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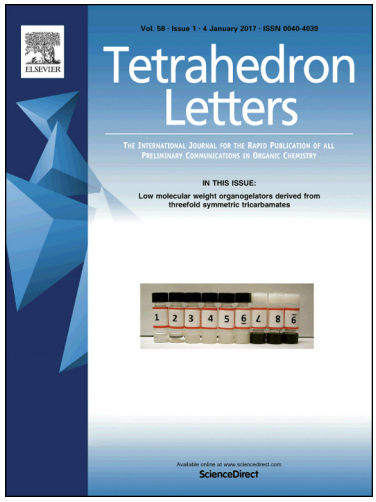

An eco-friendly tandem tosylation/Ferrier *N*-glycosylation of amines catalyzed by $Er(OTf)_3$ in 2-MeTHF

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Graphical Abstract

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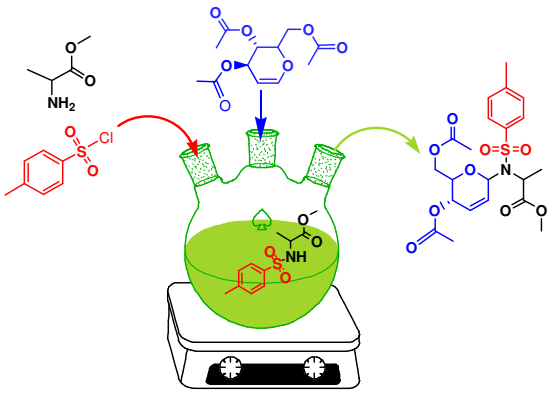

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An eco-friendly tandem tosylation/Ferrier *N*-glycosylation of amines catalyzed by $Er(OTf)_3$ in 2-MeTHF.

Monica Nardi,*[a,b] Natividad Herrera Cano,[c] Antonio De Nino, [a] Maria Luisa Di Gioia,[d] Loredana Maiuolo,[a] Manuela Oliverio,[e] Ana Santiago,[c] Diletta Sorrentino[a] and Antonio Procopio [e]

[a]*Dipartimento di Chimica, Università della Calabria, Cubo 12C, 87036, Arcavacata di Rende (CS), Italy*
[b] *Dipartimento di Agraria, Università Telematica San Raffaele, Via di Val Cannuta, 00166,247, Rome, Italy*
[c]*INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, Córdoba, 5000, Córdoba, Argentina*
[d] *Dipartimento di Farmacia e Scienze della Salute e della Nutrizione, Università della Calabria, Arcavacata di Rende (CS), 87036, Italy*
[e]*Dipartimento di Scienze della Salute, Università Magna Graecia, Viale Europa, 88100, Germaneto (CZ), Italia.*

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ABSTRACT

$Er(OTf)_3$ in 2-MeTHF provides a new and eco-friendly process for Ferrier glycosylation of sulfonamides and amino acids with various *N*-nucleophiles.
The stereoselective synthesis of 2,3-unsaturated-*N*-pseudoglycals was carried out with 3,4,6-tri-O-acetyl-D-glucal and different nucleophiles affording good results in a short time.

1. Introduction

Sulfonamides continue playing an important role in chemotherapy despite their discontinued use as antibiotics. It is known that several sulfonamides inhibit the carbonic anhydrase enzyme and are also used as diuretics, antiepileptics or used to reduce intraocular pressure in the treatment of glaucoma.[1-3] Other sulfonamides such as E7010, E7070, ER-67865 and ER-68487 show anticancer properties [4,5] (Figure 1) whereas some sulfonamidoglycosides show antiproliferative action against human hepatocellular carcinoma.[6]

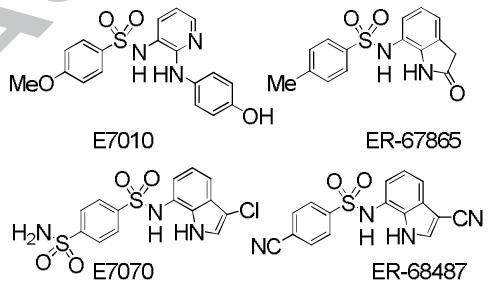


Figure 1. Sulfonamide use as Antitumor Agent

On the other hand, the classical method for the synthesis of sulfonamides involves the nucleophilic attack of amines to sulfonyl chlorides in the presence of bases or other catalysts in organic solvents at high temperature and pressure.[7,8] Furthermore the subsequent *N*-alkylation of sulfonamides requires the use of strong reaction conditions.[9-11] The environmental pollution caused by the use of non-green solvents and catalysts as well as tedious work-up makes these methods inappropriate for the synthesis of azaglycosides.[12]

The synthesis of 2,3-unsaturated glycosides has become of great interest and importance since they are basic building blocks for the production of molecules with biological activity. One of these methods is the Ferrier reaction, which involves an acid catalysis in the presence of nucleophiles (OH-, S-, etc). [13,14] Nitrogen nucleophiles have not been extensively used in the Ferrier rearrangement, azide being the typical nucleophile used to afford *N*-pseudoglycals.[15-18]

