Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

General methodology for the chemoselective *N*-alkylation of (2,2,6,6)-tetramethylpiperidin-4-ol: Contribution of microwave irradiation

Romain Membrat [a], Alexandre Vasseur [b], Laurent Giordano [a], Alexandre Martinez [a], Didier Nuel [a]

[a] Aix-Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France
[b] Université de Lorraine, CNRS, L2CM, F-54000 Nancy, France

ARTICLE INFO

Article history:
Received 2 November 2018
Revised 30 November 2018
Accepted 10 December 2018
Available online xxxx

Keywords:
Chemoselective alkylation
Functional tolerance
Microwave assisted reactions
Sterically hindered amines

ABSTRACT

A convenient method to access a broad variety of *N*-alkyl-(2,2,6,6)-tetramethylpiperidin-4-ol compounds is reported. The thermal treatment of a mixture of (2,2,6,6)-tetramethylpiperidin-4-ol and allyl or benzyl bromide derivatives gave the corresponding *N*–alkylated compounds in good yields while leaving the hydroxyl functional group intact. Whereas 40 h were needed to reach complete conversion, microwave irradiation allowed the reaction time to be reduced (20 min) and improved the yields in most cases.

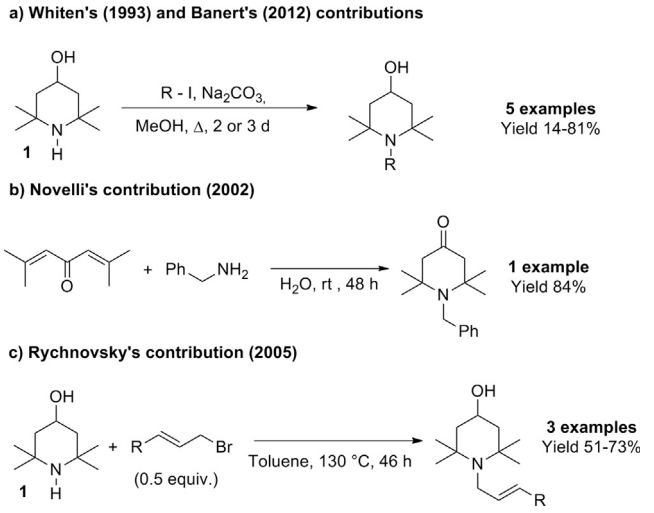
Introduction

Sterically Hindered Amine (SHA) is a term coined by Sartori and Savage in 1983 to define any primary or secondary amine derivatives in which the amino group is bonded to a tertiary carbon atom and a secondary or tertiary carbon atom, respectively [1]. They have long been known for their performance in carbon dioxide removal for gas steaming in industrial chemical processes [2–4]. (2,2,6,6)-Tetramethylpiperidin-4-ol derivatives **1** belong to this compound class and have added an extra-dimension to applications over the last two decades. Indeed, **1** is a synthetic precursor of TEMPOL [5] which is a well-known nitroxyl radical of major interest in organic synthesis [6], as well as polymer chemistry [7]. TEMPOL exhibits not only a higher oxidation potential than its TEMPO analogue [8], but also represents a low cost alternative [6]. In this context, Rychnovsky and co-workers showed that the catalytic activity of TEMPOL could be three times higher than that of TEMPO when grafted to a polymeric carrier *via* the OH moeity [9]. Using *N*-allyl (2,2,6,6)-tetramethylpiperidin-4-ol as a precursor of TEMPOL was essential to achieve the grafting procedure. In another context, **1**–derived *N*-alkylated compounds are also useful for commercial polymeric material stabilization [10,11]. In particular, *N*-alkyl substitution enables significant modulation of the photosensibilizing effects of **1** in polypropylene [10]. For at least these two reasons, the *N*-alkylation reaction of **1** has been well studied, but the development of an efficient protocol remains desirable as the literature precedent is scarce in this regard [12]. Whiten and co-workers carried out the synthesis of *N*-ethyl, *N*-methyl and *N*-hydroxymethylanthra-none-(2,2,6,6)-tetramethylpiperidin-4-ol from **1** in moderated to good yields, using classical S_N2 reaction conditions (Scheme 1, a) [13].

