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Cascade reactions between 2-substituted-3-(4-oxo-4*H*-chromen-3-yl)acrylonitriles with benzylamine and *p*-toluidine

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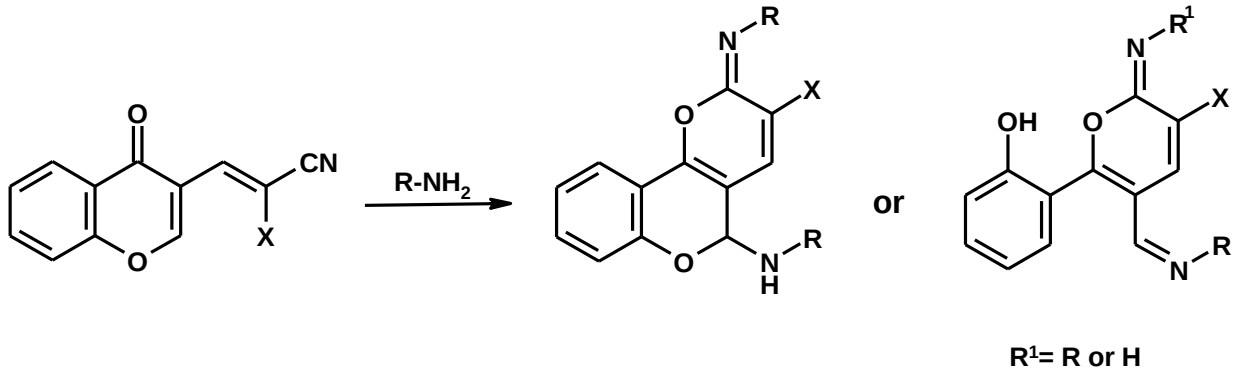
Abstract

Chemical transformations of the simple condensation products derived from 3-formylchromone and some active methylene compounds, was achieved by reaction with nucleophilic reagents namely benzylamine and *p*-toluidine to produce either 2-iminopyrane or pyrano[3,2-*c*]chromene derivatives. These transformations initially proceed through nucleophilic attack at C-2 of the γ–pyrone ring with concomitant addition of the carbonyl oxygen onto the nitrile function followed by further transformations depending on the substrate and the nucleophile used. The structures of the new synthesized products were deduced on the basis of their analytical and spectroscopic data.

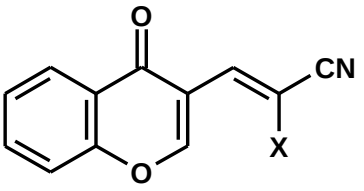


R[1]= R or H

Keywords: 3-Substituted chromones, ring transformation, pyrano[3,2-*c*]chromene**,** nucleophilic reactions

Introduction

Chromones represent an important class of oxygen containing heterocyclic compounds and reveal a diversity of biological and pharmacological activities including anticancer,[1-3] anti-HIV,[4,5] anti-inflammatory,[6-8] antimicrobial,[9,10] antimalarial,[11,12] antitumor,[13,14] anti-oxidant,[15,16] and antidiabetic,[17] as well as treatment of Alzheimer's disease.[18] The chemistry of 3-substituted chromones is of interest due to the presence of a diversity of electron-deficient centers and their reactions with nucleophilic reagents produced various heterocyclic products.[19-22] 1-(2-Hydroxyphenyl)-3-piperidin-1-ylpropenone was obtained from chromone-3-carboxaldehyde with piperidine.[23] Chromone-3-carbonitriles produced a wide range of products upon treatment with nitrogen and carbon nucleophiles.[24-28] Heating chromone-3-carboxylic acid with primary or secondary amines gives rise to a variety of products depending on the solvent used.[29,30] Treatment of chromone-3-carboxamide with nitrogen nucleophilic reagents produced 3-alkylaminomethylenechromane-2,4-diones and coumarins.[31,32] Furthermore, heating chromone-3-carboxylate with concentrated ammonium hydroxide leads to 3-formimidoyl-4-hydroxycoumarin.[33] The present investigation describes the chemical behavior of benzylamine and *p*-toluidine towards the simple condensation products **1**-**4**, derived from 3-formylchromone and cyanoacetic acid, malononitrile, ethyl cyanoacetate and/or cyanoacetamide respectively (Figure 1).



