Tetrahedron Letters 51 (2010) 5980–5983

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An economic and efficient tetrahydrofuranylation of alcohols, imines and alkynes

Luigino Troisi *, Catia Granito, Ludovico Ronzini, Francesca Rosato, Valeria Videtta

Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, University of Salento, via Prov.le Lecce-Monteroni, 73100 Lecce, Italy

ARTICLE INFO

Article history:
Received 17 June 2010
Revised 3 September 2010
Accepted 6 September 2010
Available online 15 September 2010

Keywords:
Radical reactions
Alcohols
Imines
Alkynes
Tetrahydrofuranylation

ABSTRACT

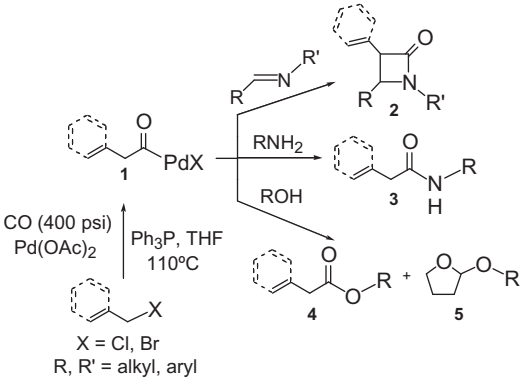
The tetrahydrofuranyl radical, generated by heating tetrahydrofuran in the presence of air and allyl or benzyl chloride, becomes a useful tool in order to transform the hydroxyl functions into ethers, or the C=N double bond into amine, or the C–C triple bond into vinyl derivatives. A radical mechanism is proposed followed by a nucleophilic substitution for the alcohol substrate and a radical addition for the iminic and the acetylenic reactants.

In the last few years our research group has been involved in the study of the Pd(0)-catalysed carbonylation reaction of allyl and benzyl halides. Through the generation of the palladium complex **1** (Scheme 1), β-lactam rings **2**, amides **3** and esters **4** could be prepared by reaction with imines,[1–5] amines[6] and alcohols,[7] respectively.

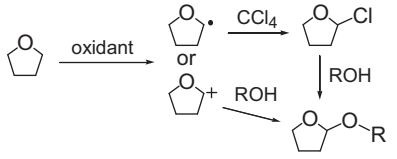
Moreover, the reaction with alcohols and phenols produced esters **4** (>90%) together with small amounts of tetrahydrofuranyl alkyl or aryl ethers **5** (1–5%), respectively.

In the literature, reactions of tetrahydrofuranylation of alcoholic centres were recently reported to be based on the use of one-electron oxidants to activate the tetrahydrofuran (THF). Peroxydisulfates,[8] cerium(IV) reagents,[9] peroxy-λ^3-iodane,[10] or alternatively, $CrCl_2$,[11] Mn(0) powder[12] or VCl_3[13] in the presence of CCl_4 were reported as good reactants in the alcohol tetrahydrofuranylation. All the mentioned studies described a prior transformation of THF to 2-tetrahydrofuranyl radical or cation which then reacted by two different ways. The radical underwent firstly halogenation by CCl_4 and then a nucleophilic substitution by the alcohol, the cation linked directly the alcoholic moiety (Scheme 2).

In order to explore the mechanism of generation of compound **5**, occurring under experimental conditions (Scheme 1) completely different from those reported in the literature, several experiments were planned. In the first instance, benzyl alcohol (1.0 mmol) and THF (20 mL) were reacted in autoclave (110 °C) for 15 h. In order to find better experimental conditions for the best yields, the operating parameters, including the presence of allyl chloride, CO, $Pd(OAc)_2$, and PPh_3, were modulated each time. The final results of this investigation are shown in Table 1.



Scheme 1. Pd(0)-catalysed carbonylation of allyl and benzyl halides.