Banert and co-workers thereafter capitalized on this contribution to reinvestigate the synthesis of triacetonamine derivatives, without however studying neither the scope nor alternatives to reduce the reaction time [14]. Alternatively, Novelli and co-workers proposed a double Michael addition-based approach for the synthesis of *N*-benzyl-(2,2,6,6)-tetramethylpiperidin-4-one from phorone and benzylamine (Scheme 1, b) [15]. Although this method provides the expected compound in a good yield, multiple purification steps by column chromatography strongly limits its attractiveness. Later, Rychnovsky's group reported the synthesis of three *N*-allyl-(2,2,6,6)-tetramethyl-piperidin-4-ol compounds in good yields [9]. The reaction was conducted in a sealed tube using two equivalents of (2,2,6,6)-tetramethylpiperidin-4-ol **1** with regard to the electrophile (Scheme 1, c). Herein, we report that this method is convenient for the preparation of *N*-benzyl and *N*-allyl-(2,2,6,6)-tetramethylpiperidin-4-ol in good to high yields, including on gram-scale when performed in an autoclave. The scope was examined and the effect of microwave irradiation on the process was also investigated to optimize its effectiveness.

E-mail address: didier.nuel@centrale-marseille.fr (L. Giordano)

https://doi.org/10.1016/j.tetlet.2018.12.020
0040-4039/



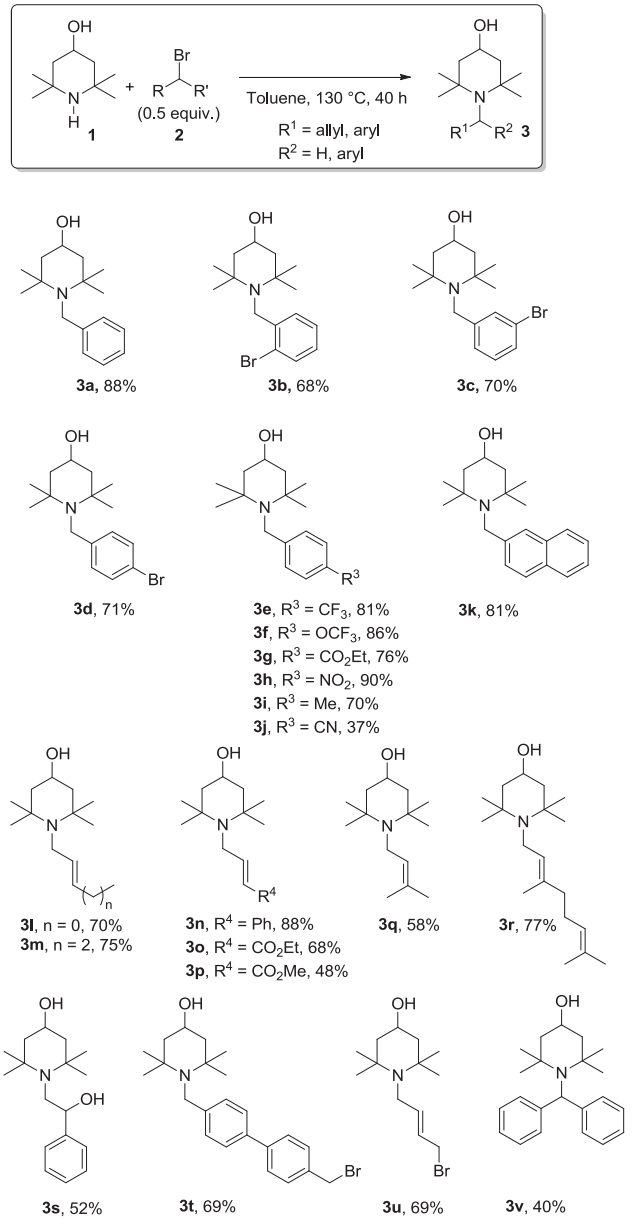
Scheme 1. Reported procedures for the *N*-alkylation of **1**.

