Accepted Manuscript

Microwave Assisted Benzylation of Naphthols and 4-Hydroxycoumarin under Catalyst & Solvent Free Conditions

Ravikrishna Dada, Garima Singh, Abhishek Pareek, Saeen Kausar, Srinivasarao Yaragorla

PII:	S0040-4039(16)30831-0
DOI:	http://dx.doi.org/10.1016/j.tetlet.2016.07.010
Reference:	TETL 47872
To appear in:	Tetrahedron Letters
Received Date:	31 May 2016
Revised Date:	1 July 2016
Accepted Date:	2 July 2016



Please cite this article as: Dada, R., Singh, G., Pareek, A., Kausar, S., Yaragorla, S., Microwave Assisted Benzylation of Naphthols and 4-Hydroxycoumarin under Catalyst & Solvent Free Conditions, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.07.010

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Graphical Abstract





Tetrahedron Letters

journal homepage: www.elsevier.com

Microwave Assisted Benzylation of Naphthols and 4-Hydroxycoumarin under Catalyst & Solvent Free Conditions

Ravikrishna Dada, ^a Garima Singh, ^a Abhishek Pareek, ^a Saeen Kausar, ^a Srinivasarao Yaragorla ^{a*}

^a SY-Organic & Medicinal Chemistry Laboratory, Department of Chemistry, Central University of Rajasthan, Bandarsindri, NH-8, Ajmer, Rajasthan, 305817, India.

ARTICLE INFO

ABSTRACT

- Article history: Received Received in revised form Accepted Available online
- Keywords: Benzylation Microwave reaction Catalyst-free Solvent-free Ethers Dehydration SN¹

An expeditious and highly practical, microwave assisted benzylation of naphthols and 4hydroxycoumarin has been developed under catalyst-free & solvent-free conditions. Alcohols undergo heat induced dehydration to form ethers, which collapse reversibly to form the carbocation which was captured immediately by a suitable nucleophile to furnish the benzylated compounds

2009 Elsevier Ltd. All rights reserved.

1

Carbon-Carbon bond formation is one of the fundamental and key reactions in the organic synthesis.¹ Nucleophilic substitution of benzylic alcohols by various nucleophiles such as naphthols²⁻⁹ or coumarins¹⁰ is one of the important and highly studied C-C bond forming reactions. In general, the direct nucleophilic substitution reaction of benzylic alcohols was achieved by the use of excess of sulphuric acid or phosphoric acid² and stoichiometric amounts of Lewis acids.³ As the hydroxyl functionality is not a good leaving group, it needs to be activated by converting into a better leaving group and then treated with a nucleophile under suitable conditions.⁴ For example benzylation of naphthols has been reported from the benzylic alcohols using *p*-TsOH.H₂O, polymer-bound *p*-TsOH,⁵ I₂,⁶ ionic liquids,⁷ metal salts⁸ such as Bi, La, Sc, Hf, Fe, Au, InCl₃ and Amberlyst-15.⁵ Similarly, benzylic alcohols were treated with hydroxycoumarin with variety of catalysts such as Pd, ^{10a} Co, ^{10b} Cu, ^{10c} BF₃OEt₂, ^{10d} InCl₃, ^{10e} Indium bromide, ^{10f} FeCl₃, ^{10g} Bi(OTf)₃, ^{10h} lanthanide triflates, ¹⁰ⁱ p-TsOH, ^{10j} dodecyl benzene sulfonia acid. (DBCA) ^{10k} sulfonic acid (DBSA),^{10k} molecular iodine,¹⁰¹ PMA/SiO₂,^{10m} 10n TMSOTf¹⁰⁰ $B(C_{6}F_{5})_{3}$ and for the preparation of pharmaceutically important C3-benzylated coumarin derivatives.¹

Owing to the global and environmental changes, scientists are very keen in developing and practicing the green chemistry approaches.¹² During the process several innovations were explored, to list a few, multicomponent reactions, Cascade/Domino/Tandem approaches, microwave reactions, on-water synthesis, solvent-free reactions, catalyst-free reactions and the reactions with atom & step economy.¹²

From Last few years, our research has been focussed to develop novel synthetic protocols for the synthesis of biologically important heterocyclic molecules maintaining some of the sustainable principles.¹³ In this process, we developed "On-Water Synthesis" of oxindole derivatives, synthesis of various benzopyran and benzofuran molecules under solvent-free conditions using environmentally benign calcium salts as catalysts. In continuation, herein we report a microwave assisted Catalyst and solvent free benzylation of naphthols and 4hydroxycoumarin with various benzylic alcohols.





