Monatshefte für Chemie - Chemical Monthly
https://doi.org/10.1007/s00706-019-02440-4

ORIGINAL PAPER

Microwave-assisted ruthenium catalysed high-pressure synthesis of N-heterocyclic compounds

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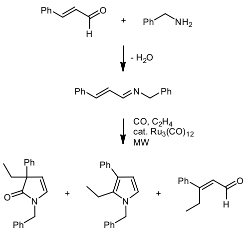
Received: 13 December 2018 / Accepted: 6 May 2019

Abstract

The four-component reaction of an *α*,*β*-unsaturated aldehyde and a primary amine with carbon monoxide and ethylene in the presence of $Ru_3(CO)_{12}$ as a precatalyst yielding mixtures of chiral γ-lactams and substituted pyrrole derivatives has, for the first time, been performed under microwave irradiation. It has also been possible to collect samples of the reaction mixture without releasing the applied pressure of the gas phase, and therefore, monitoring of substrates, intermediates, and products during the synthetic procedure became accessible. Compared to classical thermally induced reactions, microwave irradiation leads to a significant shortening of reaction times, and requires lower partial pressures of carbon monoxide and ethylene and a lower precatalyst loading.

Graphical abstract



Keywords Ruthenium · C–H activation · Lactams · Pyrroles · Microwave irradiation

Introduction

γ-Lactams or *γ*-aminobutyric acid derivatives in general have been investigated due to their potential relevance as psychotropic drugs as well as for the treatment of diseases like cancer, osteoporosis, or Alzheimer's disease or as constituents of non-natural peptide sequences [1–7]. Especially in the context of the latter research topic, it was pointed out that the use of *γ*-aminoacids enhances the stability of the respective peptides against proteases, thus, enabling the application of these peptides as active substances under physiological conditions [8]. We were able to show that γ-lactams (1,3-dihydropyrrolones) are the main products of the catalytic multi-component reaction of *α*,*β*-unsaturated imines, carbon monoxide, and ethylene (or terminal alkenes in general) in the presence of $Ru_3(CO)_{12}$ as the precatalyst [9–16]. Nevertheless, 2,3-disubstituted pyrrole derivatives have been observed as side-products of the reaction sequence (Scheme 1) [9–16]. In this context, it is not necessary to introduce the imine into the reaction, since a four-component reaction of the corresponding *α*,*β*-unsaturated aldehyde and a primary amine under CO and ethylene pressure in the presence of the same precatalyst leads to the formation of the same compounds. In addition, it became obvious that chemoselectivity of the reaction highly depends on the choice of solvent [17]. Therefore, it is possible to exclusively produce the corresponding γ-lactam if unpolar solvents as hydrocarbons are used, whereas the reaction in methanol leads to

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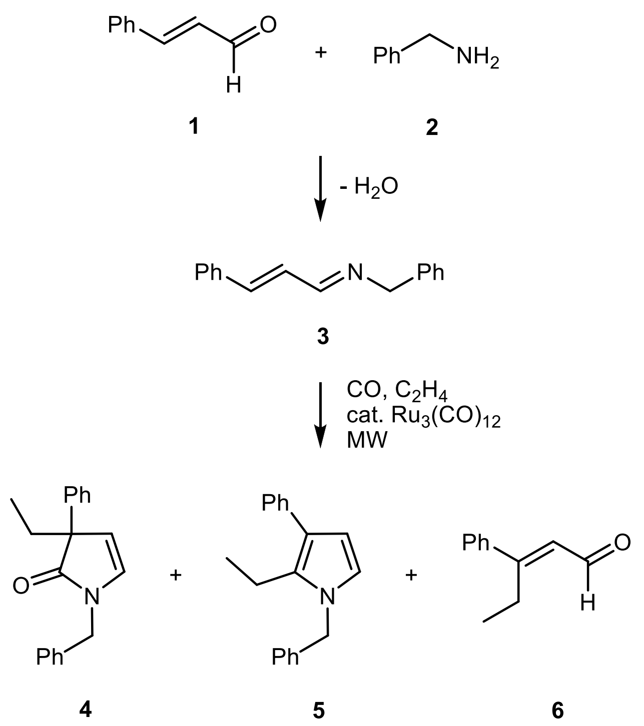
Scheme 1



the formation of the pyrrole in 65% yield [17]. It was also possible to perform the reaction in ionic liquids as solvents still leading to mixtures of both products [18].

One major drawback of the reaction is that reaction times are quite high, meaning that a complete conversion of the starting compounds needs app. 14–16 h. Another topic relating to safety issues are relatively high pressures of toxic (carbon monoxide) and inflammable (carbon monoxide, ethylene) gaseous compounds. Moreover, required reaction temperatures are considerably high.

