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$LiClO_4$- or LiOTf-accelerated 1,3-dipolar cycloaddition reactions: a facile synthesis of *cis*-fused chromano[4,3-*c*]isoxazoles

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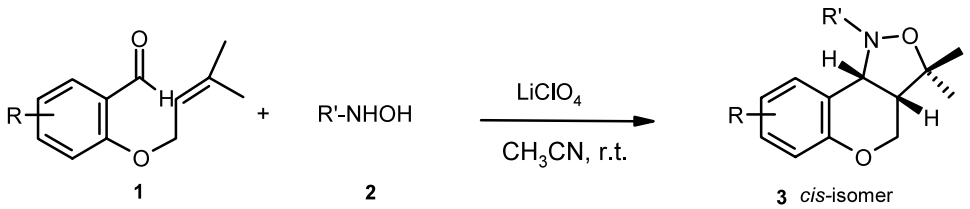
Abstract—Acetonitrile solutions of lithium perchlorate or lithium triflate are found to accelerate considerably the intramolecular 1,3-dipolar cycloaddition reactions of nitrones derived in situ from hydroxylamines and the *O*-prenyl derivatives of salicylaldehydes to afford enhanced rates and improved yields of tetrahydrochromano[4,3-*c*]isoxazole derivatives with high diastereoselectivity. The stereochemistry of the products has been assigned by using extensive NMR studies.

The construction of isoxazolidines by 1,3-dipolar cycloaddition reactions between nitrones and alkenes has been utilized by several groups in the total synthesis of alkaloids and many other nitrogen containing natural products.[1] Owing to the labile nature of the N–O bond under mild reducing conditions, isoxazolidines provide easy access to a variety of fascinating 1,3-difunctional aminoalcohols.[2] Particularly, the intramolecular nitrone cycloaddition reaction is one of the most powerful synthetic methods for the construction of fused bicyclic isoxazolidine derivatives.[3] In this context, several groups have reported the synthesis of isoxazolidines by inter- and intramolecular nitrone cycloadditions.[4] Despite their potential utility, many of these procedures involve the use of high temperatures, extended reaction times and in a few cases, the use of expensive reagents and can also give mixtures of *cis*- and *trans*-isomeric products. The development of novel reagents would widen the scope and utility of this process. In recent years, $LiClO_4$ in diethyl ether (LPDE) has evolved as a mild Lewis acid catalyst in promoting various organic transformations.[5] The lithium ion acts as a mild Lewis acid and shows enhanced rates and selectivity in cycloaddition reactions. Organic solutions of lithium perchlorate provide a convenient reaction medium to perform reactions under neutral conditions. Furthermore, lithium perchlorate in organic solutions is found to retain its activity even in the presence of amines.[6,7]

In this report, we wish to highlight our results on intramolecular nitrone cycloaddition reactions in the presence of $LiClO_4$ in acetonitrile to produce isoxazolidine derivatives in excellent yields (Scheme 1).



Scheme 1.

Keywords: lithium salts; nitrones; intramolecular cycloaddition; chromanoisoxazoles.
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For example, treatment of the *O*-prenyl derivative of salicylaldehyde with phenyl hydroxylamine in the presence of 10 mol% lithium perchlorate in acetonitrile afforded the corresponding tetrahydrochromano[4,3-*c*]isoxazole **3a** in 90% yield with *cis*-selectivity. The *cis*-stereochemistry of the products was assigned by detailed NMR studies. The five- and six-membered rings were shown to be *cis*-fused by the presence of an NOE between H_2 and H_3 and a coupling constant (J_{H2-H3}) of 6.9 Hz. The six-membered ring adopts a twisted structure, consistent with the following coupling constants: $J_{H1'-H2}=9.7$ Hz and $J_{H1-H2}=4.8$ Hz as well as the NOE's between H_1–$CH_3(6')$, H_1'–$CH_3(6')$, H_3–$CH_3(6)$ and H_2–$CH_3(6)$. The H_A of the phenyl and H_a of the *N*-phenyl both show an NOE with H_3 whilst H_a also shows an NOE with CH_3-6 (Fig. 1).

In a similar fashion, various hydroxylamines and *O*-prenyl derivatives of salicylaldehydes underwent smooth intramolecular cycloaddition to give the corresponding tetrahydrochromanoisoxazolines in excellent yields. In all cases, the reactions proceeded in acetonitrile at reflux and the products were obtained with *cis*-selectivity. The mild Lewis acidity of the lithium ion activates the nitrones to accelerate the reaction. However, condensation of (+)-citronellal with phenylhydroxylamine gave the corresponding cyclized product **4** in 92% yield with *trans*-selectivity (Scheme 2).

