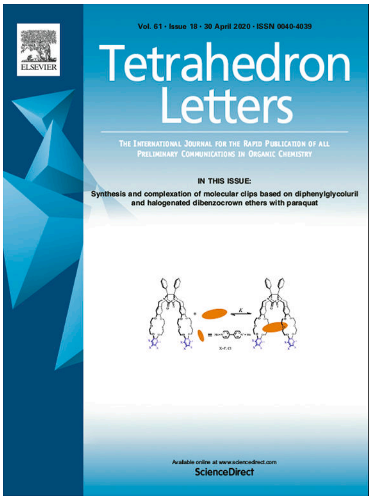


Metal-free tetrahydrofuranylation of alcohols with tertbutyl nitrite

Kang Bi, Yue-Ming Cai, Yun-Bing Zhou, Junyue Lin, Miao-Chang Liu

PII: S0040-4039(20)30718-8
DOI: https://doi.org/10.1016/j.tetlet.2020.152251
Reference: TETL 152251

To appear in: *Tetrahedron Letters*

Received Date: 28 March 2020
Revised Date: 6 July 2020
Accepted Date: 10 July 2020

Please cite this article as: Bi, K., Cai, Y-M., Zhou, Y-B., Lin, J., Liu, M-C., Metal-free tetrahydrofuranylation of alcohols with tertbutyl nitrite, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152251

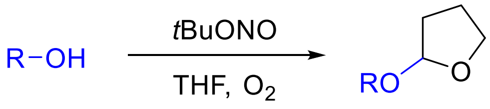
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Metal-Free Tetrahydrofuranylation of Alcohols with Tertbutyl Nitrite

Leave this area blank for abstract info.

Kang Bi[a] , Yue-Ming Cai[a] , Yun-Bing Zhou[a] , Junyue Lin[b], * and Miao-Chang Liu[a], *



- Metal-free conditions
- Excellent functional group tolerance
- Broad scope
- Gram-scale

Tetrahedron Letters
journal homepage: www.elsevier.com

Metal-Free Tetrahydrofuranylation of Alcohols with Tertbutyl Nitrite

Kang Bi[a], Yue-Ming Cai[a], Yun-Bing Zhou[a], Junyue Lin[b, *] and Miao-Chang Liu[a, *]

[a]*College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, 325035, P. R. of China*
[b]*College of Chemistry & Chemical Engineering, Jinggangshan University, Jinggangshan, 343600, P. R. of China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Tertbutyl nitrite
Alkoxyl radical
Protection of alcohols
Metal-Free
Tetrahydrofuran

ABSTRACT

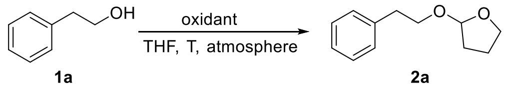
Metal-free tetrahydrofuranylation of alcohols in the presence of tertbutyl nitrite is described, providing a facile and green route for the protection of hydroxy groups. Mechanistic studies demonstrate that this transformation proceeds in a radical way, and involves alkyl nitrite of corresponding alcohol as the key intermediate.

Alcohols have always been a class of important synthetic precursors in organic synthesis on account of their availability, variety and abundance on earth. Considering their instability under harsh reaction conditions, hydroxy groups usually need to be protected in advance. Among currently existed approaches to protecting hydroxy groups, tetrahydrofuranylation of alcohols is getting more attention from organic chemists, since hydrolysis of THF-ether can proceed under milder conditions in shorter time compared with well researched THP-group.[1] In 1976, Professor Gen and coworkers disclosed the first tetrahydrofuranylation of alcohols in the presence of $SOCl_2$.[2] Then, lots of reaction conditions applied in tetrahydrofuranylation of alcohols such as $CrCl_2$,[3] alkylperoxy-λ3-iodane,[4] Mn(0) powder,[5] and VCl_3[6] in the presence of CCl_4 were established successively by Falck, Sueda, Mioskowski and Laxminarayana. In 2013, Deng's group developed a $CuBr_2$-promoted alcohol tetrahydrofuranylation,[7] but it suffered from relatively low yields. Recently, a light-promoted metal-free cross dehydrogenative coupling between ethers and alcohols was described by Vincent' group.[8] The use of other reagents including ceric ammonium nitrate,[9] p-TsCl[10] and $(Bu_4N)_2S_2O_8$[11] also successfully enabled tetrahydrofuranylation of alcohols. Despite these advances, the development of a facile and green procedure for the preparation of tetrahydrofuranether is still desired. Herein, we report a metal-free method for tetrahydrofuranylation of alcohols with tertbutyl nitrite.