Our initial investigations began by heating benzhydrol (**1a**, 1.5 mmol) and 2-naphthol (**2a**, 1 mmol) at 90 °C and found that 1benzhydrylnaphthalen-2-ol (**3a**) was formed in 35% yield after 12 h. Encouraged by this preliminary observation we repeated the reaction at 120 °C and were glad to isolate 90% of **3a** after 4 h. Neither water nor toluene was found to be useful when **1a** and **2a** were refluxed for 12 h. This indicated that the reaction works better under solvent-free conditions. The reaction was repeated in microwave irradiation¹⁴ at 110 °C and found that the reaction gave better result in 20 min (84%). The raise in temperature to 140 °C was found to yield **3a** in 90% after 20 min and hence considered to be the best condition (Figure 1). After finding the

* Corresponding author. Tel.: +91-463-238535; fax: +91-463-238722; e-mail: srinivasarao@curaj.ac.in

Tetrahedron

optimum conditions¹⁵ for the benzylation of 2-naphthol (**3a**) with benzhydrol (**1a**), we were interested to check the scope of this catalyst free and solvent free method and hence 2-naphthol was treated with 1-phenylethan-1-ol (**1b**) and the product **3b** was isolated in 90% (Table 1).

Table 1 Substrate scope of alcohols, naphthols and 4-hydroxy coumarin in microwave assisted benzylation reaction under catalyst & solvent free conditions.^a



^aReaction Conditions: Benzylic Alcohol (1, 1.5 mmol), Nucleophile (2, 1 mmol), mw, 140 °C, 20 min. ^b 110°C, 20 min. (1d, 3 mmol)

Similar way 1-(4-bromophenyl)ethan-1-ol (1c) and benzyl alcohol (1d) reacted -with 2-naphthol under microwave irradiation to furnish the benzylated naphthols 3c and 3d in 86, 81% yields. Encouraged by the scope of various benzylic alcohols in the reaction (Table 1) we aimed to check the reactivity of some more naphthols such as 6-bromo-2-naphthol (2b) and 1-naphthol (2c). As planned, benzylic alcohols 1a and 1b were treated with naphthol 2b to yield the benzyl derivatives 3e and 3f in 81, 85% yields and they furnished 3g, 3h in 88, 85% yields with 1-naphthol (Table 1, entries 5-8). Excelled by the scope of various naphthols and alcohols in the methodology, we were driven to look at the reactivity of other nucleophiles such as 4-hydroxy coumarin, indole and malanonitrile (Table 1, entries 9-15). Interestingly, benzylic alcohols 2a, 2b reacted with 4hydroxycoumarin under mw conditions at 140 °C and yielded the respective C3-benzylated 4-hydroxy coumarins 3i and 3j in 91, 84% yields after 20 min. Other benzylic alcohols 2c and 2d also showed the similar reactivity towards 4-hydroxycoumarin to furnish the respective coumarin derivatives 3k and 3l in 82, 78% yields (Table 1, entries 11,12). It was observed that indole and malononitrile could not benzylated with benzhydrol (2a) under catalyst free mw irradiation, rather we found that benzhydrol underwent dehydration to yield the respective ether. This observation lead us to investigate the plausible mechanism for the reaction process which is described in figure 2. Trityl alcohol neither reacted with naphthol nor dehydrated to give the ether (entry 15).



Scheme 1. Microwave assisted cascade benzylation/dehydration under catalyst & solvent free conditions

An interesting observation was made when 2-naphthol was heated with 2-(hydroxy(phenyl)methyl)phenol (**1e**) at 140 °C, the reaction proceeded through a cascade benzylation followed by dehydration to yield the 4-aryl-dibenzoxanthene **3m** in 72% yield. The scope of this was extended to other benzylic alcohols **1f** and **1g** with 2-naphthol to furnish the respective dibenzoxanthenes **3n** and **3o** in good yields (Scheme 1). This cascade benzylation/dehydration strategy was extended to 4-hydroxycoumarin (Scheme 2), as planned the reaction furnished the 4-aryl pyranocoumarins **3p**, **3q** and **3r** in good yields.



Scheme 2. Microwave assisted cascade benzylation/dehydration under catalyst & solvent free conditions

The plausible mechanism for the benzylation of naphthol has been described in figure 1. Initially benzylic alcohols (1a) undergo dehydration at high temperature to produce the ether (1aa), which collapse reversibly to yield the benzylic carbocation. Immediately, a suitable nucleophile (naphthol) could capture the carbocation possibly SN1 pathway to produce the desired product 3a (Figure 2). To authenticate this idea, ether 1aa was isolated and treated with 2-naphthol (2a) under the same conditions to furnish the product 3a (Scheme 3).

ACCEPTED MANUSCRIPT



Figure 2. Plausible mechanism for mw assisted, heat induces benzylation of naphthol under catalyst and solvent free conditons.



Scheme 3. Reaction of 1aa with 2- naphthol

To further support the proposed mechanism through ether formation, 1-phenylethan-1-ol (1b) was heated under mw irradiation and the mixture of ether and styrene (by dehydration) was isolated. This mixture was further treated with 1-naphthol (2c) under the optimized conditions to furnish the benzyl derivative **3h** in 85% yield (Scheme 4).



