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Condensation reactions of dialkoxy-2-phenylchroman-4-ones with 1,2-diamines: A method for the preparation of chromenoquinoxalines

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ABSTRACT

Reactions of dialkoxy-2-phenylchroman-4-ones (2,3-diethoxy-3-hydroxy-2-phenylchroman-4-one (**1**) and 2,3-dimethoxy-3-hydroxy-2-phenylchroman-4-one (**2**)) with various phenylenediamines in refluxing chloroform led to quinoxaline ring formation to produce racemic mixtures of chromenoquinoxaline molecules in good to moderate yields (**3**–**10**). The proposed mechanism involves the hemiacetals (**1** and **2**) rearranging upon heating to form a reactive dione intermediate that subsequently reacts with phenylenediamine derivatives to produce the title compounds. Reactions of **1** and **2** with asymmetric phenylenediamines led to mixtures of two regioisomers, for which the major products were dictated by the relative reactivity of the nucleophilic amine and the electrophilic carbonyl groups. The chromenoquinoxaline products were characterized by ^{1}H, ^{13}C, ^{19}F (when necessary), nuclear magnetic resonance spectroscopy, high-resolution mass spectrometry, melting point determination, and in some cases (compounds **6**–**10**) single crystal X-ray diffraction studies. Herein, the synthesis, characterization, and reactivity of this new class of molecules are discussed.

Introduction

Quinoxalines are bicyclic systems that can be best described as a benzene unit fused to pyrazine. They are commonly produced by the condensation reaction of 1,2-dicarbonyl compounds with *o*-phenylenediamine derivatives. At one time, this reaction had very little utility except as an identification tool to determine the presence of 1,2-diamine and/or 1,2-dicarbonyl groups [1]. However, today a plethora of methods have been developed to produce quinoxalines due to their increasing presence and utility. Quinoxaline motifs are commonly observed in natural and medicinal products [2], biologically active compounds [3–7], antibiotics [8,9], dyes [10,11], organic semiconductors [12], thermal plastics [13,14], insecticides [15,16], herbicides [16,17], and others [18]. Alternative means to produce quinoxalines include using catalysts to promote the condensation between diamines and dicarbonyl compounds [19–21], dehydrogenative coupling of vicinal alcohols [22] and vicinal amino alcohols [23], and sulfur-catalyzed oxidative condensations of aryl ketones with phenylenediamines [24,25]. Two thorough reviews, and the references therein, are available that highlight some of the syntheses and applications of quinoxalines [26,27].

We became interested in the formation of quinoxalines during our oxidation studies of 3-hydroxyflavone by copper(II) bromide ($CuBr_2$) in the presence of alcohols [28]. These studies revealed the ready oxidation of 3-hydroxyflavone to produce hemiacetals or hydrates, depending on reaction conditions (Fig. 1). Hydrates are preferred under heated, thermodynamic conditions, while acetals are isolated as kinetic products [28]. Based on literature precedence [29], the oxidation reaction mechanism likely involves the oxidation of the alcohol of 3-hydroxyflavone by $CuBr_2$, followed by nucleophilic acyl addition of either alcohol or water (Fig. 1).

It was also found that the kinetically accessible hemiacetals readily convert into thermodynamically stable hydrates upon heating, which was assumed to also proceed through a dione intermediate [30]. To validate the formation of the dione intermediate during the conversion of the hemiacetals to hydrates, the hemiacetal derivative was heated with phenylenediamine to trap the dione intermediate as a stable quinoxaline unit (Scheme 1) [28]. Smith *et al.* performed a similar reaction almost 60 years ago to determine the products of periodate oxidations of flavanols; however, no effort was dedicated to characterizing the quinoxaline product, nor was the scope of the reaction examined with substituted phenylenediamine analogs [30]. Moreover, Raw *et al.*

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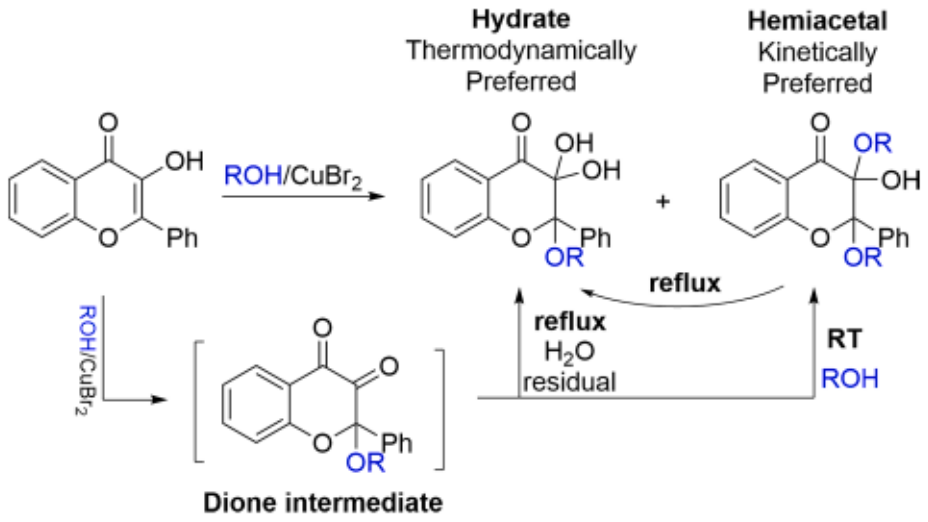
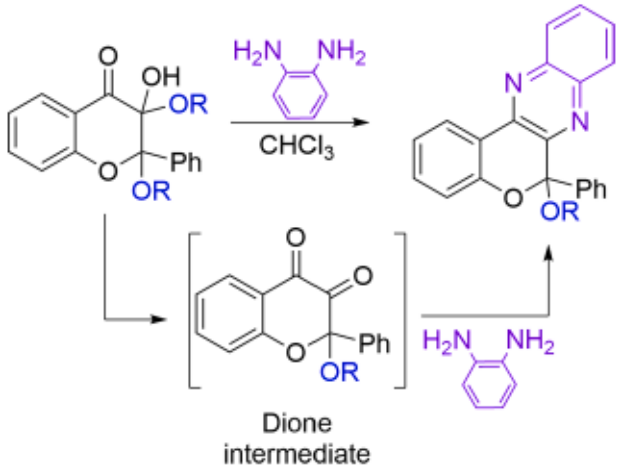