To commence our investigation, the reaction of 2-phenylethanol in THF at 80°C was chosen as a model reaction system in the presence of *t*BuONO. Gratifyingly, we found that the reaction afforded the desired product **(2a)** in 74% yield in the presence of two equivalents of *t*BuONO (Table 1, entry 1). Prolonging the reaction time led to an increased yield (Table 1, entry 2). Notably, when the atmosphere was replaced by air or nitrogen, the reaction delivered lower yields of 72% and 52% (Table 1, entry 4 and 5). Raising temperature to 90°C was beneficial to the yield of **2a** (Table 1, entry 6), whereas a further lift of temperature to 100°C showed no improvement (Table 1, entry 7). Furthermore, a lower temperature of 60°C resulted in a sharp decrease in the yield of the desired product (Table 1, entry 8), indicating that the temperature is crucial to the efficiency of this transformation. Remarkably, the use of 2.5 equivlents of *t*BuONO led to an excellent yield of **2a** (Table 1, entry 12). Further screening of oxidants (Table 1, entries 14-17) showed that *t*BuONO was identified as the most efficient oxidant. Therefore, the optimal conditions entailed the use of *t*BuONO (2.5 equiv) as an oxidant in THF at 90 °C.

With the optimal reaction conditions in hand, we further explored the possibility to extend the methodology to a variety of alkyl alcohols (Table 2). 1-Phenyl-2-propanol (**1b**) was subjected to the optimal reaction conditions, and delivered the diastereoisomers **2b** with a low yield compared to that of **2a**, indicating that steric effect showed negative influence on the efficiency of this transformation. Changing the phenyl moiety to fluorenyl or naphthyl moiety afforded the desired products in 75% (**1c**) and 91% (**1d**) yields respectively. A series of alicyclic alcohols with different sizes were successfully reacted to afford corresponding products in moderate to good yields (50-86%,**2e-2k**). In the case of macrocyclic alcohol (**1h**), an obvious decrease in yield was observed. Liner alcohols (**1l** and **1m**) also worked efficiently with excellent yields. The halogen substituents such as Br and Cl (**1m-1o**) were well tolerated under standard conditions. Alcohols containing a heterocyclic ring (**1p-1r**) or an alkyne moiety proved to be a suitable substrate and provided the desired products (**2p-2r**) in 25-89% yields. Due to the formation of aldehydes as major byproducts, allyl and propargyl alcohols afforded inferior yields (**1p** vs **1q**, **1s** vs **1t**). It is worthy to note that this method was successfully applied to the hydroxy group

