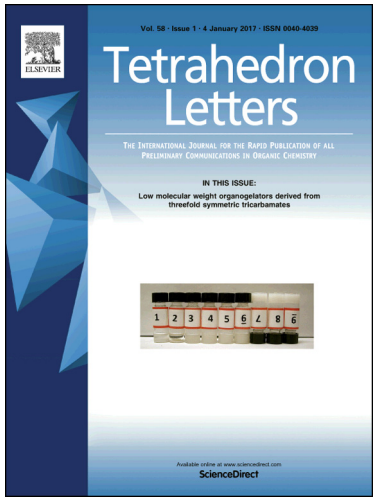

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Synthesis of *C*-glycosylmethyl isoxazoles via aerobic oxidation of ketoximes catalyzed by TEMPO

Helberth Llantén,[a] Sebastian Barata-Vallejo,[b] Alberto Postigo,[b] Pedro A. Colinas[a,*]

[a]CEDECOR, Departamento de Química, Facultad de Ciencias Exactas, CONICET, Universidad Nacional de La Plata. 47 y 115, La Plata, 1900, Argentina.

[b]Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 954 CP 1113, Buenos Aires, Argentina.

e-mail: pcolinas@quimica.unlp.edu.ar

Abstract

An efficient and high yielding synthesis of *C*-glycosylmethyl isoxazoles by oxidation of ketoximes in the presence of oxygen and mediated by TEMPO is described.

Keywords: *C*-glycosides; heterocycle; radical; *C*-cinnamoyl glycosides

Chemistry of isoxazole derivatives has attracted increasing interest due to their chemotherapeutic properties, such as hypoglycemic,[1a] anti-inflamatory,[1b] cytotoxic,[1c] and anti-bacterial activity.[1d] One of the most useful strategies to prepare 1,2-isoxazoles is the nitrile oxide cycloadditions to alkynes.[2] Nitrile oxides are normally obtained from oximes in two steps: halogenation of the aldoxime to give a hydroximoyl halide and subsequent dehydrohalogenation by base. It is also possible to combine both steps in one operation. Due to some drawbacks of this methodology (use of oxidants, metal salts, high pressure) several alternative preparations have been reported.

Dominguez et al. have described the high efficient synthesis of 4,5-diarylisoxazoles by a “one-pot” reaction of enamino ketones with hydroxylamine

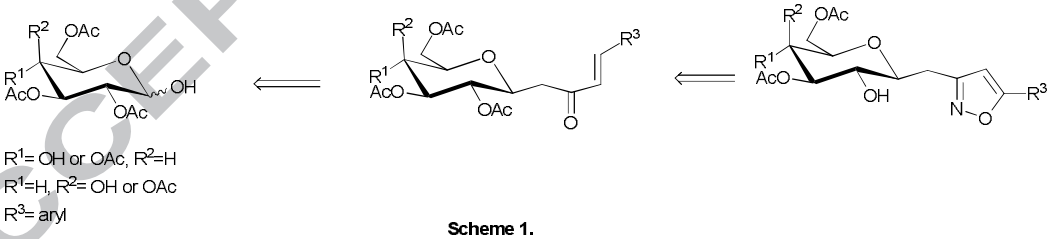
under oximation conditions.[3] A mechanism was proposed involving an amine exchange reaction followed by nucleophilic attack of the hydroxylamine derivative to the carbonyl group. Then elimination afforded the isoxazoles with high yields. Recently Liu reported an aqueous “one-pot” reaction of ethyl acetoacetate, hydroxylamine and aromatic aldehydes in the presence of sodium benzoate.[4] The methodology involves an oximation reaction, further ring closing and subsequent Knoevenagel reaction of the isoxazolone with aromatic aldehydes gave the isoxazoles in good yields. A closed related synthesis has been developed by reaction of α,β-unsaturated ketones or aldehydes and *N*-hydroxyl-4-toluenesulfonamide in the presence of potassium carbonate to afford the isoxazoles in good to moderate yields.[5] Recently Chiba´s group has described the synthesis of several pyrazoles and isoxazoles by the reaction of hydrazones and oximes in the presence of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) and K_2CO_3 under N_2 atmosphere.[6]

