Efficient method for propargylation of aldehydes promoted by allenylboron compounds under microwave irradiation

Jucleiton J. R. Freitas\textsuperscript{1}, Queila P. S. B. Freitas\textsuperscript{2}, Silvia R. C. P. Andrade\textsuperscript{2}, Juliano C. R. Freitas\textsuperscript{3}, Roberta A. Oliveira\textsuperscript{2} and Paulo H. Menezes\textsuperscript{2*}

Abstract

The propargylation of aldehydes promoted by microwave irradiation using allenylboron compounds in a chemo- and regioselective way is described. The corresponding products were obtained in short reaction time, high yield and purity without the need of any solvent when allenylboronic acid pinacol ester was used, or using a minimal amount of acetone when potassium allenyltrifluoroborate was used.

Introduction

The propargylation of carbonyl compounds is widely used in the synthesis of biologically active natural products [1]. Some examples can be found in the synthesis of histrionicotoxin [2], rhizopodin [3], baflomycin [4], bryostatin [5], vancosamine [6] and macrolactin A [7].

Although there are several stereoselective methods described for the reaction of propargyl or allenyl organometallics with carbonyl compounds [8-14], the control of the regioselectivity is still a major concern. This is mainly due to the metallotropic rearrangement of propargyl and allenyl organometallics in solution resulting in mixtures of the two reagents [15]. Thus, upon reaction with an aldehyde, mixtures of propargylic and allenic alcohols can be obtained through a chelate transition state (S\textsubscript{E2*}).

Attempts to improve the regioselectivity of the propargylation reaction by using allenic organometallic species of Cd [16], Ga
Table 1: Propargylation of 2-naphthaldehyde with allenylboronic acid pinacol ester (1) at different temperatures.

| Entry | Temp. (°C) | 2a/3a | Yield (%) |
|-------|------------|-------|-----------|
| 1     | 75         | 97:3  | 94        |
| 2     | 100        | 98:2  | 97        |
| 3     | 125        | 98:2  | 81        |
| 4     | 150        | 98:2  | 84        |

Results and Discussion

For preliminary optimization of the reaction conditions, 2-naphthaldehyde (1 mmol) and allenylboronic acid pinacol ester (1, 1.5 mmol) in a capped vial were irradiated in a MW synthesizer for 30 minutes under different temperatures. The results are depicted in Table 1. In all cases, the desired propargylic product 2a was obtained together with a small amount of the corresponding allenic product 3a. When the reaction was performed at 75 °C, good conversions of 2-naphthaldehyde into the corresponding products were observed (Table 1, entry 1). The best result was observed when the temperature was increased to 100 °C affording the products in 97% yield in a 98:2 ratio (Table 1, entry 2). Higher temperatures gave lower yields or the decomposition of the boron reagent 1 (Table 1, entries 3 and 4). It is worth to note that when the reaction was carried out with conventional heating (100 °C), the desired product was not observed after 1 h. A similar behavior was previously observed by Schaus [32].

Next, the shortest time necessary for the formation of the products at 100 °C under microwave irradiation was evaluated. The results are shown in Table 2. From Table 2, it can be seen that the increment in the reaction time resulted in higher yields without major changes in the ratio of 2a:3a.

The optimized reaction conditions, namely: 2-naphthaldehyde (1.0 mmol), 1 (1.5 mmol) under microwave irradiation (300 W) were then applied for the propargylation reaction of aldehydes containing a wide range of functional groups and the results are shown in Scheme 1. In all cases the reaction proceeded smoothly leading to the conversion of aldehydes into the corresponding homopropargylic alcohols 2 in moderate to high yields and in a very regioselective way, while the propargylated product was obtained as the major product in all cases.
Table 2: Propargylation of 2-naphthaldehyde with allenylboronic acid pinacol ester (1) using different reaction times.\(^a\)

| Entry | Time (min) | \(2a/3a\) | Yield (%)\(^c\) |
|-------|------------|-----------|-----------------|
| 1     | 5          | 98:2      | 87              |
| 2     | 10         | 98:2      | 88              |
| 3     | 15         | 97:3      | 88              |
| 4     | 20         | 98:2      | 95              |
| 5     | 30         | 97:3      | 97              |

\(^a\)Reaction conditions: Reactions were performed with 2-naphthaldehyde (1 mmol), 1 (1.5 mmol) under MW irradiation (300 W) at 100 °C for the time indicated. \(^b\)Determined by GC analysis. \(^c\)Isolated yield.

