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The effect of pressure on microwave-enhanced Diels–Alder reactions. A case study †

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It is demonstrated that microwave-assisted Diels–Alder reactions of substituted 2(1*H*)-pyrazinones with ethylene are significantly more effective utilizing pre-pressurized (up to 10 bar) reaction vessels.

High-speed microwave synthesis[1] has attracted considerable attention in recent years.[2] Processing techniques employed in microwave chemistry involve, for example, solventless (dry-media) procedures where the reagents are adsorbed onto either a microwave transparent or strongly absorbing inorganic support.[3] Alternatively, microwave-assisted synthesis can be carried out using phase-transfer catalysis (PTC),[4] or—most commonly—in solvents, employing either open[5] or closed vessel systems.[6]

However, relatively little work has been performed with gaseous reagents in sealed vessel microwave experiments. Although several publications describe this technique in the context of heterogeneous gas-phase catalytic reactions important for industrial processes,[7] the use of pre-pressurized reaction vessels in conventional microwave-assisted organic synthesis (MAOS) involving solvents is rare.[8,9] Here we report the first study on the use and the effect of pressure in microwave-assisted synthesis involving solvents.

We have previously shown that the readily accessible and broadly functionalized 2-azadiene system of the 2(1*H*)-pyrazinone scaffold can undergo a Diels–Alder cycloaddition reaction with ethylene, leading to bicyclic cycloadducts of type **2** (Scheme 1).[10] These bridged pyrazinone structures could be used as versatile intermediates for the synthesis of analogues of different piperazine drugs and for the construction of conformationally restricted dipeptide analogs, useful as β-turn mimetics.[11] Under conventional conditions, these cycloaddition reactions have to be carried out in an autoclave applying 25–40 atm ethylene pressure before the setup is heated to 110 °C for several hours or even days. Recently we have shown that some of these reactions could be run upon microwave irradiation of an *o*-dichlorobenzene (DCB) solution saturated with ethylene without pre-pressurization of the vial.[12] Unfortunately this method failed to be generally applicable for our substrates. Therefore we were particularly interested to see, how a pre-pressurized microwave protocol would compare with the elevated pressure conditions used under conventional heating. In the present study a prototype, bench-top multimode microwave reactor is used, allowing processing in either quartz or PTFE-TFM® vessels with maximum operating limits of 300 °C and 80 bar. The system features magnetic stirring, complete on-line monitoring of temperature, pressure and microwave power, and the ability to maintain inert or reactive gas atmosphere.[13] As a starting point for the development of our microwave-assisted pre-pressurized Diels–Alder reactions, we chose to investigate the moderately reactive 2(1*H*)-pyrazinone **1a** (Scheme 1, Table 1), as this would act as a sharpening stone for optimizing reaction conditions. Flushing a solution of the pyrazinone **1a** in 25 mL of DCB with ethylene at atmospheric pressure, followed by microwave-irradiation at 190 °C for 100 min (employing a 2 min linear heating ramp) resulted in 53% conversion (determined upon isolation of the product) of the starting material (entry 1). As the imidoyl chloride moiety of the crude adduct **2a** is moisture sensitive this was hydrolyzed upon treatment with aqueous NaOH at rt or at 70 °C upon microwave irradiation. The bislactam **3a** was isolated in 12% yield. On the contrary, when the reaction vessel was pre-pressurized with ethylene to 5 bar, complete conversion upon irradiation at 190 °C was achieved within 30 min, yielding the hydrolyzed compound **3a** in excellent yield (87%, entry 2). The reaction could be accelerated by raising the pressure (10 bar, entry 3) or the pressure and

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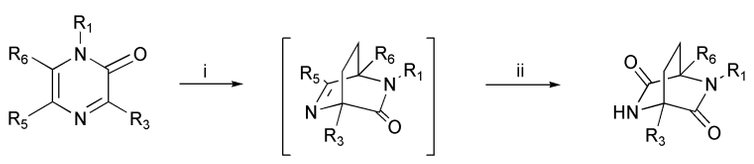

1a-i **2a-i** **3a-i**

i) ethylene, DCB, MW; ii) 1M NaOH/THF (1:2), RT, 2h or MW, 70°C, 5 min

1a R_1=Ph, R_3=Cl, R_6=H
1b R_1=Bn, R_3=Cl, R_6=H
1c R_1=PhCH$_2$CH$_2$,R_3=Cl, R_6=H
1a-h R_5=Cl; **1i** R_5=H
1d R_1=(p-MeO)Bn, R_3=Cl, R_6=H
1e R_1=Ph, R_3=CN, R_6=H
1f R_1=Ph,R_3=OMe,R_6=H
1g R_1=Bn, R_3=Ph, R_6=H
1h R_1=Ph, R_3=Cl, R_6=(p-MeOOC)Ph
1i R_1=Ph, R_3=OMe,R_6=H

Scheme 1 Microwave-assisted Diels–Alder reactions of pyrazinones **1a**–**i** with ethylene.