Ta



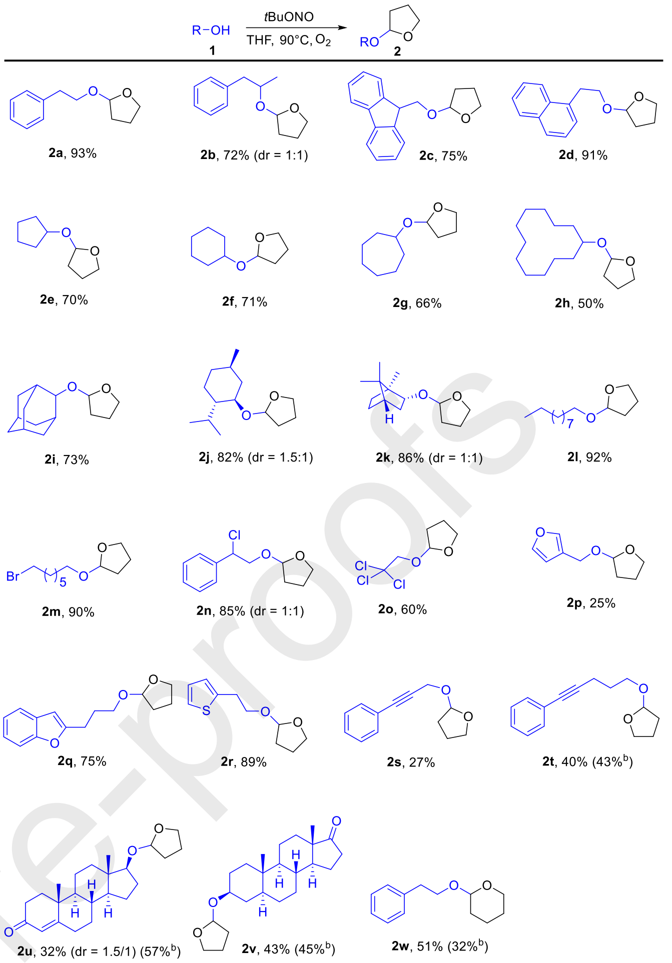
Entry	Oxidant	Temperature (°C)	t (h)	Yield (%)[b]
1	*t*-BuONO	80	12	74
2	*t*-BuONO	80	20	81
3	*t*-BuONO	80	24	82
4[c]	*t*-BuONO	80	20	72
5[d]	*t*-BuONO	80	20	52
6	*t*-BuONO	90	20	87
7	*t*-BuONO	100	20	73
8	*t*-BuONO	60	20	39
9	*t*-BuONO	70	20	79
10[e]	*t*-BuONO	90	20	58
11[f]	*t*-BuONO	90	20	79
12[g]	*t*-BuONO	90	20	93
13[h]	*t*-BuONO	90	20	89
14[g]	*n*-BuONO	90	20	79
15[g]	*i*-BuONO	90	20	82
16[g]	*t*-BuOOH	90	20	12
17[g]	$(t\text{-BuO})_2$	90	20	17

a Reaction conditions: 1a (0.5 mmol), *t*BuONO (1 mmol), solvent (2 mL), under an oxygen atmosphere.
b Isolated yields.
c Under air atmosphere.
d Under N_2 atmosphere.
e *t*-BuONO (1.0 equiv).
f *t*-BuONO (1.5 equiv).
g Oxidant (2.5 equiv).
h *t*-BuONO (3.0 equiv).

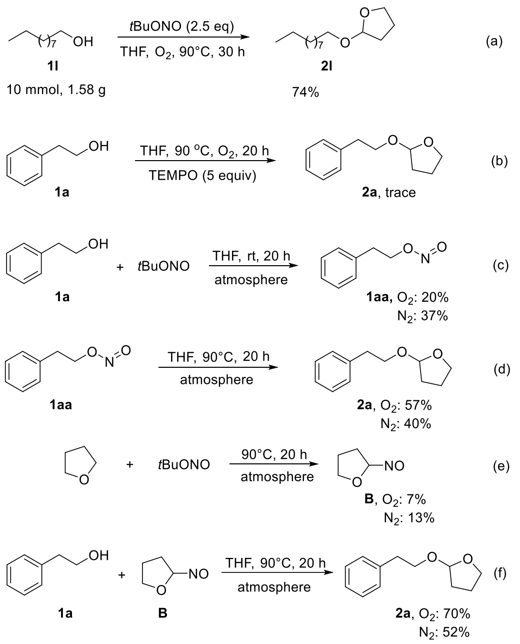
protection of natural compounds including Testosterone (**1u**) and Epiandrosterone (**1v**). Interestingly, it was found that *t*BuONO also enabled the reaction of tetrahydropyran and 2-phenylethanol to provide desired product (**2w**). The low yields of products **2t-2w** were mainly attributed to the poor conversions.

