2Cl_2	Stir, rt (48)	**5e** (10)	**6e** (Nil)	**7e** (80)
12	Ph	CH_3	CH_2Cl_2	Stir, rt (48)	**5f** (20)	**6f** (Nil)	**7f** (80)
13	H	CH_3	Benzene	Reflux (24)	**5d** (10)	**6d** (Nil)	**7d** (80)
14	CH_3	CH_3	Benzene	Reflux (24)	**5e** (15)	**6e** (Nil)	**7e** (85)
15	Ph	CH_3	Benzene	Reflux (24)	**5f** (15)	**6f** (Nil)	**7f** (85)
16	H	CH_3	Toluene	Sealed tube, 140 °C (5)	**5d** (<5)	**6d** (Nil)	**7d** (90)
17	CH_3	CH_3	Toluene	Sealed tube, 140 °C (5)	**5e** (Nil)	**6e** (Nil)	**7e** (85)
18	Ph	CH_3	Toluene	Sealed tube, 140 °C (5)	**5f** (10)	**6f** (Nil)	**7f** (85)



Scheme 2.

The products were isolated by column chromatography and have been characterized by detailed spectroscopic analysis, including a comparison of the spectroscopic data with that of related compounds.[5a,8] That the compound **5a** is derived from intramolecular 1,3-dipolar cycloaddition of an in situ formed nitrone was established from its mass spectrum, which revealed a M^+ ion peak at *m/z* 396. Its ^1H NMR spectrum indicated the absence of resonances attributable to olefinic protons of the allylic moiety or aldehydic-H and indicated the presence of an isoxazolidine moiety.[5a,8] The assigned stereochemistry around the isoxazolidine moiety is based on the value of $J_{3a,11b}$=8.4 Hz, indicating a cis relationship between these hydrogens.[5a,8] Overall ^1H and ^{13}C NMR spectral assignments, aided by ^1H–^{13}C hetero-COSY experiments, corroborated the assigned structure. The assigned C3a–C11b cis geometry in the case of obtained

cycloadducts **5a** and **c–f** has been further established by an X-ray crystallographic analysis of **5d** (Fig. 1).[9]

In the case of isomeric cycloadduct **6c** the C1–H was observed as a doublet at δ 5.8 (J=4.3 Hz) and C11b–H as a broad singlet at δ 4.23; lack of observable coupling between C11b–H and C3a–H was indicative of a trans relationship. The changes in the chemical shift values of C11b–H, C3a–H, and C3–H on going from **5c** to **6c** are as anticipated.[5a,10] It may be mentioned here that an alternative structure **8** for the obtained products was rigorously ruled out on the basis of obtained ^{1}H NMR spectral data, including ^{1}H–^{1}H connectivities, though formation of such products has been reported in intramolecular cycloadditions of nitrones in related systems.[8e] The structural assignments of **7a–f** are also based on spectroscopic analysis.

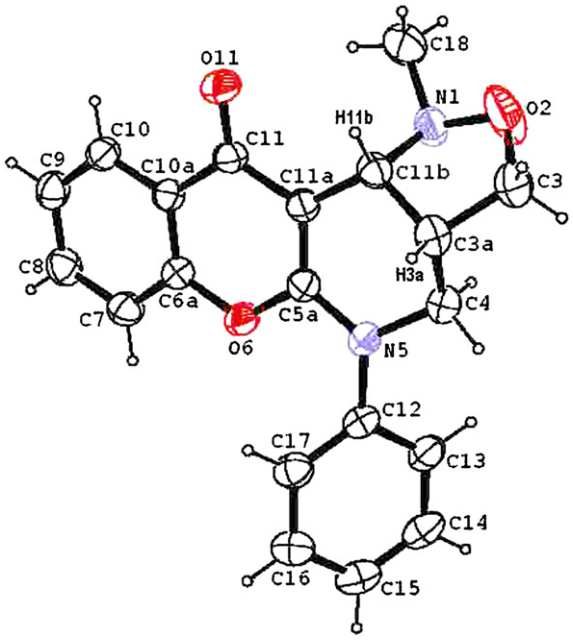
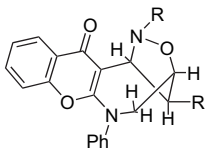


Figure 1. ORTEP diagram of **5d**.



(8)

Mechanistically, the regio- and stereo-chemical outcomes of intramolecular cycloadditions of nitrones are dependent on an interplay of various factors; the major contributing factors being the conformational constraints and steric influences of the substituents.[8e,11] The formation of the obtained products in the present investigations can be rationalized in term of various approaches outlined in Figure 2.

