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In-situ mechanochemical synthesis of nitrones followed by 1,3-dipolar cycloaddition: a catalyst-free, "green" route to *cis*-fused chromano[4,3-*c*]isoxazoles

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An efficient and catalyst-free method for the synthesis of *cis*-fused chromano[4,3-*c*]isoxazoles via intramolecular 1,3-dipolar nitrone cycloaddition involving hand-grinding in a mortar–pestle has been developed. The mechanochemical agitation was sufficient for dehydrative nitrone formation by condensation of various *O*-allyl salicylaldehyde derivatives and alkyl / aryl hydroxylamines. The corresponding nitrones undergo intramolecular 1,3-dipolar cycloaddition leading to regioselective formation of *cis*-fused tetrahydrochromeno[4,3-*c*]isoxazole derivatives in high yields. The key features of this new method are cleaner reaction profiles, catalyst-free condition, high yields, and short reaction times.

Introduction

Isoxazolidines,[1] an important class of nitrogen containing five-membered heterocycles, is ubiquitous structural motif of a wide spectrum of organic molecules of both natural origin and synthetic background, many of which are pharmaceutically important.[2] 1,3-Dipolar nitrone cycloaddition is the most facile way for the construction of these heterocycles as documented by different research groups.[3] In particular, intramolecular nitrone-olefin cycloadditions are often employed to achieve structurally more complex bi- or tri-cyclic isoxazolidines of biological significance and also to synthesize key intermediates of several natural products.[4] Notably, fused isoxazoles / isoxazolidines with chromano moiety are known to possess biomedical properties (Fig. 1) such as antidepressant, antipsychotic and antianxiolytic activities.[5] Due to the labile nature of N-O bond chromanoisoxazoles are used as synthetic precursors for the construction of pharmaceutically important amino alcohols.[6] Surprisingly, however, not many methods are available for the construction of these pharmacologically important heterocyclic systems.[6a–c,7,8] Moreover, most of the existing methods are based on conventional synthetic protocols that use hazardous reagents, toxic solvents and / or relatively harsh reaction conditions and are facilitated by the presence of a catalyst.[6a–c,7] Although few eco-friendly methods for chromano-isoxazoles are available,[8] such a method can be turned more economical by avoiding use of catalysts, additional reagents and solvents.

Use of toxic chemicals and solvents for chemical transformations is a serious environmental concern for last few decades. At present, most of the chemical processes at an industrial scale use toxic organic solvents for various transformations which account for 80–90% of the waste generated in a typical pharmaceutical/fine chemical operational process.[9] To counter this growing environmental problem, significant research efforts have been focused on solvent-free reactions,[10] which are often associated with several other advantages such as faster reaction rates, lower energy consumption and easy separation giving rise to products in higher yields and with higher purities. One common technique employed in solvent-free reactions is mechanical grinding,[11] which has gradually become a powerful tool in the paradigm of synthetic organic chemistry.[12] In a typical mechanochemical process, reactions are initiated and progressed under frictional force provided either by grinding in a mortar-pestle or by milling in a ball-mill. Recently, mechanosynthesis by "ball milling" has emerged as effective technique for various organic transformations[13,14] including aldol condensation,[14a,b] Michael additions,[15c,d] Knoevenagel condensation,[14e] Morita–Baylis–Hillman reactions,[14f] cross-coupling reactions,[14h-k] click reactions[14l,m] etc. On the other hand, manual grinding[15] with a mortar and pestle is mostly limited to condensation reactions[16] including Schiff's base formation,[16a-c] oxime formation,[16d] Knoevenagel condensation,[16e] with occasional exceptions.[17] However, this a very useful method at laboratory scale due to simple and hazardless experimental set-up and is found

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to be equally effective for the construction of heterocyclic compounds of biological interest in last few years.[18] In this purview, we envisaged, development of an environment friendly and a catalyst-free mechanochemical route to chromano-isoxazoles is a worthy pursuit. As per our current research focus of exploring the scope of hand-grinding techniques for organic transformation,[18b] herein, we report a one-pot process for nitrone formation followed by its intarmolecular cycloaddition to afford a variety of cis-fused tetrahydrochromeno [4,3-*c*] isoxazole derivatives in high yields.