Results and discussion

During preliminary investigations, we observed that classical Hoffmann alkylation conditions relying on the use of an inorganic Brønsted base such as K_2CO_3 or $CsCO_3$ in DMF were unsuccessful. Specifically, the nucleophilicity gap between oxygen and nitrogen is narrowed due to the high steric hindrance caused by the four methyl groups positioned at the two carbons adjacent to the nitrogen atom. Accordingly, all our attempts led to an intractable mixture of *O*- and *N*-alkylated products [14]. Moreover, acylation of the hindered amine and subsequent reduction of the amide using a hydride source ($LiAlH_4$, $PhSiH_3$, or BH_3·THF) only allowed recovery of the starting material. Buchwald–Hartwig coupling reaction-based strategies [16,17] also proved to be poorly chemoselective. In addition, it is important to note that the alkylation of (2,2,6,6)-tetramethylpiperidin-4-one was unviable because: (i) protons at the α-position of the ketone are labile even under mildly basic conditions, thus leading to enol formation and then to the corresponding *C*-alkylated and aldol products [14]. (ii) no general methodology is reported to chemically reduce the ketone without alteration of the integrity of the C–N bond. These unsuccessful attempts highlighted the difficulty in achieving the chemoselective *N*-alkylation of **1**. As the Rychnovsky's approach [9] was promising but unexplored, we first examined its scope using a slightly modified procedure.

Alkylation in an autoclave

A wide variety of electrophiles were screened under Rychnowsky's conditions (see Scheme 2) but using an autoclave instead of a sealed tube in order to achieve better control of the experiment as well as to support possible scaling up. The treatment of **1** with benzyl bromide (0.5 equiv.) as the electrophile at 130 °C for 40 h gave the expected product **3a** in 88% isolated yield after simple filtration through a short pad of silica gel (Scheme 2). We then explored the aromatic ring substitution effect. Using bromobenzyl bromide as the electrophile gave the corresponding *N*-alkylated product in similar yield whatever the position of the halide atom on the aromatic ring (Scheme 2, see **3b**–**d**). A large number of 4-substituted benzyl bromides also reacted smoothly under these conditions (Scheme 2, see **3e**–**i**), indicating that the reaction proceeds independently of the electron density localized on the aromatic ring moiety. Electron withdrawing or donating group-possessing electrophiles were efficiently reacted, including



Scheme 2. Scope of the process *via* thermal treatment. Reagents and conditions: **1** (12.7 mmol), **2** (6.35 mmol), toluene (20 mL), 130 °C, 40 h, autoclave; [a]Isolated yield.

Scheme 3. Model reaction for optimizing the microwave assisted alkylation.

when strong electron-withdrawing groups were involved (Scheme 2, see **3e** and **3h**). Allylic bromide derivatives could also be used as electrophiles (Scheme 2, see **3l**–**q**). The important point of this strategy lies in the absence of a Brønsted base in the reaction mixture, thus enabling base sensitive substrates to be accessed. Nitrile (Scheme 2, see **3j**) as well as ester groups (Scheme 2, see **3g**, **3o**–**p**) were also compatible with these condi-

