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Microwave activation of an asymmetric Michael reaction: unexpected behaviour of chiral α-alkoxy imines

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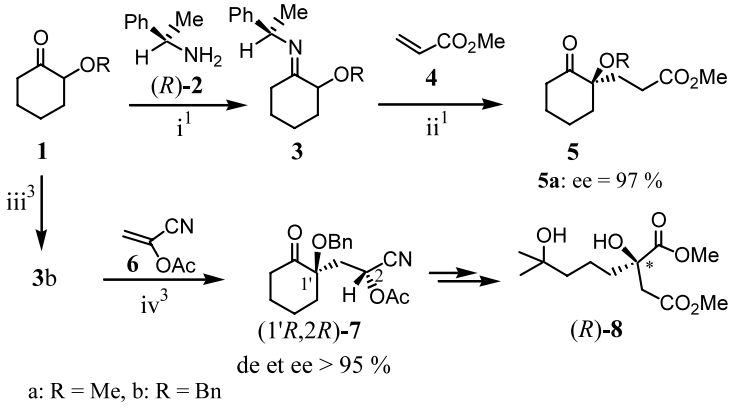
Abstract—While it has been previously established that chiral α-alkoxy imines undergo thermal rearrangement at temperatures above 50°C, the microwave activation of the Michael addition between chiral imine **3b** and methyl acrylate at 100°C led cleanly to the corresponding Michael adduct **5b** without the formation of any rearranged product and with the same regio- and stereoselectivity as the corresponding thermal condensation at 40°C (ee 95%).

1. Introduction

Construction of C–C bonds plays a fundamental role in organic synthesis and in particular, elaboration of stereodefined, fully substituted carbon centers remains a major challenge. Recently, Desmaële et al. showed that replacement of the alkyl substituent by an alkoxy one α to the carbonyl group in ketone **1**, does not modify the outcome of the asymmetric Michael reaction of the corresponding imine **3** with electrophilic alkenes such as methyl acrylate **4**. This thereby allows the more substituted Michael adducts **5** to be obtained with a high degree of regio- and stereocontrol (Scheme 1).[1] Such adducts featuring a stereogenic tetrasubstituted carbon center are useful synthons for the asymmetric synthesis of a variety of bioactive compounds.[2] For example, we have recently developed the use of α-acetoxyacrylonitrile **6** as an electrophilic equivalent to acetaldehyde in the Michael condensation of imine **3b**,[3] allowing the first asymmetric synthesis of enantiopure (*R*)-**8** methyl



Scheme 1. *Reagents and conditions*: i: (*R*)-**2**, catalyst, cyclohexane, 20°C, 24 h. ii: excess methyl acrylate, neat, 40°C, 4 days then AcOH 20%, 20°C, 75%. iii: (*R*)-**2**, SiO_2, Al_2O_3, 5 Å MS, cyclohexane, 20°C, 3 h. iv: 2 equiv. **6**, 20°C, 36 h then AcOH 20%, 20°C, 4 h, 72%.

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ester of the side chain of homoharringtonine (HHT),[4] a potent antileukemic alkaloid (Scheme 1).[5] In this context, we were interested in the synthesis of HHT side chain analogues starting for instance from the known Michael adduct (*R*)-**5b**. Herein, we report on the successful microwave activation of the Michael addition of the chiral imine **3b** and methyl acrylate leading regio- and stereoselectively, to this adduct **5b** in a very short time.[6]