Approaches **A** and **B** differ in the conformation around the N–C1′ bond and consequently lead to different π-facial selectivities, with approach **A** leading to the cis arrangement between C11b–H and C3a–H (**5a**, **c–f**) and approach **B** leading to the trans relationship (**6c**). Approach **A** is favored both at higher and lower temperatures and corresponds to an *endo*-orientation of the substitutient R and *exo*-orientation of the relatively bulky substituient on the dipolarophile in the transition state. For steric reasons the *endo*-orientation of the bulky substitutient (R=Me, Ph) raises the barrier to cycloaddition and alternative pathway of isomerization of nitrone to amide becomes the predominant mode; for R′=Ph and R=Me, and Ph cycloaddition is completely prohibited. Carrying out the reactions of **4a–c** with *N*-methylhrdoxylamine at a low temperature and slowly bringing the reaction mixture to the room temperature suppresses the competitive formation of amide and leads to the formation of cycloadducts in high yields. Mechanistically, the rearrangement leading to the formation of amides from nitrones is known to involve oxaziridines as intermediates.[12]

3. Conclusions

The investigations have provided easy access to chromone-fused isoxazolidines by carrying out reactions at low

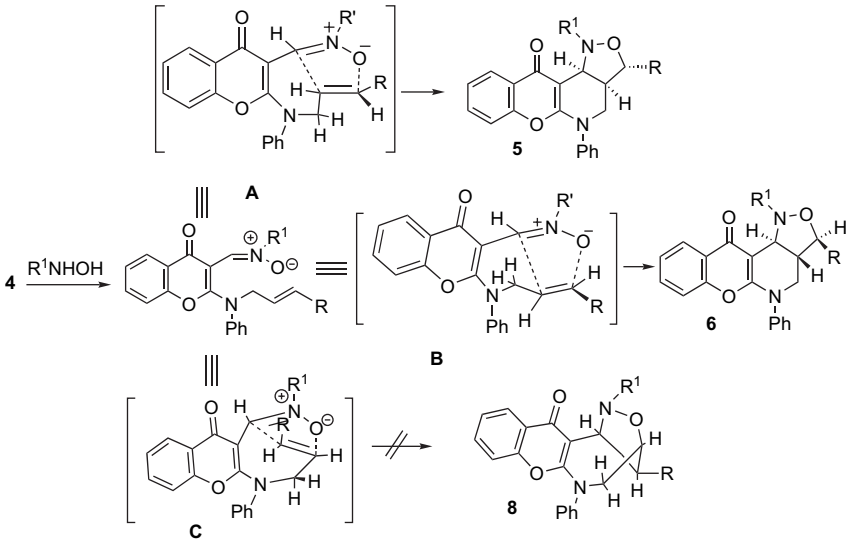


Figure 2.

temperature, which helps to circumvent the isomerization of nitrones to the corresponding amides.

4. Experimental

4.1. General information

Starting materials and reagents were purchased from commercial suppliers and used after further purification (crystallization/distillation). Bruker AC-200 FT (200 MHz) and JEOL (300 MHz) NMR spectrometers were used to record the ^{1}H NMR and ^{13}C NMR (50 and 75 MHz) spectra. Chemical shifts are reported in parts per million, tetramethylsilane is used as the internal standard and *J* values in hertz. IR spectra were recorded on Shimadzu 8400 S FT-IR spectrophotometer as KBr pellets. Mass spectra, EI and ESI-methods, were recorded on Shimadzu GCMS-QP-2000A and Bruker Daltonics Esquire 300 mass spectrometers, respectively. Elemental analyses were carried out on a Perkin–Elmer 240C elemental analyzer and are reported in percent atomic abundance. All melting points are uncorrected and measured in an open glass-capillaries using Veego Precision Digital Melting Point Apparatus.

4.1.1. Reaction of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (4a–c) with *N*-phenyl/methyl-hydroxylamine at room temperature. To a solution of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (300 mg) in dry CH_2Cl_2 (50 mL) was added *N*-phenyl/methyl-hydroxylamine (1 M equiv) and the solution was stirred at room temperature. After the completion of reaction (TLC), solvent was removed under vacuum and the residue was resolved by column chromatography over silica gel (60–1200 mesh, packed in hexane) using hexane/ethyl acetate gradient as an eluent to obtain adduct **5a** and **5c**–**f** along with amide **7a**–**c**.