In order to investigate the practicality of this reaction, we carried out a gram-scale reaction using **1l** as a substrate (Scheme 1a). After 30 h, the reaction successfully delivered the desired product **2l** in 74% yield with 20% of **1l** to be recovered.

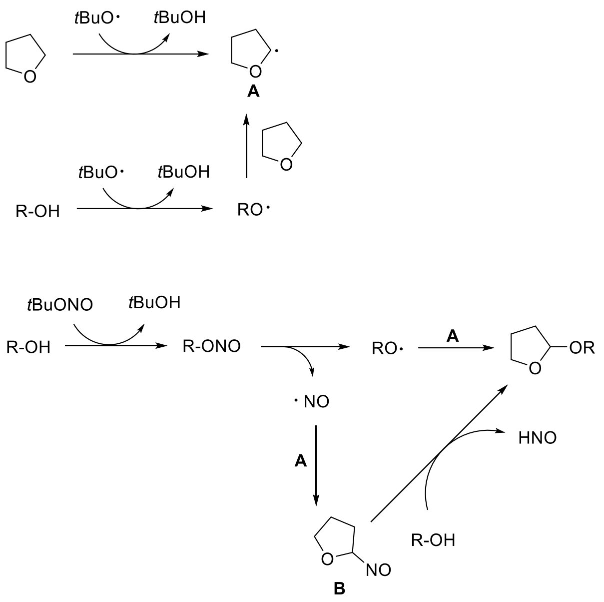
Some control experiments were conducted to shed light on the mechanism of this procedure. The presence of 5 equivalents of TEMPO led to only trace of product, supporting a radical way (Scheme 1b). The reaction between 2-phenylethanol and *t*BuONO under O_2 or N_2 atmosphere gave 20% and 37% yields of intermediate **1aa** respectively (Scheme 1c). In the absence of *t*BuONO, the resulting intermediate **1aa** could react with THF to give the desired product **2a** (Scheme 1d). The employment of O_2 atmosphere delivered a better yield of **2a** because oxygen could abstract a hydrogen atom from THF to afford a radical intermediate.[7] We also detected the formation of 2-nitrosotetrahydrofuran (**B**) during the reaction (Scheme 1e). The presence of O_2 brought a negative impact on the reaction efficiency probably due to the instability of **B** under O_2 atmosphere. The intermediate **B** could react well with **1a** to produce the desired product **2a** (Scheme 1f). These results indicated that both **1aa** and **B** served as the reaction intermediates.



a Reaction conditions: **1** (0.5 mmol), *t*BuONO (1.25 mmol), solvent (2 mL), under oxygen atmosphere, isolated yields.
b Recovered starting material.



Scheme 1. Gram-Scale synthesis and some control experiments.



Scheme 2. Proposed reaction mechanism.

Based on the results of control experiments and previous references,[12] a plausible mechanism was described in Scheme 2. First, a *t*BuO radical and a NO radical are generated from homolytic cleavage of *t*BuONO. The *t*BuO radical or oxygen abstracts a hydrogen atom from tetrahydrofuran to form a carbon-centred radical **A**. Moreover, radical **A** could be accessed via hydrogen atom transform between THF and oxygen radicals generated from substrates. [13] On the other hand, alcohol reacts with *t*BuONO to give corresponding alkyl nitrite which fragments into an alkoxyl radical and a NO radical. Subsequently, alkoxyl radical is coupled with radical **A** to afford tetrahydrofuranylation product. Alternatively, NO radical is trapped by **A** to generate intermediate **B** which undergoes a nucleophilic substitution reaction with alcohol to form target product.