During the last years one of our groups has been interested in the synthesis of *C*-glycosides analogues of biologically active molecules. The replacement of the naturally occurring *O*-glycoside bond by *C*-glycoside bond is an approach practiced in the synthesis of carbohydrate-containing compounds for the downstream biological applications.[7] This isosteric replacement seeks to enhance stability of the small molecule glycoside toward enzymatic hydrolysis of the glycosidic bond while retaining vital molecular recognition interactions with the biological target.[8]

Several glycosyl isoxazoles have been prepared by cycloaddition of nitrile oxides to propargyl glycosides.[9] Dondoni´s group has developed the synthesis of *C*-glycosyl amino acids that feature an isoxazole heterocycle as a tether of

the carbohydrate and glycinyl moiety.[10] Interesting some glycosyl isoxazoles showed to be good inhibitors of galectins.[11] Ismael´s group has reported the synthesis of furanosyl isoxazoles by intramolecular oxidative cyclization of α,β-unsaturated oximes with iodine, potassium iodide and sodium hydrogen carbonate.[12] Somzák´s group reported the synthesis of one *C*-glycosyl isoxazole by reaction of a glucopyranosyl alkynyl ketone with hydroxylamine. The compound was tested as inhibitor of glycogen phosphorylase b showing no activity.[13]

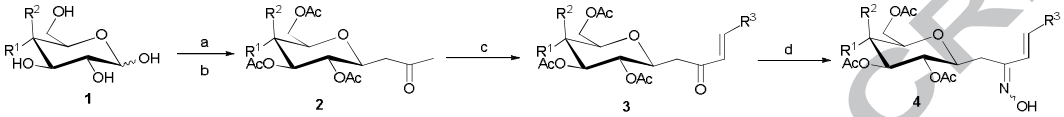
Recently we have described the synthesis and biological activities of several *C*-glycosides, which have been prepared by aldol condensation of β-*C*-glucosyl and β-*C*-galactosyl ketones with aryl aldehydes at room temperature in the presence of pyrrolidine as catalyst.[14] It could be envisioned that the ketoximes of those glycosides could be used in the synthesis of the corresponding *C*-glycosylmethyl isoxazoles (Scheme 1). Here we describe the synthesis of *C*-glycosyl isoxazoles via aerobic oxidation of glycosyl ketoximes.



Scheme 1.

1-(β-D-Glycosyl)-propan-2-ones were prepared by Knoevenagel condensation with 2,4-pentanedione in the presence of sodium carbonate using water as solvent.[15] Crude mixtures containing the *C*-glycosyl ketones were acetylated and then purified to afford the peracetylated compounds **2** in good yields. *C*-

cinnamoyl glycosides **3** have been prepared by aldol condensation of β-*C*-glucosyl or β-*C*-galactosyl ketones with different aromatic aldehydes at room temperature in the presence of pyrrolidine as catalyst.[14] Then the reaction of the *C*-glycosides with hydroxylamine hydrochloride under oximation conditions afforded the corresponding ketoximes **4** in very good yields (Scheme 2).

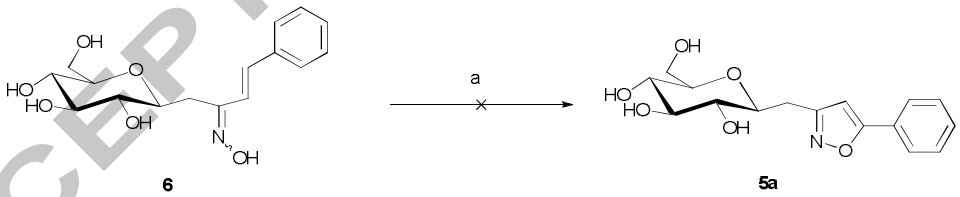


R^1= OH or OAc, R^2=H
R^1=H, R^2= OH or OAc
R^3= aryl

a) 2,4-pentanodione, $NaHCO_3$, H_2O, 90 °C; b) $(AcO)_2O$, pyr., r.t., 48 h., 96-98%; c) R^3CHO, pyrrolidine, CH_2Cl_2, r.t., 24 h., 64-72%; d) NH_2OH, pyr., EtOH, reflux, 2 h., 73-87%