Scheme 4. Reaction of 1b with 2-naphthol. dr = diastereomeric ratio

The reaction of 1-phenylethan-1-ol (1b) showed that styrene as an intermediate in the reaction (Scheme 4). Taking this as advantage we extended the scope of the benzylation methodology to styrene (Scheme 5) and synthesized the naphthol derivatives **3b** and **3h** in good yields.



Scheme 5. Reaction of styrene (1h, 1.5 mmol) with 2-naphthol (2a, 1 mmol) &1-naphthol (2c, 1 mmol).

In summary, we developed a facile microwave assisted catalyst and solvent free benzylation of naphthols and 4-hydroxy coumarin. This methodology was also extended to a cascade benzylation/dehydration to furnish the unsymmetric dibenzoxanthenes. Control experiments suggested that the reaction proceeds through SN^1 pathway.

Acknowledgments

RD, GS and AP thank Central University of Rajasthan for the fellowship and SY thank Council of Scientific and Industrial Research (CSIR)-India for the financial support under Extramural Research Grant -No. 02(0200)/14/EMR-II.

References

- (a) Corey, E. J. Angew. Chem., Int. Ed. 1991, 30, 455. (b) Chemler, S. R.; Danishefsky, S. J. Angew. Chem., Int. Ed. 2001, 40, 4544.
- (a) Khalaf, A. A.; Roberts, R. M. J. Org. Chem. 1973, 38, 1388. (b) Khalaf, A. A.; Roberts, R. M. J. Org. Chem. 1972, 37, 4227. (c) Khalaf, A. A.; Roberts, R. M. J. Org. Chem. 1969, 34, 3571. (d) Khalaf, A. A.; Roberts, R. M. J. Org. Chem. 1971, 36, 1040. (e) Sundberg, R. J.; Laurino, J. P. J. Org. Chem. 1984, 49, 249. (f) Davis, B. R.; Johnson, S. J.; Woodgate, P. D. Aust. J. Chem. 1987, 40, 1283.
- (a) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron Lett.* **1989**, *30*, 3581. (b) The benzylic alcohol bearing strong electron-donating group reacts without any catalyst. See: Takahashi, H.; Kashiwa, N.; Kobayashi, H.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2002**, *43*, 5751.
- For reactions of benzyl acetates, benzyl halides, benzyl ethers, and benzyl carbonates for nucleophilic substitution reactions, see: (a) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. Angew. Chem. Int. Ed. 2005, 44, 3913. (b) Shiina, I.; Suzuki, M. Tetrahedron Lett. 2002, 43, 6391. (c) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. Angew. Chem. Int. Ed. 2005, 44, 238.
- Sanz, R.; Martinez, A.; Miguel, D.; Alvarez-Gutierrez, J. M.; Rodriguez, F. Adv. Synth. Catal. 2006, 348, 1841
- Srihari, P.; Bhunia, D. C.; Sreedhar, P.; Yadav, J. S. Synlett. 2008, 1045.
- Earle, M. J.; McCromac, P. B.; Seddon, K. R. Chem. Commun. 1998, 2245.
- (a) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. Adv. Synth. Catal. 2006, 348, 1033. (b) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. J. Org. Chem. 2003, 68, 9340. (c) Noji, M.; Konno, Y.; Ishii, K. J. Org. Chem. 2007, 72, 5161. (d) Liu, J.; Muth, E.; Flore, U.; Henkel, G.; Merz, K.; Sauvageau, E.; Schwake, E.; Dyker, G. Adv. Synth. Catal. 2006, 348, 456. (e) Yasuda, M.; Somyo, T.; Baba, A. Angew. Chem. Int. Ed. 2006, 45, 793.
- 9. Das, B.; Veeranjayanelu, B.; Krishnaiah, M.; Balasubramanyam, P. *Synthetic Commun.* **2009**, *39*, 1929.
- 10. (a) Muzart, J. Tetrahedron 2005, 61, 4179. (b) Mukhopadhyay, M.; Iqbal, J. Tetrahedron Lett. 1995, 36, 6761. (c) Baruah, J. B.; Samuelson, A. G. J. Organomet. Chem. 1989, 361, 57. (d) Li, Y.; Yu, Z.; Wu, S. J. Org. Chem. 2008, 73, 5647. (e) Bisaro, F.; Pretat, G.; Vitale, M.; Poli, G. Synlett 2002, 1823. (f) Yasuda, M.; Somyo, T.; Baba, A. Angew. Chem., Int. Ed. 2006, 45, 793. (g) Vicennati, P.; Cozzi, P. G. Eur. J. Org. Chem. 2007, 2248. (h) Jana, U.; Biswas, S.; Maiti, S. Tetrahedron Lett. 2007, 48, 4065 and references cited therein. (i) Salehi, P.; Iranpoor, N.; Behbahani, F. K. Tetrahedron 1998, 54, 943. (j) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. Org. Lett. 2007, 9, 825. (k) Huang, W.; Wang, J.; Shen, Q.; Zhou, X. Tetrahedron Lett. 2007, 48, 3969. (1) Sang, R.; Martinez, A.; Miguel, D.; Alvarez-Gutierrez, J. M.; Rodriguez, F. Adv. Synth. Catal. 2006, 348, 1841. (m) Shirakawa, S.; Kobayashi, S. Org. Lett. 2007, 9, 311. (n) Rao, W.; Tay, A. H. L.; Goh, P. J.; Choy, J. M. L.; Ke, J. K.; Chan, P. W. H. Tetrahedron Lett. 2008, 49, 122. (o) Yadav, J. S.; Subba Reddy, B. V.; Pandurangam, T.; Rao, K. V. R.; Praneeth, K.; Narayanakumar, G. G. K. S.; Madavi, C.; Kunwar, A. C. Tetrahedron Lett. 2008, 49, 4296. (p) Reddy, C. R.; Jithender, E. Tetrahedron Lett. 2009, 50, 5633. (q) Theerthagiri, P.; Lalitha, A. Tetrahedron Lett. 2010, 51, 5454.
- (a) Naser-Hijazi, B.; Stolze, B.; Zanker, K. S. Second Proceedings of the International Society of Coumarin Investigators; Springer: Berlin, 1994. (b) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. Bioorg. Med. Chem. Lett. 2000, 10, 59. (c) Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. J. Med. Chem. 2001, 44, 3932. (d) Itoigawa, M.; Ito, C.; Tan, H. T.-W.; Kuchide, M.; Tokuda, H.; Nishino, H.; Furukawa, H. Cancer Lett. 2001, 169, 15. (e) Spino, C.; Dodier, M.; Sotheeswaran, S. Bioorg. Med. Chem. Lett. 1998, 8, 3475.
- (a) Matlin, M. A.; Mehta, G.; Hopf, H.; Krief, A. *Nature Chemistry*, 2015, 7, 941. (b) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.*,