However, several protocols have been developed for the synthesis of *N*-pseudoglycals with sulfonamides,[19] carbamates, amides and azides from 3,4,6-tri-*O*-acetyl-D-glucal using

boron trifluoride etherate[19] Amberlyst 15,[20] $ZnCl_2/Al_2O_3$, [21] ruthenium trichloride,[22] iodine catalysis[23] and Mitsunobu reaction conditions. [24]

We previously studied the synthesis of *O*-, *C*-, *N*- and *S*-glycal derivatives, describing a highly efficient and simple procedure for the synthesis of *O*- and *S*-alkyl and aryl 2,3-unsaturated glycosides using erbium(III) trifluoromethanesulfonate as a Lewis acid catalyst.[25-27] Erbium (III) is a water-tolerant Lewis acid, used as catalyst for the synthesis of Acetonides [28] and ring opening of epoxides.[29]

We have successfully applied microwave heating to the addition of different organic moieties on the surface of the mesoporous silica to obtain a new hybrid mesoporous silica–supported Er III catalyst.[30] This catalyst has proved to be very efficient in a series of frequent organic reactions such as the C-C bond formation, [31] protection and de-protection of alcohols [32] and carbonyl compounds,[33] the synthesis of benzodiazepines [34,35] and trans-4,5-diaminocyclopent-2-enones.[36]

In the last decade, some considerable interest has developed around the innovative synthetic protocols in organic synthesis adopting a more eco-sustainable approach.[37,38]

Based on these results and in view of the numerous biological properties of glycosides,[39,40] we proposed the development of a low-cost environmentally friendly procedure for *N*-glycosylation of tri-O-acetyl-D-glucal with different *N*-nucleophiles employing 2-MeTHF as solvent.

According to Anastas and Warner's 12 Principles of Green Chemistry, [41,42] this solvent can be considered a real alternative to toxic solvents. Tetrahydrofuran (THF) and diethyl ether (DEE) as a reaction solvent can be substituted in some reactions by 2-MeTHF. This is of great importance since it comes from renewable resources like corncobs and bagasse.[43] 2-MeTHF improves extraction yields by reducing the number of extraction steps as it forms a water-rich azeotrope at atmospheric pressure. [44-46]

Furthermore, 2-MeTHF is recognized by GSK (GlaxoSmithKline) as a new "green" alternative solvent[46] and considered negative for genotoxicity and mutagenicity.[47]

Lanthanides (III) prove as environmentally friendly oxophilic Lewis acids for activation of glycosyl donors.[48] In recent years a number of important contributions to the chemistry of Ferrier *N*-glycosidation have appeared. In many cases, these catalysts are used in traditional organic solvents or under dry conditions.[49]

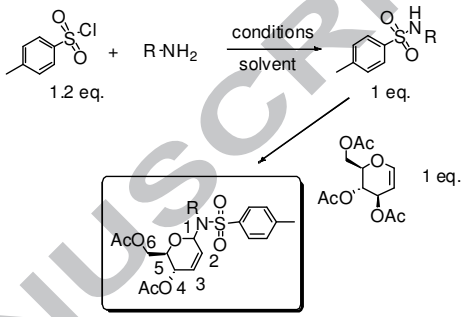
We studied the system $Er(OTf)_3$/2-MeTHF for the reduction reaction of α,β-unsaturated carbonyl compounds. We proposed this protocol as a cheap, efficient, and environmentally sustainable reduction system for the synthesis of allylic alcohols.[50]

The results reported here are comparable to those of the classical Ferrier azaglycosylation; however, the proposed method involves a significant greening of the whole process compared to several previous protocols that required the use of toxic solvents. In addition, the protocol is applicable to biologically important products such as amino acids, showing good yields and high stereoselectivity.

2. Results and Discussion

Very recently, we developed a new aqueous MW-assisted protocol for the rapid and efficient *N*-protection of amino acids and amines using carbonate and sulfonyl chlorides as protecting groups.[51]

This sustainable protection method has stimulated the development of a synthetic way for the synthesis of 2,3-unsaturated-*N*-pseudoglycals. Thus, we investigated the Ferrier azaglycosylation reaction for providing 2,3-unsaturated-*N*-pseudoglycals using the *N*-protected amines obtained according to our previous protocol (Scheme 1).



Scheme 1: One-pot synthesis of azaglycosilated sulfonamides.

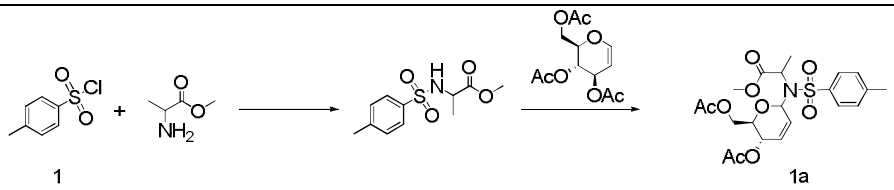
The same method was extended to the synthesis of L-amino acid-glycosides and *N*-tosyl-L-amino acid-glycosides, considered potential drugs, and to the preparation of azidotrimethyl-silanes used as precursors for the synthesis of glycosyl amines (*N*-glycosides), *N*-glycopeptides and *N*-glycoproteins.