Scheme 2. Preparation of C-glycosyl ketoximes

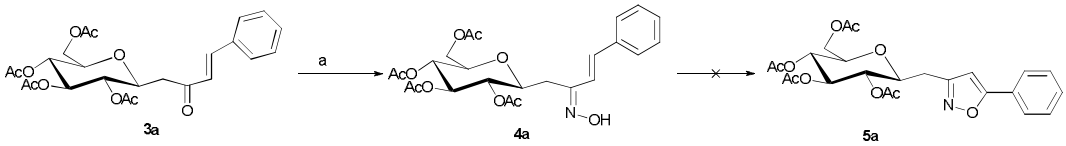
We have studied several reactions conditions to obtain the desired C-glycosylmethyl isoxazoles. We have employed She´s methodology[5] using the deprotected *C*-cinnamoyl glycoside **6** (Scheme 3), easily prepared from compound **3a** by reaction with triethylamine in methanol/water. Unfortunately the product was not observed and only starting material was recovered.



a) TsNOH (8 equiv), K_2CO_3 (8 equiv), MeOH/H_2O, 40 to 60 °C, 34 h.

Scheme 3.

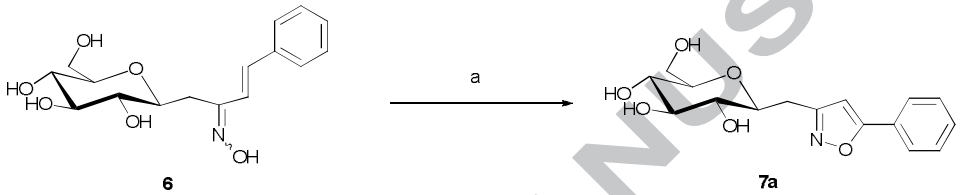
Recently Joshi´s group has prepared several isoxazoles by reaction of chalcones with hydroxylamine hydrochloride and sodium acetate in the presence of glacial acetic acid.[1d] We applied this methodology to the per-*O*-acetylated C-glycoside **3a** but only the corresponding ketoxime **4a** could be isolated from the reaction mixture (Scheme 4).



a) $NH_2.HCl$ (1 equiv), CH_3COONa (1 equiv), CH_3COOH/EtOH, reflux, 20 h.

Scheme 4.

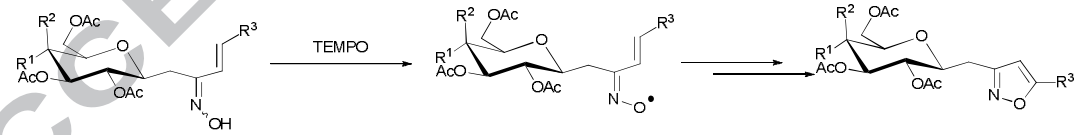
Next we applied the conditions developed by Ismael´s group to the deprotected oxime **6** (Scheme 5).[12] Although it was possible to obtain the desire isoxazole, the yield was low and the purification step was complicated due to the presence of several compounds in the reaction mixture.



a) KI (3.5 equiv), I_2 (1 equiv), K_2CO_3 (4 quiv), THF/H_2O, reflux, 60%

Scheme 5.

In view of the methodology reported by Chiba´s group[6] and that steric hindrance around the double bond of oximes decreases the O-H bond dissociation energy,[16] we decided to study if an iminoxyl radical generated from the oximes of *C*-cinnamoyl glycosides by TEMPO could led to the corresponding *C*-glycosylmethyl isoxazoles through an intramolecular cyclization (Scheme 6).



R^1= OAc, R^2= H or
R^1=H, R^2= OAc
R^3= aryl

Scheme 6. Synthesis of C-glycosylmethyl isoxazoles

We began studying the preparation of *C*-glycosylmethyl isoxazole **5a** from ketoxime **4a** under different reaction conditions (Table 1).