Microwave irradiation represents an alternative method of energy input into chemical systems compared to classical thermal reaction regimes. Major advantages of microwave irradiation are the uniform heating of the complete system as well as the high heating rates that might be achieved. If heating is performed by a heat source outside the reaction vessel (typically an oil bath), a temperature gradient from the vessel wand to the inside is observed. Avoiding these "wall effects" by the use of microwave heating is one of the major advantages of this method. On the other hand, microwave irradiation holds for a rapid and local heating directly at microwave absorbing molecules being part of the reaction mixture or at specific additives which are not reactive components, but, due to their ability of effectively absorbing microwave irradiation, allow for the heating of the reaction mixture. These "thermal microwave effects" occur at the same time in the complete volume of the reaction mixture and, therefore, provide identical reaction conditions in the reaction mixture. In a given setting of reactive compounds, solvent, and specific reaction vessel, the effect of microwave irradiation is a mixture of different influencing factors quite commonly (although not necessarily) leading to shorter reaction times, enhanced selectivities, and better turnover numbers, and was referred as the "microwave effect" [19–22].

As a further development of typical microwave systems, devices were introduced in which procedures under enhanced pressures are possible. Mostly, these are used for pulping processes in conjunction with analytical issues or as a possibility to work under conditions that allow for the heating of the respective reaction mixtures above the boiling point of the solvent. The latter of course leads to enhanced pressures in the reaction system. Nevertheless, surprisingly few reports on the use of these microwave systems for synthetic applications, in which gaseous reactive substrates under high partial pressures were used, have been published. The first-transition metal-catalysed reactions in this respect being induced by microwave irradiation were hydrogenation reactions [23–29]. The use of carbon monoxide has been described in conjunction with hydroformylation, aminoformylation, alkoxyformylation, hydroxyformylation, and cycloaddition reactions, and also has recently been reviewed [30–38].

Results and discussion

Scheme 1 shows the model reaction that we used for our investigation. We chose benzyl amine (**2**) as one of the components, because, on one hand, aliphatic primary amines show an enhanced reactivity due their higher basicity compared to aromatic amines [12, 14] and because CH_2 protons are diastereotopic in case of the formation of the dihydropyrrolone **4**, which means that the formation of **4** is easily detected from ^{1}H NMR spectra even of crude reaction mixtures. Since we already showed the scope of this one-pot reaction, we concentrated on the optimization of reaction conditions using microwave heating instead of classical external heating devices.

Due to the enhanced chemoselectivity of the catalytic reaction described herein towards the formation of chiral γ-lactams in unpolar hydrocarbon solvents, we decided to use toluene as the solvent in our experiments. On the other hand, unpolar solvents are not the solvents of choice for reactions under microwave irradiation, because low relative permittivities also mean that interaction of the respective molecules with microwave irradiation is not effective [39]. We, therefore, utilized additives with different particle sizes and different specific surfaces, respectively, as additives to ensure effective heating of a toluene-based reaction mixture by microwave irradiation. The use of reaction vessels made of SiC in comparison with glass vessels was reported before and has also been thoroughly reviewed [40].

Figure 1 shows the results of heating experiments in glass vessels under different conditions and with different additives. If 15 g SiC (0.2–1 mm) were suspended in 200 cm^3 of toluene and the mixture was irradiated with microwaves at a constant power of 300 W, the system reaches a temperature of slightly above 150 °C after circa 10 min [Fig. 1, curves indicated (a)]. After 6 min, the heating rate diminishes, because SiC particles and the solvent show only small differences in their temperature. Nevertheless, the experiment had to be stopped after 25 min due to the fact that overall reflections, i.e., the fraction of the irradiated microwave power that is not absorbed by the additive or the solvent, were too high. In all other experiments, a glass inset into the PTFE reactor was used which reduced this phenomena. If SiC with a bigger specific surface is used, higher solvent temperatures might be achieved. Moreover, it is possible to reduce the amount of SiC. In Fig. 1, curves indicated (b) show the heating of 200 cm^3 toluene by microwave irradiation in the presence of 5 g SiC (29.1 µm). A higher constant heating rate (650 W) was applied and a maximum temperature of 180 °C was defined to maintain the temperature below the boiling point of toluene at a pressure of 10 bar. The observed *T*/*t* curve clearly demonstrates that 180 °C might be achieved under these conditions in approximately 10 min. Further reduction of particle size using SiC (1.7 µm) did not lead to any improvement of the situation, although reflection phenomena again became a more pronounced issue leading to the situation that experiments had to be stopped at a temperature of 100 °C.

If pyrographite with a specific surface of 1200 m^2/g is used as the additive to toluene heating of the solvent to temperatures up to 200 °C was easily achieved. In Fig. 1, curves indicated (c) show a corresponding experiment in which, in contrast to experiments with SiC, no constant power was used, but the power was adjusted by the system according to the set parameter that heating should be finished after exactly 10 min.