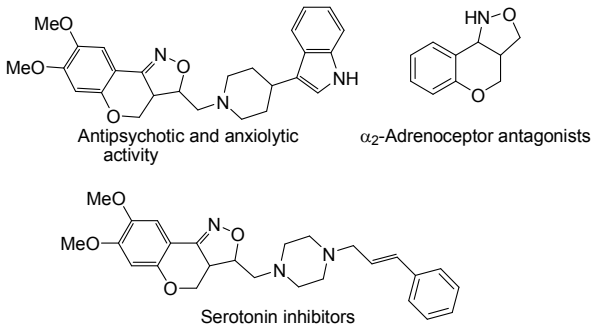
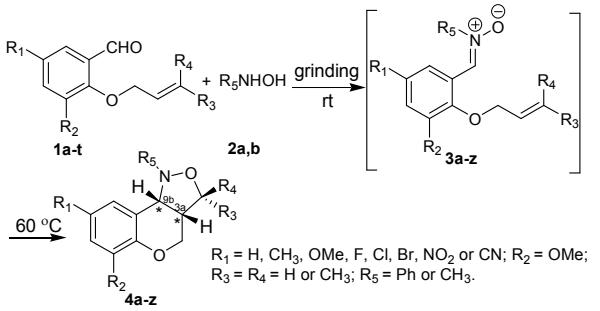


Fig. 1. Chemical structures of few bioactive chromano[4,3-*c*]isoxazoles.

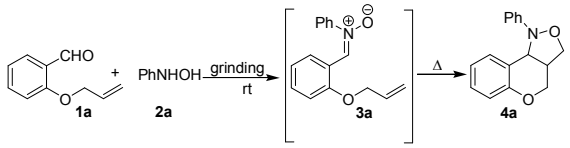
Results and discussion



Scheme 1. Mechanochemical route to *cis*-fused chromano[4,3-*c*]isoxazoles.

At first, we focused our attention on optimizing the reaction conditions. Thus, a model reaction was conducted between equimolar mixture of *O*-allyl salicylaldehyde (**1a**) and phenylhydroxylamine (**2a**) in an Agate mortar by manual grinding at room temperature to examine whether grinding under neat condition is useful or liquid assisted grinding (LAG)[19] is more effective. The first reaction was conducted in neat condition. The reaction produced a viscous liquid after 5 min of gentle grinding. Although out of the two reactants *N*-phenylhydroxylamine is solid (m.p. 79-80 °C) the reaction mixture forms a melt phase presumably because of the transient heat generated during frictional force. The formation of nitrone was monitored by taking

Table 1. Optimization of the reaction condition for chromano[4,3-*c*]isoxazoles



Entry	Solvent	Temp (°C)	Time (h)[a]	(%) **3a**[b]	(%) **4a**[b]
1	Neat	Rt	0.25	100	Nil
			2	70	20
			12	Nil	86
		60	1.5	Nil	84
2	$CHCl_3$	Rt	0.25	100	Nil
			2	57	26
3	EtOH	Rt	0.17	100	Nil
			2	70	18
4	CH_3CN	Rt	0.34	100	Nil
			2	64	25

[a]Reactions were ground for 10-120 min followed by heating, [b]Ratio of **3** and **4** was obtained from ^{1}H NMR of reaction mixture.

TLC after every 5 min. It was observed that grinding for 15 min in neat condition is sufficient for complete conversion of aldehyde (**1a**) and hydroxylamine (**2a**) to corresponding nitrone (**3a**). It is noteworthy to mention that rate of the reaction is dependent on the force applied for grinding the reaction mixture. As a matter of fact, fast and relentless grinding of the same reaction led to nitrone (**3a**) formation with about two third reduction in the reaction time (10 min). Since the nitrone formation is relatively fast even by gentle grinding the remaining reactions were carried out by gentle grinding only. However, intramolecular cycloaddition of nitrone to obtain chromano isooxazoles was bit slower. Only 20% of product (**4a**) was obtained even after 2 h of grinding of the intermediate nitrone (Table 1, entry 1). Cycloaddition was complete only after standing the mixture for 12 h at room temperature with intermittent grinding (Table 1, entry 1). However, gentle heating of the reaction mixture at 60 °C was helpful in almost 10 fold reduction of the reaction time. On the other hand, LAG effect was studied using three polar solvents viz. chloroform, ethanol and acetonitrile (0.5 mL per 1 mmol of substrate) in which all the starting materials, intermediates and products are freely soluble. Although nitrone formation was as fast as the neat reaction, there was practically no difference in the rate of conversion of nitrone (**3a**) into the chromano-isooxazole (**4a**) in each case of LAG. In addition, solvent got evaporated after sometimes and time to time addition of solvent (0.5 mL per 1 mmol of substrate each time) was required to continue LAG. Therefore, "neat grinding" was preferred over LAG for the synthesis of tetrahydrochromeno[4,3-*c*]isoxazole derivatives unless all the reactants are solid; in such cases, little amount of EtOH

