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Proclivity of chromonyloxazolone towards some nitrogen nucleophiles

Hamed A. Derbala, Manal M. El-Shahawi**,** Marwa S. Salem, Eman A. E. El-Helw*

Synthetic Organic Chemistry Laboratory, Chemistry Department, Faculty of Science, Ain Shams University, Abbasiya, 11566, Cairo, Egypt.

**E-mail: eman.abdo89@hotmail.com*

Abstract: The proclivity of 4-((6-chloro-4-oxo-4*H*-chromen-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one **1** towards some nitrogen nucleophiles has been investigated under different reaction conditions. The reaction with benzylamine led to the formation of the open ring structures, chromenyl and chromanyl benzamide derivatives **2**-**4**, respectively. Conduct compound **2** in either EtOH/AcOH mixture, EtOH /AcOH/ HCl mixture or HCl/AcOH mixture yielded *N*-benzoylaminopyridone **5**, aminopyridone **6** and chromenopyrole **7**. On the other hand, the two alternative chromenylbenzamide derivatives **8** and **9** were obtained by refluxing compound **1** with benzidine in ethanol/acetic acid mixture and in acetic acid alone, respectively. All newly synthesized compounds were characterized by IR, ^{1}H-NMR and MS.

Keywords: Oxazolone, 6-Chlorochromone-3-carboxaldehyde, Imidazolone, Chromenopyrrole.