In principle, the use of additives like SiC or pyrographite is well suited to realize heating of unpolar solvents by microwave irradiation under high-pressure conditions. Nevertheless, in the end, we decided to use a stirrer made of Weflon, which is Teflon with a certain amount of carbon incorporated, instead of additives for two reasons. First of all, the use of additives leads to an additional work-up step, because the additive has to be filtered off after the reaction induced by microwave irradiation is finished. Second, we observed that precipitation of the solid additives takes place even if the suspension is intensively stirred. We, therefore, envisaged the potential problem that the efficiency of the heating process, which is also depending on the even distribution of additive particles in the reaction mixture, might be depending on the stirring rate or even on the geometrical design of the stirrer itself.

In orienting experiments, we, first of all, applied reaction conditions concerning concentration of substrates and precatalyst, partial pressures of gaseous substrates, reaction

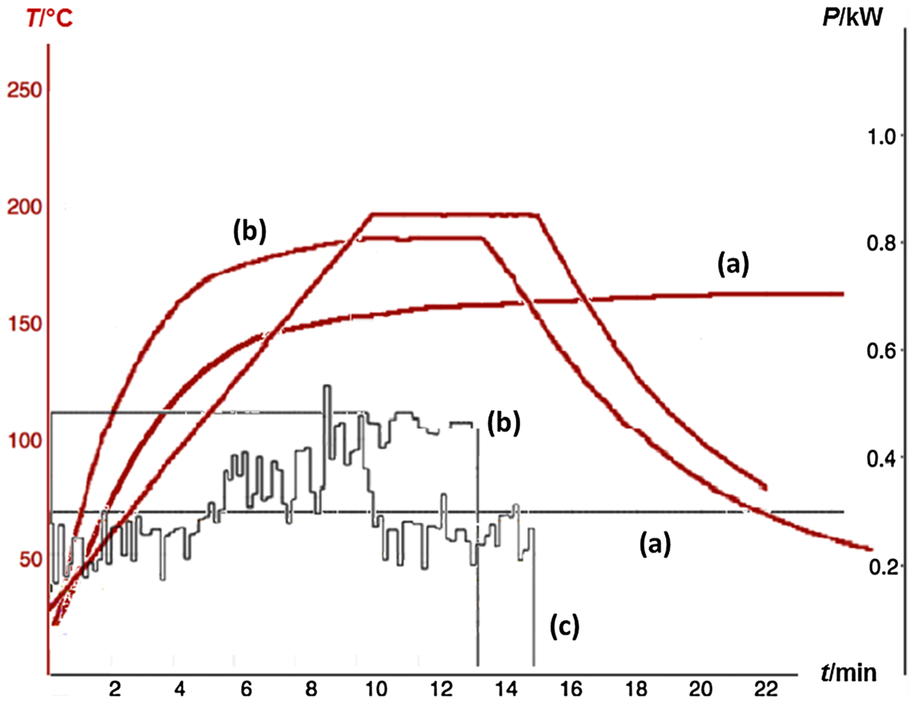


Fig. 1 Heating of (a) 15 g SiC (0.2–1 mm) in 200 cm^3 toluene at a constant power of 300 W; (b) 5 g SiC (29.1 µm) in 200 cm^3 toluene at a constant power of 650 W; (c) 5 g pyrographite (1200 m^2/g) in 200 cm^3 toluene at variable power [red: temperature of the solution (°C), black: power (kW)]

time, and reaction temperature that were identical to those used for analogous reactions in stainless steel autoclaves under external heating [14, 15]. This experiment showed that the same products **4** and **5** were produced in a comparable ratio under microwave activation. Figure 2 shows a section of the corresponding ^{1}H NMR spectrum of the crude reaction mixture from which signals being indicative for the formation of compounds **4** and **5** are easily detectable.

In additional experiments, we investigated changes in the above-mentioned parameters. First of all, we had a look on the question whether anhydrous solvents have to be used for the catalytic reactions. During the formation of intermediate **3**, water is produced as a side-product, anyway (cf. Scheme 1). Nevertheless, the more water is present in the reaction mixture, the more the ratio of **4** : **5** is expected to be shifted towards the formation of **5,** because the polarity of the reaction mixture is increased by the formation of water [17]. Due to the fact that the amount of water produced by condensation of substrates **1** and **2** is considerably higher than the water content of commercially available toluene, we, indeed, saw no significant difference concerning chemoselectivity of the reaction if either anhydrous or aqueous toluene is used. Nevertheless, we observed another possibility to enhance the selectivity of the reaction to make **4** the main product of the reaction. In our experiments in connection with the combinatorial synthesis of derivatives of **4** and **5** using a multi-reactor station [14], we used 1 mmol of the starting compounds in 2 cm^{3} of toluene, which means that the concentration of **1** and **2** was 0.5 mol/dm^{3}. In the microwave high-pressure reactor used for the experiments described herein, the reaction vessel is much bigger and we, therefore, had a look whether solutions with a lower concentration of **1** and **2** would also work. Therefore, we conducted three experiments with solutions of 0.5, 0.25, and 0.05 mol/dm^{3} **1** and **2,** and performed the catalytic reactions under microwave irradiation using 8 bar ethylene and 12 bar carbon monoxide, a reaction temperature of 140 °C, and a reaction time of 8 h and 3 mol % $Ru_3(CO)_{12}$. The result is depicted in Fig. 3, and shows that the lower the concentration of **1** and **2** is at the start of the reaction, the higher is the yield of **4** relative to **5** at the end of the catalytic reaction.