This study takes the best reaction condition for the MW-assisted *N*-protection of amines recently published[51] which are evaluated in the Ferrier azaglycosylation with the aim of developing a one-pot methodology.

N-glycosylation of *O*-methyl alanine (2.0 mmol) with 3,4,6-tri-O-acetyl-D-glucal (2.0 mmol) was chosen as a model reaction (Table 1). Opposite to what happens for the simple tosylation reactions, in tosylation/Ferrier glycosylation reaction poor yields were obtained using CH_2Cl_2 (entries 1-3, Table 1).

The result found was the same, increasing reaction time (entry 4, Table 1). By contrast, good product yields were obtained when the reaction was performed in EL (ethyl lactate) and 2-MeTHF (entries 5-10, Table 1). The reaction carried out in the absence of Er (III) did not lead to the formation of the product which means that the Lewis acid catalyst, not involved in the tosylation reaction of amine, is essential for the Ferrier azaglycosylation reaction to occur (entry 11, Table 1). Thus, in order to decrease reaction time, we carried out the same reaction under microwave activation, but lower yields were observed due to decomposition of glucal (entry 12, Table 1). The reaction carried out in water did not lead to the formation of the product, not even when the reaction system was subjected to microwave irradiation (entries 13 - 20, Table 1). The reaction carried out in 2-MeTHF with $Er(OTf)_3$ under reflux showed the best results (entry 9, Table 1, only α) as described in the references section.[52]

Table 1. Tosylation/Azaglycosidation reactions of *O*-methyl alanine with 3,4,6-tri-*O*-acetyl-D-glucal.[a]



1 1a

Entry	Lewis acid	Solvent	T °C	Time (min)[b]	Yield (%)[c]
1	$ErCl_3 \cdot 6H_2O$	CH_2Cl_2	60	150	40
2	$Er(OTf)_3$	CH_2Cl_2	60	150	40
3	$ErCl_3$	CH_2Cl_2	60	150	40
4	$ErCl_3 \cdot 6H_2O$	CH_2Cl_2	60	240	40
5	$ErCl_3 \cdot 6H_2O$	EL	60	150	60
6	$Er(OTf)_3$	EL	60	150	60
7	$ErCl_3$	EL	60	150	60
8	$ErCl_3 \cdot 6H_2O$	2-MeTHF	60	240	70
9	$Er(OTf)_3$	2-MeTHF	60	240	80
10	$ErCl_3$	2-MeTHF	60	240	73
11	-	2-MeTHF	60	240	0
12	$Er(OTf)_3$	2-MeTHF	60	15	20
13	$Er(OTf)_3$	H_2O	60	150	trace
14	$ErCl_3$	H_2O	60	150	trace
15	-	H_2O	60	150	10
16	$ErCl_3 \cdot 6H_2O$	H_2O	60	150	0
17[d]	$Er(OTf)_3$	H_2O	60	15	0
18[d]	$ErCl_3$	H_2O	80	15	0
19[d]	-	H_2O	110	15	0
20[d]	$ErCl_3 \cdot 6H_2O$	H_2O	60	15	0

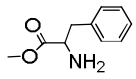
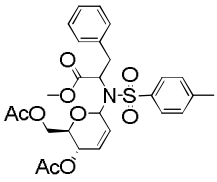
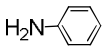
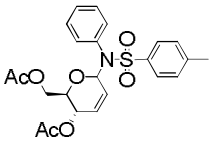
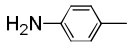
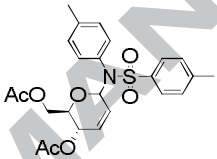
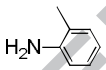
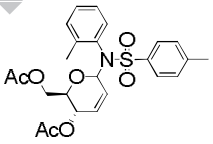
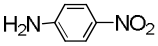
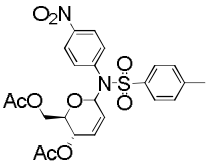
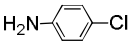
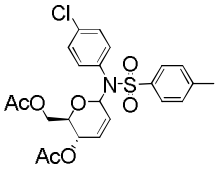
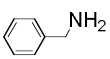
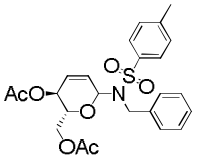
[a] Reaction conditions: *O*-methyl alanine (2 mmol), tosyl chloride (2.2 mmol) and the Lewis acid (0.2 mmol) were dissolved in the solvent (3 mL). After the formation of *N*-tosyl alanine, 3,4,6-tri-*O*-acetyl-D-glucal (2 mmol) was added to the mixture.
[b] After the addition of 3,4,6-tri-*O*-acetyl-D-glucal.
[c] Isolated yield. α only product is formed.
[d] The reactions were conducted in a Synthos 3000 microwave oven (Anton-Paar).