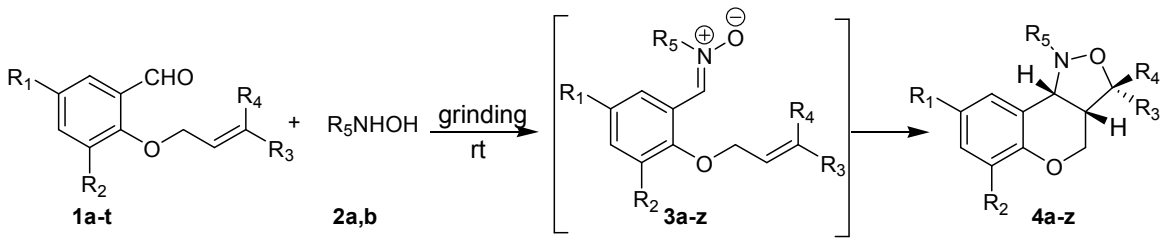
or 50% EtOH-H_2O was used to form a paste which was ground further. It is noteworthy to mention that the reaction undergoes spontaneously without addition of any catalyst or additive making this a highly atom-efficient method for the synthesis of *cis*-fused chromano isooxazoles. In a separate study, the necessity of grinding for smooth formation of intermediate nitrone (**3**) was established by carrying out the same reaction in conventional ways (see ESI for details). It was observed that nitrone formation is very sluggish in solution phase. At the same time, just mixing the reactants under neat condition without "grinding" is also not very effective. The nitrone formation was not complete even after 48 h. The formation of intermediate nitrone (**3a**) and the cyclized product (**4a**) was monitored by recording IR spectra of the reaction mixture at regular interval (see ESI for details). It was observed that the characteristic stretching bands of starting materials like carbonyl of aromatic aldehyde at 1682 cm^{-1} and phenylhydroxylamine O-H and N-H bands at 3240 cm^{-1} and 3118 cm^{-1} almost disappeared after 10 min of hand grinding and a new peak at 1545 cm^{-1} (presumably, C=N stretching band of intermediate nitrone) appeared in the IR spectrum. The same band significantly diminished after gentle heating of the reaction mixture for 1.5 h indicating conversion of intermediate nitrone to chromano isooxazoles.

