Actions of Bisnucleophiles on (E)-3-[3-(2-Hydroxyaryl)-3-oxoprop-1-en-1-yl]chromones: Versatile Transformations into Oxygen- and Nitrogen-Containing Heterocycles

Ridha Hassaine*a,b
Oualid Talhi*b,c
Nadia Taibib
Filipe A Almeida Pazd
Okkacha Bensaid*a
Khaldoun Bacharib
Artur M. S. Silva*c

R. Hassaine et al.
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Abstract

The transformations of (E)-3-[3-(2-hydroxyaryl)-3-oxoprop-1-en-1-yl]chromones in the presence of methylhydrazine and aromatic bisnucleophiles are described. The reactions generally lead to chromone ring transformation via pyrone ring-opening and heterocyclization to give novel diazoles and (Z)-3-aminomethylenechromanones, respectively. Piperazine catalyzes chromanone ring closure of the starting substrate to afford chromone–chromanone dyads.

Key words chromones, α,β-unsaturated carbonyl systems, Michael additions, bisnucleophiles, X-ray diffraction, heterocycles, 2D NMR

Chromones and chromanones (2,3-dihydrochromones) are generally recognized as medicinally active heterocycles.1–3 Hence, the important biological properties of these compounds explain their use in many synthetic scaffolds.4 Indeed, these types of compounds have long been employed in cancer therapy and anti-inflammatory drug design, especially the flavones.2 In addition to their bioactivity, chromones are used as synthetic precursors due to their ability to undergo versatile ring transformations that utilize the intracyclic α,β-unsaturated carbonyl system of the pyrone ring, leading to enaminochromanones,6 aurones7 and polyheterocyclic compounds.8

In an effort to develop novel biologically active chromanones following new synthetic methods,6,9 a considerable amount of work was focused on chromone ring modifications and transformations involving conformational rearrangements10 and various cyclizations through hetero-Michael additions.11a,b The large majority of reactions are nitrogen and oxygen nucleophilic additions promoting ring opening of the pyrone leading to a large diversity of heterocycles.5–11 A good example concerns 2-(N-methylanilino)-3-formylchromones which have demonstrated broad synthetic applications, especially when incorporating a chromone moiety. A variety of heterocyclized chromones, novel macrocycles, and tetradentate ligands can be prepared upon reactions with bisnucleophiles, such as hydrazines and phenylenediamines, via substitution of the N-methylanilino moiety and/or condensations with the 3-formyl group.12 Other studies have involved the reaction of 3-formylchromones with active methylene compounds to access different heterocyclic systems, mainly via pyrone ring-opening upon nucleophilic attack13 with thiosemicarbazine. Further chelation with nickel(II) yields cytotoxic and DNA-binding agents,14 or with diazoles under microwave-assisted conditions to prepare a series of chromone–diazole dyads.15

We envisaged that (E)-3-[3-(2-hydroxyaryl)-3-oxoprop-1-en-1-yl]chromones 1a,b might undergo further transformations on reactions with bisnucleophiles at their different electrophilic centers, namely the intracyclic α,β-unsaturat-
ed carbonyl system (the pyrone ring) along with the exocyclic 3-oxoprop-1-enyl moiety. In this study, methylhydrazine and aromatic-derived bisnucleophiles exhibited different reactivity toward chromones 1a,b leading to diazoles 2a,b and 3-aminomethylenechromanones 3aa,ab, respectively (Scheme 1). Moderate to good yields (43–76%) were achieved overnight at room temperature using tetrahydrofuran as the solvent. Monitoring the reaction progress by thin-layer chromatography showed that the best results were obtained after stirring the reaction for 20 hours at room temperature. Longer reaction times and higher temperatures led to the formation of several other minor products.

Scheme 1 Synthesis of diazoles 2a,b, 3-aminomethylenechromanones 3aa,ab, and chromone–chromanone dyads 4a,b18

The two transformations of interest involve a domino sequence of nucleophilic attack at the chromone C-2 with pyrone ring opening and pyrazole ring closure,16 together with a 1,4-aza-Michael addition to the exocyclic 3-oxoprop-1-enyl moiety followed by formation a 2-pyrazoline ring,17 and subsequent nucleophilic attack at the chromone C-2 with pyrone ring opening followed by chromanone ring closure (Scheme 2).5

It is worth noting that C-2 of chromones 1 is highly reactive toward nucleophiles due to the presence of the oxygen atom at position 1 and the mesomeric electron-withdrawing effects caused by the two carbonyl groups. The presence of a second electrophilic center at C-1’ on the 3-[(2-hydroxyaryl)-3-oxoprop-1-en-1-yl] moiety of 1, even though relatively less electrophilic, allows its participation in a consecutive (or simultaneous) attack of a second molecule of methylhydrazine to form the intermediate A. These events are followed by heterocyclization to afford the diazoles 2 (Scheme 2).