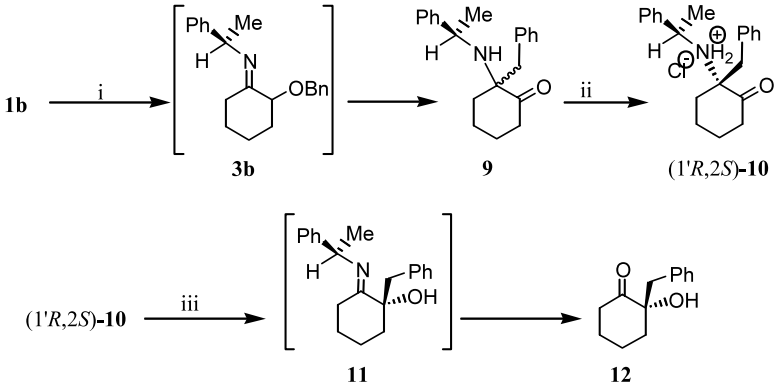
We were encouraged to exploit the potential of microwave irradiation as a non-conventional energy source known for the promotion of organic reactions associated with slow reaction rates such as the Michael reaction leading to **5b**. Microwave (μW) flash heating has become a popular and efficient way of promoting organic transformations, mainly in solvent-free systems, giving rise to significant increases in reaction rates, along with cleaner reactions that are easier to work up together with improvements in yields, when compared to the corresponding conventional thermal reactions.[7] Concerning most of the studied reactions, the chemical reactivity is unchanged and no variation in the isomeric distribution is observed. However, the temperature profiles achieved under microwave irradiation are not accessible by conventional heating and can allow some differentiation in reaction pathways.[8] Consequently, interest in microwave assisted organic reactions has increased considerably in recent years. Since 1986,[9] the importance of μW in organic synthesis has been amply demonstrated by more than 1000 publications in this field, although few examples of microwave-promoted asymmetric Michael reactions have been reported to date.[10] Due to the slow rate of the asymmetric Michael reaction under consideration (**3b**+**4**→**5b**), and to the fact that both the regio- and the stereoselectivity of the process are unchanged at high reaction temperatures, coupled with the asynchronous nature of the transition state of this concerted reaction[11] leading to its polarization, microwave activation of this reaction seemed promising, provided that the remarkable regio- and stereocontrol of the process could be maintained.[12]

At this point, it should be noted that these chiral α-alkoxy imines **3** have to be prepared at room temperature in the presence of an acid–base catalyst and molecular sieves[1] since, above 50°C, such imines undergo a thermal rearrangement.[13] Indeed, Frahm reported that imine **3b** was not obtained when a mixture of ketone **1b** and 1-phenylethylamine (*R*)-**2** was refluxed in toluene. Instead the α-aminoketone **9** was formed in a non stereoselective manner, from which the enantiopure hydrochloride **10** could be separated by fractional crystallization. Compound **10** led in turn to the formation of α-hydroxyketone **12** upon heating in aqueous ethanol for one day, via hydrolysis of the corresponding α-hydroxyimine **11** (Scheme 2).[14] Such thermal rearrangements could be a major drawback in the case of microwave-assisted asymmetric Michael reaction. Nevertheless, this flash heating could be beneficial if the expected Michael reaction of imine **3b** is faster than its undesired rearrangement pathway.

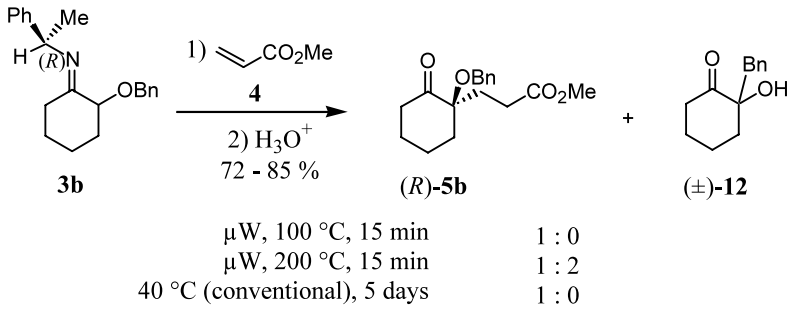
2. Results

A first set of experiments was conducted using mixtures of imine **3b** and excess methyl acrylate **4** under conventional heating, at temperatures below 50°C (Scheme 3). This condensation did not go to completion at 20°C even after 1 week, and at 30°C for the same time the yield of **5b** was only 61%. The best result was obtained at 40°C for 5 days after which the keto ester (2*R*)-**5b**[1] was obtained regioselectively in 85% yield without any trace of the hydroxyketone **12**. In order to compare the stereoselectivities of the microwave and the conventional processes, a method for the accurate determination of enantiomeric excess in Michael adduct **5b** was desirable. In contrast to the keto ester **5a**[1,15] and the Michael adduct **7**,[3] however, the determination of the ee of ketone **5b** was not possible using NMR experiments in the presence of the chiral shift reagent $Eu(hfc)_3$. Fortunately, this ee could be determined as 95% by using chiral HPLC, in comparison to (±)-**5b** obtained similarly from imine **3b** prepared from racemic 1-phenylethylamine **2**.