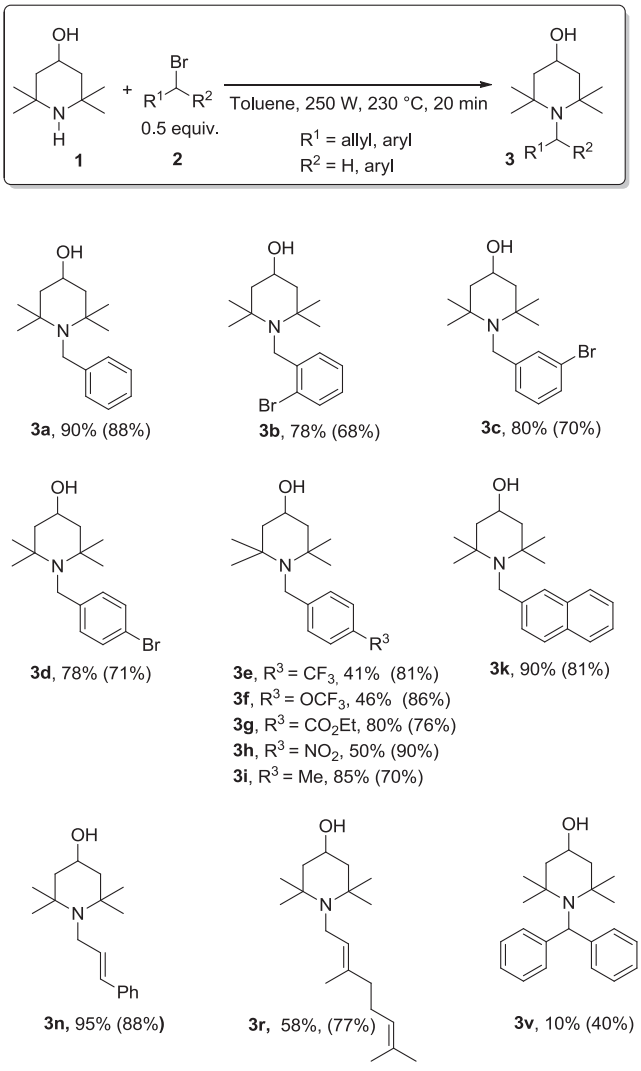
Please cite this article as: R. Membrat, A. Vasseur, L. Giordano et al., General methodology for the chemoselective *N*-alkylation of (2,2,6,6)-tetramethylpiperidin-4-ol: Contribution of microwave irradiation, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2018.12.020

Table 1
Optimization of the process using microwave irradiation.[a]

Entry	Solvent	T (°C)	Time (min.)	**1** (%)[b]	*N*-Alkyl **1** (%)[b]	*O*-Alkyl **1** (%)[b]
1	Neat	230	5	66	28	6
2	Neat	230	10	48	44	8
3	Neat	230	20	35	53	10
4	Neat	250	5	21	66	20
5	Neat	250	2	44	52	7
6	Neat	180	30	35	60	5
7	DMF	230	20	22	54	24
8	Toluene	230	5	75	24	1
9	Toluene	230	20	3	90	7
10	Toluene	250	20	1	86	14

[a] Reagents and conditions: **1** (0.127 mmol), **2a** (0.0635 mmol), dry solvent (0.2 mL) or Neat in a G10 tube at 250 W.
[b] Conversion measured by ^{1}H NMR spectroscopy.

tions. Interestingly, the use of styrene oxide as the electrophile allowed the synthesis of **3s** possessing a benzyl alcohol in 52% isolated yield and without any trace of elimination products. Starting from allyl or benzyl dibromide resulted in the formation of **3t** and **3u**, respectively, in 69% yield. It is noteworthy that the method left the second electrophilic moiety intact even in the presence of a large excess of **1**, therefore offering the opportunity to increase the functional diversity of the structure. Finally, the reaction was conducted on a large scale (8 g) for the synthesis of **3a** and an isolated yield similar to that previously discussed was obtained (81%). It should be stressed that the excess of **1** could be recovered as the ammonium salt from the aqueous layer and recycled after treatment with base (93%). However, despite the good yields and remarkable chemoselectivity, this strategy is limited by the reaction duration.



Scheme 4. Scope of the microwave assisted transformation. Reagents and conditions: **1** (12.7 mmol), **2** (6.35 mmol), dry toluene (20 mL) in a G30 tube, 250 W, 230 °C, 20 min; [a]Isolated yield; yields obtained *via* thermal treatment are in parentheses.