Scheme 1: Scope of the propargylation reaction. Reactions were performed with the appropriate aldehyde (1 mmol), 1 (1.5 mmol) under microwave irradiation (300 W) at 100 °C for 30 min. Isolated yields are given. The number in parentheses refers to the mixture of propargyl and allenyl regioisomers determined by GC analysis.
Aromatic aldehydes such as benzaldehyde, 2-methylbenzaldehyde and 3,5-dimethylbenzaldehyde gave the corresponding products 2b–d in good yields in a regioselective way regardless of the position of the substituent on the aromatic ring.

When aldehydes containing electron-donating groups such as 2-, 3- or 4-methoxybenzaldehyde or 3,4,5-trimethoxybenzaldehyde were used, the corresponding products 2e–h were obtained in good yields and regioselectivities. In the same way, aldehydes containing electron-withdrawing groups such as the nitro group also reacted without influence of the substituent location to give the corresponding homopropargylic alcohols 2m and 2n in good yields. It is interesting to note that the nitro group remained intact under the reaction conditions. Usually, this group is sensitive to reduction when alternative methods involving zinc or tin are used [33].

In addition, aldehydes containing halogens also gave the corresponding products 2j–l in moderate yields. These results indicated that the substituent nature, whether electron-donating or electron-withdrawing, has no dramatic influence on the product yields.

When the α,β-unsaturated aldehyde, cinnamaldehyde was used, the corresponding 1,2-addition product 2i was obtained exclusively.

The chemoselectivity of the method was evaluated using aldehydes containing different functionalities. For example, the use of vanillin, an aldehyde containing the acidic phenol group as substituent, gave the corresponding product 2o in 93% yield in an 82:18 ratio of regioisomers. In the same way, when aldehydes containing an ester or nitrile group were used, the corresponding products 2q and 2r were obtained in good yields. The use of a heteroaromatic or an aliphatic aldehyde as substrates under the optimized conditions gave the corresponding homopropargylic alcohols 2s,t in moderate yields.

The development of a solvent-free protocol for propargylation of aldehydes based on microwave irradiation should take into account not only the reaction itself but also an effective method for the extraction of the obtained products. Despite the excellent results described on Scheme 1, a factor that must be taken into consideration is the removal of the desired alcohols 2a–t from pinacol – the byproduct obtained in the reaction. There are some examples in the literature based on the removal of pinacol by distillation in vacuo (50 °C/0.05 mbar) [34]. However, this technique can only be applied for non-volatile samples. More recently, Aggarwal and co-workers [35] described an efficient method for removal of pinacol based on the formation of an azeotrope with water under moderate vacuum. Thus, a test experiment was performed using compound 2h. The crude product obtained from the reaction was dissolved in 50% aqueous methanol and the volatile materials were removed using a rotary evaporator. The procedure was monitored by gas chromatography and was repeated until the crude mixture contained less than 1 mol % of pinacol remaining. The results are described in Table 3.

Although the desired products 2a–t having been obtained along with a small proportion of the corresponding regioisomer in some cases, in the development of new synthetic methods, it is desirable that it gives the corresponding product as a single compound. Our group described the synthesis of homopropargylic alcohols using potassium allenyltrifluoroborate as the propargylating agent in a very regioselective way [36,37]. Thus,
Potassium allenyltrifluoroborate (4) is a crystalline solid and despite several microwave promoted reactions can be conducted without the use of solvents, the propargylation reaction using 2-naphthaldehyde and 4 under the previously optimized conditions gave the desired product in only low conversion (Table 4, entry 1).

In order to find an appropriate and suitable solvent that could be used in small amounts to promote the reaction different solvents were screened and the best result was observed when a small amount of acetone was used, where 2a was obtained in 92% yield as a single regioisomer (Table 4, entry 2). Low conversions were observed when water or a 1:1 mixture of acetone and water was used in the reaction (Table 4, entries 3 and 4). The use of alcohols also gave the desired product in lower yields (Table 4, entries 5–7). Finally, when a less polar solvent was used, the observed conversion was only 10% (Table 4, entry 8).

Two factors must be considered when allylboron species are used in the propargylation reaction. The first is that the atomic efficiency [40] using potassium allenyltrifluoroborate (4, 62%) or allylboronic acid pinacol ester (1, 58%) is higher when compared to the commercially available allyltributyltin (22%) for similar reactions.

The second refers to the regioselectivity of the reaction. Despite the reaction using 2-naphthaldehyde led only to the propargyl isomer 2a, when the same reaction conditions were applied to 4-nitrobenzaldehyde, the desired product 2m was once again obtained with a small amount of the corresponding regioisomer 3m in a 97:3 ratio (Scheme 3).

