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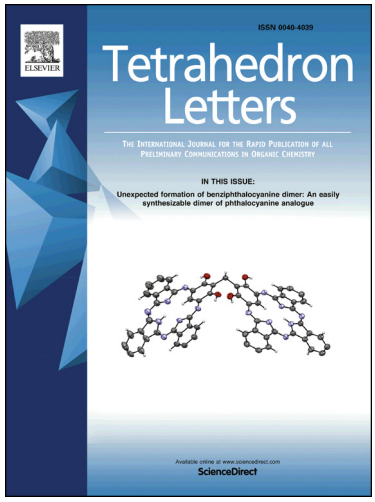

Reduction of chromano–piperidine-fused isoxazolidines: Tandem intramolecular rearrangements leading to 2-(methylamino)-4-oxo-*N*-phenyl-*N*-propyl-4*H*-chromene-3-carboxamide

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Graphical Abstract

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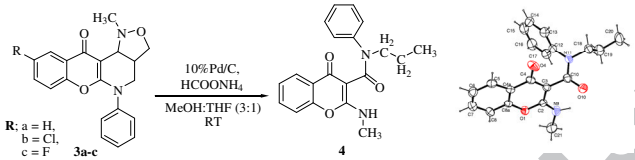

ORTEP view of compound **4**

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Reduction of chromano–piperidine-fused isoxazolidines: Tandem intramolecular rearrangements leading to 2-(methylamino)-4-oxo-*N*-phenyl-*N*-propyl-4*H*-chromene-3-carboxamide

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ABSTRACT

Reductive ring opening of isoxazolidine moiety of chromano–piperidine-fused isoxazolidines (**3a-c**) with $HCOONH_4$ and 10% Pd/C in a mixture of solvents (THF/MeOH) at ambient temperature, affords novel 2-(methylamino)-4-oxo-*N*-phenyl-*N*-propyl-4*H*-chromene-3-carboxamide (**4**), which is apparently, derived from reductive N-O bond cleavage followed by tandem intramolecular rearrangements. Plausible mechanistic rationale for the formation of compound **4** is proffered.

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Chromones and flavones are ubiquitous structures that occur in a variety of natural products and synthetic compounds exhibiting various important pharmacological activities such as anti-inflammatory/analgesic,[1a] antitumoral,[1b] P-glycoprotein binding (to overcome multidrug resistance),[1c] neuroprotective,[1d] HIV-inhibitory,[1e] antioxidant, [1f] antifungal and antimicrobial.[1g] Inhibition of enzymes such as oxidoreductases,[2a] kinases,[2b] tyrosinases,[2c] and cyclooxygenases[2d] have also been reported for chromone based molecules. Additionally, 3-formylchromone possessing three electrophilic centers,[2d] is a highly reactive and versatile synthon for constructing various heterocycles; consequently, chromone chemistry continues to draw considerable interest of synthetic organic and medicinal chemists. On the other hand, it is well established that highly regio- and stereoselective 1,3-dipolar cycloaddition reactions of nitrones with olefins is a very useful methodology for the formation of isoxazolidines,[3] which are present in different bioactive compounds and have been reported as precursors for the asymmetric synthesis of natural products;[4] isoxazolidines are also important precursors to β-amino acids, β-lactams, 1,3-amino alcohols, pyrrolidinones, and can be further transformed to obtain variety of heterocycles such as modified nucleosides, carbohydrate mimics, and diverse range of alkaloids.[5]

We have recently reported the synthesis of peptidomimetic constrained $\beta^{2,3,3}$–amino alcohols,[6a] indole based natural product analogs and peptidomimetic precursors[6b,6c] via reductive cleavage of N-O bond of substituted isoxazolidine moiety.

Inspired by this development[6] and in continuation of our work to develop new synthetic pathways for constructing heterocyclic scaffolds possessing chromone moiety,[7] it was decided to attempt the reductive cleavage of N-O bond of chromano–piperidine-fused isoxazolidine moiety, which was anticipated to provide novel chromone based peptidomimetic precursor, however, the reaction followed a more complex pattern with tandem rearrangements providing substituted chromone-3-(*N*-phenyl)carboxamide (**4**).