*Microwave assisted chemoselective N-alkylation of **1***

Microwave irradiation represents a powerful tool to improve the efficiency of organic reactions [18]. The basic principle of microwave heating relies on the ability of polar compounds to selectively absorb the radiation and to convert electromagnetic energy into heat by dielectric losses [19]. This technology enables significant improvements in reactivity, namely chemical rate acceleration, higher yields, or modifications in selectivity [20]. Since microwave irradiation has been largely used for amine alkylation [21–24], we decided to investigate the effect of this technology on the reaction duration. In order to optimise the microwave parameters, the model reaction presented in Scheme 3 was studied. Results of the optimization experiments are given in Table 1.

Using the same **1**/**2a** ratio as in Scheme 2 under neat conditions at 250 W and 230 °C gave 34% conversion after 5 min including 6% of the undesired *O*-alkylated product (Table 1, entry 1). Changes to the temperature and/or the reaction duration resulted in either poor conversions or the loss of chemoselectivity (Table 1, entries 2–6). Use of the good irradiation absorbing solvent DMF led to significant formation of the *O*–alkylated product (Table 1, entry 7). Finally, the best reactivity/selectivity ratio was obtained when the reaction was carried out in toluene at 230 °C for 20 min. Under these conditions, a 97% conversion was attained with excellent chemoselectivity towards the *N*-alkyl product (Table 1, entries 8–10). These microwave based-conditions were then applied to a selection of electrophiles in order to compare the results with those obtained by the standard thermal treatment. For the majority of compounds, microwave heating allowed the reaction time to be reduced (20 min) and improved the yields (Scheme 4, see **3a**–**d**, **3g**, **3i**, **3k**, 2–15% increase in isolated yield). However, lower yields were obtained for products **3e**–**f**, **3h** and **3r**. Regarding compound **3v,** the disappointing result could be explained by its sensitivity to degradation as a result of C—N bond cleavage. For the other products we propose that energy absorption is partly enabled from the polar moiety of the electrophiles which act as a molecular radiator [25,26]. This assumption is supported by the reactivity observed under neat conditions (Table 1, entries 2–7). Very polar substituents such as trifluoromethoxy, trifluoromethyl or nitro (Scheme 4, see **3e**–**f**, **3h**) could promote very high energy transfer

Please cite this article as: R. Membrat, A. Vasseur, L. Giordano et al., General methodology for the chemoselective *N*-alkylation of (2,2,6,6)-tetramethylpiperidin-4-ol: Contribution of microwave irradiation, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2018.12.020

causing degradation while a less polar long carbon chain-possessing compound such as geranyl (Scheme 3, **3r**) is probably not absorbent enough to inhibit the reactivity. Finally, these conditions were tested on a large scale (5 g) for product **3a** without alteration of the yield (89%).

In conclusion, we have developed a general method to access *N*-alkyl-(2,2,6,6)-tetramethylpiperidin-4-ol derivatives which constitute a particularly valuable class of compounds. Chemoselectivity issues were solved by using an excess of the *N*-H starting material as a Brønsted base, providing access to products with a base sensitive moiety. The synthesis of a broad range of *N*–alkyl-(2,2,6,6)-tetramethylpiperidin-4-ol compounds in moderate to excellent yields was achieved although a long reaction time was required. This drawback could be overcome by using microwave assistance. In this case, the reaction time can be reduced to 20 min and gave improved yields in most cases. We hope that this synthetic contribution will help the community to explore new applications of these *N*-alkyl derivatives.

Acknowledgments

This work was supported by Ministère de l'Enseigenement supérieur et de la Recherche (R. Membrat PhD grant, French Ministry). We thank Dr. Valérie Monnier and Dr. Christophe Chendo for HRMS analysis (Spectropole, Fédération des Sciences Chimiques de Marseille). Special thanks to Arnaud Treuvey for his efficient technical support.

Appendix A. Supplementary data

Supplementary data (Experimental procedures for the transformations described in Schemes 3 and 4 are provided, along with ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra and spectral data for all compounds) to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.12.020.