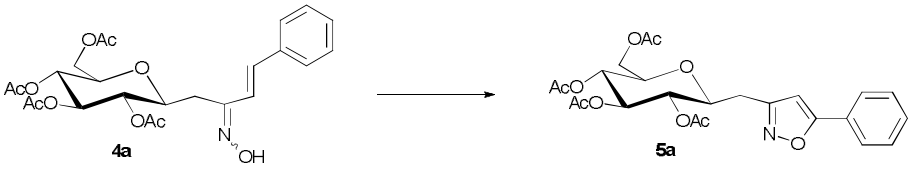


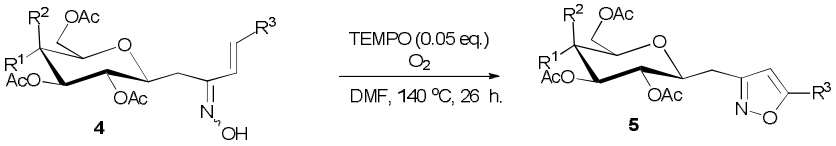
Table 1. Preparation of C-glycosylmethyl isoxazole **5a** [a]

entry	TEMPO (equiv)	Solvent	Temp (°C)	Additives	time(h)	Yield(%)
1[b]	3	DMF	140	K_2CO_3 (2 equiv)	2	80
2	3	DMF	140	**O_2 (1 atm)**	3	99
3	1	DMF	140	O_2 (1 atm)	5	99
4	0.5	DMF	140	O_2 (1 atm)	13	99
5	0.2	DMF	140	O_2 (1 atm)	18	99
6	**0.05**	**DMF**	**140**	**O_2 (1 atm)**	**26**	**99**
7	0.05	DMF	120	O_2 (1 atm)	32	99
8	0.05	DMF	80	O_2 (1 atm)	40	99

[a] The reactions were performed using 0.04 mmol of **4a** en 0.2 mL of solvent. [b] Under argon and with degassed solvent.

When **4a** was heated with TEMPO (3 equiv.) in DMF at 140 °C under argon in the presence of potassium carbonate (2 equiv) the reaction afforded a good yield of the *C*-glycosyl isoxazole **5a** (entry 1). Unfortunately purification of the product was very difficult due to the presence of partial deacetylated derivatives. It is very well known that TEMPO could be regenerated by oxygen thus we decided to perform the reaction under 1 atm of oxygen.[17] Under those conditions the best yield is found using 0.05 equiv. of TEMPO at 140 °C (entry 6) with full conversion and shorter reaction times (entries 7-8).
Based on the results shown in Table 1, it is possible to conclude that the reaction rate depends on amount of TEMPO and the temperature.

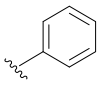
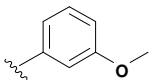
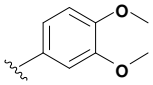
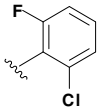
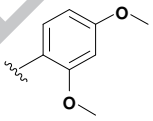
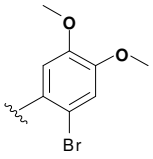
With this knowledge in hand, the selected conditions were applied to a variety of *C*-glycosyl ketoximes to examine the scope of the reaction.



4 5

R^1= OAc, R^2= H or
R^1=H, R^2= OAc

Table 2. Preparation of *C*-glycosylmethyl isoxazoles [a]

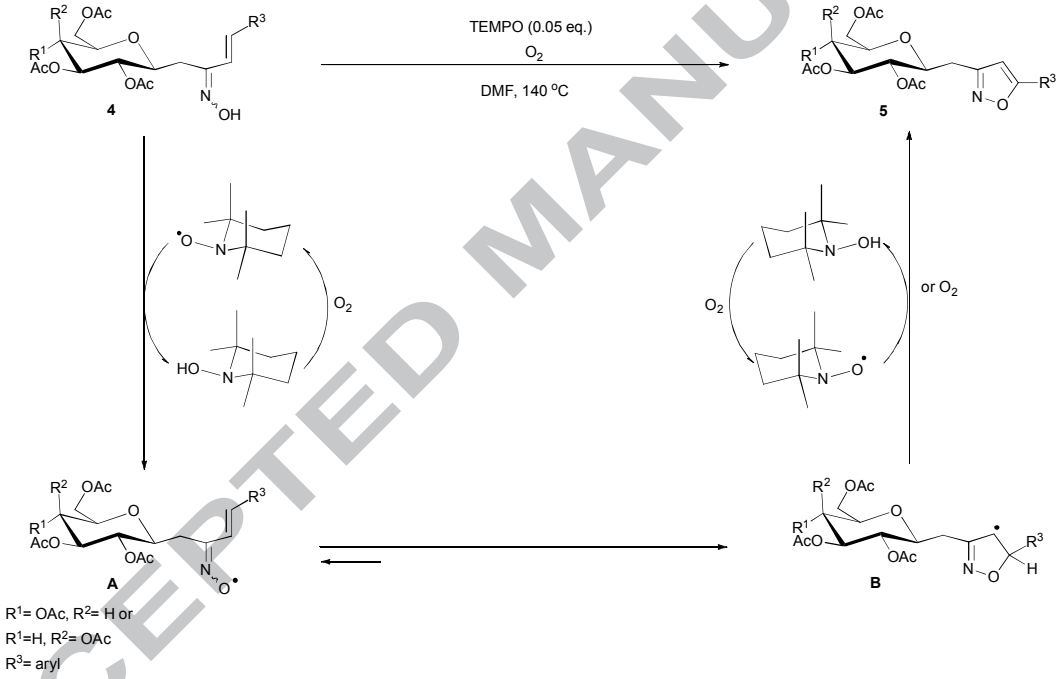
entry	*C*-glycosyl	R^3	Product	Time	Yield(%)
1	*C*-glucosyl		**5a**	26	99
2			**5b**	15	99
3			**5c**	10	99
4			**5d**	35	77
5			**5e**	22	99
6	*C*-galactosyl		**5f**	8	99
7			**5g**	33	86