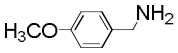
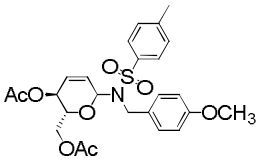
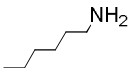
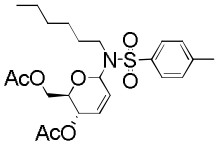
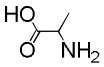
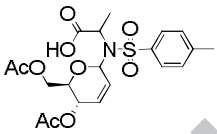
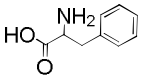
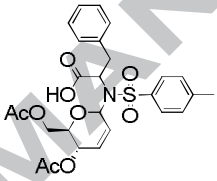
Therefore we decided to test a series of amines in the one-pot synthesis of 2,3-unsaturated-*N*-pseudoglycals (Table 2).

Glycal and various sulfonamides were coupled in the presence of $Er(OTf)_3$ (10 mol%) in 2-MeTHF affording the corresponding *N*-glycosyl sulfonamides (**1a-10a**). In good yields with high anomeric selectivity, *N*-(phenyl)-4 methylbenzene sulfonamide, *N*-(phenyl)-2-methylbenzenesulfonamide and *N*-(4-chlorophenyl)-4- Ts-L-phenylalanine methyl ester (**2**) gave new *N*-glycosyl *N*-Ts-L-alanine/methyl 2-(4 methylphenylsulfonamido)propanoate methyl ester and *N*- amino acid sulfonamides which could be potential anticancer drugs. However, no amino acid tested was useful for this type of reaction (entries 10-11, Table 2). This is probably due to amino acids that act as zwitterions, decreasing the nucleophilicity on nitrogen atom.

Methylbenzenesulfonamide reacted smoothly to afford 2,3-unsaturated-*N*-glycosides (entries 3, 4 and 6, Table 2).

Table 2: One pot tosylation/Azaglycosidation of amine reactions with 3,4,6-tri-*O*-acetyl-D-glucal. [a]

Entry	Substrate	Product	Yield (%)[b] α:β
1	 **2**	 **2a**	73 90:10
2	 **3**	 **3a**	90 90:10
3	 **4**	 **4a**	98 α only
4	 **5**	 **5a**	91 α only
5	 **6**	 **6a**	85 75:25
6	 **7**	 **7a**	83 α only
7	 **8**	 **8a**	87 90:10

8	 **9**	 **9a**	90	87:13
9	 **10**	 **10a**	86	α only
10	 **11**	 **11a**	NR	
11	 **12**	 **12a**	NR	

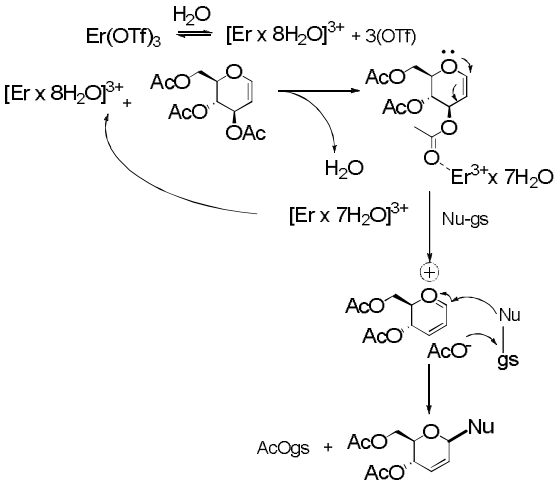
[a]General reaction conditions: the N-nucleophile (2.0 mmol) and $Er(OTf)_3$ (0.2 mmol) were added to a stirred solution of tosyl chloride (2.2 mmol) in 2-MeTHF (3 mL). The reaction was conducted in a two neck round bottom flask using reflux system. After 2 hours tri-O-acetyl-D-glucal (2.0 mmol) was added.

[b]Anomeric selectivity was determined by ^{1}H-NMR.

The reaction mechanism proposed is shown in Scheme 2.

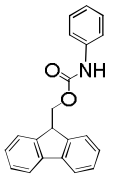
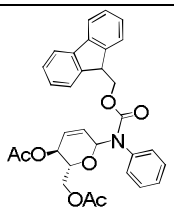
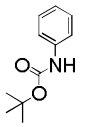
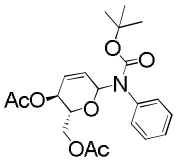
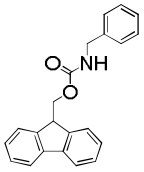
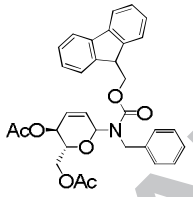
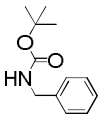
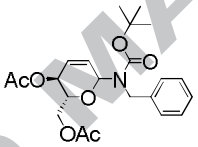
The Ferrier process starts with the coordination of Er and one of the oxygen atom lone pairs of the glycal molecule producing the release of a glycoxil group. A delocalized cation is formed and then attacked by a nucleophile affording a product.