**Table 4: Propargylation of 2-naphthaldehyde with potassium allenyltrifluoroborate (4) using different solvents.**

| Entry | Solvent         | Time (min) | 2a:3a | Yield (%) |
|-------|-----------------|------------|-------|-----------|
| 1     | –               | –          | –     | –         |
| 2     | acetone         | 30         | 100:0 | 92        |
| 3     | water           | 30         | 100:0 | 3         |
| 4     | acetone/water   | 30         | 100:0 | 10        |
| 5     | ethylene glycol | 20         | 100:0 | 45        |
| 6     | ethanol         | 20         | 100:0 | 45        |
| 7     | methanol        | 20         | 100:0 | 30        |
| 8     | dichloromethane | 20         | 100:0 | 10        |

aReaction conditions: Reactions were performed with 2-naphthaldehyde (1 mmol), 4 (1.5 mmol) under MW irradiation (300 W) at 100 °C for the time indicated using the appropriate solvent (500 μL). bDetermined by GC analysis. cIsolated yield.
Conclusion

In summary, we have shown an efficient method for the propargylation of aldehydes promoted by microwave irradiation using allenylboron compounds in a chemo- and regioselective way. The corresponding products were obtained after a short reaction time in high yield and purity without the need of a solvent when allenylboronic acid pinacol ester was used, or using a minimal amount of acetone when potassium allenyltrifluoroborate was used. The method is simple, fast and general allowing further applications in the synthesis of more complex compounds.

Supporting Information

Supporting Information File 1
Experimental procedures and 1H, 13C, 11B and 19F NMR spectra for all synthesized compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-19-S1.pdf]

Funding

This work was jointly supported by grants from CNPq and FACEPE.

ORCID® IDs

Jucelin J. R. Freitas - https://orcid.org/0000-0001-6349-8764
Silvia R. C. P. Andrade - https://orcid.org/0000-0002-0929-715X
Juliano C. R. Freitas - https://orcid.org/0000-0003-4617-4084
Roberta A. Oliveira - https://orcid.org/0000-0001-7905-2433
Paulo H. Menezes - https://orcid.org/0000-0002-0327-6032

Preprint

A non-peer-reviewed version of this article has been previously published as a preprint doi:10.3762/bxiv.2019.138.v1