I. Introduction

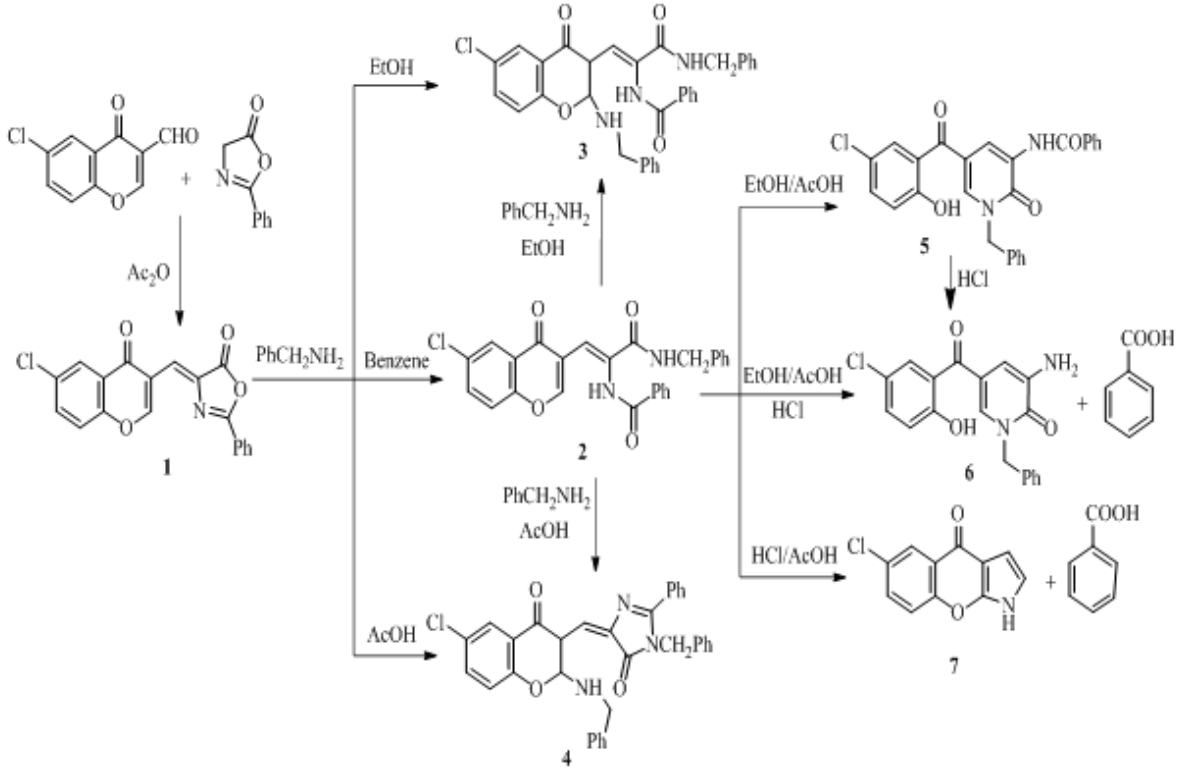
The development of new anticancer therapeutic agents is one of the fundamental goals in medicinal chemistry. Surpassing cardiovascular diseases, it is taking the position number one killer due to various factors (Noolvi et al., 2011; Young, 1975; Yang et al., 2007). Besides, treatment of cancer is associated with various side effects which include bone marrow depression, alopecia, drug induced cancer, hepatotoxicity, and many more. The compounds containing imidazolone are known to have a wide range of biological activities like anticancer, anti-inflammatory, cardioactivity and angiotensin II receptor antagonistic activity (Siamaki et al., 2008). A trisubstituted imidazolone (MZ3) induced high degree of apoptosis in human leukemia cells and also have prominent cytotoxicity (Fang et al., 2007). Pyrrole and fused pyrrole compounds exhibit a broad spectrum of biological activities such as antimicrobial (Dang and Gomez-Galeno, 2002), analgesic (Danchev et al., 2006), anti-inflammatory (Jarvis et al., 2002), antiviral (Gangjee et al., 2005) and anticancer activity (De Clercq et al., 1987; Finch et al., 1997; Krawczyk et al., 1995). Several natural products with chromonic derivatives exhibit interesting biological and pharmacological properties *e.g.* anticancer (Huang et al., 2009; Nam et al., 2010), anti-HIV active (Hesse and Kirsch, 2002), antiviral, insecticidal (Lee et al., 1998), anticoagulant (Jung et al., 1999; 2001), antioxidant (Atassi et al., 1985; Pietta, 2000) and antimicrobial (Salem et al., 2013). These findings and our continued research program targeting synthesis of new heterocycles (Salem et al., 2013; 2015; Salem and Ali, 2016; Salem and Errayes, 2016; El-Kady et al., 2016) with anticancer activity have prompted us to make use of the reactivity of 4-((6-chloro-4-oxo-4*H*-chromen-3-yl)methylene)-2-phenyloxazol-5(4*H*)-one **1** towards various nitrogen nucleophiles with the aim of developing new heterocycles of anticipated biological activity.

II. Results and Discussion

The key starting material, 4-((6-chloro-4-oxo-4*H*-chromen-3-yl)methylene)-2-phenyloxazol-5-(4*H*)-one **1** was prepared *via* the reaction of *N*-benzoylglycine, and 6-chlorochromone-3-carboxaldehyde in acetic anhydride (Ghosh and Bandyopadhyay, 1984). Compound **1** can suffer attack at oxazolone ring as a multifunctional moiety and are known to react at C=C, C=N, C=O bonds. Besides, the chromone nucleus participates similar reactions at C=O and *C-2*, a position may undergo Michael addition, as well (Salem et al., 2013). The chemoselectivity of these reactions depends mainly on the nature of the nucleophile, as well as the utilized solvent. Herein, proclivity of chromonyloxazolone **1** towards some nitrogen nucleophiles was investigated with the aim of synthesizing some novel heterocyclic systems.