Fig. 1. Oxidation of 3-hydroxyflavone by copper(II) bromide in the presence of alcohols, showing the reactive dione intermediate and its conversion to hydrates and hemiacetals.



Scheme 1. Reaction of chromane hemiacetal with phenylenediamine to form chromenoquinoxalines.

reported a similar reaction wherein the alcohol of α-hydroxy ketones was oxidized (*in situ)* with MnO_2, followed by the treatment with diamines to produce diazines [31].

The product obtained from the condensation reaction between chromane hemiacetals and phenylenediamine can be described as a chromane fused to a quinoxaline unit, which we have aptly named chromenoquinoxalines (CQ). Indeed, some chromanes (known as benzopyrans) can be found in numerous natural products such as flavonoids and tocopherols (e.g., vitamin E) [32]. They have been implicated in various therapeutic applications, including anticancer agents [33], antioxidants [34], antibacterials [35,36], antifungals [37], anti-inflammatory [38,39], antiviral [40], and treatments for cardiovascular diseases [41–43]. The structural complexity of the title chromenoquinoxalines, especially its similarity to steroids, with its three, six-membered, A, B, and C rings, suggests its potential use for preparing molecules for endocrine therapies, especially for ER + breast cancers [44,45]. The merging of two biologically active units into a single, unique molecular entity with distinguishing biological properties is an interesting construct to investigate new leads into pharmacological development.

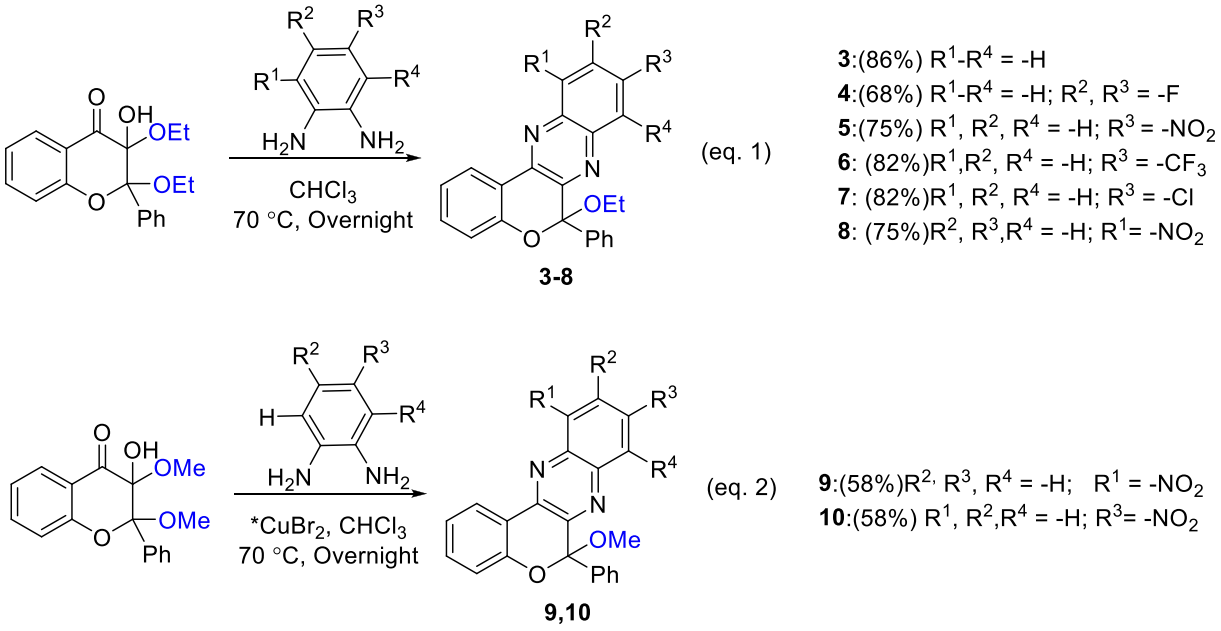
Herein, we describe the synthesis, reactivity, and characterization of several chromenoquinoxalines. We aimed to further examine the scope of the reaction between chromane hemiacetals and various phenylenediamines to produce a library of chromenoquinoxalines. Ultimately, we plan to test their biological activity against cancer cells, bacteria, and fungi.