4.1.2. Reaction of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (4a–c) with *N*-phenyl/methyl-hydroxylamine in dry benzene. To a solution of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (300 mg) in dry benzene (50 mL) was added *N*-phenyl/methyl-hydroxylamine (1 M equiv) and the solution was stirred with refluxing under anhydrous conditions, After the completion of reaction (TLC), solvent was removed under vacuum and the residue was resolved by column chromatography over silica gel (60–1200 mesh, packed in hexane) using hexane/ethyl acetate gradient as an eluent to obtain adduct **5a**–**c** along with amide **7a**–**c**.

Adduct (% yield) **5a** (5); **5b** (nil); **5c** (10); **5d** (10); **5e** (15); **5f** (15); *Amide* **7a** (70); **7b** (75); **7c** (80); **7d** (80); **7e** (85); **7f** (85).

4.1.3. Reaction of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (4a–c) with *N*-phenyl/methyl-hydroxylamine in dry toluene (sealed tube). To a solution of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (300 mg) in dry toluene (50 mL) was added *N*-phenyl/methyl-hydroxylamine (1 M equiv) and the solution was heated in Pyrex glass sealed tube at 140 °C for 5 h. After the completion of reaction (TLC), solvent was removed under vacuum and the residue was resolved by column chromatography over silica gel (60–1200 mesh, packed in hexane) using hexane/ethyl acetate gradient as an eluent to obtain adduct **5a**–**c** along with amide **7a**–**c**.

Adduct (% yield) **5a** (5); **5b** (nil); **5c** (10); **5d** (<5); **5e** (nil); **5f** (10); *Amide* ***7a*** (90); **7b** (80); **7c** (80); **7d** (90); **7e** (85); **7f** (85).

4.1.3.1. Adduct (5a). Colorless crystalline solid (37%); mp 112–113 °C ($CHCl_3$/hexane, 1:2); [Found: C, 75.82; H, 4.96; N, 6.98; $C_{25}H_{20}N_2O_3$ requires C, 75.74; H, 5.08; N, 7.07]; ν_{max} (KBr) 1646, 1628, 1596, 1592, 1516, 1504, 1487, 1443, 1382 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.19 (dd, 1H, *J* 7.7 & 1.4 Hz, C10–H), 7.49–7.41 (m, 4H, Ar–Hs), 7.32–7.26 (m, 6H, Ar–Hs), 7.07 (d, 2H, *J* 8.3 Hz, Ar–H), 6.97 (t, 1H, *J* 7.2 Hz, Ar–Hs), 5.39 (d, 1H, *J* 8.4 Hz, C11b–H), 4.43 (t, 1H, *J* 8.1 Hz, C3–H), 4.07–3.99 (m, 2H, C3–H & C4–H), 3.75 (dd, 1H, *J* 12.4 & 2.2 Hz, C4–H), 3.21–3.17 (m, 1H, C3a–H); δ_C ($CDCl_3$, 75 MHz) 175.2(C11), 159.1 (C5a), 152.9 (C6a), 150.7 (q), 141.6 (q), 132.0 (CH), 129.0 (CH), 128.5 (CH), 125.8 (CH), 125.1 (CH), 124.4 (CH), 124.1 (CH), 123.1 (C10a), 121.7 (CH), 116.3 (C7), 114.8 (CH), 98.7 (C11a), 68.9 (C3), 62.3 (C11b), 50.8 (C4), 40.5 (C3a); *m/z* (EI) 396 (M^+, 21), 381 (21), 380 (24), 355 (19), 169 (100).

4.1.3.2. Adduct (5c). A cream colored semi-solid (8%); mp 102–104 °C ($CHCl_3$/hexane, 1:3); [Found: C, 78.95; H, 5.27; N, 5.76; $C_{31}H_{24}N_2O_3$ requires C, 78.79; H, 5.12; N, 5.93]; δ_H ($CDCl_3$, 200 MHz) 8.10 (dd, 1H, *J* 7.6 & 1.4 Hz, C10–H), 7.71 (d, 1H, *J* 7.12 Hz, Ar–H), 7.62–7.21 (m, 9H, Ar–Hs), 7.19–7.00 (m, 8H, Ar–Hs), 5.31 (d, 1H, *J* 6.8 Hz, C3–H), 5.23 (d, 1H, *J* 7.4 Hz, C11b–H), 4.12 (dd, 1H, *J* 12.3 & 3.9 Hz, C4–H), 3.78 (dd, 1H, *J* 12.3 & 5.4 Hz, C4–H), 3.04–2.98 (m, 1H, C13–H); *m/z* (ESI) 474.4 (M^++2, 32), 473.3 (M^++1, 100).