Due to the extensive use of fluorenylmethyloxycarbonyl chloride (Fmoc-Cl) and *tert*-butyloxycarbonyl (Boc) as amino-protecting groups and their significant synthetic utility,[53] we examined the scope of the present reagent system with series of Fmoc- and Boc-protected amines, exploring the generality of this azaglycosylation method (Table 3). Unfortunately, we observed that *N*-Fmoc and *N*-Boc amines failed to react in the usual reaction conditions (Table 3).



Scheme 2: Mechanism hypothesized for Ferrier glycosylation

Table 3: Azaglycosidation reactions of *N*-Boc and *N*-Fmoc protected amines [a]

Entry	Substrate	Product	Yield (%)[b]
1	 **13**	 **13a**	NR
2	 **14**	 **14a**	NR
3	 **15**	 **15a**	NR
4	 **16**	 **16a**	NR

[a]General reaction conditions: the *N*-nucleophile (2.0 mmol) and $Er(OTf)_3$ (0.2 mmol) were added to a stirred solution of tri-O-acetyl-D-glucal (2.0 mmol), in 2-MeTHF (3 mL). The reaction was performed in a two neck round bottom flask using reflux system.

[b]Substrate recovered.

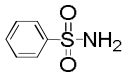
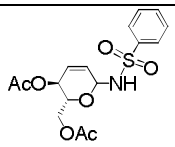
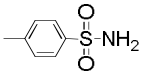
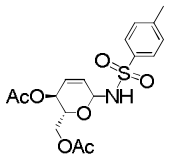
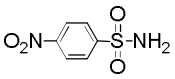
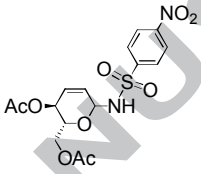
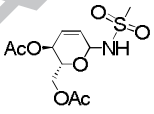
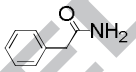
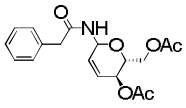
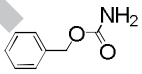
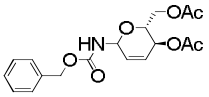
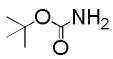
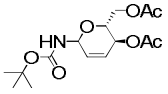
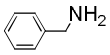
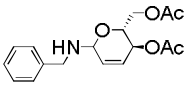
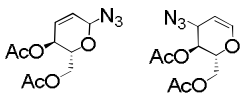
We then decided to test the efficiency of sulfonamides, carbamates and primary amines, using the same protocol proposed for Ferrier azaglycosylation. Excellent results were obtained for primary sulfonamides (entries 1-4, Table 4).[54] The reaction with benzylamide gave moderate yields (entry 5, Table 4). This result encouraged us to further exploit Ferrier azaglycosylation with benzyl carbamate, *t*-butyl carbamate and trimethylsilyl azide ($TMSN_3$) (entries 6, 7 and 9, Table 4) as nucleophiles. Reaction of carbamates with glucal provided the corresponding pseudoglycals (**22a** and **23a**), in good yields and selectivities. These products can be transformed into the corresponding amines by elimination of the protecting moiety. In contrast, reaction of benzylamine was unsuccessful (entry 8, Table 4). Likewise, glycosylation of glucal with $TMSN_3$ gave the corresponding α- and β-1-azido-3-deoxy (**25a**) and a- and b-3-azido-3-deoxy (**26a**) glycoside in 90% yield (entry 9, Table 4).

Although the nucleophilicity (N) of the amines studied is difficult to predict in our systems, we could make estimates of the trend. For instance, when the hydrogens of ammonia (N = 9.48) are successively replaced by one ($MeNH_2$, N = 13.85) and two methyl groups (Me_2NH, N =17.12), a small increase in nucleophilicity was observed.[55] Thus, a secondary amine is more nucleophilic than a primary amine. This could explain the fact that *N*- Benzyl benzene sulfonamide (**8**) is more reactive than *N*- benzylamine (**24**). Conversely, Fmoc- and Boc-protected amines did not react to afford the corresponding pseudoglycals, probably due to high steric hindering (Table 3, entries 1-4).

Even though the reaction did not perform well on amino acids without methyl group, probably because amino acids behave like zwitterions reducing nucleophilicity, the reaction provided good yields for azaglycosylation using amino acids with methyl group.

The results reported here are comparable to those of the classical Ferrier azaglycosylation; however, the proposed method involves a significant greening of the whole process compared to several previous protocols that required the use of toxic solvents. In addition, the protocol is applicable to biologically important products such as amino acids, showing good yields and high stereoselectivity.