Initially, reaction of compound **1** with benzylamine was dependent mainly on the reaction conditions. Thus, when the reaction was carried out in refluxing dry benzene as a solvent, lactone ring opening occurred to afford chromone derivative **2**. IR spectrum of the latter compound showed the disappearance of $\nu_{C=O}$ of oxazolone and appearance of ν_{NH}, $\nu_{C=O}$ of chromone moiety at 3233, 1644 cm^{-1}, respectively. ^{1}H-NMR spectrum

revealed the existence of 2 N-H signals at δ 10.00 and 8.69 ppm, respectively. Reflux chromonyloxazolone **1** with benzylamine in ethanol afforded benzamide derivative **3**. Presumably, it was formed *via* lactone ring opening followed by Michael addition of another molecule of benzylamine on chromone C_2-position. The structure of benzamide **3** was confirmed by comparison with an authentic sample (mp, mixed mp and TLC) prepared from reaction of chromone derivative **2** with benzylamine in refluxing ethanol.

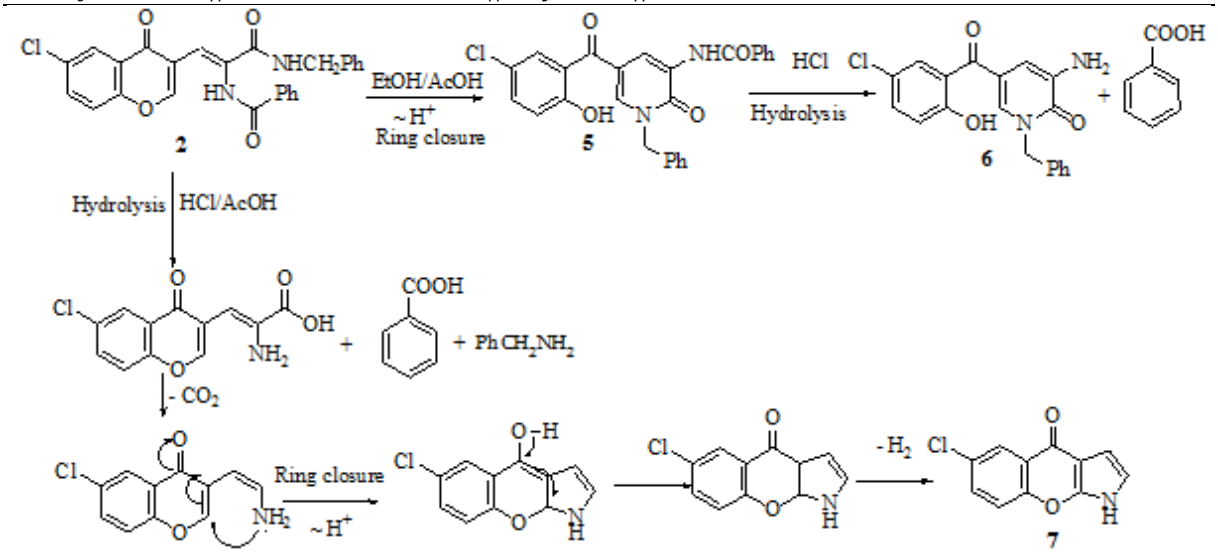


Scheme 1

Furthermore, treating chromonyloxazolone **1** with benzylamine in glacial acetic acid yielded the imidazolone derivative **4** which was suggested to occur *via* lactone ring opening followed by ring closure, then Michael-type addition of another molecule of benzylamine on chromone C_2-position. A compelling evidence for the formation of imidazolone **4** *via* this reaction route was provided by refluxing chromone derivative **2** with benzylamine in acetic acid that gave the former derivative (cf. **Scheme 1**). It is noteworthy to mention herein, that under the preceding circumstances, the reactivity of oxazolone ring moiety towards nucleophilic attack by benzylamine is higher than electrophilic sites in chromone nucleus.