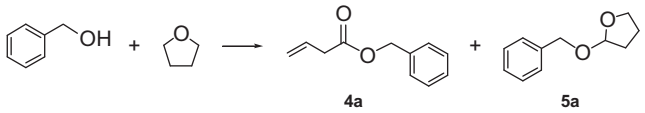


Scheme 2. Tetrahydrofuranylation of alcoholic centres using one-electron oxidants to activate the THF unit.

* Corresponding author. Fax: +39 0832298732.
E-mail address: luigino.troisi@unisalento.it (L. Troisi).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.014

Table 1
Reaction of benzyl alcohol with THF modulating the experimental conditions



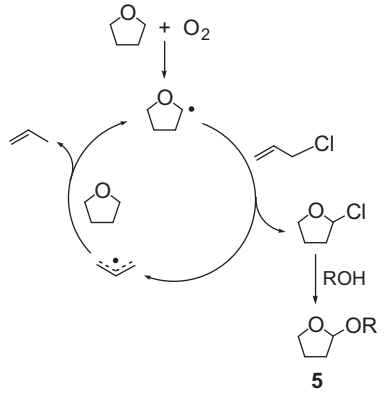
4a **5a**

Entry	RCl (mmol)	Gas (psi)	$Pd(OAc)_2$ (mmol)	PPh_3 (mmol)	T[a] (°C)	Yield[b] (%)	Products distribution[c] (%)	
							4a	**5a**
1	CH_2=$CHCH_2$– (1.2)	CO (400)	0.1	0.4	110	50	97	3
2	–	CO (400)	0.1	0.4	110	–	–	–
3	CH_2=$CHCH_2$– (1.2)	–	0.1	–	110	45	–	100
4	CH_2=$CHCH_2$– (1.2)	CO (400)	–	0.4	110	43	–	100
5	CH_2=$CHCH_2$– (1.2)	CO (400)	–	–	110	45	–	100
6	CH_2=$CHCH_2$– (1.2)	–	–	–	Reflux	60	–	100
7	CH_2=$CHCH_2$– (1.2)	N_2 (400)	–	–	110	–	–	–

[a] The reactions at 110 °C were carried out in autoclave; all the reactions were carried out for 15 h.
[b] Transformation yield calculated by GC, no other products were formed and unreacted alcohols were recovered.
[c] Products distribution measured by GC.

The presence of allyl chloride, CO, $Pd(OAc)_2$, and PPh_3 in THF afforded the butenoyl-palladium-complex **1**, which, by reaction with the benzyl alcohol, gave mostly ester **4a** with a small amount of the tetrahydrofuranyl ether **5a** (entry 1, Table 1). In the absence of allyl chloride, the benzyl alcohol–THF mixture under CO pressure, with $Pd(OAc)_2$ and PPh_3, did not afford any product (entry 2, Table 1). These preliminary results suggested the great importance of allyl chloride in the tetrahydrofuranylation reaction. Then, more reactions were performed using allyl chloride and benzyl alcohol in THF, but without $Pd(OAc)_2$ and/or PPh_3 and/or CO, with the aim of understanding a possible influence of the other reactants. Ether **5a** was obtained selectively in modest yields (entries 3–5, Table 1), excluding the Pd(II) and the Pd(0) as possible initiator of a supposed radical mechanism in these kind of reactions. Moreover, these results allowed us to deduce that the process did not need to be carried out under CO pressure. Thus, in order to find milder operating conditions, the reaction of allyl chloride and benzyl alcohol in THF was performed at reflux temperature, instead of 110 °C in autoclave (entry 6, Table 1). Ether **5a** was selectively obtained in a reasonable transformation yield of 60%, in the same reaction time, while a 40% of unreacted alcohol was recovered by chromatography. Finally, allyl chloride and benzyl alcohol in THF were reacted in autoclave under N_2 pressure, removing any O_2 traces. Ether **5a** was not observed (entry 7, Table 1); this result drove us to an important consideration: even in small amounts oxygen was necessary for the reaction to progress.

Therefore, all these results clearly highlight that the benzyl alcohol tetrahydrofuranylation is mostly dependent on the presence of the allyl chloride and on the O_2 traces.