The reactions of aromatic bisnucleophiles, such as phenylenediamine and 2-aminophenol, with chromones 1 are expected to proceed through a similar mechanistic pathway, thus favoring the initial nucleophilic attack of nitrogen on the chromone C-2 of the pyrone ring affording intermediate B. Due to the weaker nucleophilic character and bulky nature of these bisnucleophiles, the heterocyclization and/or attack of a second molecule on the electrophilic C-1’ center of 3-[(2-hydroxyphenyl)-3-oxoprop-1-enyl] moiety...
is not possible. Nevertheless, intermediate B was able to undergo regioselective intramolecular heterocyclization via an oxo-Michael addition using the hydroxy group of the 2-hydroxyphenyl side chain (resulting from the ring-opening of the pyrone) to yield the corresponding 3-aminomethylenechromanones 3 (Scheme 2).

Piperazine, taken as an example of a secondary cyclic diamine, catalyzed the chromanone ring closure of substrates 1 giving rise to the novel chromone–chromanone dyads 4 (Schemes 1 and 2).  

2D NMR spectroscopic analysis and single-crystal X-ray diffraction studies were employed to reveal the exact spatial description of structures 2–4. Distinguishing between the 2-(3,4-dihydro-1H-pyrazol-3-yl)phenol and 2-(1H-pyrrozol-3-yl)phenol moieties of the diazoles 2a,b was rather straightforward.  

'H NMR spectroscopic analysis clearly showed the AMX spin-system resulting from the aromatic carbon C-3 (δC 63.8–63.9) with three doublets of doublets at δH 2.97–2.98 (H-4[A]), 3.65–3.69 (H-4[M]), and 4.40–4.42 (H-3[X]). The vinylic proton H-5 of the 1H-pyrazole was assigned to a singlet at δH 7.61. Nevertheless, only analysis of the HMBC connectivities permitted the assignment of the imino carbon at δC=N 152.9–153.1 for the 3,4-dihydro-1H-pyrazole, and at δC=N 148.0–147.9 for the 1H-pyrazole, as both are involved in intramolecular hydrogen bonding with phenolic hydroxy groups (δC=O-H 10.56–10.73 and δC=O-H 10.56–10.97) as was clearly observed from the crystallographic studies (vide infra). The latter proton signals could also be differentiated from their HMBC cross-peak correlations as depicted in Figure 1.

The 3-aminomethylenechromanones 3aa,ab21,22 displayed an ABX spin-system in their 1H NMR spectra (δH 3.38–3.43 and 3.69–3.71 for H-1[AB], and 5.73–5.74 for H-2[X]) attributable to the 2-(2-hydroxyaryl)-2-oxoethyl side chain. It was found that the amino protons 1″-NH appeared as a doublet at δH 11.80–11.99 due to coupling with the vinylic proton H-1″ (JH-1″,1″-NH = 12.0 Hz) which appear under a multiplet of the aromatic protons (δH 7.35–7.57). The HMBC connectivities allowed the unequivocal assignment of all the non-protonated carbons (Figure 1). For example, H-2[X] showed correlations with the neighboring carbons C-4 (δC 181.4–181.6), C-2' (δC 203.2–203.3), C-3 (δC 103.8–103.9) and C-9 (δC 157.3–157.5) of the chromanone ring.

The structures of the novel chromone–chromanone dyads 4a,b23,24 were established unequivocally on the basis of 1H NMR spectroscopic analysis, showing an ABX spin-system for the intracyclic aliphatic protons H-3'[AB] and H-2'[X] resulting from the presence of the asymmetric carbon at C-2' (δC 73.0–73.1) of the chromanone unit. Carbons C-4' (δC 191.3–191.5) and C-4 (δC 175.7) could be distinguished using HMBC cross-peak correlations with H-5' and H-5, respectively, as shown in Figure 1.

Single-crystal X-ray diffraction studies provided additional insight on the 3D structures of the chelating hexacyclic iminenol and enaminone systems in diazoles 2 and 3-aminomethylenechromanones 3, respectively.

Crystals of 2a25 were isolated by slow evaporation at 6 °C from a solution of a 1:1 mixture of hexane–dichloromethane. The crystallographic structural features of the diazole 2a were in good agreement with those derived from the 2D NMR studies (Figure 2, top). The 3,4-dihydro-1H-pyrazole group was almost co-planar with the attached phenol group, with the two rings subtending a dihedral angle of 5.18(7)°. On the other hand, the 1H-pyrazole group subtended a prominent 25.66(7)° angle with its corresponding phenol ring. Nevertheless, as depicted in Figure 2, both groups were engaged in O–H···N intramolecular hydrogen bonds. It is worth emphasizing that the bulky (3,4-dihydro-1H-pyrazol-3-yl)phenol and (1H-pyrazol-3-yl)phenol groups of the molecular unit of compound 2a were located in different planes subtending a dihedral angle of 68.10(4)°.