References

1. Ding, C.-H.; Hou, X.-L. Chem. Rev. 2011, 111, 1914–1937. doi:10.1021/cr100284m
2. Adachi, Y.; Kamei, N.; Yokoshima, S.; Fukuyama, T. Org. Lett. 2011, 13, 4446–4449. doi:10.1021/ol2018032
3. Pulukuri, K. K.; Chakraborty, T. K. Org. Lett. 2014, 16, 2284–2287. doi:10.1021/ol5008179
4. Marshall, J. A.; Adams, N. D. Org. Lett. 2000, 2, 2897–2900. doi:10.1021/ol000344b
5. Trost, B. M.; Dong, G. Nature 2008, 456, 485–488. doi:10.1038/nature07543
6. Parker, K. A.; Chang, W. Org. Lett. 2003, 5, 3891–3893. doi:10.1021/ol035479p
7. Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. J. Am. Chem. Soc. 2002, 124, 1664–1668. doi:10.1021/ja0177171
8. Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. J. Am. Chem. Soc. 1982, 104, 7667–7669. doi:10.1021/ja00399a052
9. Ikeda, N.; Arai, I.; Yamamoto, H. J. Am. Chem. Soc. 1986, 108, 483–486. doi:10.1021/ja00263a020
10. Reddy, L. R. Org. Lett. 2012, 14, 1142–1145. doi:10.1021/ol300075n
11. Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. Angew. Chem., Int. Ed. 2012, 51, 1391–1394. doi:10.1002/anie.201107407
12. Fernández, S.; González, J.; Santamaría, J.; Ballesteros, A. Angew. Chem., Int. Ed. 2019, 58, 10703–10707. doi:10.1002/anie.201905159
13. Horino, Y.; Murakami, M.; Ishibashi, M.; Lee, J. H.; Watanabe, A.; Matsumoto, R.; Abe, H. Org. Lett. 2019, 21, 9594–9598. doi:10.1021/acs.orglett.9b03710
14. Wisniewska, H. M.; Jarvo, E. R. J. Org. Chem. 2013, 78, 11629–11636. doi:10.1021/jo4019107
15. Yamashita, Y.; Cui, Y.; Xie, P.; Kobayashi, S. Org. Lett. 2015, 17, 6042–6045. doi:10.1021/acs.orglett.5b03045
16. Zheng, Y.; Bao, W.; Zhang, Y. Synth. Commun. 2000, 30, 3517–3521. doi:10.1080/0039791008087264
17. Lee, P. H.; Kim, H.; Lee, K. Adv. Synth. Catal. 2005, 347, 1219–1222. doi:10.1002/adsc.200505046
18. Lin, M.-J.; Loh, T.-P. J. Am. Chem. Soc. 2003, 125, 13042–13043. doi:10.1021/ja037410i
19. Millán, A.; de Cienfuegos, L. A.; Martín-Lasanta, A.; Campaña, A. G.; Cuerva, J. M. Adv. Synth. Catal. 2011, 353, 73–78. doi:10.1002/adsc.201000655
20. Guo, L.-N.; Gao, H.; Mayer, P.; Knochel, P. Chem. – Eur. J. 2010, 16, 9829–9834. doi:10.1002/chem.201000523
21. Kobayashi, S.; Kitanosono, T.; Ueno, M. Synlett 2010, 2033–2036. doi:10.1055/s-0030-1258485
22. Keck, G. E.; Krishnamurthy, D.; Chen, X. Tetrahedron Lett. 1994, 35, 8323–8324. doi:10.1016/s0040-4039(00)74397-8
23. Yu, C.-M.; Kim, J.-M.; Shin, M.-S.; Cho, D. Tetrahedron Lett. 2003, 44, 5487–5490. doi:10.1016/s0040-4039(03)01335-5
24. Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. Angew. Chem., Int. Ed. 1998, 37, 2392–2395. doi:10.1002/1521-3733(19980818)37:17<2392::aid-anie2392>3.0.co;2-d
25. Chen, J.; Captain, B.; Takenaka, N. Org. Lett. 2011, 13, 1654–1657. doi:10.1021/ol200102c
26. Grayson, M. N.; Goodman, J. M. J. Org. Chem. 2013, 78, 8796–8801. doi:10.1021/jo401611q
27. Grayson, M. N.; Goodman, J. M. J. Am. Chem. Soc. 2013, 135, 6142–6148. doi:10.1021/ja4122137
28. Wang, M.; Khan, S.; Milordos, E.; Chen, M. Org. Lett. 2018, 20, 3810–3814. doi:10.1021/acs.orglett.8b01399
29. Tri-n-butyltin compounds [MAK Value Documentation, 1990]. The MAK Collection for Occupational Health and Safety (2012) 316.
30. Kappe, C. O. Angew. Chem., Int. Ed. 2004, 43, 6250–6284. doi:10.1002/anie.200400655
31. Sheldon, R. A. Green Chem. 2017, 19, 18–43. doi:10.1039/c6gc02157c
32. Barnett, D. S.; Schaus, S. E. Org. Lett. 2011, 13, 4020–4023. doi:10.1021/ol201535b
33. Chan, T. H.; Isaac, M. B. Pure Appl. Chem. 1996, 68, 919–924. doi:10.1351/pac199668040919
34. Murphy, J. M.; Tszchucke, C. C.; Hartwig, J. F. Org. Lett. 2007, 9, 757–760. doi:10.1021/ol062903o
35. Bagutski, V.; Ros, A.; Aggarwal, V. K. Tetrahedron 2009, 65, 9956–9960. doi:10.1016/j.tet.2009.10.002

Beilstein J. Org. Chem. 2020, 16, 168–174.
36. Freitas, J. J. R.; Couto, T. R.; Cavalcanti, I. H.; Freitas, J. C. R.; Barbosa, Q. P. S.; Oliveira, R. A. Tetrahedron Lett. 2016, 57, 760–765. doi:10.1016/j.tetlet.2016.01.017

37. Couto, T. R.; Freitas, J. J. R.; Freitas, J. C. R.; Cavalcanti, I. H.; Menezes, P. H.; Oliveira, R. A. Synthesis 2015, 47, 71–78. doi:10.1055/s-0034-1379163

38. Lennox, A. J. J.; Lloyd-Jones, G. C. Angew. Chem., Int. Ed. 2012, 51, 9385–9388. doi:10.1002/anie.201203930

39. Oliveira, R. A.; Silva, R. O.; Molander, G. A.; Menezes, P. H. Magn. Reson. Chem. 2009, 47, 873–878. doi:10.1002/mrc.2467

40. Trost, B. M. Science 1991, 254, 1471–1477. doi:10.1126/science.1962206

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0). Please note that the reuse, redistribution and reproduction in particular requires that the authors and source are credited.

The license is subject to the Beilstein Journal of Organic Chemistry terms and conditions: (https://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.16.19