Initially, chromano–piperidine-fused isoxazolidines (**3a-c**) were prepared as reported earlier,[7h] by mixing respective aldehydes (**2a–c**), with *N*-methylhydroxylamine in dichloromethane at an ice-cold temperature (0^oC-4^oC) with continuous stirring 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 [**A**] led to chromano–piperidine-fused isoxazolidines **3a–c** in very good yields and the results are summarized in **Scheme-1** and **Table-1**. Column chromatographic resolution (silica gel 60–120 mesh, eluant hexane/ethylacetate; as gradient mixture) of the crude product afforded the cycloadducts **3a–c**, which were characterized by rigorous spectroscopic analysis (^{1}H NMR, ^{13}C NMR and HRMS), including a comparison of the spectroscopic data with that of related compounds.[8]

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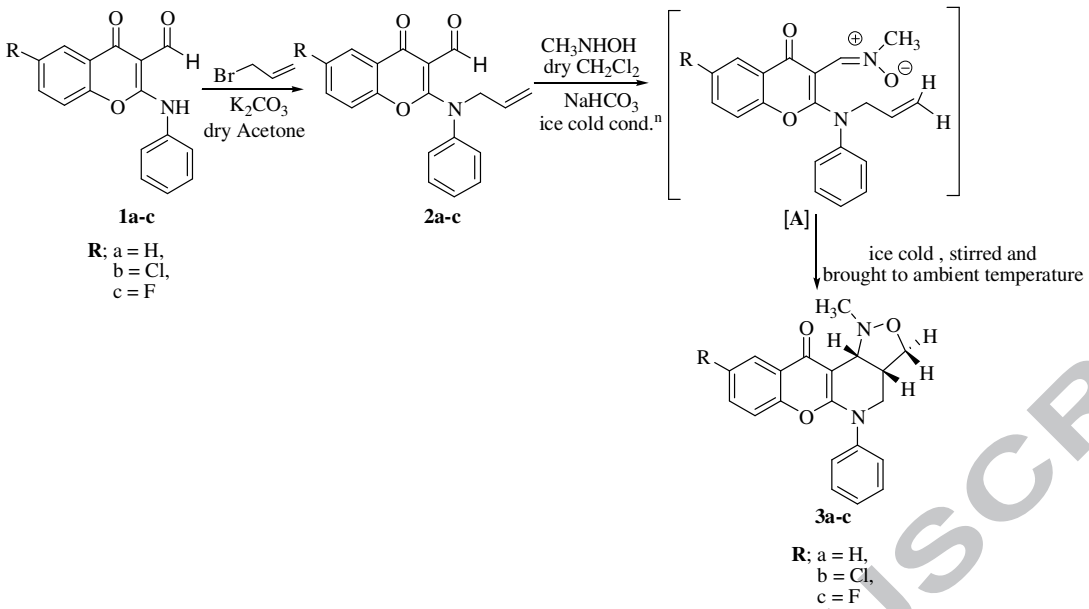
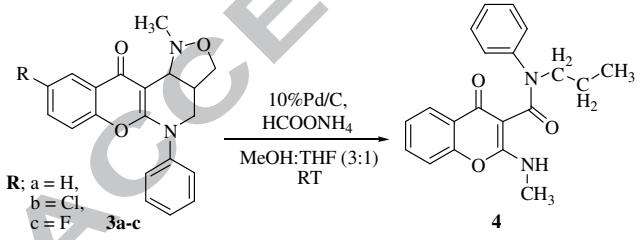


Scheme-1: Synthesis of chromano-piperidine fused isoxazolidine (**3a-c**)

Table 1: Reaction time and Yields (%) of products **3a-c**

Serial No.	R	Reaction time (h)	Yield (%) of various products
1	**3a**; R = -H	4	80%
2	**3b**; R = -Cl	4	78%
3	**3c**; R = -F	4	75%

In the next step, reductive ring opening of obtained fused-isoxazolidines (**3a-c**) via cleavage of N-O bond was attempted under mild reductive conditions as employed earlier.[6a] Thus, compounds **3a-c** were subjected to reduction with $HCOONH_4$ and 10% Pd/C (10 equiv.) in a mixture of solvents (THF/MeOH) at room temperature, till the completion of reaction as monitored by Tlc. The reaction was very neat and clean as monitored by Tlc, affording a single product **4**[6d] in good yield (**Scheme 2** and **Table 2**). The final products were purified by column chromatography and characterized spectroscopically (^{1}H NMR, ^{13}C NMR, 2D-NMR and HRMS).