Table 4: Ferrier azaglycosylation of tri-O-acetyl-D-glucal with sulfonamides and carbamates primary [a]

Entry	Substrate	Product	Yield (%)[b] (α:β)
1	 **17**	 **17a**	89 92:8
2	 **18**	 **18a**	93 85:15
3	 **19**	 **19a**	83 90:10
4	 **20**	 **20a**	95 72:28
5	 **21**	 **21a**	60 70:30
6	 **22**	 **22a**	90 90:10
7	 **23**	 **23a**	85 80:20
8	 **24**	 **24a**	N.R[c]
9	 **25**	 **25a** **26a**	90 (25a) 70:30 (26a) 80:20.

[a] General reaction conditions: the *N*-nucleophile (2.0 mmol) and $Er(OTf)_3$ (0.2 mmol) were added to a stirred solution of tri-O-acetyl-D-glucal (2.0 mmol), in 2-MeTHF (3 mL). The reaction was performed in a two neck round bottom flask using reflux system.

[b] The anomeric ratio was determined by integration of the anomeric hydrogen in the ^{1}H NMR spectrum.

[c] Substrate recovered.

Conclusion

In summary, we describe an efficient, eco-friendly and simple procedure for the synthesis of sulfonamides and 2,3-unsaturated-*N*-pseudoglycals. The application of erbium (III) trifluoromethanesulfonate as a Lewis acid catalyst in 2-MeTHF shows good results. Although this new protocol does not perform well on *N*-Cbz and *N*-Boc amines, the same method affords good yields and excellent selectivity for azaglycosylation using primary amine carbamates.

Compared to the classical procedures, the present protocol ($Er(OTf)_3$/2-MeTHF) offers several advantages including use of green solvent, use of water alone for the work-up (use of H_2O and 2-MeTHF as an organic solvent), recovery and reusability of the catalyst, use of mild reaction conditions and wide range of applicability.