To test the generality of this method, the phenolic –OH group of several salicylaldehyde derivatives were first alkylated with allyl group or prenyl group adopting reported procedure.[20] Next, a series of *O*-allyl/prenyl derivatives of salicylaldehyde (**1a-t**) were ground with *N*-substituted hydroxylamines (**2a,b**) in an Agate mortar and pestle for several minutes to afford corresponding nitrones (Table 2). Once nitrone formation was complete (as revealed by TLC), the reaction mixture was heated on a sand bath at 60 °C for several hours to afford racemic *cis*-fused 1-aryl-1,3a,4,9b-tetrahydro-3H-chromano[4,3-*c*]isoxazoles (**4a-z,aa**) in excellent yields via *in situ* intramolecular cycloaddition in a stereoselective manner (Table 2). It is worthy to mention that all the intermediate nitrones (**3**) underwent complete conversion into chromano[4,3-*c*]isoxazoles (**4**) and the crude products were found to be sufficiently pure. Most of the crude products were purified by recrystallization from a mixture of ethyl acetate and petroleum ether. Only few of the final products, which were obtained as viscous liquid, were purified by passing them through a short bed of silica gel. It is noteworthy to mention that *N*-methylhydroxylamine (**2b**) was generated from corresponding hydrochloride salt *in situ* by addition of sodium carbonate to the reaction mixture. For these reactions few drops of 50% EtOH-water was added at the beginning and the resulting paste was ground thoroughly with portionwise addition of Na_2CO_3. It was observed that the nitrone formation was much faster in the presence of little amount of solvent than at neat condition. Most likely, EtOH-water mixture dissolves a part of $CH_3NHOH.HCl$ and Na_2CO_3 making release of *N*-methylhydroxylamine easy. The products derived from *N*-methylhydroxylamine (**2b**) were taken in ethyl acetate and washed with water to remove sodium carbonate if any and then purified either by crystallization or by column chromatography. All the chromano[4,3-*c*]isoxazoles were characterized by ^1H NMR, ^{13}C NMR, ESI-MS and CHN analysis. The spectra of known compounds were in well agreement with the reported values.[7b,c,8b] Notably, Jadav et al.[7b] and we[8b] separately demonstrated that 1,3-dipolar cycloaddition of nitrones derived from *O*-allyl salicylaldehyde derivatives preferably form chromano[4,3-*c*]isoxazoles with *cis*-stereochemistry at the junction of six- and five-membered rings. The expected *cis* stereochemistry was verified by comparing the coupling constant ($J_{H3a-H9b}$) of ring junction protons of the compounds synthesized using the current method with chromano[4,3-*c*]isoxazoles that are previously reported by our group.[8b] A relatively small coupling constant (see Table S2 of ESI) between ring junction protons of all the chromano isoxazoles clearly indicate that the five- and six-membered rings adopt a *cis*-fused twisted structure.[7b,8b] In general, the method worked well with both aliphatic and aromatic hydroxylamines and had been applied to a variety of *O*-allyl salicylaldehydes with same efficacy. Noticeably, substituents in the aromatic ring of the *O*-allyl salicylaldehyde derivatives did not pose any significant effect on the yield of chromano[4,3-*c*]isoxazoles. However, yields of chromano[4,3-*c*]isoxazoles derived from *N*-methylhydroxylamine (**2b**) (Table 2, entry 7, 19, 23 etc.) were slightly less than that of *N*-phenylhydroxylamine (**2a**) (Table 2, entry 5, 17, 21 etc.). It was also observed that the nitrone formation for a particular *O*-allyl salicylaldehyde derivative was little faster with *N*-phenylhydroxylamine (**2a**) (Table 2, entry 1, 2, 5, 18 etc.) as compared to *N*-methylhydroxylamine (**2b**) (Table 2, entry 3, 4, 7, 19 etc.). Moreover, the intramolecular cycloaddition was generally faster for nitrones derived from *N*-phenylhydroxylamine (**2a**) (Table 2, entry 1, 5, 20, 21 etc.) than that of *N*-methylhydroxylamine (**2b**) (Table 2, entry 3, 7, 19 etc.). Presumably, the electron donation ability of the methyl group makes the 1,3-dipolarophile less reactive, whereas, phenyl group acts as an electron pulling unit to make nitrone more reactive. Again, doubly substituted allyl moiety (i.e. prenyl group) although did not influence the yield of **4** but slowed down the reaction due to steric reason (Table 2, entry 2, 4, 6, 18 etc.).

Conclusion

In conclusion, we have developed a catalyst-free method for the synthesis of *cis*-fused chromano[4,3-*c*]isoxazoles via intramolecular 1,3-dipolar nitrone cycloaddition reaction involving hand-grinding in mortar-pestle. A series of *O*-allyl salicylaldehyde derivatives were successfully condensed with alkyl / aryl hydroxylamines to produce corresponding chromano[4,3-*c*]isoxazoles in high yields. Most of the