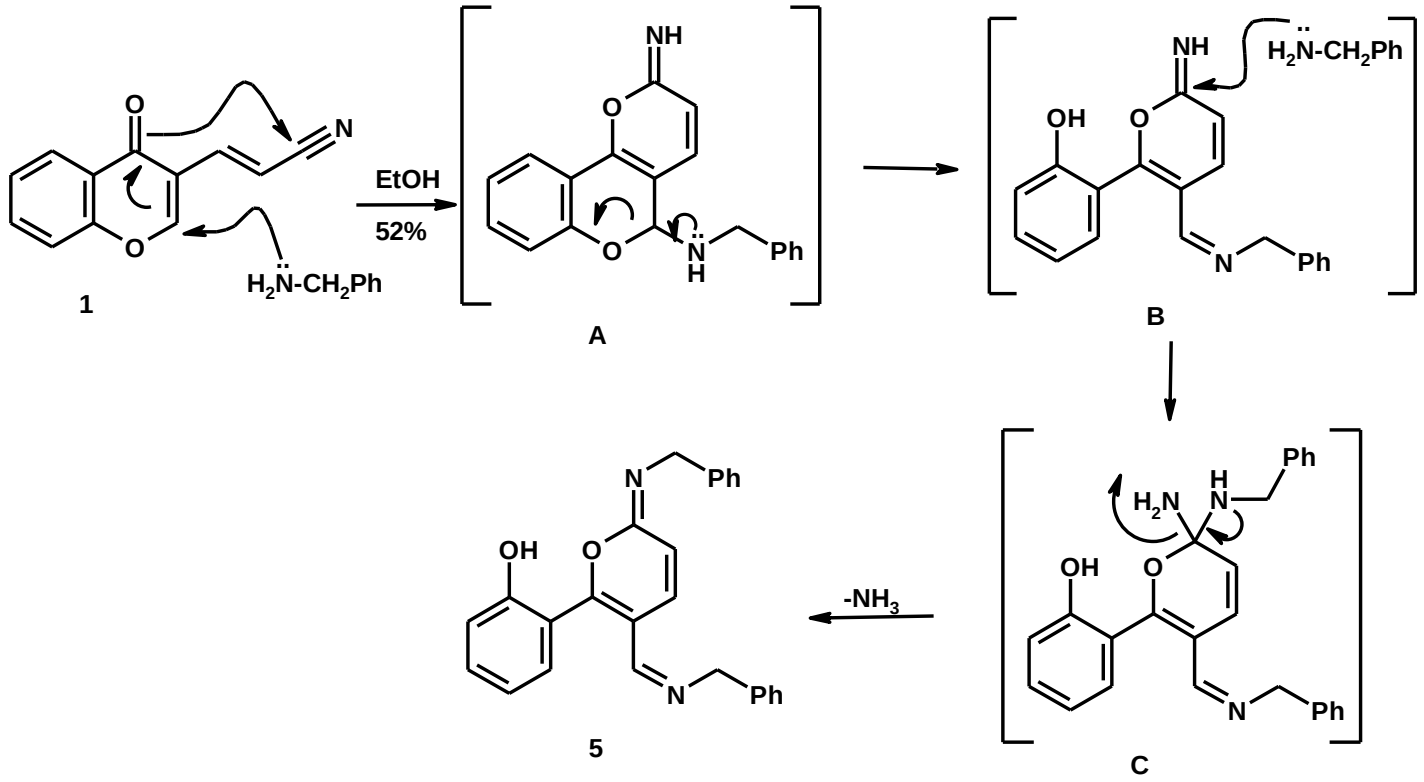
1; X = H **2; X = CN**

3; X = COOEt **4; X = $CONH_2$**

Figure 1. Condensation products **1**-**4** from 3-formylchromone.

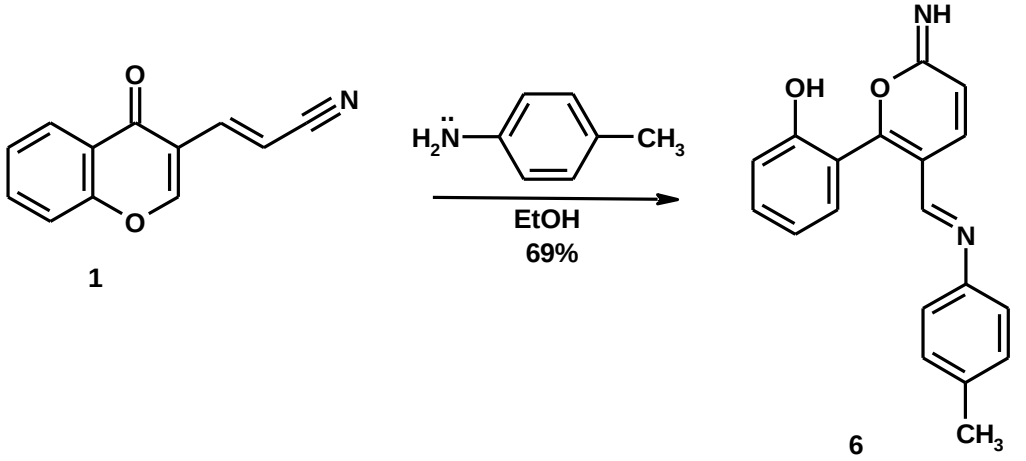
Results and Discussion

The simple condensation products **1**-**4** (Figure 1) may be of interest in the synthesis of various heterocyclic systems due to the availability of diverse electron deficient sites; C-2, C-4, exocyclic vinyl carbon, cyano group and the carbonyl group of the ester or amide functions. The present work aimed to study the chemical behavior of simple primary amines namely benzylamine and *p*-toluidine with the compounds **1**-**4**. Thus, treatment an ethanolic solution of 3-(4-oxo-4*H*-chromen-3-yl)acrylonitrile (**1**) with benzylamine under reflux for 30 minutes gave 2-{2-(benzylimino)-5-[(benzylimino)methyl]-2*H*-pyran-6-yl}phenol (**5**) (Scheme 1). The reaction may proceed through nucleophilic attack at C-2 with concomitant addition of the carbonyl oxygen at the nitrile function producing 2-iminopyranochromene intermediate **A** which can undergo ring opening generating 2-iminopyran intermediate **B**. The latter intermediate can condense with another molecule of benzylamine with elimination of ammonia, producing the final product **5** (Scheme 1). The ^{1}H NMR spectrum of compound **5** showed two characteristic two-hydrogen singlets attributed to the two methylene groups at δ 4.66 and 5.15 ppm, in addition to a characteristic singlet assigned to CH=N at δ 7.95 ppm.