4.1.3.3. Adduct (6c). A cream colored solid (5%); mp 147–148 °C ($CHCl_3$/hexane, 1:2); [Found: C, 78.61; H, 5.03; N, 5.75; $C_{31}H_{24}N_2O_3$ requires C, 78.79; H, 5.12; N, 5.93]; δ_H ($CDCl_3$, 200 MHz) 8.31(br d, 1H, *J* 6.4 Hz, C10–H), 7.71(d, 1H, *J* 7.1 Hz, ArH), 7.21–7.62(m, 9H, Ar–Hs), 7.19–7.00 (m, 8H, Ar–Hs), 5.80 (d, 1H, *J* 4.3 Hz, C3–H), 4.23(br d, 1H, C11b–H), 3.97–3.90 (m, 2H, C4–Hs), 2.79–2.74 (m, 1H, C3a–H); δ_C ($CDCl_3$, 75 MHz) 176.0 (C11), 159.0 (C5a), 153.0 (C7), 150.4 (q), 141.6 (q), 141.2 (q), 132.3 (CH), 129.3 (CH), 129.0 (CH), 128.3 (CH), 127.8 (CH), 127.0 (CH), 126.4 (CH), 126.0 (CH), 125.4 (CH), 124.9 (C10a), 121.1 (CH), 116.3 (C9), 114.6 (CH), 95.0 (C11a), 73.0 (C3), 68.6 (C11b), 50.9 (C4), 47.9 (C3a); *m/z* (ESI) 495 (M^++Na), 472 (M^+).

4.1.3.4. Amide (7a). A cream colored solid (44%); mp 95–96 °C ($CHCl_3$/hexane, 1:3); [Found: C, 75.34; H, 4.82; N, 6.95; $C_{25}H_{20}N_2O_3$ requires C, 75.74; H, 5.08; N, 7.07]; ν_{max} (KBr) 3350, 1635, 1605, 1583, 1502, 1466, 1441, 1395 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 9.94 (s, 1H, D_2O exchangeable, amidic-H), 7.83 (br d, 1H, *J* 7.5 Hz, C5–H), 6.83–7.47 (m, 13H, Ar–Hs), 5.93–6.06 (m, 1H, C2′–H), 5.37 (d, 1H, *J* 17.2 Hz, C3′–H), 5.17 (d, 1H, *J* 10.1 Hz, C3′–H), 4.53 (d, 2H, C1′–Hs); δ_C ($CDCl_3$, 75 MHz) 171.4 (C4), 167.5 ($CONH_2$), 160.8 (C2), 152.1 (C8a), 142.9 (q),

136.2 (q), 132.4 (CH), 129.1 (CH), 128.8 (CH), 128.2 (CH), 127.5 (CH), 126.5 (CH), 125.0 (CH), 125.7 (CH), 125.1 (CH), 123.1 (C4a), 122.1 (CH), 117.3 (CH_2), 116.2 (CH), 96.9 (C3), 53.2 (C1′); *m/z* (EI) 305 (M^+-91, 23), 132 (100).

4.1.3.5. Amide (7b). A cream colored solid (90%); mp 99–100 °C ($CHCl_3$/hexane, 1:3); [Found: C, 76.49; H, 5.63; N, 6.56 $C_{26}H_{22}N_2O_3$ requires C, 76.08; H, 5.40; N, 6.82]; ν_{max} (KBr) 3310, 1639, 1609, 1591, 1512, 1491, 1482, 1462, 1425 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 9.92 (s, 1H, D_2O exchangeable, amidic-H), 7.83 (br d, 1H, *J* 7.5 Hz, C5–H), 7.47–7.06 (m, 13H, Ar–Hs), 5.73–5.57 (m, 2H, C2′–H & C3′–H), 4.46 (br d, 2H, C1′–Hs), 1.64 (d, 3H, *J* 4.8 Hz, $-CH_3$); δ_C ($CDCl_3$, 75 MHz) 171.4 (C4), 167.3 ($CONH_2$), 160.5 (C2), 152.2 (C8a), 142.8 (q), 136.3 (q), 132.36 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.8 (CH), 126.5 (CH), 125.8 (CH), 125.7 (CH), 125.0 (CH), 123.1 (C4a), 122.0 (CH), 116.2 (CH), 97.2 (C3), 52.6 (C1′), 17.6 (CH_3); *m/z* (EI) 318 (M^+-92, 19), 317 (M^+-93, 17), 169 (100).