5

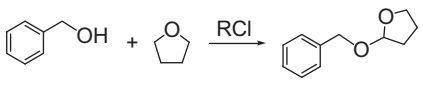
Scheme 3. Proposed mechanism for tetrahydrofuranylation reaction of alcohol.

According to these results, obtained in the absence of any metal or peroxide catalyst, we suggest a radical mechanism initiated by the atmospheric oxygen, where the tetrahydrofuranyl radical is favored by slightly high temperature, and the allyl radical is a propagator of the radical chain (Scheme 3).

For better investigating this mechanism, we performed more experiments. Adding benzyl chloride (entry 2, Table 2), instead of allyl chloride (entry 1, Table 2), into benzyl alcohol and THF mixture at reflux temperature, compound **5a** was obtained in similar isolated yield (45%).

The presence of a primary halide such as the 1-Cl-hexane instead of the allyl or benzyl chloride did not afford any reaction product (entry 3, Table 2). Therefore, the allyl or benzyl chlorides are strategic for the reaction because of the easy formation and high stability of the corresponding radicals. The reaction performed with lower amount of allyl chloride gave ether **5a** in lower isolated yields (entry 4, Table 2). The same reaction carried out without allyl chloride produced **5a** in traces (entry 5, Table 2). The reaction performed with de-aerated THF did not give, in 15 h, any product (entry 6, Table 2). Thus, it is reasonable to conclude that the proposed mechanism needs oxygen as the initiator and the allyl chloride as the propagator of the radical chain (Scheme 3). These considerations were furthermore supported by more experiments:

Table 2
Reaction of benzyl alcohol with RCl in THF at refluxing temperatures for 15 h



5a

Entry	RCl	mmol	Yield[a] (%)
1	CH_2=$CHCH_2$–	(1.2)	57
2	$C_6H_5CH_2$–	(1.2)	45
3	$CH_3(CH_2)_4CH_2$–	(1.2)	–
4	CH_2=$CHCH_2$–	(0.3)	5
5	–	–	Traces
6[b]	CH_2=$CHCH_2$–	(1.2)	–
7[c]	CH_2=$CHCH_2$–	(1.2)	–
8	CH_2=$CHCH_2$–	(3.0)	70

[a] Isolated yield.
[b] Reaction performed in de-aerated THF.
[c] Reaction carried out in the presence of 1.2 mmol of 2,2,6,6-tetramethyl-1-oxypiperidine (TEMPO).

(a) Adding the 2,2,6,6-tetramethyl-1-oxy-piperidine (TEMPO, 1.2 mmol) to a benzyl alcohol–THF and allyl chloride mixture, ether **5a** was not formed (entry 7, Table 2). This result supports, once more, the radical mechanism of the reaction as the TEMPO is responsible for neutralizing the formed radical, inhibiting the radical mechanism and then the tetrahydrofuranyl ether formation.

(b) A greater isolated yield was observed increasing the allyl chloride amount (3.0 mmol), under same operating conditions (entry 8, Table 2). This result supports the hypothesis of the allyl radical as the propagator of the radical chain.

(c) A solution of the only allyl chloride in THF, at reflux temperature for few hours, gave the 2-Cl-tetrahydrofuran. This compound is the outcome of the radical mechanism (Scheme 3), which undergoes, in a second instance, a nucleophilic substitution by the alcohol.

As the commercial THF (Aldrich) contains stabilizers, the different results reported in the literature for similar reactions are probably due to the different kinds of THF used. For instance, the THF used for each process reported in this manuscript was previously distilled in order to free it of any radical stabilizers. The distilled solvent was then ready to allow the tetrahydrofuranyl radical formation by simple action of the atmospheric oxygen (Scheme 3). Moreover, when the THF was used for alcohol tetrahydrofuranylation without distillation, the products were not observed or observed only in traces. These considerations highlight that the use of the stabilized THF should need, as reported in the literature, the addition of an oxidant that firstly reacts with the stabilizer and then can form the furanyl radical. In order to support this hypothesis, the tetrahydrofuranylation reaction was performed on benzyl alcohol and allyl chloride using the commercial stabilized THF. After 15 h of refluxing, only few traces of the functionalised alcohol were observed. When the oxidant $CrCl_2$ (1.0 mmol)[11] was added to this reaction mixture, the expected ether was formed very quickly, as reported in the literature.