In summary, we have disclosed a new method to synthesize tetrahydrofuran ether via the oxidative coupling between THF and alcohols in the presence of *t*BuONO. Mechanism exploration shows that this reaction proceeds in a radical way. The advantages of this protocol include no need for metal, easy operation, simple conditions and excellent functional group tolerance, enabling it to be an attracting alternative method for the protection of alcohols.

Acknowledgments

nal Natural Science Foundation of China (21372177 and 21901187).

References and notes

1. Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449. (a) Miyashita, R.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772-3774; (b) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618-620; (c) Morizawa, Y.; Mori, I.; Hiyama, T.; Nozaki, H. *Synthesis* **1981**, 899-901; (d) Olah, G.; Husain, A.; Singh, B. P. *Synthesis* **1985**, 703-704; (e) Bolitt, V.; Mioskowski, C.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1988**, *29*, 4583-4586; (f) Ranu, B. C.; Saha, M. *J. Org. Chem.* **1994**, *59*, 8269-8270; (g) Bhalerao, U. T.; Davis, K.J.; Rao, B. V. *Synth. Commun.* **1996**, *26*, 3081-3085; (h) Habibi, M.H.; Tangestaninejad, S.; Mohammadpoor-Baltork, I.; Mirkhani, V.; Yadollahi, B. *Tetrahedron Lett.* **2001**, *42*, 2851-2853; (i) Stephens, J. R.; Butler, P. L.; Clow, C. H.; Oswald, M. C.; Smith, R. C.; Mohan, R. *Eur. J. Org. Chem.* **2003**, *19*, 3827-3831.
2. Kruse, C. G.; Broekhof, N. L. J. M.; van der Gen, A. *Tetrahedron Lett.* **1976**, *20*, 1725-1726.
3. Baati, R.; Valleix, V.; Mioskowski, C.; Barma, D. K.; Falk, J. R. *Org. Lett.* **2000**, *2*, 485-487.
4. Ochiai, R.; Sueda, T. *Tetrahedron Lett.* **2004**, *45*, 3557-3559.
5. Falck, J. R.; De Run, L.; Bejot, R.; Mioskowski, C. *Tetrahedron Lett.* **2006**, *47*, 5111-5113.
6. Das, B.; Krishnaiah, M.; Reddy, V. S.; Laxminarayana, K. *Helv. Chim. Acta* **2007**, *90*, 2163-2166.
7. Wang, M.; Zhou, Z.; Tang, R.; Zhang, X.; Deng, C. *Synlett*. **2013**, *24*, 737-740.
8. Beniazza, R.; Abadie, B.; Remisse, L.; Jardel, D.; Lastécouères, D.; Vincent, J. *Chem. Commun*. **2017**, *53*, 12708-12711.
9. Maione, A. M.; Romeo, A. *Synthesis* **1987**, 250-251.
10. Yu, B.; Hui, Y. *Synth. Commun.* **1995**, *25*, 2037.
11. Jung, J. C.; Choi, H. C.; Kim, Y. H. *Tetrahedron Lett*. **1993**, *34*, 3581-3584.
12. (a) L. Troisi, C. Granito, L. Ronzini, F. Rosato, V. Videtta, *Tetrahedron Lett.* **2010**, *51*, 5980-5983; (b) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J.* **2011**, *17*, 4085-4089; (c) Kabasakalian, P.; Townley, E.; Yudis, M. *J. Am. Chem. Soc.* **1962**, *84*, 2716-2718; (d) Akhtar, M.; Barton, D. H. R.; Sammes, P. G. *J. Am. Chem. Soc.* **1965**, *87*, 4601-4607.
13. Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937–1949.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

1. The protection of alcohols.
2. Synthesizing asymmetric ethers via *t*BuONO-promoted oxidative coupling between tetrahydrofuran and alcohols.
3. Exploring the potential applications of tertbutyl nitrite in the organic synthesis.