4.1.3.6. Amide (7c). A cream colored solid (80%); mp 104–105 °C ($CHCl_3$/hexane, 1:3); [Found: C, 78.93; H, 5.27; N, 5.39 $C_{31}H_{24}N_2O_3$ requires C, 78.79; H, 5.12; N, 5.93]; ν_{max} (KBr) 3320, 1640, 1615, 1582, 1520, 1478, 1455, 1418 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 10.20 (s, 1H, D_2O exchangeable, amidic-H), 8.20 (br d, 1H, *J* 7.80 Hz, C5–H), 7.42–7.27 (m, 18H, Ar–Hs), 6.58 (d, 1H, *J* 15.9 Hz, C3′–H), 6.37–6.26 (dt, 1H, *J* 15.9 & 5.9 Hz, C2′–H), 4.75 (d, 2H, *J* 5.9 Hz, C1′–Hs); *m/z* (EI) 381 (M^+-91, 30), 380 (M^+-92, 45), 116 (100).

4.1.4. Reaction of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (4a–c) with *N*-methyl-hydroxylamine-hydrochloride at low temperature. To an ice-cold solution of 2-(*N*-allyl/crotyl/cinnamyl-anilino)-3-formylchromone (300 mg) in dry CH_2Cl_2 (50 mL) were added *N*-methyl-hydroxylamine-hydrochloride (1 M equiv) and $NaHCO_3$ (excess), suspension was stirred for an hour, the stirred suspension was brought to ambient temperature in 30 min and was stirred in excess for another 30 min at room temperature. After the completion of reaction (TLC), the suspension was filtered and $NaHCO_3$ was washed with CH_2Cl_2 (2×20 mL), combined extracts were evaporated under reduced pressure and the residue was resolved by column chromatography over silica gel (60–120 mesh, packed in hexane) using hexane/ethyl acetate gradient as an eluent to obtain adduct **5d–f** along with amide **7d–f**.

4.1.4.1. Adduct (5d). A cream colored solid (80%); mp 182–184 °C ($CHCl_3$/hexane, 1:3); [Found: C, 71.93; H, 5.52; N, 8.13 $C_{20}H_{18}N_2O_3$ requires C, 71.84; H, 5.43; N, 8.38]; ν_{max} (KBr) 1614, 1589, 1548, 1479, 1467, 1433, 1423, 1361, 1298, 1267 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.13 (dd, 1H, *J* 7.7 & 1.5 Hz, C10H), 7.84–7.48 (m, 4H, Ar–Hs), 7.36–7.26 (m, 3H, Ar–Hs), 7.01 (d, 1H, *J* 7.6 Hz, Ar–H), 4.31 (t, 1H, *J* 7.2 Hz, C3H), 4.11 (d, 1H, *J* 4.2 Hz, C4H), 4.04 (d, 1H, *J* 11.5 Hz, C11b-H), 3.68–3.63 (m, 2H, C3-H & C4-H), 2.96 (s, 3H, N–CH_3), 2.80–2.78 (m, 1H, C3a-H); δ_C ($CDCl_3$, 75 MHz) 175.1 (C═O), 158.7 (C5a), 152.8 (C6a), 141.6 (q), 131.9 (CH), 129.3 (CH), 127.1 (CH), 125.8 (CH), 125.7 (CH), 124.7 (CH), 122.8 (C10a), 116.3 (C7), 93.2 (C11a), 68.5 (C3), 61.1 (11b), 51.5 (C4), 44.9 (N–CH_3), 38.2 (C3a); *m/z* (ESI) 356.97 (M^++Na), 334 (M^+).

4.1.4.2. Adduct (5e). A cream colored solid (85%); mp 92–93 °C ($CHCl_3$/hexane, 1:3); [Found: C, 72.63; H, 5.82; N, 7.87 $C_{21}H_{20}N_2O_3$ requires C, 72.40; H, 5.79; N, 8.04]; ν_{max} (KBr) 1612, 1591, 1548, 1494, 1465, 1429, 1407, 1311, 1274, 1217, 1174 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.14 (dd, 1H, *J* 7.7 & 1.4 Hz, C10-H), 7.49–7.38 (m, 4H, Ar–H), 7.34–7.32 (m, 3H, Ar–Hs), 7.01 (d, 1H, *J* 8.1 Hz, Ar–H), 4.16 (d, 1H, *J* 5.6 Hz, C3H), 4.06 (d, 1H, *J* 11.4, C11b–H), 3.95–3.89 (m, 1H, C4H), 3.70–3.61 (m, 1H, C4H), 3.37–3.29 (m, 1H, C3aH), 2.93 (s, 3H, N–CH_3), 1.38 (d, 3H, *J* 6.1 Hz, CH_3); δ_C ($CDCl_3$, 75 MHz) 175.3 (C═O), 159.1 (C5a), 152.7 (C6a), 141.3 (q), 132.1 (CH), 129.2 (CH), 127.1 (CH), 125.7 (CH), 125.5 (CH), 124.7 (CH), 122.6 (C10a), 116.2 (C7), 92.3 (C11a), 76.2 (C3), 60.2 (C11b), 51.3 (C4), 44.9 (N–CH_3), 14.0 (CH3); *m/z* (ESI) 370.99 (M^++Na), 348 (M^+).