Tetrahedron

2009, 38, 2993 and references cited therein. (c) Malacria, M. Chem. Rev., 1996, 96, 289. (d) Tietze, L. F. Chem. Rev., 1996, 96, 115. (e) Climent, M. J.; Corma, A.; Iborra, S.; Sabater, M. J. ACS Catal. 2014, 4, 870.

- 13. (a) Yaragorla, S.; Dada, R.; Pareek, A.; Singh, G. RSC Adv. 2016, 6, 28865. (b) Yaragorla, S.; Saini, P. L.; Pareek, A.; Almansour, A. I.; Arumugam, N. Tetrahedron Lett. 2016, 57, 2034. (c) Yaragorla, S.; Saini, P. L.; Vijaya Babu, P.; Almansour, A. I.; Arumugam, N. Tetrahedron Lett. 2016, 57, 2351. (d) Yaragorla, S.; Dada, R.; Singh, G. Synlett 2016, 27, 912. (e) Yaragorla, S.; Singh, G.; Dada, R. Tetrahedron Lett. 2016, 57, 591. (f) Yaragorla, S.; Singh, G.; Dada, R. Tetrahedron Lett. 2015, 56, 5924. (g) Yaragorla, S.; Pareek, A.; Dada, R. Tetrahedron Lett. 2015, 56, 4770. (h) Yaragorla, S.; Saini, P. L.; Singh, G. Tetrahedron Lett. 2015, 56, 1649. (i) Yaragorla, S.; Singh, G.; Saini, P.; Reddy, M. K. Tetrahedron Lett. 2014, 55, 4657.
- domestic mw (IFB) with mw output 900W, power source 230 V~50 14. Hz, mw frequency 2450 MHz.
- 15. General experimental procedure for the synthesis Benzyl derivatives 3: A mixture of benzylic alcohol (1, 1.5 mmol) and nucleophile (2, 1 mmol, naphthol/4-hydroxycoumarin) was weighed into a microwavable glass tube (regular microwave vials with screw-cap) and subjected to mw-irradiation14 at 120 °C for 20 minutes. After completion the reaction mixture was diluted with minimum amount of dichloromethane and absorbed on silicagel (work up procedure is not required) and was purified on silica gel column chromatography using ethyl acetate and petroleum ether as the eluents to afford the desired benzylated product (3). See the supporting information for the spectral data and copies of ¹H and ¹³C NMR spectra.

4

ACCEPTED MANUSCRIPT

<u>Highlights of the Work:</u>

- Acception A Catalyst free method for benzylation of •
- •
- •
- •
- •