Results and discussions

Reaction of 2,3-dialkoxy-3-hydroxy-2-phenylchroman-4-one (1 and 2) with o-phenylenediamines to produce chromenoquinoxalines

The reaction of 2,3-dialkoxy-3-hydroxy-2-phenylchroman-4-ones (1 and 2) with *o*-phenylenediamines in chloroform at 70℃ resulted in quinoxaline ring formation to produce chromenoquinoxalines as racemic mixtures in moderate to good yield, (eq. 1 and 2). Though a similar reaction was reported as an assay to validate 1,2-diketone formation during flavanol oxidation studies [46], to our knowledge the ready formation of quinoxalines by reacting oxidized 3-hydroxyflavone products with phenylenediamines has not been examined for nearly 60 years. With the advent of readily available modern technologies (e.g., nuclear magnetic resonance spectroscopy and single crystal X-ray diffraction), reexamining this chemistry provided an opportunity to better understand these molecules from both a structural and spectroscopic perspective. Recent studies present similar reactions involving the reaction of phenylenediamines with 2,5-dihydroxy-*p*-benzoquinone and α-hydroxy ketones to produce quinoxalines; [31] however, the authors disclosed that the reaction conditions did not provide successful condensation with 3-hydroxyflavones. Raw *et al.* demonstrated that quinoxalines could be prepared by reacting α-hydroxy ketones with diamines in the presence of an oxidant [31]. In addition, Kundu *et al.* recently reported the formation of quinoxalines by reaction of 1,2-diols with phenylenediamines in the presence of a nickel catalyst and a sacrificial base [22]. Considering these previous studies required alcohol oxidation prior to condensation with diamines, initial investigations in this study were carried out with a catalytic amount of copper(II) bromide (20 mol %) with the assumption that it would be necessary to oxidize the hemiacetal to produce the 1,2-dione intermediate. Through control studies, it was determined that the copper bromide additive was unnecessary when using compound 1. In fact, the use of the additive slowed the reaction rate severely, requiring as much as 7–8 days at 70℃ for reaction completion. Whereas reactions conducted without $CuBr_2$ only required ~ 12–24 h for reaction completion (overnight). This suggests compound 1, a kinetic accessible product, can autoxidize in the absence of excess alcohol [47,48]. The retarded reactivity of 1 in the presence of $CuBr_2$ is likely a consequence of copper arresting the diamine, preventing it from reacting with the carbonyl groups [49].

Unlike **1**, reactions of **2** with phenylenediamines required the $CuBr_2$ additive for the reaction to proceed. Without the additive, the reactions of **2** were very sluggish and required more than a week to observe 50 % reaction completion.



The reactions of 2,3-diethoxy-3-hydroxy-2-phenylchroman-4-one (**1**) with various phenylenediamine derivatives (*o*-phenylenediamine, 4,5-difluoro-*o*-phenylenediamine, 4-nitro-*o*-phenylenediamine, 4-trifluormethyl-*o*-phenylenediamine, 4-chloro-*o*-phenylenediamine, and 3-nitro-*o*-phenylenediamine) led to their respective chromenoquinoxaline (**3** **8**) (eq. 1). Compound **2** (2,3-dimethoxy-3-hydroxy-2-phenylchroman-4-one) was only reacted with 4-nitro-*o*-phenylenediamine and 3-nitro-*o*-phenylenediamine to produce **9** and **10** to examine regiochemical outcomes (*vide infra*) (eq. 2).

The properties of the chromenoquinoxaline products are somewhat similar. For example, they are sparingly soluble in common organic solvents (THF, diethyl ether, DMSO, acetone, acetonitrile, toluene, benzene, and water), regardless of phenylenediamine substituents. However, they show appreciable solubility in halogenated solvents such as chloroform and dichloromethane. A generic numbering scheme for the chromenoquinoxaline is shown in Fig. 2 and will be referred to throughout the synthesis, characterization, and reactivity discussions. All the synthesized chromenoquinoxalines were characterized by ^{1}H, ^{13}C, and ^{19}F (when appropriate) NMR spectroscopy, IR spectroscopy, melting point analysis, high-resolution mass spectrometry, and in some cases single crystal X-ray crystallography (Compounds **6** **10**).

The ^{1}H NMR spectra of the 6-*alkoxy*-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline derivatives (**3** **10**) have some common features. In general, the resonances for the protons at the 2-, 3-, and 4-positions of the *a*-ring are significantly overlapped and appear as a multiplet (3H, 7.3 7.6 ppm) and are often overlapped with the triplet resonance for the proton at the *para*-position of the phenyl ring at the 6-position (7.5 ppm). The resonance for the proton at the 1-position on the *a*-ring is very distinct, often appearing as the most downfield signal (~8.5 ppm). The ^{1}H NMR resonance signal for the CH_2 group (2H) of the flanking ethyl group appears as a broad quartet at ~ 3.7 ppm, which is probably a consequence of the diastereotopic nature of the CH_2 group.

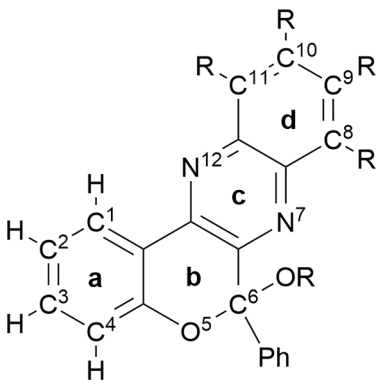


Fig. 2. IUPAC numbering scheme for naming the chromenoquinoxalines.

Reactions of **1** with the symmetrical phenylenediamines (phenylenediamine and 4,5-difluorophenylenediamine) afforded 6-ethoxy-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (**3**) and 6-ethoxy-9,10-difluoro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (**4**), respectively, in good yield (86 % and 92 %, respectively). These compounds were assigned by their ^{1}H NMR spectra using mainly the multiplicity of the protons on the quinoxaline d-ring. The four protons on the quinoxaline d-ring of compound **3** appear as two upfield triplets (7.62 and 7.72 ppm, respectively) for the 9/10-positions and two downfield doublets (7.97 and 8.12 ppm) for the 8/11 positions. The protons of the quinoxaline d-ring of **4** appear as a pair of doublet of doublets (due to H-F coupling ($^{3}J_{HF}$ 11 Hz and $^{4}J_{HF}$ 9 Hz)) that appear at 7.86 ppm and 7.72 ppm, respectively.