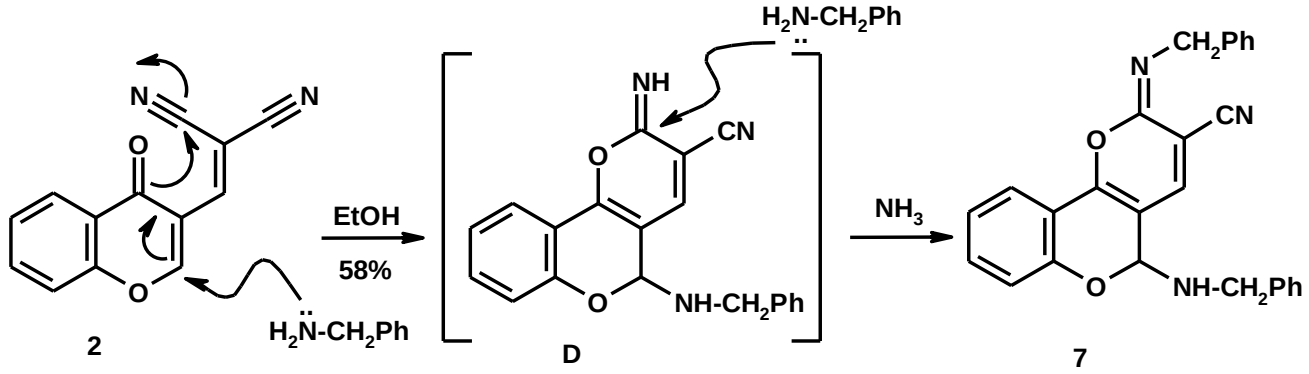
Scheme 1. Reaction of chromonylacrylonitrile **1** with benzylamine.

In contrast, reaction of acrylonitrile **1** with *p*-toluidine occurred in 1.1 molar ratio affording 2-(2-imino-5-{[(4-methylphenyl)imino]methyl}-2*H*-pyran-6-yl)phenol (**6**) (Scheme 2). The elemental analysis and spectroscopic data of the latter reaction confirms the participation of one molecule of *p*-toluidine in the reaction. The ^{1}H NMR spectrum of compound **6** showed two singlet signals attributed to CH_3 and CH=N at δ 2.26 and 8.43 ppm, in addition to D_2O-exchangeable signals assigned to NH and OH protons at δ 9.55 and 10.27 ppm, respectively. The ^{13}C NMR spectrum of compound **6** agrees well with the proposed structure and revealed characteristic signals at δ 20.3 (CH_3) and 193.8 (C-OH).



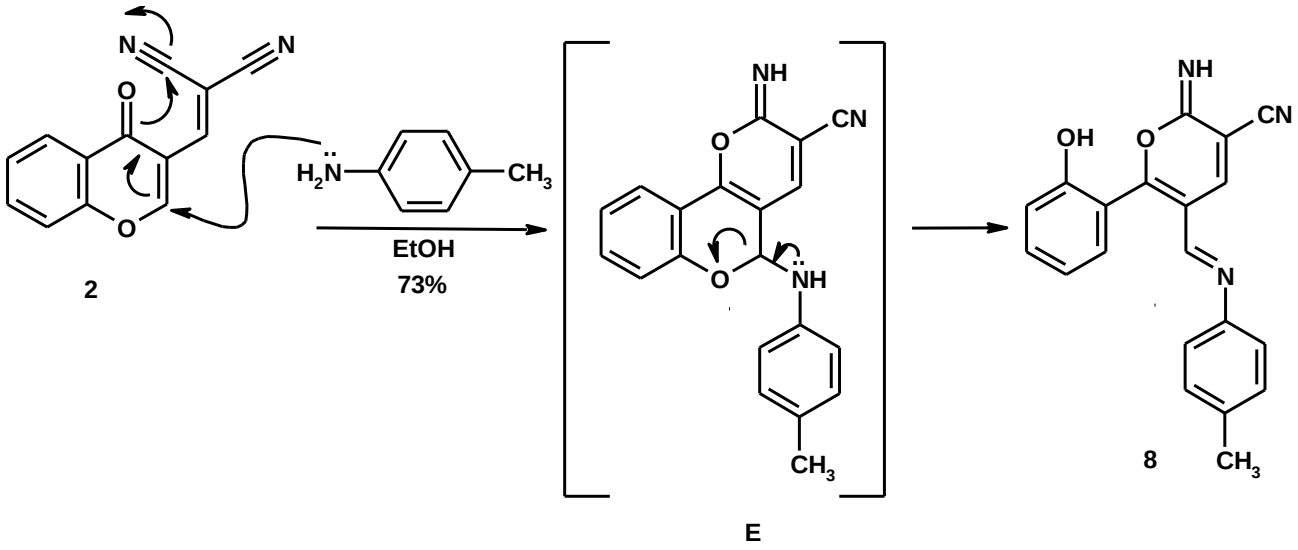
Scheme 2. Reaction of chromonylacrylonitrile **1** with *p*-toluidine.

Next, the effect of benzylamine and *p*-toluidine on the [(4-oxo-4*H*-chromen-3-yl) methylidene]propanedinitrile (**2**) was studied. Thus, refluxing an ethanolic solution of the substrate **2** with benzylamine afforded a white crystalline product identified as 5-(benzylamino)-2-(benzylimino)-2*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (**7**) (Scheme 3). Formation of compound **7** may proceed *via* nucleophilic attack at C-2 of the γ–pyrone ring with concomitant addition onto the nitrile group producing intermediate **D** which would react with another molecule of benzylamine to afford the final product **7** as depicted in Scheme 3. The IR spectrum of compound **7** showed characteristic absorption bands at 3376 (NH), 2209 (C≡N) and 1601 cm^{-1} (C=N). The ^{1}H NMR spectrum of compound **7** showed characteristic signals attributed to the two methylene groups at δ 3.95 (singlet) and δ 4.66 ppm (doublet exchanged to singlet in D_2O), in addition to a characteristic doublet exchanged to singlet in D_2O at δ 5.84 ppm assigned to H-5. The spectrum also revealed a singlet signal at δ 7.87 ppm assigned to the H-4_{pyran}. The ^{13}C NMR spectrum of compound **7** showed characteristic signals at δ 44.2 (CH_2), 47.9 (CH_2), 86.5 (C-3), 88.9 (C-5 as O-CH-NH) and 116.9 (C≡N).