Crystals of 3-aminomethylenechromanone 3aa26 were obtained from a mixture of hexane–dichloromethane (1:1) by slow evaporation at 6 °C. Crystallographic studies clearly showed that the chromanone and the phenylenediamine groups were almost coplanar, with their average planes subtending a dihedral angle of only 5.83(5)°. In addition, the intramolecular hydrogen bonding interaction involving these two moieties further promoted the typical Z-configuration, ultimately delineating a hexacyclic enaminoine ring (Figure 2, middle). Attached to the C-2 asymmetric center, the 2-(2-hydroxyaryl)-2-oxoethyl side chain subtended a dihedral angle of 31.27(4)° with that formed by the conjugation of both the chromanone and the phenylenediamine groups.

A similar recrystallization procedure [hexane–dichloromethane (1:1) at 6 °C] allowed the isolation of good quality crystals of the novel chromone–chromanone dyad 4b.27 Crystallographic studies showed that the chromane and...
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Supporting Information

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References and Notes

ARKIVOC 2009, (xii), 161.


   (b) Santos, C. M. M.; Silva, A. M. S.; Jekó, J.; Léai, A. ARKIVOC (v), 265.


(20) 2′-[3′-(2-Hydroxyphenyl)-1′,2-dimethyl-3,4-dihydro-1′H,2′H 
[3′,4′-bispyrazole]-3′,5-diyl]diphenyl (2a)

Yield: 0.20 g (57%); M₉ = 348.41 g/mol; colorless crystals; mp 205–206 °C. ¹H NMR (300 MHz, CDCl₃); δ = 2.88 (s, 3 H, 1-N-CH₃), 2.98 (dd, J = 18.0, 14.0 Hz, 1 H, H-4[AB]); 3.69 (dd, J = 18.0, 10.0 Hz, 1 H, H-4[AB]); 3.95 (s, 3 H, 1′-N-CH₃), 4.40 (dd, J = 14.0, 10.0 Hz, 1 H, H-3[X]), 6.83–6.94 (m, 2 H, H-5), 6.97–7.14 (m, 3 H, H-3′, H-4′, H-6′), 7.20–7.28 (m, 2 H, H-4′, H-5′), 7.47 (dd, J = 7.8, 1.6 Hz, 1 H, H-6′), 7.61 (s, 1 H, H-5′), 7.10 (s, 1 H, 2′-[OH]), 10.97 (s, 1 H, 1′-OH). ¹C NMR (75 MHz, CDCl₃); δ = 39.1 (1′-N-CH₃), 42.1 and 42.2 (1-N-CH₃ and C-4), 63.8 (C-3), 116.1 (C-1′), 116.5 (C-3′), 117.2 (C-1′′), 117.3 (C-3′′), 118.3 (C-4′), 119.1 (C-5′), 121.9 (C-5′′), 127.2 (C-6′), 127.3 (C-6′′), 129.1 (C-4′′′), 130.4 (C-3′′′), 147.9 (C-3), 153.1 (C-5), 155.7 (C-2′), 157.6 (C-2′′). HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₄H₂₀N₂O₄Na: 423.1321; found: 423.1318.

2′-[3′-(2-Hydroxyphenyl)-1′,2-dimethyl-3,4-dihydro-1′H,2′H 
[3′,4′-bispyrazole]-3′,5-diyl]diphenyl (2a)

Yield: 0.20 g (57%); M₉ = 348.41 g/mol; colorless crystals; mp 205–206 °C. ¹H NMR (300 MHz, CDCl₃); δ = 2.88 (s, 3 H, 1-N-CH₃), 2.98 (dd, J = 18.0, 14.0 Hz, 1 H, H-4[AB]); 3.69 (dd, J = 18.0, 10.0 Hz, 1 H, H-4[AB]); 3.95 (s, 3 H, 1′-N-CH₃), 4.40 (dd, J = 14.0, 10.0 Hz, 1 H, H-3[X]), 6.83–6.94 (m, 2 H, H-5), 6.97–7.14 (m, 3 H, H-3′, H-4′, H-6′), 7.20–7.28 (m, 2 H, H-4′, H-5′), 7.47 (dd, J = 7.8, 1.6 Hz, 1 H, H-6′), 7.61 (s, 1 H, H-5′), 7.10 (s, 1 H, 2′-[OH]), 10.97 (s, 1 H, 1′-OH). ¹C NMR (75 MHz, CDCl₃); δ = 39.1 (1′-N-CH₃), 42.1 and 42.2 (1-N-CH₃ and C-4), 63.8 (C-3), 116.1 (C-1′), 116.5 (C-3′), 117.2 (C-1′′), 117.3 (C-3′′), 118.3 (C-4′), 119.1 (C-5′), 121.9 (C-5′′), 127.2 (C-6′), 127.3 (C-6′′), 129.1 (C-4′′′), 130.4 (C-3′′′), 147.9 (C-3), 153.1 (C-5), 155.7 (C-2′), 157.6 (C-2′′). HRMS (ESI): m/z [M + Na]⁺ calcd for C₂₄H₂₀N₂O₄Na: 423.1321; found: 423.1318.
(24) 3-(6-Methoxy-4-oxochroman-2-yl)-4H-chromen-4-one (4b)