At the end of this deep investigation, the best experimental conditions for a good yield in ether **5a** resulted those reported on Table 2, entry 8. For instance, a representative experimental procedure for the tetrahydrofuranylation of alcohols is hereafter reported. A solution of benzyl alcohol (1 mmol) and allyl chloride (3 mmol) in unstabilized THF (20 mL) was refluxed for 15 h. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (ethyl ether/petroleum ether = 2:8) to afford the pure ether **5a**. The same synthetic protocol was then applied for the tetrahydrofuranylation of simple alcohols. The use of ethanol, 2-butanol and cyclohexanol gave compounds **7**–**9**, in 60%, 55% and 55% of isolated yields, respectively (Chart 1).

The phenolic function underwent the tetrahydrofuranylation too, being transformed into ether **10** in slightly lower isolated yields (35%). We then decided to extend this protection methodology to more complex alcohols, encouraged by these results. The tyrosol and the *p*-hydroxybenzyl alcohol were transformed into compounds **11** and **13** in 45% and 40% of isolated yields, respectively (Chart 1), the tetrahydrofuranylation occurring at the alcoholic function only. The methoxytyrosol was transformed into product **12** in 61% of isolated yield. The hydroxytyrosol, a known powerful antioxidant present in the olive tree leaves, underwent a degradation: no tetrahydrofuranylation product was isolated. Rather, protecting the two phenolic functions by methoxy groups, the tetrahydrofuranylation of the free alcoholic group of the protected hydroxytyrosol afforded ether **14** in an isolated yield of 88% (Chart 1).

The reaction easiness allowed us to functionalise also more complex molecules such as the cholesterol and the 1,2,5,6-di-*O*-isopropyliden-α-D-glucofuranose: ethers **15** and **16** were formed in fairly good isolated yields of 55% and 60%, respectively. For instance, compound **15** (as epimer at the THF ring), already isolated in a diastereoisomeric mixture by Hon et al.,[14] was formed with a diastereomeric enrichment (de) >99% as the sole diastereomer ($[\alpha]_D^{22} - 25.6$).[15] The high stereoselectivity observed for this reaction could be due to a better asymmetric induction which seems to be favoured by our synthetic methodology (with no metal or peroxide catalyst). Product **16** was obtained with a de = 20% and was isolated as a diastereomeric mixture, according to what was previously reported in the literature.[12]

Because of the easy 2-tetrahydrofuranyl radical formation, the THF was also reported in the literature to be widely used in the radical addition reactions to C=N and C=O bonds, but in the presence of Me_2Zn and air. Under similar conditions, arylamines, alkoxyamines and dialkylhydrazines were reported to react with THF to give amino alcohols, oximes and hydrazones, respectively.[16]

In order to show that the tetrahydrofuranyl radical generation if performed in unstabilized THF did not need oxidant addition, except for the atmospheric oxygen already present, the same kind of reaction described above was carried out with some imines. The obtained results are reported in Table 3.

The reactions were carried out in freshly distilled and unstabilized THF, at reflux temperature for 15 h. The addition to the C=N double bond occurred regioselectively: the THF radical carbon bore the imine carbon while the THF hydrogen linked the imine nitrogen, respectively. The supposed mechanism is still radical, having oxygen as the initiator and the allyl system increasing the THF radical formation. The resulting tetrahydrofuranyl amine was the outcome of the THF radical addition to the C=N double bond (Scheme 4).