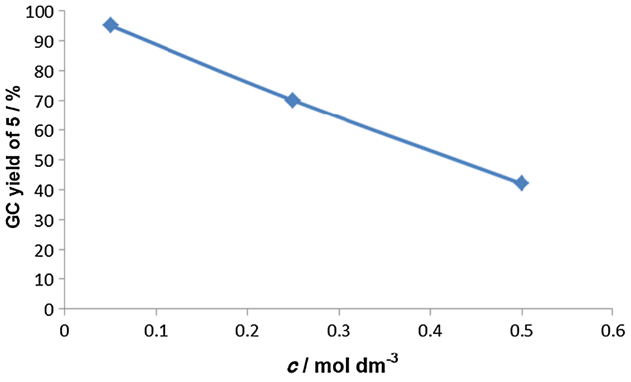


Fig. 3 Dependence of the yield of the γ-lactam **4** on the starting concentration of the starting compounds **1** and **2**

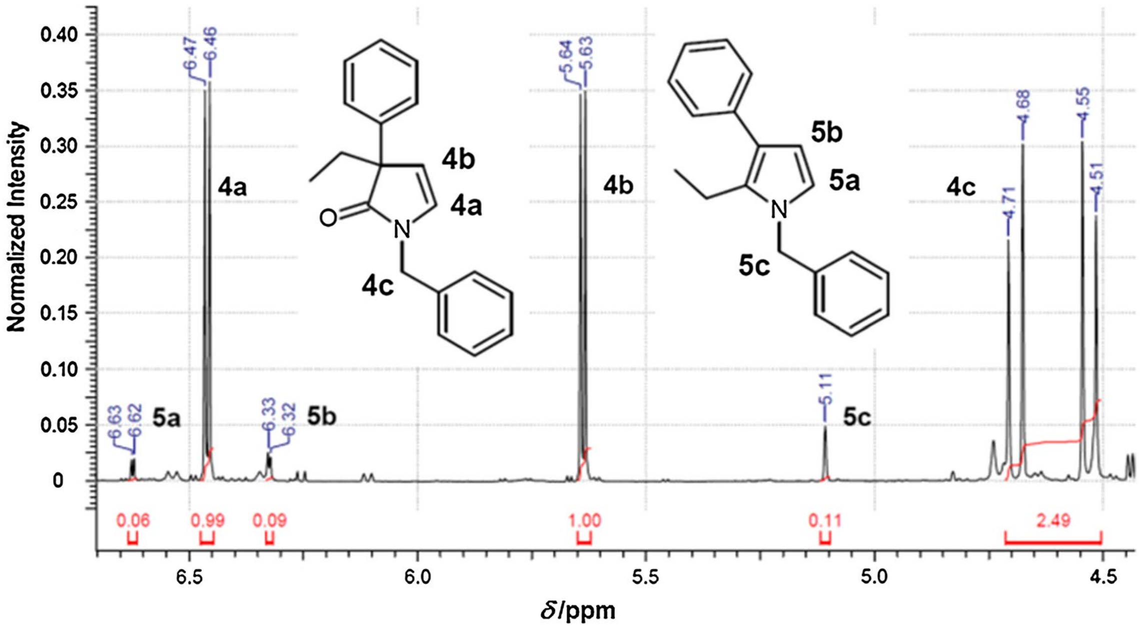


Fig. 2 Section of the ^{1}H NMR spectrum of a crude reaction mixture obtained from the reaction depicted in Scheme 1 (next to **4** and **5** traces of **3** still are detectable)

Concerning reaction temperatures, we already knew from the investigations under a thermal reaction regime that temperatures below 100 °C do not lead to the formation of any of the expected product molecules. Only non-reacted starting compounds **1** and **2** as well as the intermediate **3** may be recovered from the solution. We, therefore, tested three temperatures of 120 °C, 140 °C, and 160 °C, and had a look on the composition of the reaction mixture every hour. The other reaction conditions were 0.05 $\mathrm{mol/dm}^3$ of **1** and **2**, 8 bar ethylene and 12 bar carbon monoxide and 3 mol % $\mathrm{Ru}_3(\mathrm{CO})_{12}$. The results of the experiments at 120 °C and 140 °C are depicted in Fig. 4. The reaction at 160 °C had to be stopped after 2 h due to problems with cooling of the high-pressure reactor leading to a situation in which no constant temperature could be maintained. From Fig. 4, it gets obvious that, at a temperature of 120 °C after 1 h, a small amount of the starting compounds still is detectable. However, the reaction mixture mainly consists of the intermediate imine **3**. After 1 h, the amount of **3** slowly decreases and, to the same extent, concentrations of product molecules rise. After approximately 7–8 h, the reaction is finished and the main product **4** is produced with a GC yield of about 90%. At 140 °C, the reaction proceeds much faster. Therefore, after 1 h, the amount of **3** already is quite low and the combined ratio of **4** and **5** already reached almost 60%. After approximately 5 h, the composition of the reaction mixture stays constant and the reaction is finished. Nevertheless, the amount of the main product **4** now only is circa 80%. In addition, we observed the formation of another side-product **6** which, according to MS spectra, is a derivative of **3** with one molecule of ethylene having been inserted in β-position with respect to the C=N double bond. After the reaction at 160 °C was stopped after 2 h, we observed that 80% of the starting compounds had been consumed, but the combined yield of **4** and **5** was about 50% and the before-mentioned side-product **6** was formed to a higher extend. Therefore, higher temperatures as expected lead to enhanced reaction rates but, on the other hand, to decreased selectivity. Under thermal reaction conditions, reaction times of 16 h were needed for complete consumption of starting material. Under microwave activation, a complete reaction with high selectivity is achieved after 8 h at 120 °C and a reaction with acceptable selectivities is observed after a reaction time of 5 h at 140 °C.