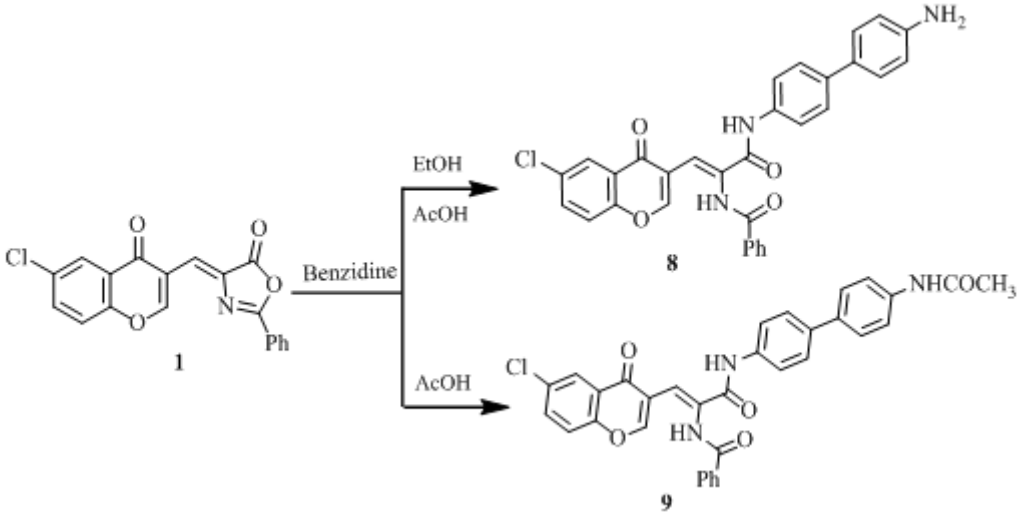
As a point of interest, the variation of reaction conditions effect on the nature of the resulted product in preparative organic chemistry was obtained when chromone derivative **2** underwent cyclization to the pyridone derivative **5** *via* reflux in EtOH/AcOH mixture, while a mixture of pyridone derivative **6** and benzoic acid was provided by reflux compound **2** in EtOH /AcOH/ HCl mixture. Probably, the formation of **6** occurred *via* hydrolysis of the amide bond in pyridone **5** under the effect of HCl (cf. **Scheme 2**).

On the other hand, the given compound **2** was transformed to chromenopyrrole derivative **7** and benzoic acid as it was submitted to react with HCl/AcOH (1:1). Formation of these compounds can be visualized to occur as depicted in **Scheme 2**. The structures of these compounds deduced from their analytical and spectral data.



Scheme 2. Mechanistic pathways for the formation of compounds **5-7**.

Recently, reaction of chromonyloxazolone **1** with benzidine in absolute ethanol containing few drops of glacial acetic acid furnished the amide derivative **8**. The ^{1}H-NMR spectrum of product **8** revealed that it exists in solution, in dynamic equilibrium of (*Z*) and (*E*) isomers in a ratio of 45.99 % and 54.01 % respectively. However, the acetamide derivative **9** was obtained by refluxing **1** with benzidine in glacial acetic acid. This means that both reactions occurred *via* a similar route which involved only ring cleavage of oxazolone ring moiety. Nevertheless, the existence of more concentration of acetic in the latter reaction made no difference except acetylation of 4-amino group. All the foregoing reactions are presented in **Scheme 3**.



Scheme 3

III. Experimental

Melting points were measured on a Gallenkamp Electric melting point apparatus. The IR spectra were recorded using potassium bromide disks on infrared Thermo Electron Nicolet 7600 (USA) spectrometer at the Central Laboratory of Faculty of Science, Ain Shams University. The ^{1}H-NMR spectra were run at 400 *MHz* on a GEMINI 400 BB NMR spectrometer using tetramethyl silane (TMS) as internal standard in deuterated dimethylsulfoxide (DMSO-d_6) at the Main Defense Chemical Laboratory. The mass spectra were recorded on a Shimadzu GC-MS-QP-1000EX mass spectrometer operating at 70 eV at the Micro analytical Center of Cairo University. The reactions were monitored by the thin layer chromatography using Merck Kiesel gel 60 F_{254} obtained from Fluka.

4-((6-Chloro-4-oxo-4H-chromen-3-yl)methylene)-2-phenyloxazol-5(4H)-one (1)

mp. 250-252^{o}C [(Ghosh and Bandyopadhyay, 1984) mp. 249-250^{o}C].