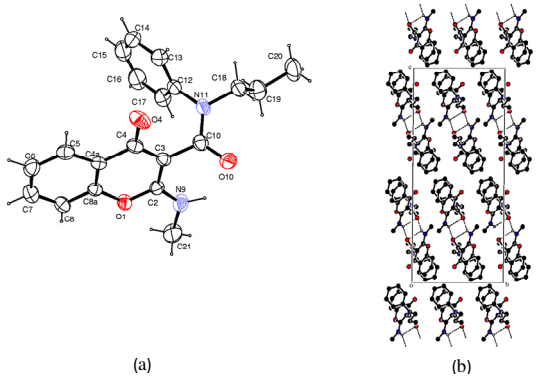
Scheme 2: Transformation of fused-isoxazolidines (**3a-c**)

Table 2: Reaction times and Yields (%) of product **4**

Entry	Reducing agent	Reaction times (h)	Yield (%)* of various products
3a	10% Pd/C-$HCOONH_4$ (10 equiv.)	2	**4** (80%)
3b	10% Pd/C-$HCOONH_4$ (10 equiv.)	3	**4** (72%)
3c	10% Pd/C-$HCOONH_4$ (10 equiv.)	3	**4** (65%)

* Based on isolated pure products.

The ^{1}H NMR spectrum of compound **4** showed signals at δ 3.12 ppm (d, 3H, J = 5.0 Hz) and δ 7.84 ppm (m, 1H, exchangeable with D_2O) ascribed to NH-CH_3 and N*H* protons, respectively, which confirms the presence of NH-CH_3 moiety. Resonances at δ 3.83 (m, 2H, CH_2), δ 1.62 (q, 2H, J = 7.5Hz, CH_2), and δ 0.92 (t, 3H, J = 7.5 Hz, CH_3) were indicative of the presence of propyl chain, and the structure was also corroborated by ^{13}C NMR spectral assignments. Overall ^{1}H and ^{13}C NMR spectral assignments, aided by ^{1}H-^{13}C hetero-COSY experiments, corroborated the assigned structure. Finally, the structure of compound **4** was established by X-ray crystallography (**Figure-1**).[9]



(a) (b)

Figure-1: (**a**) ORTEP view of compound **4**; (**b**) Packing arrangement of molecules (**4**) viewed down the a-axis

Thus, it was found that contrary to anticipated amino alcohol product, the attempted reductive ring opening reaction of **3a-c**, afforded 2-(methylamino)-4-oxo-*N*-phenyl-*N*-propyl-4*H*-chromene-3-carboxamide (**4**, **Scheme-2**), derived from reductive cleavage of N-O bond of isoxazolidine moiety, followed by subsequent tandem ring opening-recyclization rearrangements (**Scheme-3**) with concomitant reductive loss of halogens[6a] in the case of **3b**,**c**.

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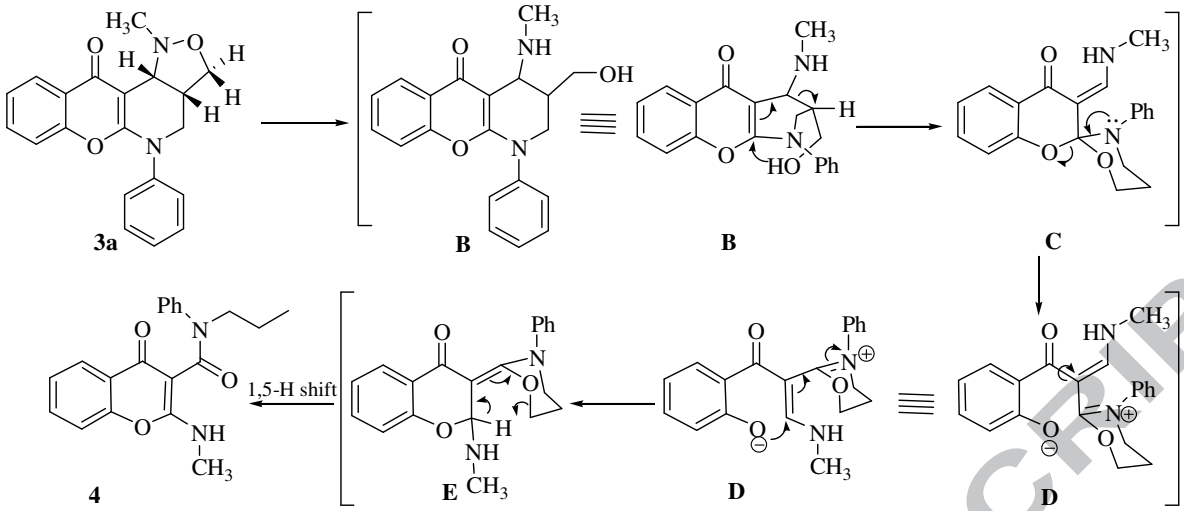