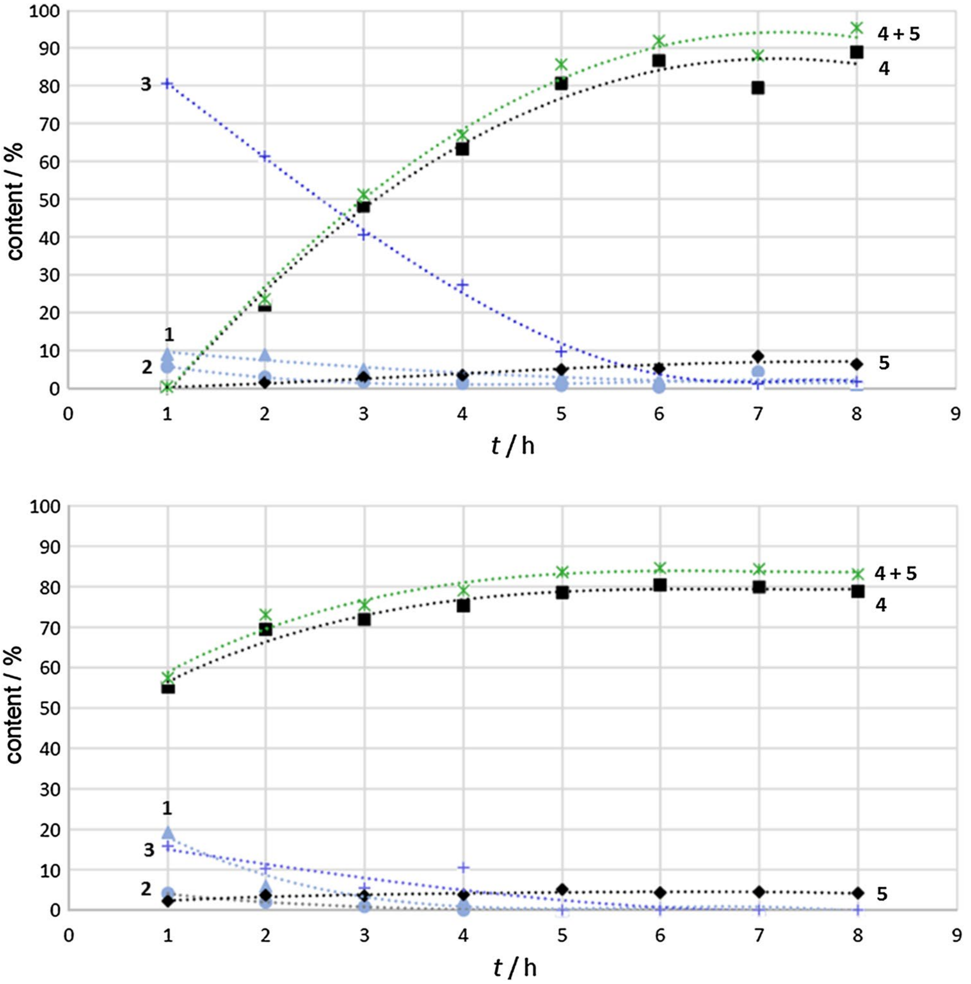


Fig. 4 Composition of the reaction mixture at 120 °C (above) and 140 °C (below)

We also performed experiments concerning precatalyst loading on the outcome of the reaction by simultaneously reacting five samples in a multi-reactor inset. Each test tube was charged with a solution of 0.6 mmol (0.079 g) cinnamaldehyde and 0.6 mmol (0.064 g) benzylamine in 12 cm^3 toluene. The test tubes were additionally charged with different amounts of $Ru_3(CO)_{12}$ (11.5, 8.6, 5.7, 2.9, and 0 mg), resulting in precatalyst loadings of 3, 2.25, 1.5, 0.75, and 0 mol % based on the amount of substrates. The first four experiments showed almost no influence on the outcome of the catalytic reaction. Only a slight decrease in the formation of the side-product **6** may be observed. If no precatalyst is introduced to the reaction mixture no formation of any of the products **4**, **5**, or **6** is observed.