References

[1] G. Sartori, D.W. Savage, Ind. Eng. Chem. Fundam. 22 (1983) 239–249.
[2] Z. Idris, K.J. Jens, D.A. Eimer, Energy Proc. 63 (2014) 1424–1431.
[3] P.M.M. Blauwhoff, G.F. Versteeg, W.P.M. van Swaaij, Chem. Eng. Sci. 39 (1984) 207–225.
[4] R.J. Hook, Ind Eng Chem Res. 36 (1997) 1779–1790.
[5] P. Phukan, R.S. Khisti, A. Sudalai, J. Mol. Catal. Chem. 248 (2006) 109–112.
[6] R. Ciriminna, M. Pagliaro, Org. Process Res. Dev. 14 (2010) 245–251.
[7] J. Kulis, C.A. Bell, A.S. Micallef, M.J. Monteiro, Aust. J. Chem. 63 (2010) 1227–1236.
[8] K. Zhang, B.B. Noble, A.C. Mater, M.J. Monteiro, M.L. Coote, Z. Jia, Phys. Chem. Chem. Phys. 20 (2018) 2606–2614.
[9] C.D. Anderson, K.J. Shea, S.D. Rychnovsky, Org. Lett. 7 (2005) 4879–4882.
[10] T. Kurumada, H. Ohsawa, O. Oda, T. Fujita, T. Toda, T. Yoshioka, J. Polym. Sci. Polym. Chem. Ed. 23 (1985) 1477–1491.
[11] J.L. Hodgson, M.L. Coote, Macromolecules 43 (2010) 4573–4583.
[12] M. Dagonneau, E.S. Kagan, V.I. Mikhailov, E.G. Rozantsev, V.D. Sholle, Synthesis 1984 (1984) 895–916.
[13] H. Gan, D.G. Whitten, J. Am. Chem. Soc. 115 (1993) 8031–8037.
[14] K. Banert, K. Fink, M. Hagedorn, F. Richter, Arkivoc 2012 (2012) 379.
[15] F. Novelli, F. Sparatore, Il Farm. 57 (2003) 871–882.
[16] P. Ruiz-Castillo, S.L. Buchwald, Chem. Rev. 116 (2016) 12564–12649.
[17] W.K. Walker, D.L. Anderson, R.W. Stokes, S.J. Smith, D.J. Michaelis, Org. Lett. 17 (2015) 752–755.
[18] A. Loupy (Ed.), Microwaves in Organic Synthesis, second ed., Wiley-VCH, Weinheim, 2006, Completely Revised and Enlarged edition.
[19] M.A. Surati, S. Jauhari, K.R. Desai, Arch. Appl. Sci. Res. 4 (2012) 645.
[20] A. de la Hoz, Á. Díaz-Ortiz, A. Moreno, Chem. Soc. Rev. 34 (2005) 164–178.
[21] B.M. Choudary, S. Madhi, N.S. Chowdari, M.L. Kantam, B. Sreedhar, J. Am. Chem. Soc. 124 (2002) 14127–14136.
[22] W.-C. Shieh, M. Lozanov, O. Repič, Tetrahedron Lett. 44 (2003) 6943–6945.
[23] D. Delledonne, F. Rivetti, U. Romano, Appl Catal Gen. 221 (2001) 241–251.
[24] A. Loupy, S. Régnier, Tetrahedron Lett. 40 (1999) 6221–6224.
[25] N.-F.K. Kaiser, U. Bremberg, M. Larhed, C. Moberg, A. Hallberg, Angew. Chem. Int. Ed. 39 (2000) 3595–3598.
[26] A. Steinreiber, A. Stadler, S.F. Mayer, K. Faber, C.O. Kappe, Tetrahedron Lett. 42 (2001) 6283–6286.

Please cite this article as: R. Membrat, A. Vasseur, L. Giordano et al., General methodology for the chemoselective *N*-alkylation of (2,2,6,6)-tetramethylpiperidin-4-ol: Contribution of microwave irradiation, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2018.12.020