Scheme-3: Plausible mechanistic transformation of **3a**

Mechanistically, the formation of compound **4** can be rationalized in terms of initial reductive cleavage of N-O bond of isoxazolidine moiety **B**, which rearranges to form a 1,3-oxazinane ring intermediate **C** along with concomitant pyrone ring opening leading to intermediate **D**. The rotation around C-C single bond in **D** followed by recyclization to yield **E** and the latter after a 1,5-H shift leads to formation of compound **4**. Such opening of the chromone ring via nucleophilic attack at C2-position of pyrone moiety and subsequent recyclization has precedents,[10] and earlier, we had also reported[7f,7g,11a-b] a similar intramolecular reorganization in some chromone derivatives. Literature also reveals a number of examples for Pd-catalyzed C-H activation/C-O cyclization reactions directed by a proximate hydroxyl group, 1,5-H shift, 1,3-H and [3,3] sigmatropic rearrangements.[11c-j] Apparently, Pd has played significant role in the observed reorganizations and sigmatropic H-shifts, leading to the formation of 2-(methylamino)-4-oxo-*N*-phenyl-*N*-propyl-4H-chromene-3-carboxamide (**4**).

In conclusion, we report that the attempted reductive cleavage of N-O bond of obtained chromano–piperidine-fused isoxazolidines (**3a-c**) with ammonium formate in the presence of 10% Pd/C followed a novel pathway of reductive *N-O* bond cleavage–intramolecular tandem rearrangements providing a concise access to chromone-3-(*N*-phenyl)carboxamide analog (**4**). As it is well established that substituted chromones bearing the carboxamide moiety at position 3 of the pyrone nucleus are selective MAO-B inhibitors with IC_{50} values in the micro or nanomolar range, and the nature and position of the substituents of the aromatic ring at the carboxamide nitrogen modulates affinity and selectivity for the hMAO-B,[12] therefore, the inhibition potential and mechanism of compound **4** at molecular levels (*in vitro* and *in vivo*) to act as monoamine oxidase-B (MAO-B) inhibitor is in progress and the results will be reported in due course.

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Conflict of interest

The authors declare they have no conflict of interests.

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solution and stirred the mixture for 2-3 hours (monitored by Tlc). The reaction mixture was filtered and the filtrate extracted with ether (30 ml). The aqueous phase was basified with aqueous sodium hydroxide (10%) and extracted with dichloromethane (3x 50 ml). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and vacuum. Purification by column chromatography (70% ethyl acetate in hexane) afforded compound **4**; $\mathbf{R}_f$ 0.30 ($CHCl_3$/EtOAc 7:3) as colourless solid, yield (65-80%), **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.85-7.82 (m, 2H, Ar-H and NH), 7.47-7.44 (m, 1H, Ar-H), 7.24-7.18 (m, 6H, Ar-Hs), 7.10-7.07 (m, 1H, Ar-H), 3.83(m, 2H, CH_2), 3.12 (d, 3H, J = 5.0 Hz, NH-CH_3), 1.62 (q, 2H, J = 7.5Hz, CH_2), 0.92 (t, 3H, J = 7.5Hz, CH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 170.42, 168.13, 164.40, 152.36, 142.96, 131.85, 128.17, 126.85, 126.29, 125.94, 124.78, 123.17, 115.93, 95.59, 52.09, 27.77, 21.27, 11.35; **HRMS** (ESI, m/z): calculated for $C_{20}H_{20}N_2O_3$ [M]+, 336.1474, found 336.1469.

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Highlights

- Reductive cleavage of N-O bond of isoxazolidines (**3a-c**) has been attempted.
- Reductive N-O bond cleavage followed by intra-molecular tandem rearrangements.
- Providing chromene-3-carboxamide (**4**) having potential medicinal significance.
- Plausible mechanistic rationale for the formation of compound **4** is proffered.

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