References and notes

1. Supuran CT. *Exp Opin Invest Drugs*, 2003; 12: 283.
2. Wilkinson BL, Bornaghi LF, Wright AD, Houston TA, Poulsen SA. *Bioorg Med Chem Lett*. 2007; 5*:* 1355.
3. Carta F, Maresca A, Scozzafava A, Vullo D, Supuran CT. *Bioorg Med Chem.* 2009; 20: 7093.
4. Medina JC, Roche D, Shan B, Learned M, Frankmoelle WP, Clark DLT, Rosen JC. *Bioorg Med Chem Lett*. 1999; 9*:* 1843.
5. Colinas PA, Bravo RD. *Org Lett*. 2003; 5: 4509.
6. (a) Kuromitsu AJ, Kawai T, Nagasu T, Sugi NH, Yoshimatsu K, Yoshino HT. *Mol Cancer Ther*. 2002; 1: 275. (b) Colinas PA, Bravo RD, Vullo D, Scozzafava A, Supuran CT, *Bioorg. Med. Chem. Lett*. 2007, 17, 5086–5090.
7. Cremlyn, R. Organosulfur Chemistry: An Introduction, John Wiley and Sons, New York, 1996.
8. Anderson, K.K.; Barton D.H.R.; Ollis W.D.; Jones D.N. Sulfonic Acids and Their Derivatives in Comprehensive Organic Chemistry Ed.; Pergamon: Oxford, 1979; Vol. 3, 331-350
9. De Marco R, Di Gioia ML, Liguori A, Perri F, Siciliano C, Spinella M. *Tetrahedron* 2011; 67: 9708 -9714.
10. Di Gioia ML, Leggio A, Liguori A, Perri F, Siciliano C, Viscomi MC. *Amino Acids* 2010; 38: 133-143.
11. Di Gioia ML, Leggio A, Malagrinò F, Romio E, Siciliano C, Liguori A. *Mini Rev Med Chem*. 2016; 16(9): 683.
12. Meshram GA, Patil VD. *Tetrahedron Lett*. 2009; 50: 1117.
13. (a) Ferrier RJ, *J Chem Soc C*. 1964; 5443-5449. (b) Ferrier RJ. *Adv Carbohydr Chem Biochem*. 1969; 24: 199 -266.
14. Gomez AM, Lobo F, Uriel C, Lopez J. C. *Eur. J. Org. Chem.* 2013, 7221–7262
15. (a) Ferrier RJ, Ciment DM. *J. Chem. Soc. C*. 1966; 441-445 (b) Ferrier RJ, Prasad N. *Chem Commun*. 1968; 476 -477. (c) Ferrier RJ, Prasad N. *J Chem Soc C*. 1969; 570 -575.
16. Ferrier RJ. Topics in Current Chemistry; Springer: Berlin/Heidelberg, 2001; 215: 153-175.
17. Ferrier RJ, Furneaux RH. *Carbohydrate Research*, 1976; 52(1): 63-68.
18. Tèmpera CA, Colinas PA, Bravo RD. *Tetrahedron Lett*. 2010; 51: 5372-5374.
19. (a) Chandrasekhar S, Reddy CR, Chandrashekar G, *Tetrahedron Lett*. 2004, 45, 6481–6484. (b) Ding F, William R, Kishan Gorityala BJ, Wang S, Wei Liu X. *Tetrahedron Lett*. 2010; 51: 3146.
20. (a) Colinas PA, Bravo RD. *Carbohydr Res*. 2007; 342: 2297-2302. (b) Témpera CA, Colinas PA, Bravo RD, *Tetrahedron Lett*. 2010, 51, 5372–5374.
21. Houston TA, Chervin SM, Koreeda M. *ITE Lett*. 2002; 3: 23.
22. Michigami K, Hayashi M. *Tetrahedron*, 2012; 68: 1092.
23. Procopio A, Dalpozzo R, De Nino A, Nardi M, Tagarelli A, Russo B. *Synthesis*, 2006; 2: 332- 338.
24. Procopio A, Dalpozzo R, De Nino A, Nardi M, Oliverio M, Russo B. *Synthesis*, 2006; 15: 2608 -2612.
25. Procopio A, Dalpozzo R, De Nino A, Maiuolo L, Nardi M, Oliverio M, Russo B. *Carbohydr Res*. 2007; 342: 2125 -2131.
26. Procopio A, Gaspari M, Nardi M, Oliverio M, Rosati O. *Tetrahedron Lett.* 2008; 49, 14: 2289-2293
27. Procopio A, Dalpozzo R, De Nino A, Maiuolo L, Nardi M, Russo B. *Adv Synth Catal*. 2005; 347: 1447-1450.
28. Procopio A, Das G, Nardi M, Oliverio M, Pasqua L. *ChemSusChem*, 2008; 1: 916.
29. Procopio A, Cravotto G, Oliverio M, Costanzo P, Nardi M, Paonessa R. *Green Chem*. 2011; 13: 436-443.
30. Nardi M, Cozza A, De Nino A, Oliverio M, Procopio A. *Synthesis,* 2012; 44: 800-804.
31. Procopio A, Das G, Nardi M, Oliverio M, Pasqua L, *ChemSusChem,* 2008; 1: 916- 919.
32. Procopio A, Cravotto G, Oliverio M, Costanzo P, Nardi M, Paonessa R. *Green Chem*. 2011; 13: 436-443.
33. Nardi M, Cozza A, Maiuolo L, Oliverio M, Procopio A. *Tetrahedron Lett.* 2011; 52: 4827–4834.
34. Nardi M, Cozza A, De Nino A, Oliverio M, Procopio A. *Synthesis*, 2012; 44: 800-804.
35. Procopio A, Costanzo P, Curini M, Nardi M, Oliverio M, Sindona G. *ACS Sustainable Chem. Eng*. 2013; 1: 541–544.
36. De Nino, A.; Maiuolo, L.; Merino, P.; Nardi, M.; Procopio, A.; Roca-López, D.; Russo, B.; Algieri, V. *ChemCatChem.* 2015; 7: 830–835.
37. Di Gioia ML, Barattucci A, Bonaccorsi P, Leggio A, Minuti L, Romio E, Temperini A, Siciliano C. *RSC Adv*. 2014; 4: 2678–2686.
38. Sneed RA, Grimes A, Schultze E, Brown PE. *Toxicol Appl Pharmacol.* 1997; 144: 77-87.
39. Karas M, Chakrabarti SK. *J Environ Pathol Toxicol Oncol*. 2001; 20: 155 -164.
40. Anastas PT, Warner JC. *Green Chemistry: Theory and Practice*, ed.; Oxford University Press, Oxford, 1998; Vol. 1.
41. Anastas PT, Williamson TC. *In Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes,* Anastas PT, Williamson TC, Eds.; Oxford University Press: USA, 1998, Vol. 1.
42. Amir S, Ayyaz M, Shahid S, Ziad A, Usman Saeed HM, Umar F. *Int J Chem Eng Appl*. 2015; 6: 381-384.
43. Pace V, Castoldi L, Holzera ARWA. *Green Chem*. 2012; 14: 1859-1863.
44. Aycock DF. *Org Proc Res Dev*. 2007; 11: 156-159.
45. Comanita B, Aycock D. *Industrie Pharma Magazine*, 2005; 17: 54-56.
46. Henderson RK, Jiménez-Gonzàlez C, Constable JC, Alston SR, Inglis GGA, Fisher G, Blinks JSPS, Curzons AD. *Green Chem.* 2011; 13: 854-862.
47. Antonucci V, Coleman J, Ferry JB, Johnson N, Mathe M, Scott JP, Xu J. *Org Process Res Dev*. 2011; 15: 939-941.
48. Kobayashi S, Sugiura M, Kitagawa H, Lam WWL *Chem. Rev*. 2002, 102, 2227–2302.
49. (a) Crasto C F, Jones G B, *Tetrahedron Lett*., 2004, 45, 891–4894. (b) Christensen H, Christiansen M S, Petersen J, Jensen H H, *Org. Biomol. Chem.Microreview* 2008, 6, 3276–3283;
50. Nardi M, Oliverio M, Costanzo P, Sindona G, Procopio A. *Tetrahedron*, 2015; 71: 1132-1135.
51. Nardi M, Herrera Cano N, Costanzo P, Oliverio M, Sindona G, Procopio A. *RSC Adv*. 2015; 5: 18751- 18760.
52. *General Procedure one pot tosylation/azaglycosidation reaction of amine with 3,4,5-tri-O-acetyl- D-glucal*, *exemplified with* ***1a***: To a stirred solution of tosyl chloride (2.2 mmol), in 2-MeTHF (3 mL) was added the *O*-methyl alanine (2.0 mmol) and $Er(OTf)_3$ (0.2 mmol). The reaction was conducted in a two neck round bottom flask using a reflux system. The reaction process was monitored by TLC using ultraviolet illumination at 254 nm or staining with ninhydrin solution. After 2 hours is added 2 mmol of tri-O-acetyl-D-glucal and it is left in the same conditions for