Reactions of **1** with the 4-substituted phenylenediamines (4-nitrophenylendiamine, 4-trifluoromethylphenylenediamine, and 4-chlorophenylenediamine) afforded a mixture of regioisomers with the substituent appearing on either the 9- or 10-position of the 6-ethoxy-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline unit. The relative proportions of the two isomers were determined by ^{1}H NMR spectroscopy by comparing the integrations of the resonances of the d-ring (8- and 11-positions) or the resonances for the 1-position of the a-ring, depending on resonance overlap. The major isomer in all cases was the 9-positional regioisomer. For example, 6-ethoxy-9-nitro-6-phenyl-6H-chromeno [3,4-*b*]quinoxaline (**5**) was isolated as the major product (90 %), while the 10-nitro isomer (**5a**, minor product) was 10 %. Likewise, the major product of the reaction of **1** with 4-trifluormethyl-*o*-phenylenediamine

afforded 6-ethoxy-6-phenyl-9-(trifluoromethyl)-6H-chromeno[3,4-*b*]quinoxaline (6) as the major product (66 %) with its 10- trifluoromethyl positional regioisomer (6a) constituting 33 % of the sample. The 4-chlorophenylenediamine gave almost no selectivity. The 9-Cl isomer (7) was slightly favored with a 7/7a (9:10-regioisomeric ratio) ratio of 52:48 %. In all cases, it was difficult to fully isolate the minor isomers to complete their full characterization. It was particularly difficult to separate compounds 7 and 7a using conventional methods, forgoing their characterization by ^{1}H or ^{13}C NMR spectroscopy. High-resolution mass-spectrometry identified both 7 and 7a with minor differences in their retention times. Attempts to separate the two regioisomers by crystallization also failed. In fact, both compounds can be seen in their single crystal X-ray structure, wherein 7a is partially occupied in the structure. This can be best ascertained by the unexpected chlorine atom at the 10-position. This artifact gives the impression that a second chlorine is present (*vide infra*).

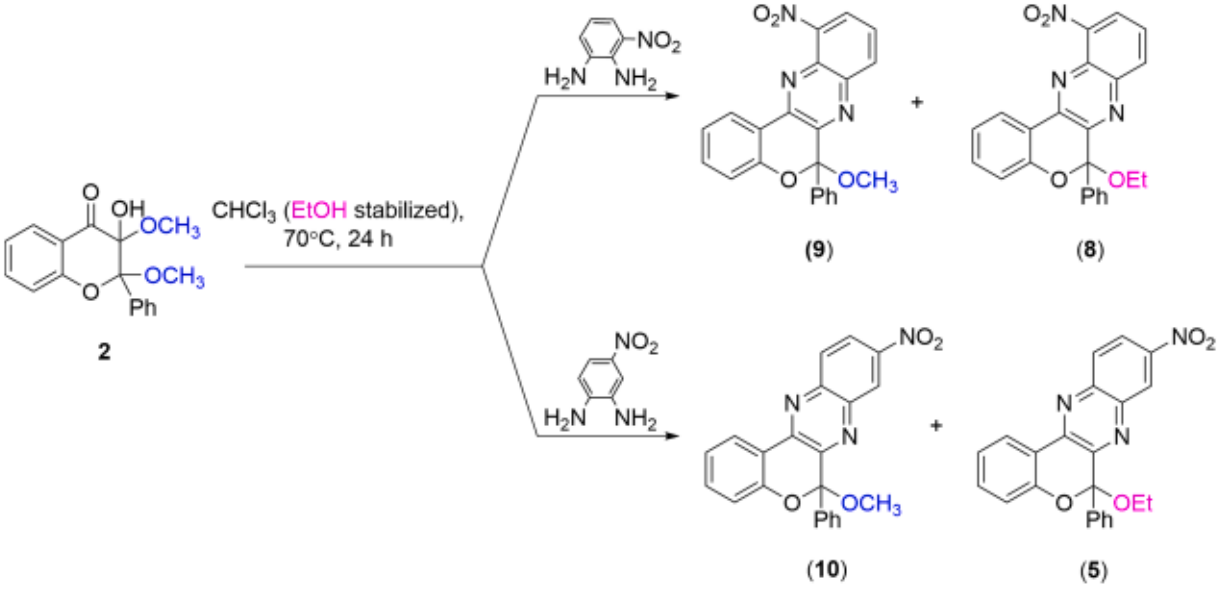
Lastly, reaction of 1 with 3-nitro-*o*-phenylenediamine produced the 11-nitro regioisomer (6-ethoxy-11-nitro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (8)) as the major isomer (90 %) along with the 8-nitro regioisomer (6-ethoxy-8-nitro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (8a)) as the minor isomer (10 %).