We next turned our attention to the focused-microwave experiments. Since we were looking for rapid reactions, high temperatures were selected, typically between 100 and 200°C, far above the rearrangement temperature limit (50°C). Mixtures of imine **3b** and 2 equivalents of



Scheme 2. *Reagents and conditions*: i: (*R*)-**2**, $PhCH_3$, 110°C, 3 h, 100%. ii: HCl, Et_2O, 33%. iii: EtOH–H_2O, 100°C, 24 h, 66%.



Scheme 3.

methyl acrylate **4** were placed in sealed,[16] 10 mL heavy-walled Pyrex tubes[17] and introduced into the cavity of a single-mode[18] device allowing control of the irradiation power, temperature and pressure.[19] Although it has been established that microwave heating induces localized enhancements of reaction rates, thus providing non-isothermal and heterogeneous kinetics,[20] the experiments were conducted with continuous magnetic stirring in order to achieve as much as possible homogeneous temperature of the reaction medium. The μW power was adjusted to reach the desired reaction temperature in less than 2 min (100 W for experiments at 100°C and 250 W for reactions at 200°C). Maximum observed reaction pressures were 1.7 bars at 100°C and 4.2 bars at 200°C. The reactions were run for 15 or 30 min, and analyzed after hydrolysis of the crude reaction mixtures (AcOH 20%: THF 1:2, 17 h, 20°C). All of the starting imine **3b** was consumed in 15 min. No incidence of the reaction time on either yields (72–85%) or regio- and stereoselectivities (>95%) was observed. At 100°C, the only reaction product was the expected Michael adduct **5b**.[21] Measurement of the optical activity of Michael adduct **5b** showed that both the sense and the extent of the asymmetric induction of the microwave experiment correlated with that obtained with conventional heating. This was further demonstrated by chiral HPLC analysis of adduct **5b** (ee 96%). In contrast, under forcing conditions (μW, 200°C) the rearranged compound, 2-hydroxy-2-benzylcyclohexanone **12** was formed as the major product (**12**:**5b** = 2:1, combined yield 72%).

3. Conclusion

In summary, we have developed a convenient microwave-promoted high-speed (in minutes rather than days) asymmetric synthesis of Michael adduct **5b** for the first time, with regio- and stereoselectivities analogue to those obtained in the conventional thermal reaction (40°C, 5 days). Moreover, we have demonstrated that under these conditions at 100°C, the thermal rearrangement of the starting chiral imine **3b** was not observed, contrasting with the results of previous studies under conventional thermal conditions (50 or 110°C). The salient features of this activation mode lie in enhanced reaction rates, simplified manipulations and higher purity of the final product. To the best of our knowledge, this is the first report concerning the use of microwave for this asymmetric Michael reaction of chiral imines in neutral media. Work is currently in progress to expand the scope of this μW-promoted asymmetric Michael addition.

Acknowledgements

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16. This technique was chosen in order to contain the toxic and volatile Michael acceptor in the reaction vessel, and to monitor the possible extent of pressure elevation during the microwave irradiation. The possibility of running reactions in an inert gas atmosphere is another distinct advantage with the sealed reaction vessel strategy. However, despite the water sensitivity of chiral imines, this was not necessary in this case.
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21. Spectroscopic data of compound **5b** matched those already reported,[1] $[\alpha]_D^{20}=+32$ (*c* 10, $EtOH_{abs}$), lit.:[1] $[\alpha]_D^{20}=+32.5$ (*c* 10, EtOH), ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 7.4–7.2 (m, 5H), 4.47 (d, $J=11.2$ Hz, 1H), 4.14 (d, $J=11.2$ Hz, 1H), 3.63 (s, 3H); 2.74 (m, 1H), 2.39–1.39 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 211.9 (C); 173.5 (C); 137.8 (C); 128 (2CH); 127.2 (2CH); 126.9 (CH); 81.8 (C); 64 (CH_2); 51.2 (CH_3); 39.2 (CH_2); 36.7 (CH_2); 27.4 (CH_2); 27.2 (CH_2); 26.6 (CH_2); 20.5 (CH_2). IR (neat, ν cm^{-1}): 2944, 2864, 1735, 1716.