The *trans*-stereochemistry of **4k** was assigned by NOE experiments and from the coupling constants of the hydrogens at the ring junction. NOE cross peaks were observed between H_1–H_3, H_1–H_5, H_3–H_5, H_4'–H_6, H_2'–H_6 and H_2'–H_4'. This information suggested that the six-membered ring had a chair conformation. The H_1 proton gave a strong NOE with $CH_3(8)$ of the five-membered ring, the H_6 proton gave an NOE with $CH_3(9)$, and H_5' gave an NOE with $CH_3(8)$ and also with $CH_3(9)$. Therefore this information shows that the two rings are *trans*-fused and hence H_1 and H_6 are *trans* to one another. The H_A proton of the *N*-phenyl group showed an NOE with H_1, H_2 and $CH_3(8)$. In this chair conformation ω coupling is observed between H_2 and H_4, i.e. $J_{H2'-H4}=1.0$ Hz. A value of $J_{H1-H6}=11.1$ Hz indicates that the five- and six-membered rings are *trans* fused. The six-membered ring adopts a $^3C_6$ chair con-

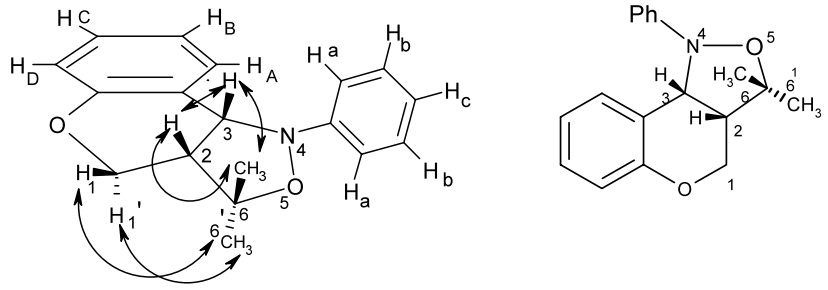
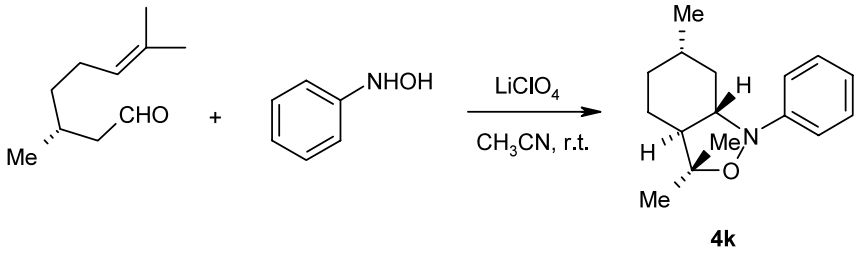


Figure 1. Important NOE's and the chemical structure of product **3a**.



4k

Scheme 2.

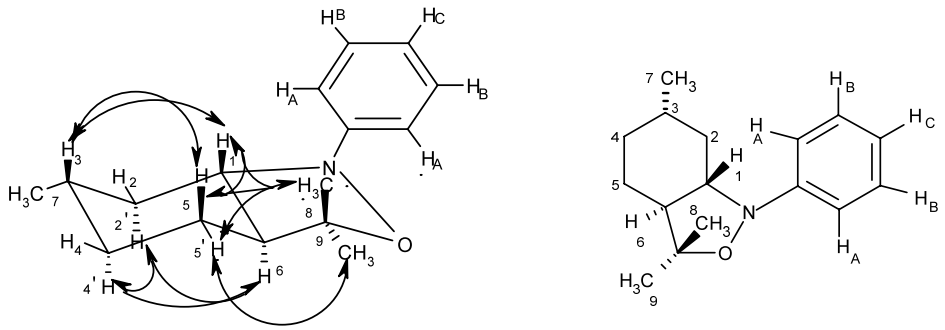
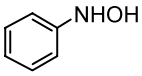
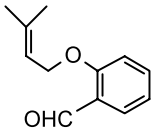
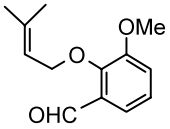
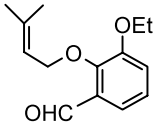
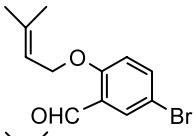
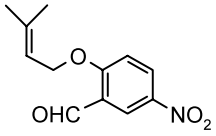
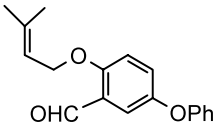
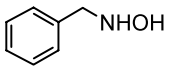
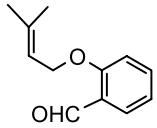
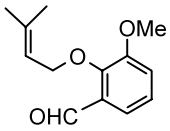
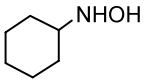
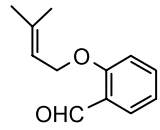
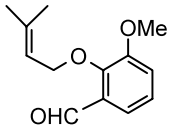
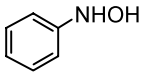
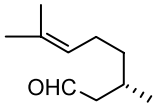
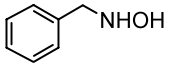