N-(3-(Benzylamino)-1-(6-chloro-4-oxo-4H-chromen-3-yl)-3-oxoprop-1-en-2-yl)benzamide (2):

Benzylamine (0.21 ml, 2 mmol) was added dropwise to a solution of chromonyloxazolone **1** (0.7g, 2 mmol) in dry benzene (20 ml) and refluxed for one hour. The precipitated solid while hot was collected by filtration and recrystallized from benzene/ethanol mixture (3:1) to give benzamide derivative **2** as white crystals, mp.183-184^{o}C (decomp.), yield 87%. IR (KBr) (ν, cm^{-1}): 3233 (NH), 3062 ($CH_{aromatic}$), 2924 ($CH_{aliphatic}$), 1644 (C=O). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.00 and 8.69 (2s, 2H, 2 N-H, D_2O-exchangeable), 8.58-7.18 (m, 14H, Ar-H), 6.98 (s, 1H, CH=), 4.37 (s, 2H, CH_2). MS (*m/z* (%)): 458 ($M^{\dot{+}}$, 00.0), 353 (0.7), 211 (44.0), 210 (17.8), 134 (0.7), 122 (18.9), 105 (100.0), 91 (10.7), 77 (52.3).

N-(3-(Benzylamino)-1-(2-(benzylamino)-6-chloro-4-oxochroman-3-yl)-3-oxoprop-1-en-2-yl)benzamide (3):

Method I:

A solution of chromonyloxazolone **1** (0.7 g, 2 mmol) and benzylamine (0.21 ml, 2 mmol) in absolute ethanol (20 ml) was refluxed for 2 h. The precipitated solid during hot was filtered off and recrystallized from ethanol to give benzamide derivative **3** as orange crystals, mp 236-238 ^{o}C, yield 76%. IR (KBr) (ν, cm^{-1}): 3306 (NH), 3062 ($CH_{aromatic}$), 2966 ($CH_{aliphatic}$), 1723, 1665, 1646 (C=O). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.16 (s, 1H, -CH=CH-NH, D_2O-exchangeable), 8.66 (s, 1H, $NH_{benzamide}$, D_2O-exchangeable), 8.49 (s, 1H, $NHCH_2$, D_2O-exchangeable), 7.82-7.07 (m, 18H, Ar-H), 6.62 (d, 1H, CH=, *J* = 8.8 *Hz*), 5.27 (d, 1H, CH-NH, *J*= 9.6 *Hz*), 4.94-4.93 (m, 1H, CH-CO), 4.38-4.29 (m, 2H, -CONH-CH_2Ph), 4.18-4.13 (m, 2H, $NHCH_2$Ph). MS (*m/z* (%)): 565 ($M^{\dot{+}}$, 1.6), 531 (16.0), 459 (43.6), 444 (10.7), 297 (15.3), 105 (100.0), 92 (13.4), 90 (11.7).

Method II:

A mixture of amide derivative **2** (0.92 g, 2 mmol) and benzylamine (0.21 ml, 2 mmol) in absolute ethanol (20 ml) was refluxed for one hour. The precipitated solid while hot was collected by filtration to afford the amide derivative **3**, yield 81%.

1-Benzyl-4-((2-(benzylamino)-6-chloro-4-oxochroman-3-yl)methylene)-2-phenyl-1H-imidazol-5(4H)-one (4):

Method I:

A mixture of chromonyloxazolone **1** (0.7 g, 2 mmol) and benzylamine (0.21 ml, 2 mmol) in glacial acetic acid (15 ml) was refluxed for 2 h. The precipitated solid while hot was filtered off and recrystallized from ethanol to furnish the imidazolone derivative **4** as orange crystals, mp. 295-297^{o}C, yield 70%. IR (KBr) (ν, cm^{-1}): 3285 (NH), 3064 ($CH_{aromatic}$), 2965 ($CH_{aliphatic}$), 1725, 1670 (C=O), 1632 (C=N). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.62 (s, 1H, N-H, D_2O-exchangeable), 8.25-7.16 (m, 18H, Ar-H), 6.87 (d, 1H, CH=, *J* = 8.8 Hz), 5.72 (d, 1H, CH-NH, *J*= 6.8 *Hz*), 5.01-4.97 (m, 1H, CH-CO), 4.33 (s, 2H, -NCH_2Ph), 4.19-4.15 (m, 2H, -$NHCH_2$Ph). MS (*m/z* (%)): 547 ($M^{\dot{+}}$, 4.5), 514 (6.8), 476 (20.8), 468 (28.4), 431 (25.0), 427 (44.3), 425 (80.47), 352 (28.9), 345 (44.5), 324 (26.5), 294 (24.7), 278 (46.9), 271 (41.8), 247 (15.6), 122 (13.4), 110 (26.1), 105 (32.2), 43 (100.0).

Method II:

A solution of amide derivative **2** (0.92 g, 2 mmol) and benzylamine (0.21 ml, 2 mmol) in glacial acetic acid (15 ml) was refluxed for one hour. The precipitated solid while hot was collected by filtration to afford the imidazolone derivative **4**, yield 77%.

N-(1-Benzyl-5-(5-chloro-2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridin-3-yl)benzamide (5):

A solution of amide derivative **2** (0.92 g, 2 mmol) in absolute ethanol (20 ml) containing few drops of acetic acid was heated under reflux for 3 h. The precipitated solid while hot was filtered off and recrystallized from ethanol to give pyridone derivative **5** as orange crystals, mp 211-213 ^{o}C, yield 60%. IR (KBr) (ν, cm^{-1}): 3358 (*br*. OH), 3219 (NH), 3064 ($CH_{aromatic}$), 2926 ($CH_{aliphatic}$), 1713, 1660, 1642 (C=O). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.00 (s, 1H, NH, D_2O-exchangeable), 8.74 (s, 1H, OH, D_2O-exchangeable), 8.59 (s, 1H, CH^{-6} pyridone), 8.04-7.29 (m, 13H, Ar-H), 6.98 (s, 1H, CH^{-4} pyridone), 4.37 (s, 2H, -NCH_2Ph). MS (*m/z* (%)): 458 ($M^{\dot{+}}$, 0.0), 430 (0.1), 246 (4.3), 210 (21.5), 154 (7.7), 121 (5.0), 105 (100.0), 91 (14.0), 77 (55.9), 65 (5.2), 51 (14.2).

3-Amino-1-benzyl-5-(5-chloro-2-hydroxybenzoyl)pyridin-2(1H)-one (6)*:*

Method I:

A solution of amide derivative **2** (0.92 g, 2 mmol) in absolute ethanol (20 ml) containing few drops of acetic acid/HCl was heated under reflux for 8 h. The precipitated solid while hot was filtered off and recrystallized from ethanol to produce the pyridone derivative **6** as orange crystals, mp.154-156 ^{o}C, yield 60%. The filtrate was evaporated under vacuum to give benzoic acid (recrystallized from light petroleum). IR (KBr) (ν, cm^{-1}): 3405, 3306 (OH), (NH_2), 3065 ($CH_{aromatic}$), 2925 ($CH_{aliphatic}$), 1728, 1692 (C=O). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 9.21 (s, 1H, OH, D_2O-exchangeable), 8.36 (s, 1H, CH^{-6} pyridone), 7.95-7.22 (m, 9H, Ar-H), 4.33 (s, 2H, -NCH_2Ph), 3.97 (s, 2H, NH_2, D_2O-exchangeable).

Method II:

A suspension of **5** (0.92 g, 2 mmol) in dil. HCl (10 ml) was heated under reflux for 2 h. The precipitated solid while hot was collected by filtration to afford pyridone derivative **6** in 55 % yield. The filtrate was evaporated under vacuum to give benzoic acid.