4.1.4.3. Adduct (5f). A cream colored solid (90%); mp 148–49 °C ($CHCl_3$/hexane, 1:3); [Found: C, 76.19; H, 5.46; N, 6.69 $C_{26}H_{22}N_2O_3$ requires C, 76.08; H, 5.40; N, 6.82]; ν_{max} (KBr) 1627, 1614, 1593, 1552, 1483, 1465, 1434, 1309, 1299, 1271, 1255, 1222 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 8.16 (dd, 1H, *J* 7.7 & 1.6 Hz, C10–H), 7.50–7.43 (m, 7H, Ar–Hs), 7.39–7.28 (m, 5H, Ar–Hs), 7.0 (d, 1H, *J* 7.8 Hz, Ar–H), 4.74 (d, 1H, *J* 2.7 Hz, C3H), 4.36 (d, 1H, *J* 5.5 Hz, C11b–H), 4.22 (d, 1H, *J* 11.3 Hz, C4H), 3.85–3.76 (m, 1H, C4H), 3.07 (s, 3H, NCH_3), 2.65–2.58 (m, 1H, C3aH); δ_C ($CDCl_3$, 75 MHz) 174.9 (C═O), 158.8 (C5a), 152.6 (C6a), 141.4 (q), 140.3 (q), 131.9 (CH), 129.1 (CH), 128.3 (CH), 127.9 (CH), 127.0 (CH), 126.2 (CH), 126.4 (CH), 125.6 (CH), 124.5 (CH), 122.6 (C10a), 116.1 (C7), 95.9 (C11a), 82.1 (C3), 60.5 (C11b), 51.3 (C4), 46.1 (NCH_3), 44.5 (C3a); *m/z* (ESI) 433.1 (M^++Na), 410 (M^+).

4.1.4.4. Amide (7d). A cream colored solid; mp 99–100 °C ($CHCl_3$/hexane, 1:3); [Found: C, 71.92; H, 5.51; N, 8.13 $C_{20}H_{18}N_2O_3$ requires C, 71.84; H, 5.43; N, 8.38]; ν_{max} (KBr) 3305, 1615, 1604, 1556, 1529, 1487, 1429 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 7.78 (dd, 1H, *J* 7.1 & 1.4 Hz, C5–H), 7.41–7.36 (m, 3H, Ar–Hs), 7.33–7.18 (m, 5H, Ar–Hs), 6.10–5.87 (m, 1H, C2′–H), 5.30 (dd, 1H, *J* 17.1 & 1.3 Hz, C3′–H), 5.13 (dd, 1H, *J* 10.2 & 1.2 Hz, C3′–H), 4.47 (d, 2H, *J* 5.4 Hz, C1′–Hs), 3.88 (s, 3H, NCH_3); δ_C ($CDCl_3$, 75 MHz) 171.0 (C═O), 167.5 (CONH), 160.5 (C2), 149.5 (C8a), 142.4 (q), 136.0 (q), 131.8 (CH), 129.3 (CH), 128.4 (CH), 128.1 (CH), 126.4 (CH), 126.2 (CH), 126.0 (CH), 124.8 (CH), 115.9 (CH), 52.6 (C1′); *m/z* (ESI) 357 (M^++Na), 334 (M^+).

4.1.4.5. Amide (7e). A cream colored solid; mp 110–112 °C ($CHCl_3$/hexane, 1:3); [Found: C, 72.52; H, 5.84; N, 7.91 $C_{21}H_{20}N_2O_3$ requires C, 72.40; H, 5.79; N, 8.04]; ν_{max} (KBr) 3305, 1614, 1593, 1550, 1497, 1463, 1434, 1406, 1218, 1107 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 7.79 (d, 1H, *J* 6.3 Hz, Ar–H), 7.45–7.43 (m, 2H, Ar–Hs), 7.42–7.31 (m, 2H, Ar–Hs), 7.26–7.16 (m, 4H, Ar–Hs), 5.64–5.53 (m, 2H, C2′H & C3′H), 4.40 (d, 2H, *J* 4.8 Hz, C1′Hs), 3.14 (d, 3H, *J* 5.2 Hz, NH–CH_3), 1.65 (d, 3H, *J* 4.8 Hz, C3′H); δ_C ($CDCl_3$, 50 MHz) 171.0 (C═O), 167.5 (CONH), 160.5 (C2), 149.5 (C8a), 142.4 (quat.), 136.0

(quat.), 131.8 (CH), 129.3 (CH), 128.4 (CH), 128.1 (CH), 126.4 (CH), 126.2 (CH), 126.0 (CH), 124.8 (CH), 115.9 (CH), 97.3 (C3), 52.6 (C1′), 27.7 (NH–CH_3), 17.7 (C3′CH_3); *m/z* (ESI) 370.98 (M^++Na), 348.98 (M^+).