In a last series of experiments concerning reaction conditions, we investigated the dependence of the formation of **4** and **5** on the partial pressures of ethylene and carbon monoxide (Fig. 5). If partial pressures are lowered from 8 bar ethylene and 12 bar carbon monoxide to 6 bar ethylene and 9 bar carbon monoxide, respectively, a slight increase of the formation of **4** and a decrease in the formation of the side-product are observed. If partial pressures are lowered to 4 bar ethylene and 6 bar carbon monoxide, the alkylated imine **6** is the main product of the reaction. Further investigations if this might be a suitable way to selectively synthesize derivatives of compounds of type **1**, which are alkylated in β-position with respect to the C=N double bond, are on their way.

In all investigations, we performed so far [9–18] samples of the reaction mixture which could only be taken by releasing the pressure from the autoclaves which means that the reaction came to a standstill. Due to the construction of the high-pressure reactor used in this investigation, it was possible to take samples without releasing pressure or lowering the temperature of the reaction mixture. Therefore, for the first time, it was possible to have a closer look on the initial stages of the reaction. We, therefore, chose a reaction temperature of 120 °C to slow down the reaction rate and collected a sample for GC/MS analysis every quarter of an hour with the first sample being taken after 10 min, which was the moment the reaction mixture reached its final temperature. The results are shown in Fig. 6. It gets obvious that, already after 10 min, the content of intermediate **3** already is higher than the amount of the starting compounds **1** and **2**. Nevertheless, the fraction of **3** reaches a maximum after about 45 min and then decreases as the content of the products **4** and **5** increases. Therefore, the assumption that **3** really is an intermediate in the formation of **4** and **5** and not just another side-product could be experimentally proven for the first time. Catalytic C–H activation as the common initial elementary reaction for all catalytic reaction pathways only starts after **3** is produced from **1** and **2**. The amount of the side-product **6** being formed by the insertion of ethylene into the C–H bond in β-position with respect to the C=N double bond is constant. This means that it has already been produced to this amount when the reaction temperature of 120 °C has been reached. Therefore, this reaction obviously is very fast, but the equilibrium at the given reaction temperature of 120 °C only holds for the formation of approximately 5–7% of **6**.

Conclusion

The catalytic formation of heterocyclic compounds **4** and **5** is possible using microwave heating as an alternative to external heating to activate substrates and catalysts. Since toluene has to be used as the solvent to enhance the selectivity of the formation of **4**, either stirrers made of Weflon or the addition of additives like SiC or pyrographite have to be

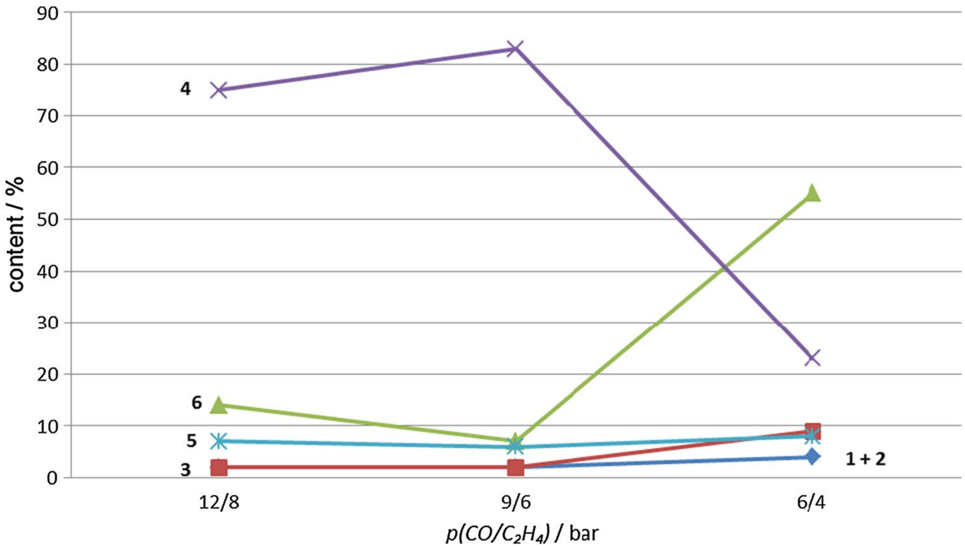


Fig. 5 Influence of partial pressures of CO and ethylene on the composition of the reaction mixture