6-Chlorochromeno[2,3-b]pyrrol-4(1H)-one (7):

A mixture of amide derivative **2** (0.92 g, 2 mmol) and HCl/CH_3COOH, 1:1 (20 ml) was heated under reflux for 2 h. The solvent was evaporated under vacuum. The residue was found to be a mixture of benzoic acid (recrystallized from Light Petroleum) and the chromenopyrrole **7** (recrystallized from ethanol).

7: Orange crystals, mp 205-207 ^oC, yield 43%. IR (KBr) (ν, cm^{-1}): 3100 (NH), 3057 ($CH_{aromatic}$), 2973 ($CH_{aliphatic}$), 1696 (C=O). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 8.99-7.73 (m, 5H, Ar-H), 6.59 (s, 1H, N-H, D_2O-exchangeable).

N-(3-(4'-Aminobiphenyl-4-ylamino)-1-(6-chloro-4-oxo-4H-chromen-3-yl)-3-oxoprop-1-en-2-yl)benzamide (8):

A solution of chromonyloxazolone **1** (0.7 g, 2 mmol) and benzidine (0.36 g, 2 mmol) in absolute ethanol (20 ml) containing few drops of glacial acetic acid was heated under reflux for 4 h. The precipitated solid while hot was filtered off and recrystallized from benzene/ethanol mixture (2:1) to afford **8** as yellow crystals, mp. 256-258^oC (decomp.), yield 74%. IR (KBr) (ν, cm^{-1}) 3358, 3225 (NH_2), 3065 ($CH_{aromatic}$), 1657 (C=O). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.42 (s, 1H, N-$H_{benzidine}$, D_2O-exchangeable), 9.46 (s, 1H, N-$H_{benzamide}$, D_2O-exchangeable), 8.78 - 7.31 (m, 17 H, Ar-H), 6.95 & 6.62 (2s, 1H, *E*- & *Z*-isomers, CH=), 5.29 (s, 2H, NH_2, D_2O-exchangeable). MS (*m/z* (%)): 535 ($M^{\dot{+}}$, 0.0), 430 (0.2), 402 (18.3), 400 (26.6), 385 (31.4), 358 (13.4), 345 (8.9), 248 (25.9), 246 (61.2), 220 (75.7), 155 (100.0), 105 (7.9), 99 (28.8).

N-(3-(4'-Acetamidobiphenyl-4-ylamino)-1-(6-chloro-4-oxo-4H-chromen-3-yl)-3-oxoprop-1-en-2-yl)benzamide (9):

When a solution of chromonyloxazolone **1** (0.7g, 2 mmol) and benzidine (2 mmol) in glacial acetic acid (15 ml) was refluxed for 4 h. The precipitated solid while hot was filtered off and recrystallized from dioxane to afford **9** as orange crystals, mp 279-281^oC, yield 70%. IR (KBr) (ν, cm^{-1}) 3404, 3302 (NH), 3059 ($CH_{aromatic}$), 1675 (C=O chromone), 1655 (C=O amide). ^{1}H-NMR (DMSO-d_6): δ_H (ppm) 10.30, 10.23, 9.96 (3s, 3H, 3NH, D_2O-exchangeable), 8.71-7.34 (m, 17H, Ar-H), 6.79 (s, 1H, CH=), 2.04 (s, 3H, CH_3). MS (*m/z* (%)): 577 ($M^{\dot{+}}$, 0.72), 535 (0.4), 284 (46.4), 255 (17.2), 185 (7.4), 145 (3.6), 105 (14.5), 77 (14.7), 73 (11.5), 60 (23.3), 57 (24.7), 43 (100.0).

IV. Conclusion

Chromonyloxazolone can be utilized to synthesize a variety of heterocycles *e.g.* pyridine and imidazolone derivatives. The regioselectivity of these products was studied.

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