4.1.4.6. Amide (7f). A cream colored solid; mp 90–91 °C ($CHCl_3$/hexane, 1:3); [Found: C, 76.12; H, 5.54; N, 6.73 $C_{26}H_{22}N_2O_3$ requires C, 76.08; H, 5.40; N, 6.82]; ν_{max} (KBr) 3305, 1627, 1552, 1487, 1427, 1402, 1255, 1217, 1157, 1112, 1074, 1026 cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 13.7 (br, 1H, NH), 7.81 (d, 1H, *J* 7.8 Hz, Ar–H), 7.75 (unresolved dd, 1H, *J*~4.7 Hz, Ar–H), 7.54–7.35 (m, 3H, Ar–Hs), 7.39–7.23 (m, 4H, Ar–Hs), 7.21–7.14 (m, 2H, Ar–Hs), 7.08–7.03 (m, 2H, Ar–Hs), 6.55 (d, 1H, *J* 15.9 Hz, C3′H), 6.30 (td, 1H, *J* 15.9 & 6.0 Hz, C2′H), 4.62 (d, 2H, *J* 6.0 Hz, C1′Hs), 2.72 (s, 3H, N–CH_3); δ_C ($CDCl_3$, 50 MHz) 171.0 (C=O), 164.6 (CONH), 158.1 (C2), 152.3 (C8a), 143.9 (quat.), 136.8 (quat.), 133.2 (quat.), 132.0 (CH), 129.1 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 126.5 (CH), 126.4 (CH), 126.3 (CH), 125.9 (CH), 124.8 (CH), 123.1 (CH), 115.9 (CH), 99.1 (C3), 52.9 (C1′), 27.7 (NH–CH_3); *m/z* (ESI) 433.08 (M^++Na), 410 (M^+).

Acknowledgements

The work was supported by research grant [E-7-14/2003 (FD-III)] from University Grants Commission (UGC), Govt. of India. Gurpinder Singh also thanks UGC for Project Fellowship. NMR, 300 MHz, facility funded by Department of Science and Technology, Govt. of India, at Guru Nanak Dev University, Amritsar, is gratefully acknowledged.