Figure 2. Important NOE's and chemical structures of product **4a**.

Table 1. $LiClO_4$-catalyzed synthesis of tetrahydrochromanoisoxazoles[8]

Entry	Hydroxylamine	Salicylaldehyde	Product[a]	Time (h)	Yield [b] (%)
a			**3a**	6.5	90
b	"		**3b**	7.0	87
c	"		**3c**	6.5	85
d	"		**3d**	9.0	80
e	"		**3e**	9.5	75
f	"		**3f**	6.0	90
g			**3g**	7.5	85
h	"		**3h**	6.0	90
i			**3i**	8.0	79
j	"		**3j**	6.0	82
k			**4k**	6.5	92
l		"	**4l**	7.5	85

a: All products were characterized by ^1H NMR, IR and mass spectroscopy.

b: Isolated and unoptimized yields

formation, which is consistent with the large values of $J_{H1-H2'} = 11.1$ Hz, $J_{H2'-H3} = 11.1$ Hz, $J_{H4'-H5} = 12.5$ Hz and $J_{H5-H6} = 12.5$ Hz as well as with the strong 1,3-diaxial NOE's H_1–H_3, H_1–H_5, H_3–H_5, H'_2–H'_4, H'_2–H_6 and H'_4–H_6. In this conformation all the substituents in the six-membered rings are placed equatorially. The proposed structure is supported by NOE's between $CH_3(8)$-H_1, $CH_3(8)$-H_5, $CH_3(8)$-H_A, $CH_3(8)$-H'_5, H_1–H_A and H_2–H_A (Fig. 2).

Similarly, benzylhydroxylamine also reacted smoothly with citronellal to give the *trans*-fused cycloadduct in 85% yield. All products were characterized by ^1H, ^{13}C NMR, IR and mass spectroscopy. However, in the absence of catalyst, the products were obtained in lower yields (35–40%) as mixtures of *cis*- and *trans*-isomers in acetonitrile at reflux temperature. Amongst the various lithium salts such as $LiClO_4$, LiOTf and $LiBF_4$, lithium triflate and lithium perchlorate were found to be most efficient in terms of conversion. Furthermore, a 5 M ether solution of $LiClO_4$ (5 M LPDE) was also found to effect this transformation at room temperature. Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$ and TMSOTf or metal triflates afforded lower yields due to rapid hydrolysis of prenyl ethers under strongly acidic conditions. Thus, this method provides a convenient procedure to carry out 1,3-dipolar cycloaddition reactions under mild conditions. The scope and generality of this process is illustrated with respect to various hydroxylamines and *O*-prenyl derivatives of salicylaldehydes and the results are presented in Table 1.

In summary, acetonitrile solutions of lithium perchlorate or lithium triflate proved to be excellent and convenient reaction media to perform intramolecular cycloaddition reactions under essentially neutral conditions. This method offers several advantages including enhanced rates, selectivity, improved yields, the ready availability of the reagents at low cost, simplicity in operation, compatibility with unstable nitrones, cleaner reaction profiles and neutral reaction/work-up procedures, which makes it a useful and attractive strategy for the synthesis of tetrahydrochromanoisoxazoline derivatives.