Table 2. Mechanochemical synthesis of chromano[4,3-*c*]isoxazoles



Entry	Salicyaldehyde derivatives	R_5	Time (min)[a] Nitrone	Time (h)[b] Product	Product	% Yield[c]	Ref.
1	**1a**: $R_1 = R_2 = R_3 = R_4 = H$	Ph	15	1.5	**4a**	86	8(b)
2	**1b**: $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$	Ph	15	3.0	**4b**	79	8(b),7(b)
3	**1a**: $R_1 = R_2 = R_3 = R_4 = H$	CH_3	20	3.0	**4c**	71	7(c)
4	**1b**: $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$	CH_3	20	4.0	**4d**	70	–
5	**1c**: $R_1 = Br$, $R_2 = R_3 = R_4 = H$	Ph	15	2.0	**4e**	80	8(b)
6	**1d**: $R_1 = Br$, $R_2 = H$, $R_3 = R_4 = CH_3$	Ph	15	2.5	**4f**	87	8(b),7(b)
7	**1c**: $R_1 = Br$, $R_2 = R_2 = R_3 = H$	CH_3	20	3.0	**4g**	68	–
8	**1e**: $R_1 = OMe$, $R_2 = R_3 = R_4 = H$	Ph	30	4.0	**4h**	88	–
9	**1f**: $R_1 = OMe$, $R_2 = H$, $R_3 = R_4 = CH_3$	Ph	30	4.0	**4i**	90	–
10	**1g**: $R_1 =$ H, $R_2 = OMe$, $R_3 = R_4 = H$	Ph	30	3.0	**4j**	89	8(b)
11	**1h**: $R_1 = H$, $R_2 = OMe$, $R_3 = R_4 = CH_3$	Ph	30	4.5	**4k**	91	8(b),7(b)
12	**1g**: $R_1 =$ H, $R_2 = OMe$, $R_3 = R_4 = H$,	CH_3	40	2.5	**4l**	70	–
13	**1i**: $R_1 = Cl$, $R_2 = R_3 = R_4 = H$	Ph	10	2.5	**4m**	83	–
14	**1j**: $R_1 = Cl$, $R_2 = H$, $R_3 = R_4 = CH_3$	Ph	20	4.0	**4n**	88	–
15	**1k**: $R_1 = CH_3$,, $R_2 = R_3 = R_4 = H$	Ph	15	2.0	**4o**	82	–
16	**1l**: $R_1 = CH_3$, $R_2 = H$, $R_3 = R_4 = CH_3$	Ph	15	4.0	**4p**	87	–
17	**1m**: $R_1 = F$, $R_2 = R_3 = R_4 = H$	Ph	10	1.5	**4q**	84	–
18	**1n**: $R_1 = F$, $R_2 = H$, $R_3 = R_4 = CH_3$	Ph	10	3.0	**4r**	87	–
19	**1m**: $R_1 = F$, $R_2 = R_3 = R_4 = H$	CH_3	15	3.0	**4s**	69	–
20	**1o**: $R_1 = NO_2$, $R_2 = R_3 = R_4 = H$	Ph	10	1.0	**4t**	84	8(b)
21	**1q**: $R_1 = CN$, $R_2 = R_3 = R_4 = H$	Ph	10	1.0	**4u**	83	–
22	**1r**: $R_1 = CN$,$R_2 = H$, $R_3 = R_4 = CH_3$	Ph	15	1.5	**4v**	85	–
23	**1q**: $R_1 = CN$, $R_2 = R_3 = R_4 = H$	CH_3	20	3.0	**4w**	63	–
24	**1s**: 2-(allyloxy)naphthalene-1-carbaldehyde	Ph	20	1.0	**4x**	91	–
25	**1t**: 2-(3-methylbut-2-enyloxy)naphthalene-1-carbaldehyde	Ph	30	1.0	**4y**	94	–
26	**1s**: 2-(allyloxy)naphthalene-1-carbaldehyde	CH_3	30	2.0	**4z**	79	–

[a]Reactions were ground for 10-40 minutes for intermediate nitrone formation, [b]the reaction mixtures were heated on a sand bath for several hours, [c]all yields refer to isolated product, characterised by ^{1}H-NMR,^{13}C-NMR, ESI-MS.

reactions were conducted under solvent-free condition and in few cases, minimum volume of ethanol-water was used for proper mixing of reactants. The approach is "greener" and more advantageous over existing methods because of drastic reduction in the use of organic solvents accompanied with clean reaction profile, high yields, and short reaction times.

Experimental

General Information

All the reagents were procured from commercial sources and were used without further purification. All solvents were obtained from local suppliers and were of research grade. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance (300 or 400 MHz, respectively) with TMS or

solvent peak as internal standard. The chemical shifts are reported in parts per million (ppm) units. Mass spectra were recorded on Agilent 6220 Accurate-Mass TOF LC-MS using ESI as the ion source. IR spectra were recorded in KBr pellets with IR Affinity 1, Shimadzu. CHN data were recorded using Vario MICRO elementar CHNS analyzer. Melting points of the compounds were determined using Melting Point Apparatus, Bio Techniques, India. The reactions were monitored by thin layer chromatography (TLC) carried out on 0.25-mm silica gel on aluminium plates (60F-254) using UV light (254 or 365 nm). Column chromatography was performed on silica gel (60–120 mesh, Merck).