Reaction of 2,3-dimethoxy-3-hydroxy-2-phenylchroman-4-one (2) with 3-nitro-o-phenylenediamine and 4-nitro-o-phenylenediamine

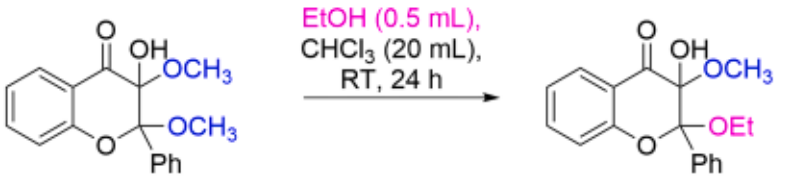
With the facile reactivity of 1 with the phenylenediamines to produce compounds 3–8, the reactivity of the dimethoxy chromane (2, 2,3-dimethoxy-3-hydroxy-2-phenylchroman-4-one) was investigated with 3-nitro-*o*-phenylenediamine and 4-nitro-*o*-phenylenediamine to examine regiochemical outcomes. Reactions of 2 with phenylenediamines required a 20 mol % of the $CuBr_2$ additive for the reaction to proceed. This suggests that the rate-determining alkoxy dissociation step is slower for 2 for autoxidation to produce the reactive dione intermediate than that of 1 [47]. A possible rationale as to why the 1 autoxidizes more readily than 2 could arise from the ability of the ethoxy groups to dissociate more readily due to steric congestion in the axial position (less thermodynamically stable) and its lessened nucleophilicity. Indeed, we have shown the conversion of the hemiacetal chromanes into their hydrates occurs faster for the bulky alkoxy groups such as isopropoxy than that of methoxy [28].

The reaction of 3-nitro-*o*-phenylenediamine with 2 in chloroform, surprisingly, led to the formation of two different major products (determined by NMR) (Scheme 2); one being the expected product with a 6-methoxy group (6-methoxy-11-nitro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (9)), as well as, the unexpected formation of 8 with a 6-ethoxy group instead of a methoxy group. The relative proportion of compounds 9 and 8 (42:58 %, respectively) was calculated using the integration values for the singlet signal (3.34 ppm) for the methyl group of 9 and the triplet signal (1.06 ppm) for the methyl group of 8. The reaction of 4-nitro-*o*-phenylenediamine with 2 also led to a mixture of the expected 6-methoxy-9-nitro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (10) and the unexpected formation of previously described compound 5 (with the methoxy replaced with an ethoxy group) as a 42/58 % mixture, respectively (Scheme 2). Attempts to separate the mixtures (9 and 8; 10 and 5) failed using column chromatography, crystallization, and/or sublimation. The source of ethoxy functionalization was found to be the result of a small amount of ethanol stabilizer present in the commercial chloroform (0.5–1.0 %). The formation of 8 and 5 can be avoided if the chloroform is first purified by removing the ethanol stabilizer. Compound 9 can be prepared in pure form by conducting the reaction in purified chloroform (9, 58 % isolated yield), while 10 and its regioisomer (10a) can be isolated as an intractable mixture, 70 % isolated yield, which could not be separated by conventional methods.

The mechanism of ethoxy incorporation into the chromenoquinoxaline products from the reaction of the phenylenediamines with the methoxy chromane (2) was deliberated. The ethoxy group could have been introduced before or after the quinoxaline formation. In either case, the minuscule amount of ethanol in the stabilized chloroform suggests the ethoxy linkage has some preference for binding over the methoxy linkage. To assess if the methoxy group could be replaced after the quinoxaline ring was formed, compound 9 was dissolved in ethanol with a catalytic amount of $CuBr_2$ and heated for 24 h. This resulted in no detectable swapping with the ethoxy group (8). This indicates that after the quinoxaline ring is formed there is little benefit to exchanging the methoxy group with an ethoxy group, thus implying the methoxy is supplanted at the starting chromane (2). To validate this hypothesis, compound 2 (40 mg) was dissolved in stabilized chloroform (20 mL) with additional absolute ethanol (0.5 mL) to speed up any potential reaction. The solution was allowed to stand at room temperature overnight (eq. 3). After removal of solvent, an ^{1}H NMR spectrum was recorded of the remaining residue. The ^{1}H NMR spectrum of the residue revealed a complicated reaction mixture with roughly a 50/50 % mixture of the starting compound 2 and another compound (2*), which we have tentatively assigned based on the NMR signatures as a complex with the 2-methoxy group swapped for an ethoxy group (eq. 3).



Scheme 2. Reaction of 2 with 3-nitro-*o*-phenylenediamine and 4-nitro-*o*-phenylenediamine in chloroform stabilized by ethanol, leading to a mixture of products.



2 2* (eq. 3)

For comparison purposes, stacked ^{1}H NMR spectra of the upfield regions of the complicated reaction mixture (bottom), the previously isolated hydrate of 2 (middle) [28], and 2 (top) are shown in Fig. 3. There was no indication of the presence of the diethoxychromane (1) in the mixture, as the CH_2 groups would have appeared as a complicated multiplet due to their diastereotopic nature [28], thus its spectrum was not included in the comparison. Moreover, both the formation of the hydrate of 2 and hydrate of 1 (where the methoxy in hydrate of 2 is replaced with ethoxy) were ruled out due to the absence of an upfield broad singlet (~2.6 ppm) for the second geminal alcohol. Attention is drawn to the two, nearly overlapping, broad singlets at 4.76 ppm (2H) in the spectrum of the reaction mixture of 2 and 2*, which indicates two distinct α-hydroxy ketone species. In addition, there is an additional singlet for a methoxy group just forward of the two singlets for the two methyl groups of 2 (Fig. 3, bottom spectrum). These data (the triplet and quartet at 0.88 and 3.38, respectively, and the distinct upfield singlet at 3.18 ppm) support the formation of a mixed methoxy/ethoxy complex (2*). With this knowledge in hand, the source of the formation of the methoxy/ethoxy mixtures (9/8- and 10/5-regioisomer mixtures) is likely due to having both 2 and 2* available in solution to react with the phenylenediamine derivative.