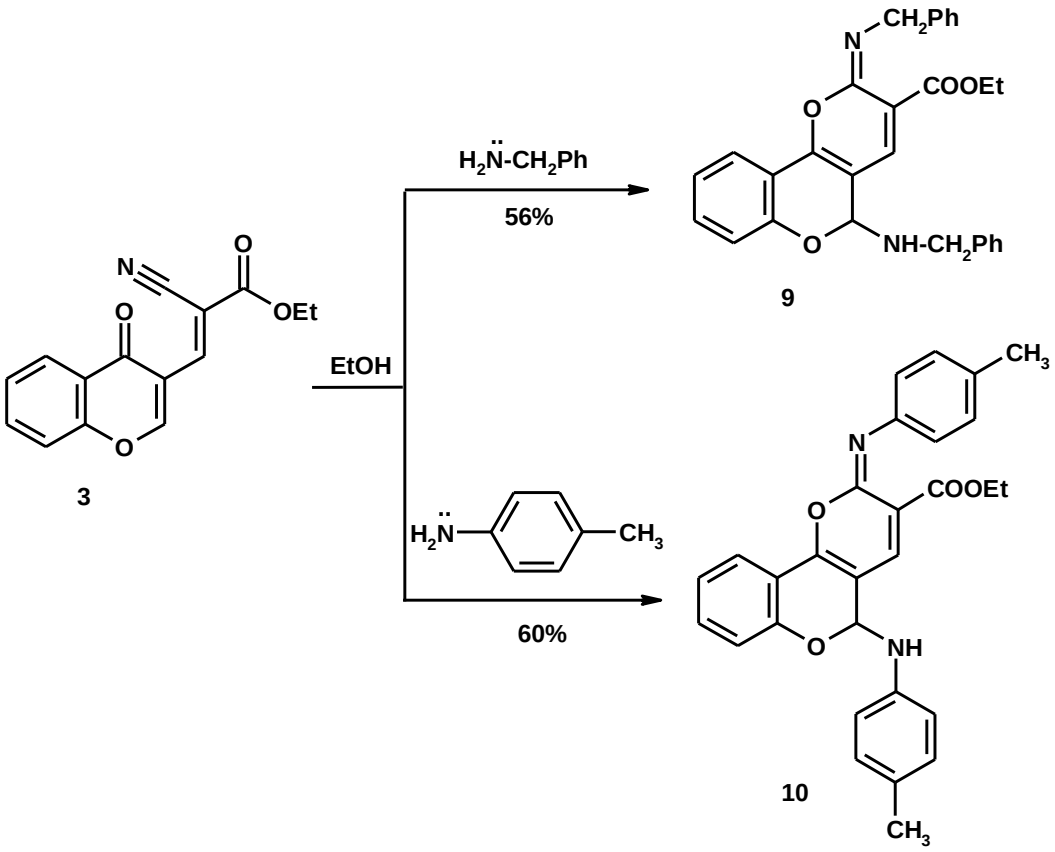
Scheme 3. Ring transformation of compound **2** with benzylamine.

Treatment of substrate **2** with *p*-toluidine in absolute ethanol showed different behavior producing the novel 6-(2-hydroxyphenyl)-2-imino-5-{[(4-methylphenyl)imino]methyl}-2*H*-pyran-3-carbonitrile (**8**), *via* intermediate **E**, as illustrated in Scheme 4. The elemental analysis and spectroscopic data confirm a 1:1 molar ratio in this reaction. The IR spectrum of compound **8** showed characteristic absorption bands at 2222 (C≡N) and 1626 cm^{-1} (C=N). The ^{1}H NMR spectrum of compound **8** showed characteristic singlet signals at δ 8.27 and 8.55 ppm attributed to the H-4_{pyran} and CH=N, respectively, in addition to two exchangeable signals at δ 9.65 and 10.32 ppm due to NH and OH protons, respectively. The ^{13}C NMR spectrum of compound **8** showed characteristic signals at δ 116.7 (C≡N) and 192.2 (C-OH). Moreover, the mass spectrum of compound **8** showed a molecular ion peak as the base peak at *m/z* 329, agreeing perfectly with the formula $C_{20}H_{15}N_3O_2$, further supporting the structural assignment.



Scheme 4. Ring transformation of compound **2** with *p*-toluidine.