General procedure for chromano[4,3-*c*]isoxazoles: synthesis of 4h.

2-(Allyloxy)-5-methoxybenzaldehyde (**1e**, 192 mg, 1 mmol) and phenylhydroxylamine (**2a**, 115 mg, 1.05 mmol) was taken in a Agate mortar and the mixture was ground thoroughly by a pestle for 30 min. The complete conversion of starting materials to nitrone (**3h**) was monitored by TLC. Next, the mortar was placed in a sand bath and the reaction mixture was heated at 60 °C for 4 h. The crude product was recrystallized from 20% EtOAc in petroleum ether to afford corresponding chromeno[4,3-*c*]isoxazole, **4h** in pure form (248 mg, 88%).

Selected spectral data of new entries

3,3a,4,9b-Tetrahydro-8-methoxy-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4h): Light brown solid, m.p.: 113-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.00-3.06 (m, 1H), 3.78 (s, 3H), 4.03-4.10 (m, 2H), 4.22 (dd, J_1 = 3.6 Hz, J_2 = 11.4 Hz, 1H), 4.29 (t, *J* = 8.4 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 6.80-6.88 (m, 2H), 6.99 (d, *J* = 3.2 Hz, 1H), 7.08 (t, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.35-7.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 41.0, 55.7, 63.6, 65.5, 68.1, 113.6, 115.4, 115.9, 117.9, 122.7, 122.8, 129.2, 149.9, 150.9, 154.4; IR (KBr): 3060, 2883, 1594, 1492, 1252, 1214, 1091 cm^{-1}; ESI-MS (*m/z*): 306 $[M + 23]^+$; Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.94; H, 6.11; N, 4.89.

3,3a,4,9b-Tetrahydro-8-methoxy-3,3-dimethyl-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4i): Light brown solid, m.p.: 66-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 3H), 1.42 (s, 3H), 2.70-2.75 (m, 1H), 3.65 (s, 3H), 4.11 (dd, J_1 = 9.6 Hz, J_2 = 11.2 Hz, 1H), 4.39 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 6.53 (d, *J* = 2.8 Hz, 1H), 6.80 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 7.09 (t, *J* = 7.0 Hz, 1H), 7.27-7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.3, 29.6, 48.8, 55.7, 62.8, 64.9, 82.7, 114.3, 116.0, 117.5, 117.7, 122.0, 123.3, 129.0, 149.3, 151.7, 153.9; IR (KBr): 3050, 2961, 1593, 1505, 1261, 1217, 1162, 1022 cm^{-1}; ESI-MS (*m/z*): 312 $[M + H]^+$; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.16; H, 6.87; N, 4.39.

8-Chloro-3,3a,4,9b-tetrahydro-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4m): Light yellow solid, m.p.: 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.04-3.10 (m, 1H), 4.05 (dd, J_1 = 5.6 Hz, J_2 = 8.0 Hz, 1H), 4.23 (dd, J_1 = 5.2 Hz, J_2 = 11.6 Hz, 1H), 4.26 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, 1H), 4.33 (t, *J* = 8.4 Hz, 1H), 4.84 (d, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.17-7.22 (m, 3H), 7.36-7.40 (m, 2H), 7.49 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.6, 63.2, 65.5, 68.2, 115.3, 118.7, 123.1, 124.0, 126.8, 129.2, 129.4, 129.9, 150.7, 154.6; IR (KBr): 3068, 2887, 1593, 1481, 1245, 1096, 1026 cm^{-1}; ESI-MS (*m/z*): 310 $[M + 23]^+$ (major peak, for ^{35}Cl), 312 $[M + 23]^+$ (minor peak, for ^{37}Cl); Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; Cl, 12.32; N, 4.87. Found: C, 66.89; H, 4.97; N, 4.81.

