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Microwave-accelerated 1,3-dipolar cycloaddition for the formation of fused [*n*]polynorbornanes

Richard C. Foitzik [a], Adam J. Lowe [b], Frederick M. Pfeffer [b,*]

[a] Department of Medicinal Chemistry and Drug Action, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville 3052, Australia
[b] School of Life and Environmental Sciences, Deakin University, Waurn Ponds 3217, Australia

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ABSTRACT

Microwave irradiation induces the 1,3-dipolar cycloaddition of cyclobutane epoxides with norbornenes to afford [*n*]polynorbornane scaffolds. Greatly enhanced reaction rates and significantly reduced levels of decomposition were observed.

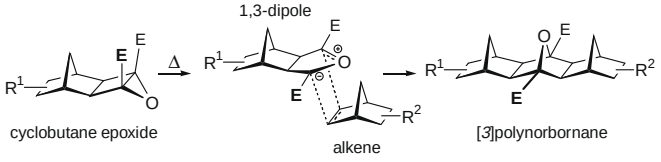
Due to their inherent conformational preorganisation, fused [*n*]polynorbornane frameworks have been employed as rigid hydrophobic scaffolds to investigate anion recognition,[1] DNA bis-intercalation[2] and through-space electron transport.[3] Typically, these frameworks are constructed using Diels–Alder and other cycloaddition reactions.[1–4]

A powerful tool for the synthesis of fused [*n*]polynorbornanes is the stereoselective 1,3-dipolar cycloaddition of a cyclobutane epoxide (which ring opens to form a carbonyl ylide) with a norbornene alkene (alkene + cyclobutane epoxide, ACE reaction, Scheme 1).[5] Whilst the reaction tolerates a range of functional groups,[1,2,4,5] it requires elevated temperatures (110–160 °C) and in some instances, long reaction times (up to 48 h), which can lead to degradation of the starting materials.

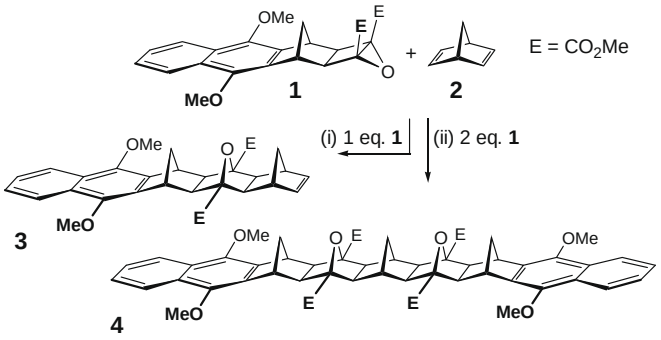
Many reactions, especially cycloadditions, have been found to proceed rapidly in high yields using microwave irradiation,[6] however, to our knowledge, no reports concerning the microwave (μw)-accelerated ACE reaction have been published. Herein, we report the first example of the microwave-assisted 1,3-dipolar cycloaddition of cyclobutane epoxides with various norbornenes, providing an efficient method for the synthesis of [*n*]polynorbornanes in moderate yields.

Two of the early substrates employed to study the ACE reaction were the dimethoxynaphthalene-based epoxide **1** and norbornadiene **2** (Scheme 2).[5] In the original report by Russell et al. reaction time for the thermal ACE reaction was 3 h in a sealed tube at 110 °C.[5] Two solvents were noted: dichloromethane and tetrahydrofuran. As such our preliminary investigations also focused on these solvents.

Using a Biotage Initiator 2.0 microwave reactor the reaction conditions were optimised on a small scale (0.3 mmol) by varying the reaction time and temperature (Table 1).[7] Following the stated time, the solutions were analysed by TLC and ^{1}H NMR spectroscopy. Analysis by TLC indicated clean conversion of compounds **1** and **2** to [3]polynorbornane **3** or [5]polynorbornane **4** with little evidence of decomposition in all cases, while NMR indicated a clear change in chemical shift of the methyl ester protons of **1** (3.77 ppm) to compound **3** (3.90 ppm) or **4** (3.92 ppm) which could be integrated to give percentage conversion.[8] From this study the optimal reaction conditions were determined to be 10 and 15 min at 180 °C for **3** and **4**, respectively, using THF as solvent.



Scheme 1. General ACE reaction: E = CO_2Me, R^1 and R^2 include aryl, alkyl, ester, amide, carbamate and urea functionality.



Scheme 2. Synthesis of **3** and **4** by microwave-mediated ACE reaction; (i) μw, 180 °C, 10 min, THF, (ii) μw, 180 °C, 15 min, THF.

* Corresponding author. Tel.: +61 3 52271439; fax: +61 3 52271040.
E-mail address: fred.pfeffer@deakin.edu.au (F.M. Pfeffer).