An analogous reaction, probably following a similar mechanism, was performed on the alkyne function. For instance, the THF

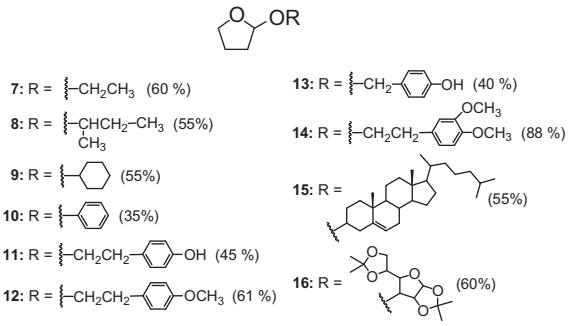
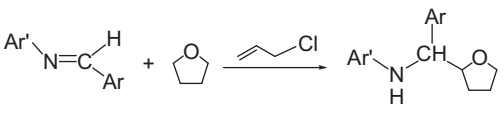


Chart 1.

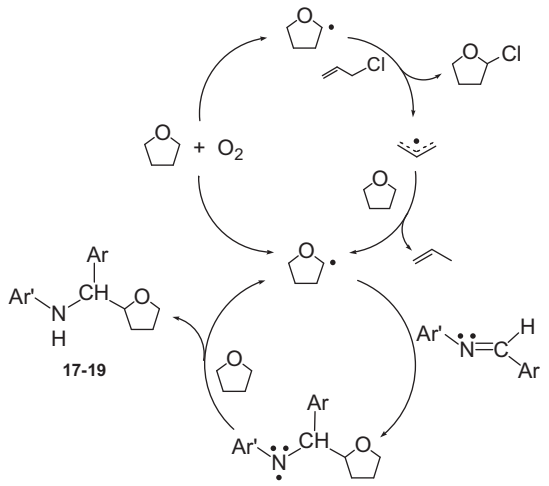
Table 3
Reaction of imines with allyl chloride in THF at refluxing temperatures for 15 h affording the tetrahydrofuranyl amines **17**–**19**



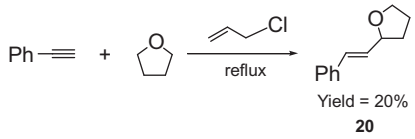
17-19

Entry	Ar′	Ar	Product	Yield[a,b] (%)
1	Ph	Ph	**17**	35
2	BTz[c]	3-Py[d]	**18**	69
3	3-Py	4-Cl–Ph	**19**	87

[a] Transformation yield calculated by GC.
[b] Diastereomeric mixture of products.
[c] BTz = 2-benzothiazolyl.
[d] 3-Py = 3-pyridinyl.



Scheme 4. Proposed mechanism for tetrahydrofuranylation reaction of imine.



Scheme 5. Tetrahydrofuranylation of phenyl acetylene.

regioselective addition to the triple bond was observed (Scheme 5) when a mixture of allyl chloride and phenyl acetylene in THF was reacted at reflux temperature for 15 h.

In conclusion, an operationally simple, inexpensive, and efficient method to prepare 2-tetrahydrofuranyl ethers has been developed. This methodology is based on the reaction of alcohols with allyl or benzyl chloride, in unstabilized THF at reflux temperature. The different behaviour of the freshly distilled THF with respect to the THF containing stabilizers has been highlighted; in this latter case the oxidant addition was necessary. The settled mild conditions, avoiding the use of any metal or peroxide catalyst, and the general tolerance of most functional groups, make this methodology widely suitable for the synthesis of complex molecules. Furthermore, 2-tetrahydrofuranyl ethers are reported in the literature as useful protecting groups for alcohols, as they can be easily removed under weakly acidic conditions.[17] Few attempts of protecting biological and pharmacological active molecules have been made in this contribution, obtaining very good yields. The same simple synthetic protocol has been applied also to the imine double bond and to the alkyne function affording 2-tetrahydrofuranyl amines and vinyls in a selective way, through a radical addition. All the reported results increase the potentiality of this methodology that becomes widely versatile for numerous synthetic applications.