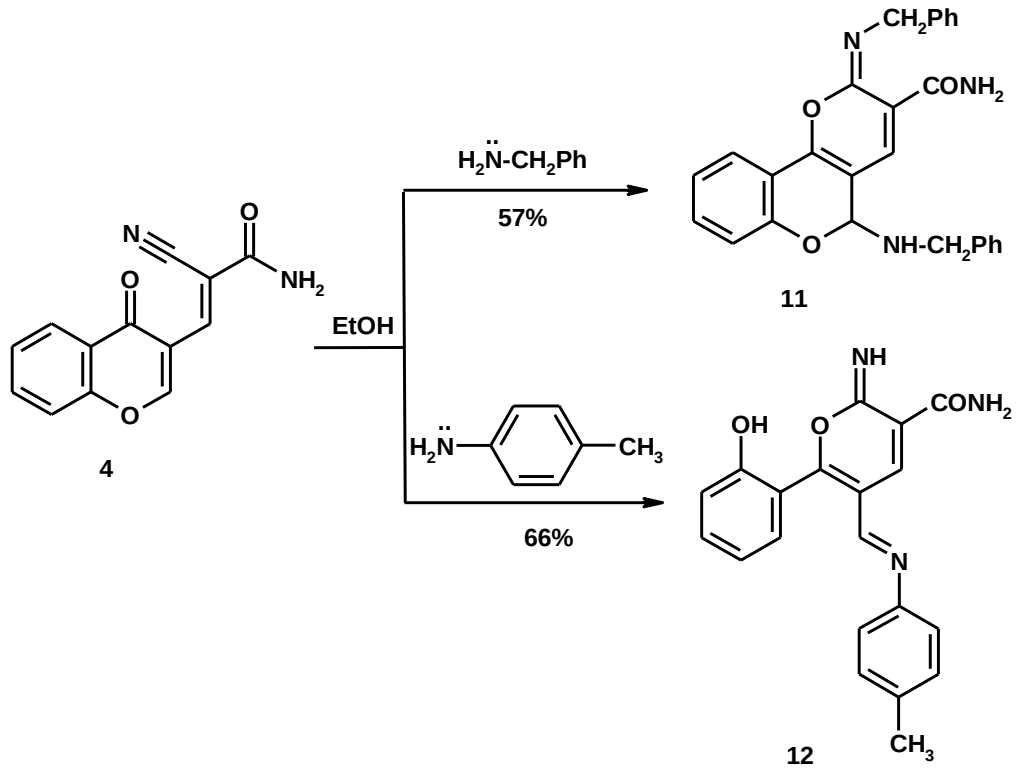
Interestingly, benzylamine and *p*-toluidine behave similarly in their reactions with ethyl 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoate (**3**) producing ethyl pyrano[3,2-*c*]chromene-3-carboxylate derivatives **9** and **10**, respectively (Scheme 5). In these reactions two moles of benzylamine and *p*-toluidine react with one mol of the substrate **3** as deduced from elemental analysis and spectral data. The IR spectra of compounds **9** and **10** showed characteristic absorption bands at 3346/3375 (NH), 1686/1674 cm^{-1} ($C=O_{ester}$), respectively. The ^{1}H NMR spectra of compounds **9** and **10** revealed the presence of characteristic doublet exchanged to singlet with D_2O at δ 5.93/6.41 ppm attributed to H-5 as well as a characteristic singlet at δ 8.07/8.29 ppm assigned to $H\text{-}4_{pyran}$. Characteristic signals appeared in the ^{13}C NMR spectrum of compound **9** at δ 14.6 ($CH_2\underline{CH_3}$), 44.5 (CH_2), 48.4 (CH_2), 61.1 ($\underline{CH_2}CH_3$), 87.4 (C-5) and 104.9 ppm (C-4a), while that of compound **10** showed characteristic signals at δ 14.4 ($CH_2\underline{CH_3}$), 20.6 (CH_3), 21.6 (CH_3), 61.8 ($\underline{CH_2}CH_3$), 81.7 (C-5) and 106.3 ppm (C-4a).



Scheme 5. Ring transformation of compound **3** with benzylamine and *p*-toluidine.

The present work was extended to study the reactivity of benzylamine and *p*-toluidine towards 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enamide (**4**). Thus, treatment of substrate **4** with benzylamine in absolute ethanol gave 5-(benzylamino)-2-(benzylimino)-2*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxamide (**11**) as described previously (Scheme 6). The ^{1}H NMR spectrum of compound **11** exhibited characteristic singlet signals at δ 4.67, 4.72 and 8.06 ppm attributed to two CH_2 and H-4_{pyran}, respectively. The spectrum also revealed exchangeable signals due to NH and NH_2 at δ 5.00 and 9.24 ppm, respectively.

Compound **4** behaved similarly to compounds **1** and **2** upon treatment with *p*-toluidine producing the novel 6-(2-hydroxyphenyl)-2-imino-5-{[(4-methylphenyl)imino]methyl}-2*H*-pyran-3-carboxamide (**12**) (Scheme 6). The ^{1}H NMR spectrum of compound **12** showed characteristic singlet signals at δ 2.28, 8.47 and 8.56 ppm attributed to the CH_3, H-4_{pyran} and CH=N, respectively, and exchangeable signals due to NH and OH at δ 10.30 and 11.53 ppm, respectively.



Scheme 6. Ring transformation of compound **4** with benzylamine and *p*-toluidine.

Conclusions

Various substituted 2-iminopyran and pyrano[3,2-*c*]chromene derivatives were efficiently prepared from the chemical transformations of simple condensation products **1**-**4** with benzylamine and *p*-toluidine. These transformations occur through nucleophilic attack at C-2 of the γ–pyrone ring with concomitant addition of the carbonyl oxygen to the nitrile function followed by further transformations.

Experimental Section

General. Melting points are uncorrected and were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on FTIR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB spectrometers, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu Gas chromatography instrument mass spectrometers (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer. 3-(4-Oxo-4*H*-chromen-3-yl)acrylonitrile (**1**),[34] [(4-oxo-4*H*-chromen-3-yl)methylidene]-propanedinitrile (**2**),[35] ethyl 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoate (**3**),[36] and 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enamide (**3**)[35] were prepared according to the published methods.