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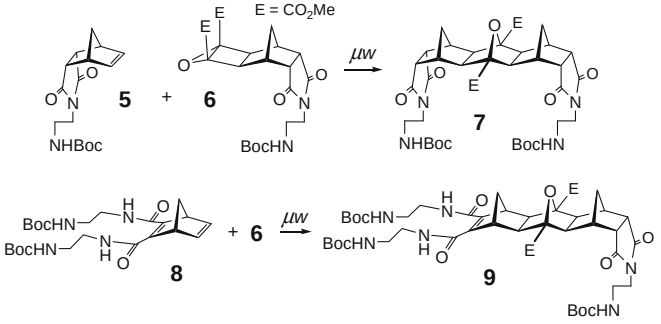
Table 1
Reaction conditions for the synthesis of **3**, **4**, **7** and **9**[7]

Product	Solvent	Temp (°C)	Pressure (PSI (bar))	Time (min)	Conversion[a] (%)
3	CH_2Cl_2	160	232 (16)	40	60
3	THF	160	203 (14)	40	55
3	THF	170	232 (16)	15	67
3	THF	180	276 (19)	10	90
4	CH_2Cl_2	160	232 (16)	60	69
4	THF	160	203 (14)	55	70
4	THF	170	232 (16)	25	72
4	THF	180	276 (19)	15	86
7	MeCN	140	131 (9)	10	12
7	CH_2Cl_2	140	189 (13)	20	11
7	THF	140	160 (11)	20	26
7	THF	160	203 (14)	10	46[b]
9	THF	140	160 (11)	20	35
9	CH_2Cl_2	140	189 (13)	20	9
9	CH_2Cl_2	160	247 (17)	10	47[b]

[a] Conversion was measured by NMR spectroscopy (see Supplementary data).
[b] Isolated yields, 44% for table entry 7 and 43% for table entry 9, following purification using column chromatography.



Scheme 3. Synthesis of functionalised [3]polynorbornanes **7** and **9** by the microwave-mediated ACE reaction.

The conversions obtained using these conditions were, in general, higher than those previously observed after 3–12 h using conventional methods.

Further ACE reactions employing substrates of interest to our current research with a focus on anion recognition (Scheme 3),[1,8] were studied in a similar fashion to those described above to see if the functional groups present would tolerate microwave irradiation. These results are also presented in Table 1.

It was immediately apparent from TLC analysis that the microwave-assisted synthesis of **7** and **9** was far cleaner than traditional thermal methods and this was confirmed by examination of the crude reaction mixtures by means of ^{1}H NMR spectroscopy. The reaction mixture did not contain any baseline material, suggesting little if any degradation of the starting materials had taken place, whereas significant decomposition occurred in previous work using conventionally heated sealed tubes at 140 °C due to the prolonged heating required (24–48 h) to effect reasonable amounts of the desired products.

Whilst the dielectric constant of the solvent is often associated with increased heating under microwave conditions,[6a–c] this investigation identified THF ($\varepsilon_s = 7.6$) as the solvent of choice (better than dichloromethane $\varepsilon_s = 9.1$ and acetonitrile $\varepsilon_s = 36$).[6a] The 46% and 47% conversion to form **7** and **9**, respectively, after 10 min at 160 °C using the microwave method were equivalent to those observed for thermal methods taking 24–72 h at 140 °C.[1] Unfortunately, prolonged periods at this temperature resulted in the thermal deprotection of the BOC groups[9] thus a 10-min timeframe was considered optimal.

Microwave irradiation can achieve 'flash' heating to give high pressures and temperatures within a short period (both pressure and temperature in the sealed tube were monitored, see Supplementary data) thereby providing enough energy for the cycloaddition to take place rapidly without significant degradation of reactants or products.[6a–c,10] It is postulated that this combination of 'flash' heating and high pressure contributed to the rapid conversions observed in this study.

As demonstrated with the additional substrates **5**, **6** and **8**, this method tolerated compounds containing amides, imides, esters, *tert*-butoxycarbonyl (BOC)-protected amines, but, as with the conventional ACE reaction, no cycloaddition reaction occurs to sterically hindered electron-poor alkenes.

In conclusion we have successfully demonstrated that, as with other cycloadditions, microwave irradiation dramatically reduces reaction times for the 1,3-dipolar cycloaddition of cyclobutane epoxides with norbornenes. As such, this powerful technique offers users a quick and convenient alternative to the conventional thermal process when synthesising [*n*]polynorbornane frameworks.

Acknowledgements

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Supplementary data

Supplementary material including a detailed synthetic method and an example of NMR analysis used to determine % conversion is available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.079.

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7. *General procedure*: A solution of the epoxide (0.3 mmol) and alkene (1 equiv) were combined in a 0.5–2.0 ml Biotage microwave vial, the lid was sealed and then reacted according to the conditions stated in Table 1. Following reaction, the vessel was allowed to cool then opened and TLC analysis performed (1:1 EtOAc/hexane). The contents of the flask were then evaporated to dryness in vacuo and the crude reaction mixture was subjected to ^{1}H NMR analysis. For more detail see Supplementary data.
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