[a] All the reactions were performed using 1 equiv of ketoxime **4**, 0.05 equiv of TEMPO, O_2 (1 atm) in DMF at 140 °C.

By varying the substituent R^3, various isoxazoles containing electron donating and electron withdrawing groups could be prepared. As can be seen in Table 2 the different groups on the aromatic moiety have almost no effect on the reaction and the corresponding isoxazoles were obtained in very good to excellent yields. Only in the compounds **5d** and **5g** the large steric hindrance of halogen atoms at ortho positions resulted in moderate yields (entries 4 and 7).

The products were easily purified by flash chromatography. The ^{1}H and ^{13}C NMR experiments and mass spectral data of the *C*-glycosyl isoxazoles were in full accordance with their structure.

Based on these results, a mechanism of this preparation of isoxazoles from ketoximes is suggested in Scheme 7. TEMPO induces generation of iminoxyl radical **A**, that undergoes 5-endo trig cyclization to give the isoxazolinyl radical **B**, this radical could participate in a disproportionation reaction with TEMPO or could be directly oxidized by oxygen.[18] Also an ionic pathway that involves trapping of *C*-radical **B** by TEMPO and successive elimination of TEMPO-H to afford the isoxazole **5,** could be suggested. However, in our conditions we have not been able to isolate or observe an intermediate that supports this pathway.



Scheme 7. Proposed mechanism for the preparation of C-glycosylmethyl isoxazoles

In conclusion, we have developed an efficient approach for the synthesis of *C*-glycosylmethyl isoxazoles from ketoximes that is quite simple and high yielding. In addition this methodology circumvents the use of metal catalysts. The reaction mechanism of our methodology includes the 5-*endo trig* cyclization of an iminoxyl radical generated from the ketoxime with TEMPO as initiator. Further applications of the above method for the synthesis of other *C*-glycosyl isoxazoles will be presented in due course.

A. Supplementary information

Experimental details including procedures, characterization, and spectra data. Supplementary data associated with this article can be found, in the online version, at

Acknowledgements

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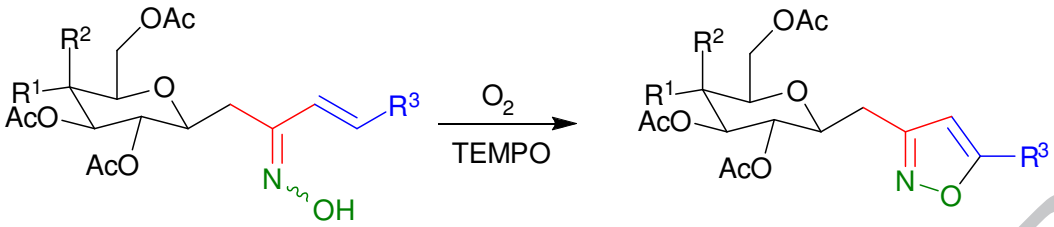

Highlights

. An efficient and high yielding synthesis of C-glycosylmethyl isoxazoles is described.

. A reaction mechanism for our methodology is proposed

. Use of metal catalysts is avoided.