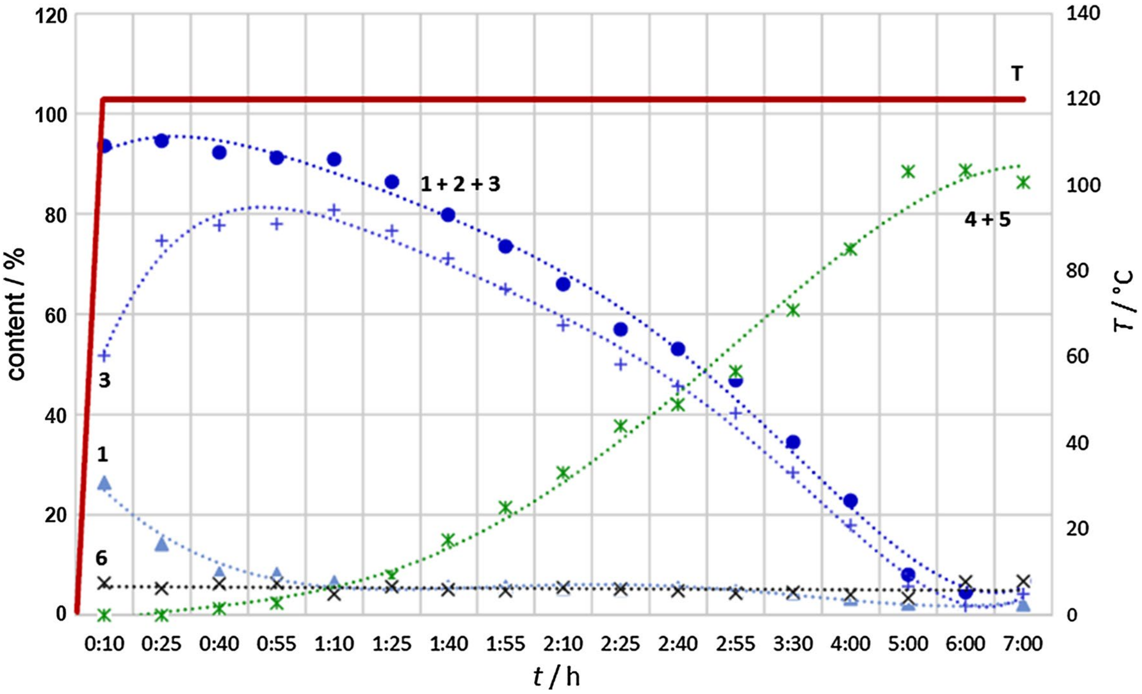


Fig. 6 Course of the reaction at 120 °C (content of **2** is not given for the sake of clarity)

taken into account to ensure effective heating of the reaction mixture by microwave irradiation. In contrast to analogous reactions under a thermal reaction, regime reaction times are lowered, less of the precatalyst is needed and partial pressures of gaseous substrates also may be reduced. In addition, it was possible, for the first time, to identify the imine **3** as an intermediate in the reaction.

Experimental

All chemicals and solvents have been checked for purity before use by GC/MS. Cinnamaldehyde, benzylamine, and all solvents have been degassed before use. The gaseous compounds carbon monoxide (4.7) and ethylene (3.5) have been used directly from the respective pressurised gas cylinder without further purification. Reactions activated by microwave irradiation have been performed in a synthWAVE 1500 microwave high-pressure reactor from MWS, Leutkirch, Germany, using a tailor-made glass container (75 × 170 mm) as the reaction vessel. For stirring, a Weflon-made stirrer was used. GC/MS measurements were performed using a GCQ plus/Polaris MS (Finnigan) device. Ionisation was done by EI; GC was performed using an OTIMA 5 MS Accent column (Macherey & Nagel, 0.25 µm, 0.25 mm × 30 m). NMR spectra were obtained using a JEOL ECZS 500 MHz spectrometer. $CDCl_3$ is used as solvent and internal standard for chemical shifts.

General procedure for catalytic reactions

Cinnamaldehyde (10 mmol, 1.322 g) and 10 mmol benzyl amine (1.072 g) were dissolved in a suspension of 200 cm^3 toluene and 0.3 mmol $Ru_3(CO)_{12}$ in the above-mentioned reaction vessel. The vessel was placed into the PTFE insert of the microwave high-pressure reactor. After closing the reactor, it was flushed with argon for 1 min, and then, a sequence of pressurizing the reactor with 5 bar argon and then releasing the pressure again was repeated three times to further remove air. Afterwards, the reactor was pressurised with the respective amounts of carbon monoxide and ethylene. Then, the reactor was heated by microwave irradiation to the required temperature. The heating rate can be controlled by the power in Watt of the microwave irradiation. Temperature is then maintained for the requested reaction time. During the reaction time, it is possible to take samples for GC/MS analysis without releasing the pressure or lowering the temperature of the system. After the reaction time is completed, microwave irradiation is turned off and the system is allowed to cool down to room temperature before the pressure is released with a rate of 3 bar/min. Evaporating the solvent results in dark brown crude reaction mixture which might directly be analysed by GC/MS and NMR techniques or purified using column chromatography to obtain pure **4** and **5**. For investigation of the influence of substrate concentration, partial pressures of CO and ethylene or precatalyst loading the amount of the respective compounds are varied correspondingly. The further procedure was performed as described above.