Acknowledgements

Thanks are due to the MIUR, the University of Salento and to the C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi) for the financial support.

References and notes

1. Troisi, L.; De Vitis, L.; Granito, C.; Epifani, E. *Eur. J. Org. Chem.* **2004**, 1357–1362.
2. Troisi, L.; Ronzini, L.; Granito, C.; De Vitis, L.; Pindinelli, E. *Tetrahedron* **2006**, *62*, 1564–1574.
3. Troisi, L.; Ronzini, L.; Granito, C.; Pindinelli, E.; Troisi, A.; Pilati, T. *Tetrahedron* **2006**, *62*, 12064–12070.
4. De Vitis, L.; Troisi, L.; Granito, C.; Pindinelli, E.; Ronzini, L. *Eur. J. Org. Chem.* **2007**, 356–362.
5. Troisi, L.; Pindinelli, E.; Strusi, V.; Trinchera, P. *Tetrahedron: Asymmetry* **2009**, *20*, 368–374.
6. Troisi, L.; Granito, C.; Rosato, F.; Videtta, V. *Tetrahedron Lett.* **2010**, *51*, 371–373.
7. Troisi, L.; Granito, C.; Rosato, F.; Videtta, V. Unpublished results.
8. Jung, J. C.; Choi, H. C.; Kim, Y. H. *Tetrahedron Lett.* **1993**, *34*, 3581–3584.
9. Maione, A. M.; Romeo, A. *Synthesis* **1987**, *3*, 250–251.
10. Ochiai, R.; Sueda, T. *Tetrahedron Lett.* **2004**, *45*, 3557–3559.
11. Baati, R.; Valleix, A.; Mioskowski, C.; Barma, D. K.; Falck, J. R. *Org. Lett.* **2000**, *2*, 485–487.
12. Falck, J. R.; De Run, L.; Bejot, R.; Mioskowski, C. *Tetrahedron Lett.* **2006**, *47*, 5111–5113.
13. Das, B.; Krishnaiah, M.; Reddy, V. S.; Laxminarayana, K. *Helv. Chim. Acta* **2007**, *90*, 2163–2166.
14. Hon, Y.-S.; Lee, C.-F.; Chen, R.-J.; Szu, P.-H. *Tetrahedron* **2001**, *57*, 5991–6001.
15. *Experimental characterization of compound* **15**. Yield: 251 mg (55%). $[\alpha]_D^{22}$ −25.6 (*c* 0.02, $CHCl_3$). White solid with mp 101–103 °C (*n*-hexane). ^1H NMR (400.13 MHz, $CDCl_3$): δ 0.67 (s, 3H), 0.86 (dd, 6H, *J* = 1.4, 6.6 Hz), 0.91 (d, 3H, *J* = 6.5 Hz), 0.99 (s, 3H), 0.94–1.70 (m, 21H), 1.77–2.02 (m, 9H), 2.15–2.36 (m, 2H), 3.41–3.48 (m, 1H), 3.80–3.94 (m, 2H), 5.28 (dd, 1H, *J* = 2.4, 4.9 Hz), 5.34 (t, 1H, *J* = 5.4 Hz) ppm. ^{13}C NMR (100.62 MHz): δ 11.8, 18.7, 19.4, 21.0, 22.6, 22.8, 23.5, 23.8, 24.3, 28.0, 28.2, 29.9, 31.9, 32.6, 35.8, 36.2, 36.7, 37.3, 37.4, 39.0, 39.5, 39.8, 42.3, 50.2, 56.2, 56.8, 66.6, 102.0, 121.5, 141.0 ppm. FTIR ($CHCl_3$): ν 2938, 2867, 1465, 1377, 1184, 1039 cm^{-1}. HRMS (ESI): calcd for $C_{31}H_{52}O_2$ 457.3967 $[M+H]^+$; found 457.3966.
16. Akindele, T.; Yamada, K.-I.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345–355.
17. Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Chemistry*; Wiley: New York, 1999. Chapter 22, pp 57 and 58.