References and notes

1. (a) Carruthers, W. R. *Cycloadditions in Organic Synthesis*; Pergamon: London, 1990; Chapter 6, p 269; (b) Black, D. C. S.; Cozia, R. F.; Davis, V. C. *Synthesis* **1975**, *205*; (c) *Synthetic Applications of 1,3-Dipolar Cycloadditions Chemistry Towards Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley Interscience: New York, NY, 2002; (d) Paquette, L. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 3; (e) Frederickson, M. *Tetrahedron* **1997**, *53*, 403; (f) Gothelf, K. V.; Jorgenson, K. A. *Chem. Rev.* **1998**, *98*, 863; (g) Padwa, A.; Schoffstall, A. M. *Advances in Cycloaddition*; Curran, D., Ed.; JAI: Greenwich, CT, 1990; p 2.
2. (a) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Goethelf, K. V.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845; (b) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2000**, *65*, 8544; (c) Aurich, H. G.; Geiger, M.; Gentes, C.; Harms, K.; Koster, H. *Tetrahedron* **1998**, *54*, 3181; (d) Goethelf, K. V.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483; (e) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Procopio, A.; Rescifena, A.; Romeo, G.; Romeo, R. *J. Org. Chem.* **2002**, *67*, 4380; (f) Knobloch, K.; Eberbach, W. *Org. Lett.* **2000**, *2*, 1117; (g) Long, A.; Baldwin, S. W. *Tetrahedron Lett.* **2001**, *42*, 5343; (h) Voinov, M. A.; Grigor'ev, I. A. *Tetrahedron Lett.* **2002**, *43*, 2445; (i) Merino, P.; Anoro, S.; Franco, F. L.; Merchan, T. T.; Tunon, V. *J. Org. Chem.* **2000**, *65*, 1590; (j) Dagoneau, C.; Tomassini, A.; Denis, J.-N.; Vallee, Y. *Synthesis* **2001**, 150; (k) Mernyak, E.; Benedek, G.; Schneider, G.; Wolfling, J. *Synlett* **2005**, 637; (l) Kanemasa, S.; Ueno, N.; Shirahase, M. *Tetrahedron Lett.* **2002**, *43*, 657.
3. (a) Frank, E.; Wolfing, J.; Aukszi, B.; Koning, V.; Schneider, T. R.; Schneider, G. *Tetrahedron* **2002**, *58*, 6843; (b) Aurich, H. G.; Geiger, M.; Gentes, C.; Harmas, K.; Coster, H. *Tetrahedron* **1998**, *54*, 3281; (c) Narayanan, I. N.; Hassner, A.; Gottlieb, H. E. *J. Org. Chem.* **1997**, *62*, 485; (d) Zaho, Q.; Han, F.; Romero, D. L. *J. Org. Chem.* **2000**, *67*, 3317; (e) Gu, Y. G.; Zhang, X.; Clark, R. F.; Djuric, S. W.; Ma, Z. *Tetrahedron Lett.* **2004**, *45*, 3051.
4. (a) Chiacchio, U.; Balestrieri, E.; Macchi, B.; Iannazzo, D.; Piperno, A.; Rescifina, A.; Romeo, R.; Saglimbeni, M.; Sciortino, T.; Vincenza, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2005**, *48*, 1389 and references cited therein; (b) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Sindona, G.; Romeo, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2717.
5. (a) Gotoh, M.; Mizui, T.; Sun, B.; Hiryama, K.; Noguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1857; (b) Gotoh, M.; Sun, B.; Hiryama, K.; Noguchi, M. *Tetrahedron* **1996**, *52*, 887; (c) Noguchi, M.; Yamada, K. *Synthesis* **1993**, 145; (d) Mora de la, M. A.; Cuevas, E.; Muchowski, J. M.; Cruz Almanza, R. *Tetrahedron Lett.* **2001**, *42*, 5351; (e) Noguchi, M.; Okada, H.; Nishimura, S.; Yamagata, Y.; Takamura, S.; Tanaka, M.; Kakehi, A.; Yamamoto, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 185.
6. (a) Morris, J.; Wishka, D. G.; Lin, A. H.; Humphery, W. R.; Wiltse, A. L.; Gammill, R. B.; Judge, T. M.; Bisaha, S. N.; Olds, N. L.; Jacob, C. S.; Bergh, C. L.; Cudahy, M. M.; Williams, D. J.; Nishijawa, E. E.; Thomas, E. W.; Gorman, R. R.; Benjamin, C. W.; Shebuski, R. J. *J. Med. Chem.* **1993**, *36*, 2026; (b) Gross, A.; Borcherding, D. R.; Friedrich, D.; Sabol, J. S. *Tetrahedron Lett.* **2001**, *42*, 1631; (c) Mori, K.; Audran, G.; Monti, H. *Synlett* **1998**, 259; (d) Pietta, P. J. *J. Nat. Prod.* **2000**, *63*, 1035.
7. Singh, G.; Singh, G.; Ishar, M. P. S. *Helv. Chim. Acta* **2003**, *86*, 168.
8. (a) Oppolozer, W.; Keller, K. *Tetrahedron Lett.* **1970**, 1117; (b) Oppolozer, W.; Weber, H. P. *Tetrahedron Lett.* **1970**, 1121; (c) Gree, R.; Carric, R. *Tetrahedron Lett.* **1972**, 2987; (d) Gree, R.; Tonnard, F.; Carric, R. *Tetrahedron* **1976**, *57*, 8323; (e) Broggini, G.; Rosa, C. L.; Tenanco, A.; Zechi, G. *Tetrahedron* **1976**, *57*, 8323.
9. Crystallographic data for compound **5d** is deposited (CCDC No. 604656).
10. (a) Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. S. *Chem. Ber.* **1968**, *101*, 2548; (b) Huisgen, R.; Hauck, H.; Seidl, H. S.; Berger, M. *Chem. Ber.* **1969**, *102*, 1117; (c) Kamaanitzky, A. V.; Levina, I. S.; Mortikora, E. I.; Shitkin, V. M.; Edyanov, B. S. *Tetrahedron* **1977**, *33*, 2135; (d) Girdhar, N. K.; Ishar, M. P. S. *Tetrahedron Lett.* **2000**, *41*, 7551 and references cited therein.
11. (a) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 4865; (b) Hems, W. P.; Tan, C. H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999**, *40*, 1393.
12. (a) Krimm, H. *Chem. Ber.* **1958**, *91*, 1057; (b) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473 and references cited therein.