This evidence suggests the 2-alkoxy group of the hemiacetal chromanes (1 and 2) is more labile than the 3-alkoxy group. This is likely due to the resulting carbocation being stabilized by resonance with the phenyl group and chromane oxygen atom. Based on the concept of microscopic reversibility, a proposed mechanism for the formation of the mixture likely involves the liberation of the 2-methoxy group to form a cation intermediate as a first step (Fig. 4) [47]. Since the alkoxides are trans in the chromane of 1 and 2, their formation likely implicates a mechanism involving anti-addition. The 3-alkoxy/hydroxy groups in this study could temporarily interact with the carbocation intermediate to form a cyclic oxonium cation intermediate. From this intermediate, either methanol or ethanol could perform a nucleophilic attack at the 2-position to produce the mixture of 2 and 2* (Fig. 4).

Regiochemical outcomes of the reactions of substituted phenylene diamines with dialkoxychromanes

The reaction of 1 and 2 with asymmetric *o*-phenylenediamine derivatives showed trends in regioselectivity, wherein the major isomer produced in the reaction was the result of the more nucleophilic amine reacting with the more electrophilic carbonyl group (intermediate)

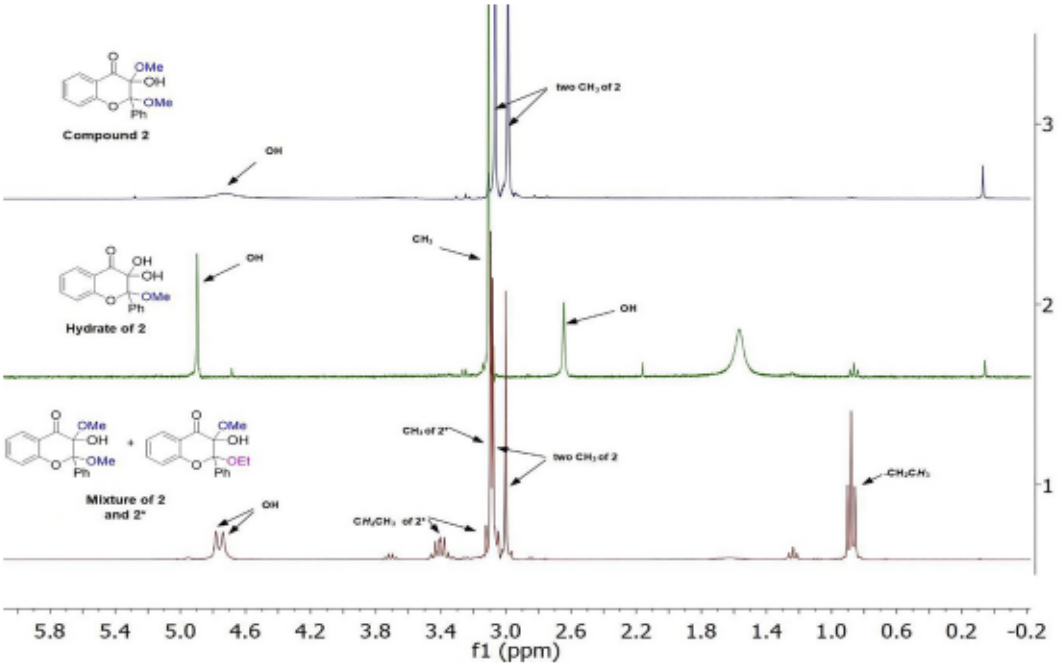


Fig. 3. Stacked ^{1}H NMR spectra of the complex reaction mixture of 2 and 2* (bottom), the hydrate of 2 (middle), and compound 2 (top).

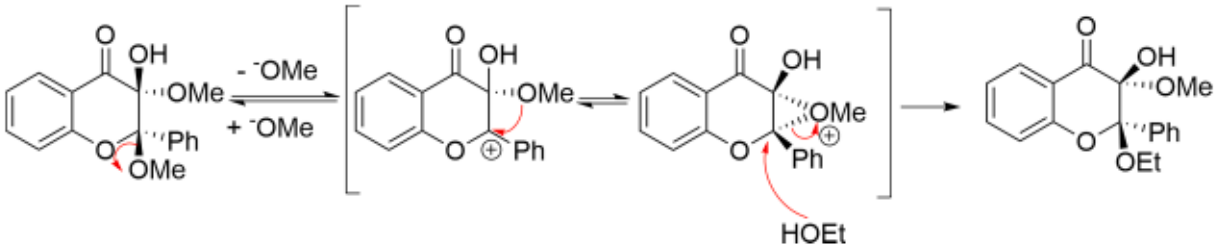


Fig. 4. Proposed mechanism for the formation of 2*.

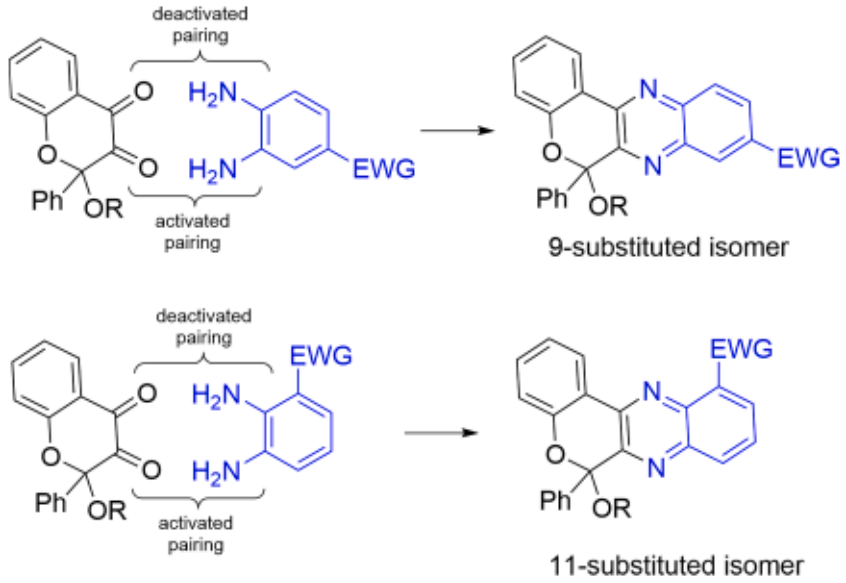


Fig. 5. Scheme showing the regiochemical selectivity in the reaction of 1 or 2 with 3- and 4- substituted o-phenylenediamines. Activated and deactivated pairing of the amine and carbonyl group which leads to regiochemical outcomes.