Acknowledgements The authors gratefully acknowledge support from MWS GmbH, Leutkirch, Germany.

References

1. Horrobin DF (1981) Pharmaceutical compositions for cancer treatment. EP 37175, Oct 7, 1981; (1982) Chem Abstr 96:24802
2. Norrby SR (1996) Drug Saf 15:87
3. Armat M, Canto M, Llor N, Escolano C, Molins E, Espinosa E, Bosch J (2002) J Org Chem 67:5343
4. Thompson LA (2002) Preparation of lactams as inhibitors of Aβ-protein production. US 20020010172, Jan 24, 2002; (2002) Chem Abstr 136:118401
5. Herzog KJ, Jacobs R, Kang J, Simpson TR, Woods JM (2004) Preparation of peptidyl lactams for treatment of neurological disorders. WO 2004080983, Sept 23, 2004; (2004) Chem Abstr 141:296296
6. Elworthy TR, Brill ER, Chiou S-S, Chu F, Harris JR (2004) J Med Chem 47:6124
7. Xu X, Che X, Gao S, Wu J, Bai X (2005) Synlett:1865
8. Frackenpohl J, Arvidsson PI, Schreiber JV, Seebach D (2001) ChemBioChem 2:445
9. Berger D, Imhof W (1999) J Chem Soc Chem Commun:1457
10. Berger D, Imhof W (2000) Tetrahedron 56:2015
11. Imhof W, Berger D, Kötteritzsch M, Rost M, Schönecker B (2001) Adv Synth Catal 343:795
12. Dönnecke D, Imhof W (2003) Tetrahedron 59:8499
13. Imhof W, Göbel A (2005) J Organomet Chem 690:1092
14. Biletzki T, Imhof W (2011) Synthesis:3979
15. Biletzki T, Elschner T, Neuwirth T, Görls H, Imhof W (2012) Arkivoc:457
16. Biletzki T, Imhof W (2012) Eur J Org Chem:6513
17. Gillies G, Dönnecke D, Imhof W (2007) Monatsh Chem 138:683
18. Biletzki T, Stark A, Imhof W (2010) Monatsh Chem 141:413
19. Younis A, Hassan AM, Mady MF, El-Haddad AF, Fayad M (2016) J Chem Pharm Res 8:193
20. Martins MAP, Frizzo CP, Moreira DN, Buriol L, Machado P (2009) Chem Rev 109:4140
21. Martinez-Palou R (2007) J Mex Chem Soc 51:252
22. Ameta SC, Punjabi PB, Ameta R, Ameta C (2015) Microwave-assisted organic synthesis: a green chemical approach. Apple Academic Press Inc, Oakville
23. Schmöger C, Stolle A, Ondruschka B, Lautenschläger W (2008) Labo:38
24. Arena G, Barreca G, Carcone L, Cini E, Marras G, Nedden HG, Rasparini M, Roseblade S, Russo A, Taddei M, Zanotti-Gerosa A (2013) Adv Synth Catal 355:1449
25. Pillai UR, Sahle-Demessie E, Varma RS (2002) J Mater Chem 12:3199
26. Gustafsson T, Hedenstrom M, Kihlberg J (2006) J Org Chem 71:1911
27. Vanier GS (2007) Synlett:131
28. Schmöger C, Stolle A, Bonrath W, Ondruschka B (2011) Curr Org Chem 15:151
29. Schmöger C, Gallert T, Stolle A, Ondruschka B, Bonrath W (2011) Chem Eng Technol 34:445
30. Pizzetti M, Russo A, Petricci E (2011) Chem Eur J 17:4523
31. Kormos CM, Leadbeater NE (2006) Synlett:1663
32. Iannelli M, Bergamelli F, Kormos CM, Paravisi S, Leadbeater NE (2009) Org Proc Res Dev 13:634
33. Petricci E, Mann A, Schoenfelder A, Rota A, Taddei M (2006) Org Lett 8:3725
34. Calcio Gaudino E, Carnaroglio D, Martina K, Palmisano G, Penoni A, Cravotto G (2015) Org Process Res Dev 19:499
35. Calcio Gaudino E, Tagliapietra S, Palmisano G, Martina K, Carnaroglio D, Cravotto G (2017) ACS Sustain Chem Eng 5:9233
36. Fukuyama T, Higashibeppu Y, Yamaura R, Ryu I (2007) Org Lett 9:587
37. Calcio Gaudino E, Rinaldi L, Rotolo L, Carnaroglio D, Pirola C, Cravotto G (2016) Molecules 21:253
38. Pineiro M, Dias LD, Damas L, Aquino GLB, Calvete MJF, Pereira MM (2017) Inorg Chim Acta 455:364
39. Kappe CO, Dallinger D, Murphree S (2008) Practical microwave synthesis for organic chemists: strategies, instruments, and protocols. Wiley-VCH, Weinheim
40. Kappe CO (2013) Acc Chem Res 46:1579