another 2 hours. The reaction mixture was extracted with H_2O and the organic phase (2-MeTHF as solvent), then dried over Na_2SO_4. The crude material was dried under vacuum (~1 mmHg) and purified by flash chromatography on silicagel ($CHCl_3$/EtOH 9.5/0.5) to isolate the desired product **1a**. *α–Methyl-2-(4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl-N-p-toluenesulfonamide)-propanoate (**1a**).* yellow oil obtained in 80 % yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ =7.76 (d, 2H, *J* = 8.2, Ar), 7.32 (d, 2H, *J* = 8.2, Ar), 5.94 (dd, 1H, *J*=9.3, 6.1 Hz, H-3), 5.82 (ddd, *J*=9.3, *J*=8.1, 1.7 Hz, 1H, H-2), 5.47-5.45 (m, 1H, H-4), 5.28 (d, *J*=8.1, Hz, 1H, H-1), 4.24-4.22 (m, 2H, H-6), 4.19-4.17 (m, 1H, H-5), 3.99-4.01 (m, *J*=7.1 Hz, 1H, CH-N), 3.55 (s, 3H, CH_3COO), 2.43 (s, 3H, CH_3Ph), 2.10 (s, 3H, CH_3COO), 2.07 (s, 3H, CH_3COO). ^{13}C NMR (75 MHz, $CDCl_3$): δ =172.7 (C=O), 170.4 (C=O), 170.0 (C=O), 143.6 (C), 138.1 (H), 130.2 (CH), 133.9 (CH), 127.5 (CH), 127.5 (2 CH), 68.0 (CH-1), 63.9 (CH-5), 63.4 (CH-4), 63.2 (CH_2-6), 52.4 (CH_3), 51.8 (CH), 21.4 (CH_3), 20.8 (CH_3COO), 20.6 (CH_3COO), 19.9 (CH_3).
IR (neat) : 3440, 3019, 2400, 1741, 1216, 1045, 749, 669.
Anal. Calcd for $C_{21}H_{27}NO_9S$: C 53.72, H 4.80, N 2.98. Found C 53.80, H 4.76, N 2.95.

53. Di Gioia ML, Gagliardi A, Leggio A, Leotta V, Romio E, Liguori A. *RSC Adv*. 2015; 5: 63407-63420.

54. General Procedure Ferrier azaglycosylation of tri-O-acetyl-D-glucal with sulfonamides and carbamates primary, exemplified with **17a** . To a stirred solution of tri-O-acetyl-*D*-glucal (2 mmol), in 2-MeTHF (3 mL) was added the benzenesulfonamide (2.0 mmol) and $Er(OTf)_3$ (0.2 mmol). The reaction was conducted in a two neck round bottom flask using a reflux system for 2 hours. The reaction process was monitored by TLC using ultraviolet illumination at 254 nm allowed for visualization for UV active materials or staining with ninhydrin solution allowed for further visualization. The reaction mixture was extracted with H_2O and the organic phase (2-MeTHF as solvent), then dried over Na_2SO_4. The crude material was dried under vacuum (~1 mmHg) and purified by flash chromatography on silica gel ($CHCl_3$/EtOH 9.5/0.5) to isolate the desired product **17a**. *4,6-Di-O-acetyl-2,3-dideoxy- α-D-erythro-hex-2-enopyranosyl-N-benzenesulfonamide (**17a**).* Straw yellow oil obtained in 89 % yield; Spectroscopic data compared to those reported in the literature.[19b]

55. Brotzel F, Chu YC, Mayr H. *J Org Chem*. 2007; 72: 3679-3688.

Supplementary Material

Supplementary data associated with this article are available.

RESEARCH HIGHLIGHTS

- convenient synthesis of sulfonamides and 2,3-unsaturated-*N*-pseudoglycals
- green procedure in 2-MeTHF
- application of erbium (III) trifluoromethanesulfonate as a Lewis acid catalyst