(Fig. 5). While the relative reactivity of the amines is due to the directing effects of the electron-withdrawing groups, the relative reactivity of the carbonyl groups is due to resonance stabilization. The regioselectivity of the chromenoquinoxaline products appears to enhance with the increasing electron-withdrawing effects of the substituent on the phenylenediamine. For example, the reaction of 1 or 2 with 4-nitro-*o*-phenylenediamines led to 90 % selectivity of the 9-substituted isomer, while the reaction with 3-nitro-*o*-phenylenediamine led to 90 % of the 11-substituted isomer. Reaction of 1 with 4-chloro-*o*-phenylenediamine, the weakest electron-withdrawing group, yielded virtually no selectivity (52 %). Finally, the regioselectivity of the phenylenediamine with the intermediate electron-withdrawing group, 4-trifluoromethyl-*o*-phenylenediamine, showed a 66 % selectivity for the 9-substituted isomer, slightly higher than the weakest electron-withdrawing group studied, but lower than the strongest withdrawing nitro group.

Single X-ray crystallography diffraction studies

The isolation of the major products of these reactions by column chromatography followed by crystallization further affirmed the structural identity of the major isomer through single crystal X-ray diffraction studies. X-ray quality crystals of compounds 6–10 suitable for single crystal X-ray diffraction examination were grown to affirm their structural identity. Their structures and numbering scheme are shown in Fig. 6. The X-ray experimental details for each are provided in Table 1. The structures reveal common features such as having a planar ring quinoxaline system fused to a puckered pyran ring with the oxygen atom resting above the pyran ring. The alkoxy group rests in the pseudo-axial position and bisects the O(1)-C(1)-C(22) bond angle in a nearly linear coplanar orientation with the C(1)-C(2) bond of the chromane system with C(22)-O(2)-C(1)-C(2) dihedral angles ranging from 173 to 175°. The phenyl group resides in the pseudo-equatorial position and is torqued with respect to the C(1)-O(1) bond of the chromane ring with varying dihedral angles for each compound (-149.83° to −159.49°). The observed arrangement of the phenyl and alkoxy groups on C(1) is likely a means to minimize steric interactions. Compounds 6 and 8–10 crystallize as a pair of R and S enantiomers. The two enantiomers associate as dimers about a center of inversion. Compound 7 is distinct from the other compounds as it co-crystallizes as two separate enantiomers. Both enantiomers of 7 were isolated in this study and crystallized in the same crystal system. Due to their similarities, only the R-enantiomer is shown. Both enantiomers of 7 show a large void that was solvent-masked in the data analysis and determined to have excess, unidentified, electron density that correlated to an ethanol (C_2H_6O) residue. Interestingly, compound 7 showed additional electron density attached to C(20) after final refinement. It was found that this excess electron residue was the result of a chlorine atom being intermittently attached at the 10-position in the lattice with a chemical occupancy of 33 %.