Yield: 0.14 g (43%); Mr = 322.31 g/mol; colorless crystals; mp 195–196 °C. 1H NMR (300 MHz, CDCl₃): δ = 2.85 (dd, J = 17.0, 13.1 Hz, 1 H, H-3′[AB]), 3.24 (dd, J = 17.0, 2.9 Hz, 1 H, H-3′[AB]), 3.83 (s, 3 H, 6′-OCH₃), 5.67 (ddd, J = 13.1, 2.9, 1.0 Hz, 1 H, H-2′[X]), 7.00 (d, J = 9.0 Hz, 1 H, H-8′), 7.13 (dd, J = 9.0, 3.2 Hz, 1 H, H-7′), 7.37 (d, J = 3.1 Hz, 1 H, H-5′), 7.40–7.52 (m, 2 H, H-6, H-8), 7.72 (ddd, J = 8.6, 7.2, 1.7 Hz, 1 H, H-7), 8.21–8.28 (m, 1 H, H-5), 8.24 (d, J = 1.0 Hz, 1 H, H-2). 13C NMR (75 MHz, CDCl₃): δ = 42.7 (C-3′), 55.8 (6′-OCH₃) 73.1 (C-2′), 107.6 (C-5′), 118.2 (C-8′), 121.0 (C-10′), 123.0 (C-3), 123.8 (C-10), 125.2 (C-7′), 125.5 (C-6), 125.9 (C-5), 134.0 (C-7), 153.3 (C-2), 154.5 (C-6′), 155.8 (C-9′), 156.3 (C-9), 175.7 (C-4), 191.5 (C-4′). HRMS (ESI): m/z [M + Na]+ calcd for C₁₉H₁₄O₅Na: 345.0739; found: 345.0748.

(25) Crystal data for compound 2a (CCDC 1404991): C₂₀H₂₀N₄O₂, Mr = 348.40, triclinic, space group P1, Z = 2, a = 8.7610(13) Å, b = 9.9194(16) Å, c = 11.871(2) Å, α = 66.580(7)°, β = 70.069(7)°, γ = 74.993(7)°. V = 880.8(3) Å³, μ(Mo-Kα) = 0.088 mm⁻¹, Dc = 1.314 g cm⁻³. Colorless block, crystal size = 0.22 × 0.16 × 0.10 mm³. Of a total of 19322 reflections collected, 4753 were independent (Rint = 0.0413). Final R1 = 0.0467 [I > 2σ(I)] and wR2 = 0.1267 (all data). Data completeness to θ = 25.24°, 99.9%.

(26) Crystal data for compound 3aa (CCDC 1404990): C₂₄H₂₀N₂O₄, Mr = 400.42, monoclinic, space group P2₁/n, Z = 4, a = 14.9755(11) Å, b = 4.7510(3) Å, c = 26.6395(16) Å, β = 93.664(5)°. V = 1891.5(2) Å³, μ(Mo-Kα) = 0.097 mm⁻¹, Dc = 1.406 g cm⁻³; orange plate, crystal size of 0.22 × 0.12 × 0.03 mm³. Of a total of 15482 reflections collected, 4999 were independent (Rint = 0.0475). Final R1 = 0.0505 [I > 2σ(I)] and wR2 = 0.1233 (all data). Data completeness to θ = 25.24°, 99.6%.

(27) Crystal data for compound 4b (CCDC 1404989): C₁₉H₁₄O₅, Mr = 322.30, triclinic, space group P1, Z = 2, a = 8.4108(9) Å, b = 8.5434(9) Å, c = 10.6878(11) Å, α = 83.293(3)°, β = 72.084(3)°, γ = 82.141(3)°. V = 721.61(13) Å³, μ(Mo-Kα) = 0.108 mm⁻¹, Dc = 1.483 g cm⁻³; colorless plate, crystal size of 0.16 × 0.12 × 0.07 mm³. Of a total of 13854 reflections collected, 2640 were independent (Rint = 0.0256). Final R1 = 0.0553 [I > 2σ(I)] and wR2 = 0.1356 (all data). Data completeness to θ = 25.24°, 99.6%.