Acknowledgements

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8. *Experimental procedure*: A mixture of a prenyl derivative of salicylaldimine (2 mmol), hydroxylamine (2 mmol) and $LiClO_4$ or LiOTf (10 mol%) in acetonitrile (10 mL) was stirred at reflux temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure chromanoisoxazoline. In the case of hydroxylamine hydrochloride as the reactant, 1.2 equiv. of triethylamine was used to generate free hydroxylamine.
3a: ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H, Me-6), 1.40 (s, 3H, Me-6^1), 2.70 (ddd, 1H, $J_{1,2} = 4.8$ Hz, $J'_{1,2} = 9.7$ Hz, $J_{2,3} = 6.9$ Hz, H_2), 4.15 (dd, 1H, $J'_{1,2} = 9.7$ Hz, $J'_{1,1} = 11.1$ Hz, H'_1), 4.33 (dd, 1H, $J_{1,2} = 4.8$ Hz, $J'_{1,1} = 11.1$ Hz, H_1), 4.61 (d, 1H, $J_{2,3} = 6.9$ Hz, H_3), 6.85 (dt, 1H, $J_{A,B} = J_{B,C} = 7.8$ Hz, $J_{B,D} = 1.1$ Hz, H_B), 6.91 (dd, 1H, $J_{C,D} = 8.2$ Hz, $J_{B,D} = 1.1$ Hz, H_D), 6.96 (dd, 1H, $J_{A,B} = 7.8$ Hz, $J_{A,C} = 1.6$ Hz, H_A), 7.06 (m, 1H, H_c), 7.18 (ddd, 1H, $J_{B,C} = 7.8$ Hz, $J_{C,D} = 8.2$ Hz, $J_{A,C} = 1.6$ Hz, H_C), 7.24 (m, 2H, H_a), 7.32 (m, 2H, H_b). ^{13}C NMR (proton decoupled, $CDCl_3$ 75 MHz): δ 22.0, 29.4, 48.4, 62.4, 64.4, 82.1, 116.7, 117.5, 121.0, 121.1, 123.1, 123.1, 128.6, 128.9, 130.6, 151.3, 154.9. EIMS: *m*/*z*: 281M$^+$, 173, 141, 131, 91, 77, 51, 43.
4k: ^1H NMR (500 MHz, $CDCl_3$): δ 1.01 (d, 3H, $J_{3,7} = 6.6$ Hz, CH_3-(7)), 1.04 (dq, 1H, $J'_{4,4} = 13.1$ Hz, $J'_{4,5} = J'_{3,4} = 12.5$ Hz, $J''_{4,5} = 4.0$ Hz, H'_4), 1.12 (s, 3H, CH_3-(8)), 1.26 (m, 1H, $J'_{5,5} = 12.7$ Hz, $J_{5,6} = J'_{4,5} = 12.5$ Hz, $J_{4,5} = 4.0$ Hz, H_5), 1.28 (m, 1H, H'_2), 1.39 (s, 3H, CH_3-(9)), 1.52 (m, 1H, H_3), 1.76 (dq, 1H, $J_{5,6} = 3.0$ Hz, $J'_{5,5} = 12.7$ Hz, $J_{4',5'} = 4.0$ Hz, $J'_{4,5} = 2.6$ Hz, H^1_5), 1.83 (ddt, 1H, $J'_{4,4} = 13.1$ Hz, $J_{3,4} = J_{4,5} = 4.0$ Hz, $J'_{4,5} = 2.6$ Hz, $J_{2,4} = 1.0$ Hz, H_4), 1.95 (ddd, 1H, $J_{1,6} = 11.1$ Hz, $J_{5,6} = 12.5$ Hz, $J'_{5,6} = 3.0$ Hz, H_6), 2.15 (ddt, 1H, $J_{1,2} = J_{2,3} = 3.5$ Hz, $J'_{2,2} = 12.1$ Hz, $J_{2,4} = 1.0$ Hz, H_2), 2.93 (dt, 1H, $J_{1,2} = 3.5$ Hz, $J_{1,6} = 11.1$ Hz, H_1), 7.01 (2t, 1H, $J_{A,C} = 1.5$ Hz, $J_{B,C} = 7.6$ Hz, H_C), 7.17 (dd, 2H, $J_{A,B} = 8.6$ Hz, $J_{A,C} = 1.5$ Hz, H_A), 7.28 (dd, 2H, $J_{A,B} = 8.6$ Hz, $J_{B,C} = 7.6$ Hz, H_B). ^{13}C NMR (proton decoupled, $CDCl_3$ 75 MHz): δ 21.8, 23.3, 24.4, 26.2, 31.1, 34.2, 40.0, 57.6, 70.5, 80.7, 117.5, 122.9, 128.5, 152.4. EIMS: *m*/*z*: 245 M$^+$, 162, 137, 95, 81, 77, 51, 41.