3,3a,4,9b-Tetrahydro-8-methyl-1-phenyl-1H-chromeno[4,3-*c*]isoxazole (4o): m.p.: 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 3H), 3.05-3.08 (m, 1H), 4.06-4.13 (m, 2H), 4.25 (dd, J_1 = 3.6 Hz, J_2 = 11.6 Hz, 1H), 4.33 (t, *J* = 8.4 Hz, 1H), 4.87 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 7.04-7.10 (m, 2H), 7.25 (dd, J_1 = 0.8 Hz, J_2 = 8.4 Hz, 2H), 7.32 (d, *J* = 1.6 Hz, 1H), 7.36-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.9, 41.1, 63.5, 65.4, 68.3, 115.4, 117.0, 122.1, 122.8, 129.3, 129.9, 130.4, 131.4, 151.2, 153.8; IR (KBr): 3033, 2875, 1593, 1491, 1296, 1219, 1088 cm^{-1}; ESI-MS (*m/z*): 268 $[M + H]^+$; Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.26; H, 6.49; N, 5.28.

3,3a,4,9b-Tetrahydro-3,3-dimethyl-1-phenyl-1H-chromeno[4,3-*c*]isoxazole-8-carbonitrile (4v): Light yellow solid, m.p.: 78-81 °C; 1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38 (s, 3H), 1.39 (s, 3H), 2.68-2.73 (m, 1H), 4.23 (dd, J_1 = 8.8 Hz, J_2 = 11.2 Hz, 1H), 4.42 (dd, J_1 = 4.8 Hz, J_2 = 11.6 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.12 (td, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.19-7.26 (m, 3H), 7.33-7.37 (m, 2H), 7.46 (dd, J_1 = 2.2 Hz, J_2 = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.5, 29.8, 47.8, 62.1, 65.0, 82.6, 104.6, 117.9, 118.2, 119.1, 122.4, 124.3, 129.2, 133.0, 135.5, 150.6, 158.8; IR (KBr): 3069, 2937, 2219, 1596, 1489, 1245, 1138, 1082 cm^{-1}; ESI-MS (*m/z*): 307 $[M + H]^+$; Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.60; H, 6.01; N, 9.07.

3,3a,4,9b-Tetrahydro-3,3-dimethyl-1-phenyl-1*H*-benzo[*f*]chromeno[4,3-*c*]isoxazole (4y): Yellow solid, m.p.: 130-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52 (s, 3H), 1.55 (s, 3H), 2.63-2.68 (m, 1H), 4.37 (dd, J_1 = 4.0 Hz, J_2 = 11.6 Hz, 1H), 4.50 (dd, J_1 = 6.8 Hz, J_2 = 11.6 Hz, 1H), 5.38 (d, *J* = 6.0 Hz, 1H), 7.01-7.06 (m, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.19-7.32 (m, 6H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.74-7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 23.7, 31.3, 47.5, 60.2, 63.9, 83.4, 111.0, 117.9, 118.6, 123.25, 123.28, 123.5, 126.6, 128.5, 129.0, 129.6, 130.5, 133.5, 150.5, 153.8; IR (KBr): 3053, 2965, 1594, 1488, 1228, 1116 cm^{-1}; ESI-MS (*m/z*): 332 $[M + H]^+$; Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.87; H, 6.36; N, 4.34.

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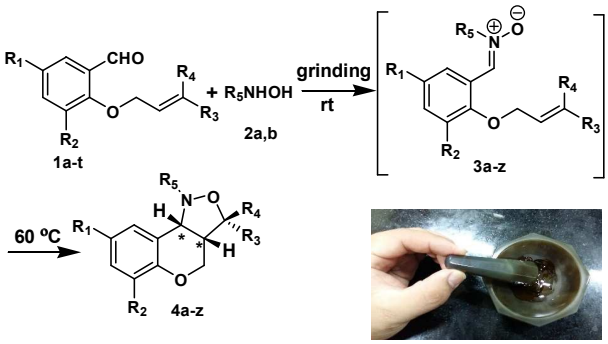

R_1 = H, CH_3, OMe, F, Cl, Br, NO_2 or CN;
R_2 = OMe; R_3 = R_4 = H or CH_3; R_5 = Ph or CH_3.
Total 26 entries, yield:

An efficient, catalyst free mechanochemical route to *cis*-fused chromano[4,3-*c*]isoxazoles has been developed via a simple mortar–pestle grinding method.