2-{2-(Benzylimino)-5-[(benzylimino)methyl]-2*H*-pyran-6-yl}phenol (5). A mixture of 3-(4-oxo-4*H*-chromen-3-yl)acrylonitrile (**1**) (0.39 g, 2 mmol) and benzylamine (0.21 g, 2 mmol) in absolute EtOH (10 mL) was heated under reflux with continuous stirring for 30 min. After cooling, the canary yellow crystals obtained were

filtered off and recrystallized from MeOH to give compound **5** as canary yellow crystals, mp 166-167 °C, yield (0.41 g, 52%). IR (KBr, cm^{-1}): 3367 (OH), 3022 ($CH_{arom.}$), 2970, 2922 ($CH_{aliph.}$), 1604 (C=N), 1559 (C=C). ^{1}H NMR (DMSO-d_6, δ): 4.66 (s, 2H, CH_2), 5.15 (s, 2H, CH_2), 6.47 (d, *J* 8.8 Hz, 1H, H-3_{pyran}), 6.69-7.77 (m, 15H, 14Ar-H and H-4_{pyran}), 7.95 (s, 1H, CH=N), 9.94 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6): 62.5 (CH_2), 63.6 (CH_2), 98.7, 108.7, 116.9, 118.0, 119.3, 119.6, 125.5, 126.5, 127.9, 128.6, 128.9, 129.1, 129.3, 130.0, 132.1, 132.6, 147.3, 154.5, 156.0, 191.3 (C-OH). Anal. Calcd for $C_{26}H_{22}N_2O_2$ (394.47): C, 79.16; H, 5.62; N, 7.10%. Found: C, 78.90; H, 5.40; N, 7.00%.

2-(2-Imino-5-{[(4-methylphenyl)imino]methyl}-2*H*-pyran-6-yl)phenol (6). A mixture of 3-(4-oxo-4*H*-chromen-3-yl)acrylonitrile (**1**) (0.39 g, 2 mmol) and *p*-toluidine (0.21 g, 2 mmol) in absolute EtOH (10 mL) was heated under reflux with continuous stirring for 30 min. After cooling, the yellow crystals obtained were filtered off and recrystallized from MeOH to give compound **6** as canary yellow crystals, mp 220-221 °C, yield (0.42 g, 69%). IR (KBr, cm^{-1}): 3234 (OH), 3195 (NH), 3029 ($CH_{arom.}$), 2920, 2880 ($CH_{aliph.}$), 1621 (C=N), 1590 (C=C). ^{1}H NMR (DMSO-d_6, δ): 2.26 (s, 3H, CH_3), 6.86 (d, *J* 9.0 Hz, 1H, H-3_{pyran}), 6.91-6.99 (m, 2H, Ar-H), 7.12 (d, *J* 8.7 Hz, 2H, Ar-H), 7.35-7.43 (m, 2H, Ar-H), 7.57 (d, *J* 8.7 Hz, 2H, Ar-H), 7.88 (d, *J* 9.0 Hz, 1H, H-4_{pyran}), 8.43 (s, 1H, CH=N), 9.55 (s, 1H, NH exchangeable with D_2O), 10.27 (s, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6): 20.3 (CH_3), 109.4, 116.5, 118.9, 119.6, 123.4, 125.0, 129.0, 129.9, 131.0, 132.5, 137.4, 137.6, 151.6, 156.3, 158.2, 193.8 (C-OH). MS (*m/z*, %): 304 (M, 100), 238 (3), 226 (6), 211 (4), 183 (59), 168 (8), 121 (12), 91 (16), 77 (11) and 65 (26). Anal. Calcd for $C_{19}H_{16}N_2O_2$ (304.34): C, 74.98; H, 5.30; N, 9.20%. Found: C, 74.80; H, 5.19; N, 9.05%.

5-(Benzylamino)-2-(benzylimino)-2*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (7). A mixture of [(4-oxo-4*H*-chromen-3-yl)methylidene]propanedinitrile (**2**) (0.44 g, 2 mmol) and benzylamine (0.21 g, 2 mmol) in absolute EtOH (10 mL) was heated under reflux with continuous stirring for 30 min. After cooling, the white crystals obtained were filtered off and recrystallized from EtOH to give compound **7** as white crystals, mp 158-159 °C, yield (0.50 g, 58%). IR (KBr, cm^{-1}): 3376 (NH), 3023 ($CH_{arom.}$), 2931, 2858 ($CH_{aliph.}$), 2209 (C≡N), 1601 (C=N), 1585 (C=C). ^{1}H NMR (DMSO-d_6, δ): 3.95 (s, 2H, CH_2), 4.10 (m, 1H, NH exchangeable with D_2O), 4.66 (d, 2H, CH_2NH, exchanged to singlet with D_2O), 5.84 (d, *J* 8.4 Hz, 1H, H-5, exchanged to singlet with D_2O), 6.93 (d, *J* 8.4 Hz, 1H, Ar-H), 7.04 (t, *J* 7.8 Hz, 1H, Ar-H), 7.22–7.44 (m, 10H, Ar-H), 7.87 (s, 1H, H-4_{pyran}), 7.95 (t, 1H, Ar-H), 8.05 (d, 1H, Ar-H). ^{13}C NMR (DMSO-d_6, δ): 44.2 (CH_2), 47.9 (CH_2), 86.5 (C-3), 88.9 (C-5 as O-CH-NH), 111.5, 115.8, 116.9 (C≡N), 117.6, 119.8, 121.2, 124.9, 126.5, 127.3, 127.7, 128.0, 128.1, 132.2, 132.5, 140.2, 140.5, 149.6, 155.0, 157.4. MS (*m/z*, %): 419 (M, 3), 418 (3), 417 (5), 401 (44), 312 (33), 106 (4), 91 (100) and 65 (13). Anal. Calcd for $C_{27}H_{21}N_3O_2$ (419.47): C, 77.31; H, 5.05; N, 10.02%. Found: C, 77.00; H, 4.85; N, 9.75%.