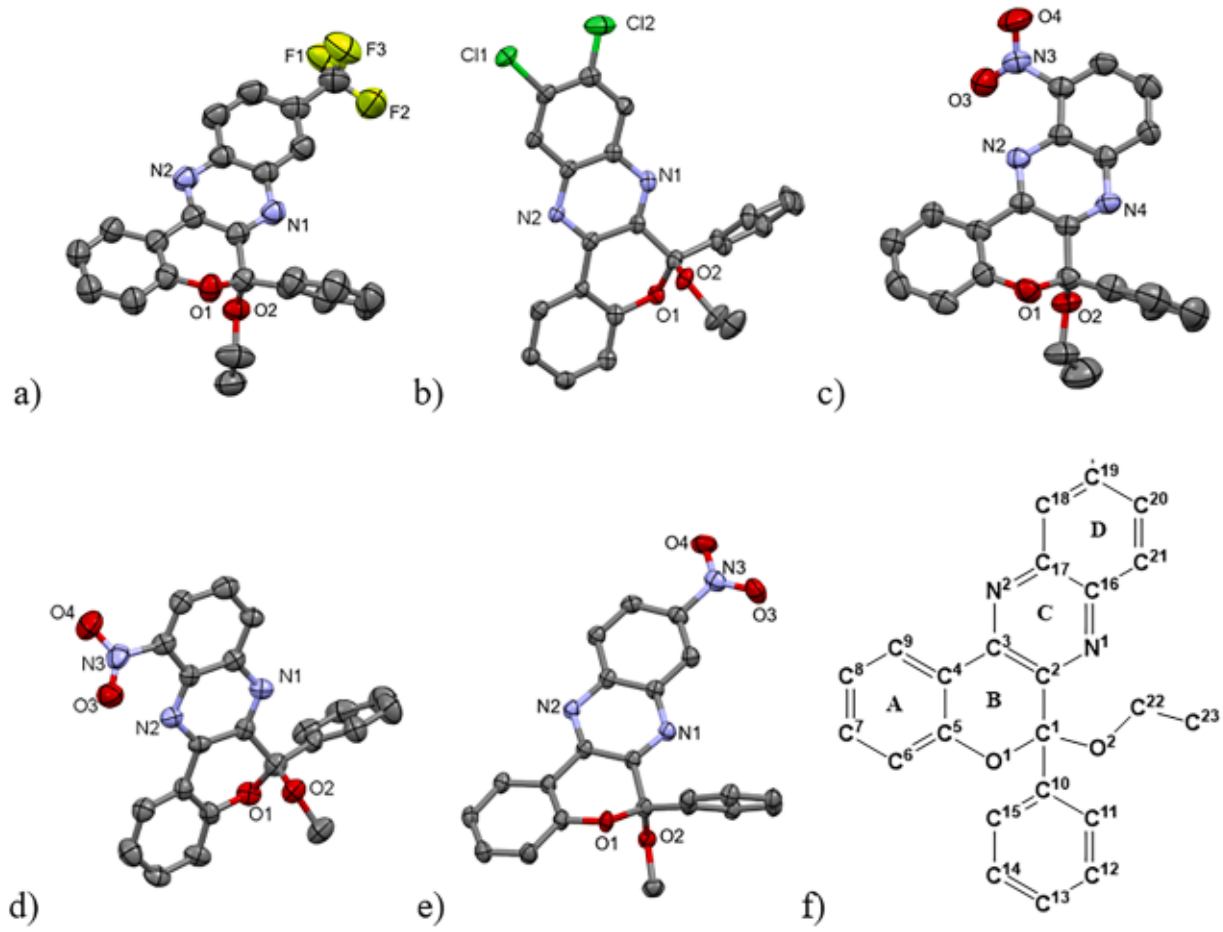


Fig. 6. Molecular structures of (a) 6-ethoxy-6-phenyl-9-(trifluoromethyl)-6H-chromeno[3,4-*b*]quinoxaline (**6**), (b) 9-Chloro-6-ethoxy-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (**7**), (c) 6-ethoxy-11-nitro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (**8**), (d) 6-methoxy-11-nitro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (**9**), (e) 6-methoxy-9-nitro-6-phenyl-6H-chromeno[3,4-*b*]quinoxaline (**10**) and (f) numbering scheme. Thermal ellipsoids are depicted at 50 % probability with hydrogen atoms omitted for clarity.

Table 1
Crystal data and structure refinement details for compounds **6–10.**

Structure	(6)	(7)	(8)	(9)	(10)
Chemical formula	$C_{24}H_{17}F_3N_2O_2$	$C_{23}H_{17}ClN_2O_2$	$C_{23}H_{17}N_3O_4$	$C_{22}H_{15}N_3O_4$	$C_{22}H_{15}N_3O_4$
M_r	422.39	388.83	399.39	385.37	385.37
Crystal system, space group	Monoclinic, $P2_1/n$	Orthorhombic, $P2_12_12_1$	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$
a, b, c (Å)	9.94153 (12), 9.58391 (11), 21.3768 (2)	19.5620 (12), 18.6482 (12), 6.0074 (4)	8.9582 (3), 9.3758 (2), 12.1119 (5)	8.8222 (2), 9.1300 (2), 11.5544 (3)	7.0961 (5), 10.6421 (8), 13.2177 (9)
α, β, γ (°)	90, 100.6340 (11), 90	90, 90, 90	86.894 (3), 75.616 (4), 74.371 (2)	91.869 (2), 96.127 (2), 105.773 (2)	112.117 (7), 91.737 (6), 98.992 (6)
V (Å^3)	2001.78 (4)	2191.5 (2)	948.87 (6)	888.66 (4)	909.01 (12)
Z	4	4	2	2	2
R_{int}	0.023	0.089	0.028	0.038	0.061
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.054, 0.172, 1.05	0.054, 0.169, 1.06	0.046, 0.148, 1.07	0.038, 0.108, 1.03	0.071, 0.232, 1.03

Conclusion

We have shown that dialkoxy-2-phenylchroman-4-ones (1) and (2) react readily with diamines to produce racemic mixtures of chromenoquinoxalines (3–10). While reactions with 1 proceeded without the aid of the transition metal catalyst, compound 2 necessitated its use, likely due to the methoxy groups' inability to dissociate to allow for autoxidation. In either case, the reaction mechanism involves the formation of a dione intermediate that undergoes a double imination reaction to close the quinoxaline ring system. The reactions with asymmetric *o*-phenylenediamines produced two regioisomers that are dominated by the relative reactivity of the amine and carbonyl groups toward nucleophilic acyl addition reactions. Regiochemical control appears to increase with the relative electron-withdrawing potential of the substituents, whereby highly deactivated diamine groups led to the best regiochemical outcomes. In the future, we will further examine this chemistry with the chromane dihydrates (3,3-dihydroxy-2-alkoxy-2-phenylchroman-4-ones) to gauge the scope of this reaction.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Brandon Quillian reports equipment, drugs, or supplies were provided by National Science Foundation. Brandon Quillian reports a relationship with the National Science Foundation that includes: consulting or advisory and funding grants.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Representative NMR and IR data spectra are available. Crystallographic data for structures **6-10** are deposited in the Cambridge Crystallographic Data Centre: CCDC-2283008 (**6**), CCDC-2283005 (**7**), CCDC-2283007 (**8**), CCDC-2283247 (**9**), and CCDC-2283009 (**10**), These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre CB2 1EZ, UK. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154820.

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