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Table 1 Microwave-assisted Diels–Alder reaction of pyrazinone **1a** with ethylene

Entry	Pressure (bar)	Temp. (°C)	Time (min)	Conversion[a] (%)	Yield[b] (%)
1	1[c]	190	100	53	12
2	5	190	30	>99	87
3	10	190	20	>99	85
4	10	220	10	>99	85

[a] Determined upon isolation of the starting material. [b] Isolated yields are given after hydrolysis. [c] Reaction run without pre-pressurization.

Table 2 Microwave-assisted Diels–Alder reactions of pyrazinones **1a**–**i** with ethylene

	Conventional conditions toluene, 25 atm, 110 °C[a]		Microwave conditions DCB, 10 bar, 190 °C	
Pyrazinone	Time (h)	Yield (%)	Time (min)	Yield (%)[b]
1a	16	86	20[c]	85
1b	16	77	30	77
1c	18	76	40	72
1d	—[d]	—[d]	20	60
1e	12	82	10[e]	80
1f	240 (**40 atm**)	58	100 (**250 °C**)	60
1g	24	83	50[f]	88
1h	—[d]	—[d]	80 (**220 °C**)	47[g]
1i	no reaction	no reaction	no reaction	no reaction

[a] Results taken from the literature (ref. 10*a*). [b] Isolated yields of **3a**–**i** after hydrolysis applying Method A and B (yields independent of the Method used). [c] If run at 1 bar for 140 min this resulted in 89% (ref. 4). [d] Not investigated. [e] If run at 1 bar for 40 min this resulted in 86% (ref. 4). [f] If run at 1 bar no reaction takes place (ref. 4). [g] Yield indicated for **2h** as hydrolysis is not possible.

the temperature (10 bar/ 220 °C; entry 4). Since for some adducts of type **2** heating above 200 °C resulted in an equilibrium between the cycloaddition and the competing retro-Diels–Alder fragmentation process,[12] a solution of the final bislactam product **3a** in DCB was irradiated at 220 °C for 60 min. No starting material was formed, confirming the stability of the adduct **3a** at 220 °C. It was established that flushing of the pyrazinone solution with ethylene before pre-pressurization has no influence on the outcome of the reaction.

The scope of our methodology was investigated upon reaction of differently substituted 2(1*H*)-pyrazinones (Scheme 1, Table 2). To prevent potential problems as a result of the competing retro-cycloaddition process all reactions were run at a preselected temperature of 190 °C and the vessels were pre-pressurized to 10 bar. A comparison is made with the conventional heating conditions,[10a] revealing that regarding the isolated product yields, the outcome is more or less the same. However, carrying out the cycloaddition reactions under sealed vessel microwave conditions dramatically speeded up the overall process. The nature of the substituent at the C3-position of the 2(1*H*)-pyrazinone strongly influences the rate of the reaction. While the electron withdrawing cyanide group of **1e** seems to favour the cycloaddition, the electron-donating methoxy group in **1f** has a strongly retarding effect, resulting in the need for a higher preselected maximum temperature of 250 °C for irradiation. The bislactam **3f** was isolated in 60% yield within 100 min (10 days under conventional conditions). Interestingly, this elevated temperature did not cause a detectable retro-cycloaddition process as was established upon microwave-irradiation of a solution of the adduct **3f** in DCB at 250 °C for 60 min. The C5-chloro-substituent appears to be essential for the cycloaddition. No reaction could be observed with pyrazinone **1i** under both conventional and microwave-irradiation conditions. Due to their moisture sensitivity, the adducts **2a**–**h** were hydrolyzed prior to isolation.

In conclusion, we have described the first systematic study on the effect of pressure on standard MAOS involving solvents. This combination was successfully applied for the Diels–Alder reaction of variously functionalized 2(1*H*)-pyrazinones with ethylene gas. These results lead us to believe that the pre-pressurized microwave technique could replace conventional autoclave chemistry in the future.

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