6-(2-Hydroxyphenyl)-2-imino-5-{[(4-methylphenyl)imino]methyl}-2*H*-pyran-3-carbonitrile (8). A mixture of [(4-oxo-4*H*-chromen-3-yl)methylidene]propanedinitrile (**2**) (0.44 g, 2 mmol) and *p*-toluidine (0.21 g, 2 mmol) in absolute EtOH (10 mL) was heated under reflux with continuous stirring for 30 min. After cooling, the yellow crystals obtained were filtered and recrystallized from MeOH to give compound **8** as white crystals, mp 196-197 °C, yield (0.48 g, 73%). IR (KBr, cm^{-1}): 3329 (OH, NH), 3040 ($CH_{arom.}$), 2940, 2870 ($CH_{aliph.}$), 2222 (C≡N), 1626 (C=N), 1602 (C=C). ^{1}H NMR (DMSO-d_6, δ): 2.29 (s, 3H, CH_3), 6.96-6.99 (m, 3H, Ar-H), 7.15 (d, *J* 8.4 Hz, 2H, Ar-H), 7.37–7.47 (m, 3H, Ar-H), 8.27 (s, 1H, H-4_{pyran}), 8.55 (s, 1H, CH=N), 9.65 (bs, 1H, NH exchangeable with D_2O), 10.32 (bs, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 20.4 (CH_3), 91.8, 115.8, 116.7, 119.3, 123.1, 123.5, 124.4, 128.8, 130.2, 133.3, 133.6, 135.8, 144.3, 154.4, 156.3, 157.4, 192.2 (C-OH). MS (*m/z*, %): 329 (M, 100), 300 (9), 208 (95), 193 (13), 121 (28), 106 (7), 93 (15), 91 (25), 77 (13) and 65 (38). Anal. Calcd for $C_{20}H_{15}N_3O_2$ (329.36): C, 72.94; H, 4.59; N, 12.76%. Found: C, 72.81; H, 4.42; N, 12.44%.

Ethyl 5-(benzylamino)-2-(benzylimino)-2*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxylate (9). A mixture of ethyl 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoate (**3**) (0.54 g, 2 mmol) and benzylamine (0.21 g, 2 mmol) in

absolute EtOH (10 mL) was heated under reflux with continuous stirring for 30 min. After cooling, the yellow crystals obtained were filtered off and recrystallized from MeOH to give compound **9** as pale yellow crystals, mp 106-107 °C, yield (0.52 g, 56%). IR (KBr, cm^{-1}): 3346 (NH), 3064 ($CH_{arom.}$), 2978, 2917 ($CH_{aliph.}$), 1686 ($C=O_{ester}$), 1612 (C=N), 1601 (C=C). ^{1}H NMR (DMSO-d_6, δ): 1.33 (t, *J* 7.2 Hz, 3H, CH_3), 3.99 (s, 2H, CH_2), 4.01 (m, 1H, NH exchangeable with D_2O), 4.31 (q, *J* 7.2 Hz, 2H, CH_2), 4.82 (d, *J* 5.7 Hz, 2H, CH_2 exchanged to singlet with D_2O), 5.93 (d, *J* 10.2 Hz, 1H, H-5 exchanged to singlet with D_2O), 6.92 (d, *J* 8.1 Hz, 1H, Ar-H), 7.05 (t, *J* 7.5 Hz, 1H, Ar-H), 7.19–7.44 (m, 11H, Ar-H), 8.07 (s, 1H, H-4_{pyran}), 8.46 (t, *J* 6.0 Hz, 1H, Ar-H). ^{13}C NMR (DMSO-d_6, δ): 14.6 (CH_2CH_3), 44.5 (CH_2), 48.4 (CH_2), 61.1 (CH_2CH_3), 87.4 (C-5), 104.9 (C-4a), 115.9, 118.1, 121.6, 121.9, 125.4, 127.0, 127.2, 127.8, 128.3, 128.5, 128.8, 132.5, 138.5, 140.7, 140.9, 150.9, 155.7, 157.7, 166.9. MS (*m/z*, %): 466 (M, 18), 439 (11), 421 (13), 408 (20), 329 (14), 313 (12), 262 (15), 234 (12), 218 (14), 116 (7), 98 (69) and 81 (100). Anal. Calcd for $C_{29}H_{26}N_2O_4$ (466.53): C, 74.66; H, 5.62; N, 6.00%. Found: C, 74.22; H, 6.17; N, 5.98%.

Ethyl 5-[(4-methylphenyl)amino]-2-[(4-methylphenyl)imino]-2*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxylate (10). A mixture of ethyl 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enoate (**3**) (0.54 g, 2 mmol) and *p*-toluidine (0.21 g, 2 mmol) in absolute ethanol (10 mL) was heated under reflux with continuous stirring for 15 min. The yellow crystals obtained during heating were filtered and recrystallized from ethanol to give compound **10** as pale yellow crystals, mp 255-256 °C, yield (0.56 g, 60%). IR (KBr, cm^{-1}): 3375 (NH), 3025 ($CH_{arom.}$), 2973, 2918 ($CH_{aliph.}$), 1674 ($C=O_{ester}$), 1612 (C=N), 1600 (C=C). ^{1}H NMR (DMSO-d_6, δ): 1.38 (t, *J* 6.9 Hz, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.37 (q, *J* 6.9 Hz, 2H, CH_2), 6.41 (d, *J* 8.1 Hz, 1H, H-5 exchanged to singlet with D_2O), 6.47 (d, *J* 6.6 Hz, 2H, Ar-H), 6.79 (d, *J* 7.6 Hz, 2H, Ar-H), 6.96 (d, 1H, Ar-H), 7.05 (d, *J* 7.8 Hz, 1H, Ar-H), 7.20 (d, *J* 8.1 Hz, 2H, Ar-H), 7.44 (t, *J* 6.6 Hz, 1H, Ar-H), 7.67 (d, *J* 8.1 Hz, 2H, Ar-H), 8.08 (d, *J* 6.9 Hz, 1H, Ar-H), 8.29 (s, 1H, H-4_{pyran}), 10.24 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 14.4 (CH_2CH_3), 20.6 (CH_3), 21.3 (CH_3), 61.8 (CH_2CH_3), 81.7 (C-5), 106.3 (C-4a), 114.3, 114.5, 116.9, 118.7, 120.6, 121.9, 125.1, 125.5, 127.2, 129.4, 131.9, 132.8, 137.2, 139.0, 143.7, 150.6, 154.9, 155.2, 167.4. MS (m/z, %): 466 (M, 14), 465 (73), 421 (18), 392 (17), 368 (32), 252 (20), 211 (8), 198 (62), 90 (6), 76 (4) and 64 (100). Anal. Calcd for $C_{29}H_{26}N_2O_4$ (466.53): C, 74.66; H, 5.62; N, 6.00%. Found: C, 74.82; H, 5.38; N, 5.88%.

5-(Benzylamino)-2-(benzylimino)-2*H*,5*H*-pyrano[3,2-*c*]chromene-3-carboxamide (11). A mixture of 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enamide (**4**) (0.48 g, 2 mmol) and benzylamine (0.21 g, 2 mmol) in absolute EtOH (15 mL) was heated under reflux with continuous stirring for 15 min. After cooling, the white crystals obtained were filtered off and recrystallized from MeOH to give compound **11** as white crystals, mp 163-164 °C, yield (0.50 g, 57%). IR (KBr, cm^{-1}): 3367, 3298 (NH_2), 3170 (NH), 3055 ($CH_{arom.}$), 2970, 2906, 2867 ($CH_{aliph.}$), 1689 ($C=O_{amide}$), 1624 (C=N), 1609 (C=C). ^{1}H NMR (DMSO-d_6, δ): 4.67 (s, 2H, CH_2), 4.72 (d, 2H, CH_2 exchanged to singlet with D_2O), 5.00 (bs, 1H, NH exchangeable with D_2O), 6.11 (d, 1H, H-5 exchanged to singlet with D_2O), 7.07-7.42 (m, 13H, Ar-H), 8.06 (s, 1H, H-4_{pyran}), 8.11 (d, *J* 7.8 Hz, 1H, Ar-H), 9.24 (bs, 2H, NH_2 exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 46.6 (CH_2), 58.7 (CH_2), 81.9 (C-3), 104.8, 115.3, 118.1, 121.5, 124.9, 127.1, 127.4, 127.8, 128.5, 129.2, 131.6, 136.5, 136.8, 139.6, 142.4, 150.0, 154.8, 158.3, 168.1, 174.7. MS (m/z, %): 437 (M, 21), 422 (M-15, 70), 393 (M-$CONH_2$, 72), 367 (78), 359 (100), 314 (62), 282 (67), 274 (75), 251 (83), 238 (50), 199 (49), 174 (85), 160 (82), 97 (26), 92 (81), 76 (50) and 65 (28). Anal. Calcd for $C_{27}H_{23}N_3O_3$ (437.49): C, 74.12; H, 5.30; N, 9.60%. Found: C, 73.75; H, 5.22; N, 9.44%.

6-(2-Hydroxyphenyl)-2-imino-5-{[(4-methylphenyl)imino]methyl}-2*H*-pyran-3-carboxamide (12). A mixture of 2-cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enamide (**4**) (0.48 g, 2 mmol) and *p*-toluidine (0.21 g, 2 mmol) in absolute EtOH (10 mL) was heated under reflux with continuous stirring for 30 min. After cooling, the yellow crystals obtained were filtered off and recrystallized from EtOH to give compound **12** as white crystals, mp 204-205 °C, yield (0.46 g, 66%). IR (KBr, cm^{-1}): 3443, 3330, 3181 (OH, NH_2, NH), 1672 ($C=O_{amide}$), 1622 (C=N), 1607 (C=C). ^{1}H NMR (DMSO-d_6, δ): 2.28 (s, 3H, CH_3), 6.94-6.99 (m, 2H, Ar-H), 7.15 (d, *J* 8.4 Hz, 2H, Ar-H), 7.39-

7.46 (m, 2H, Ar-H), 7.58 (d, *J* 8.4 Hz, 2H, Ar-H), 7.77 (bs, 2H, NH_2 exchangeable with D_2O), 8.47 (s, 1H, H-4_{pyran}), 8.56 (s, 1H, CH=N), 10.30 (bs, 1H, NH exchangeable with D_2O), 11.53 (bs, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 20.6 (CH_3), 106.3 (C-5), 116.4, 121.4, 123.5, 124.8, 125.0, 126.6, 127.9, 128.7, 133.0, 139.5, 142.7, 152.5, 158.0, 161.7, 173.4, 192.4 (C-OH). Anal. Calcd for $C_{20}H_{17}N_3O_3$ (347.38): C, 69.15; H, 4.93; N, 12.10%. Found: C, 69.69; H, 4.82; N, 12.24%.

Supplementary Material

The copies of IR, ^1H NMR, ^{13}C NMR, and Mass spectra of compounds **5-12** are presented in the Supplementary Material.

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