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Microwave accelerated aza-Claisen rearrangements

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Abstract—The microwave-assisted thermal aza-Claisen rearrangement of allylic imidates and thiocyanates to the corresponding amides and isothiocyanates is investigated. Significant accelerations of the rearrangement of allylic imidates to amides and of allylic thiocyanates to isothiocyanates in comparison with standard thermal reactions is observed.

[3,3]-Sigmatropic rearrangements, when used as a tool for the formation of carbon–nitrogen bonds, have an enormous potential for the synthesis of molecules containing nitrogen-bearing stereocentres. The prototype of this reaction is the Overman rearrangement, which provides protected allylic amines with excellent stereocontrol and constitutes one of the few possibilities for introducing an amino group at a tertiary carbon atom.[1] Stereodefined allylic amines are important building blocks for the synthesis of highly functionalized enantiomerically pure amino acid derivatives and alkaloid natural products.[2] We have recently reported thermally driven [3,3]-sigmatropic rearrangements of allylic thiocyanates as a way to synthesize protected allylic amines of varying structures.[3]

The use of microwave irradiation to assist organic reactions has shown considerable advantages over thermal reactions. Reactions that typically require high temperatures and extended reaction times have been accelerated using microwave irradiation.[4] As a continuation of our research, we herein report the microwave-assisted thermal aza-Claisen rearrangement of allylic imidates and thiocyanates to the corresponding amides and isothiocyanates (Fig. 1).

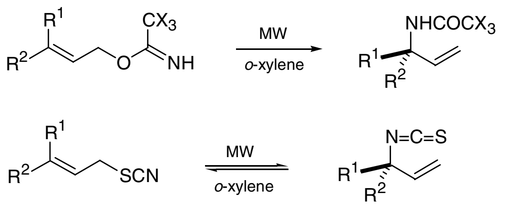

Figure 1.

We have found, that microwave irradiation[6] of thiocyanate **1** in *o*-xylene under sealed vessel conditions at 150 °C, led to the rearranged products **2** with substantial shortening of the reaction time (24 times) compared to the thermal reaction performed at 90 °C. Acceleration of the rearrangement **1**→**2** (24–80 times) in a variety of solvents was observed giving 59–72% yields of **2** (Scheme 1, Table 1).

We were also delighted to find that irradiation under solvent-free conditions on a silica gel support was applicable and provided isothiocyanate **2** in excellent isolated yield (98%) and stereoselectivity (96%).

This success encouraged us to extend this method (sealed vessel microwave irradiation) to accelerate other Overman rearrangements. The scope of this method was investigated and all the imidates shown in Table 2 were converted to the corresponding amides in considerably shorter times compared with the standard thermal rearrangement, most often performed at the reflux

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Keywords: Overman rearrangement; Imidate; Thiocyanate; Isothiocyanate; Microwave irradiation.

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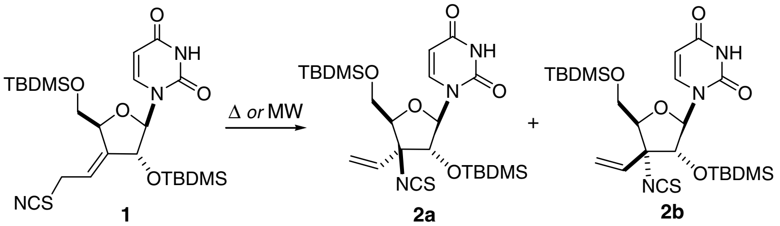


Scheme 1.

Table 1. Solvent effect on the microwave-assisted rearrangement

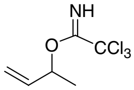
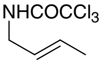
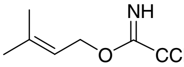
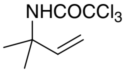
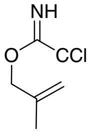
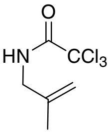
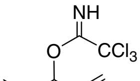
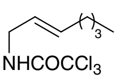
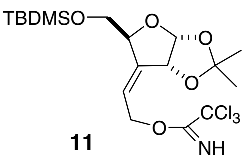
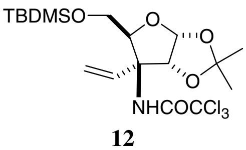
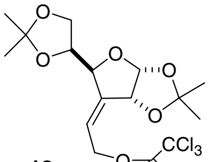
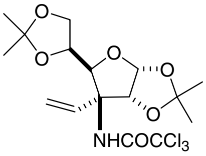
Entry	Conditions	Time	Ratio **2a**:**2b**	Yield[a] (%)
1	Δ, 90 °C, *o*-xylene [Ref. 5]	24 h	65:35	70
2	MW, 150 °C, *o*-xylene	1 h	71:29	71
3	MW, 150 °C, toluene	1 h	74:26	70
4	MW, 150 °C, hexane	20 min	79:21	70
5	MW, 150 °C, cyclohexane	30 min	80:20	59
6	MW, 150 °C, CCl_4	20 min	78:22	72
7	MW, 80 °C, silica gel support	1 h	98:2	98

[a] Isolated yield.

temperature of the solvents. In practice, the imidate was dissolved in *o*-xylene, powdered anhydrous K_2CO_3 (2 mg/mL) was added, and the solution was heated using microwave irradiation[6] with vigorous stirring. A variety of imidates including aliphatic (entries 1–4), saccharide (entries 5–9) and substituted aliphatic (entries 10 and 11) were efficiently converted to the corresponding amides.[14]

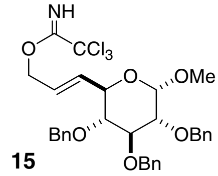
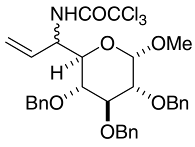
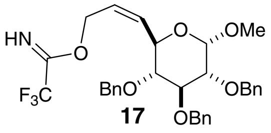
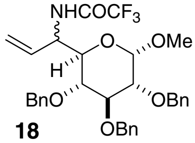
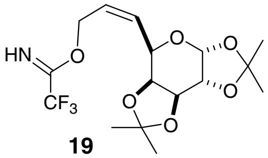
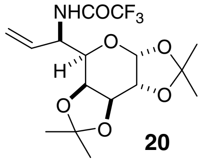
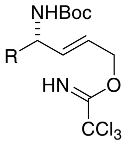
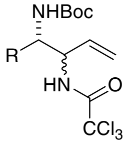
In conclusion, a significant acceleration of [3.3]-sigmatropic rearrangements and increased yields of the

Table 2. Microwave accelerated Overman rearrangements

Entry	Starting material	Product	Conditions	Time	Yield[a] (%)
1	 **3**	 **4**	Δ, 110 °C, toluene [Ref. 7] MW, 140 °C, *o*-xylene, K_2CO_3 MW, 180 °C, *o*-xylene, K_2CO_3[c]	2 h 15 min 8 min	53 93 89
2	 **5**	 **6**	Δ, 140 °C, xylene [Ref. 8] MW, 140 °C, *o*-xylene, K_2CO_3 MW, 180 °C, *o*-xylene, K_2CO_{3c}[c]	3.5 h 20 min 14 min	48 85 84
3	 **7**	 **8**	Δ, 140 °C, xylene [Ref. 8] MW, 150 °C, *o*-xylene, K_2CO_3 MW, 180 °C, *o*-xylene, K_2CO_3[c]	2.5 h 1 h 30 min	37 60 62
4	 **9**	 **10**	Δ, 140 °C, xylene [Ref. 9] MW, 140 °C, *o*-xylene, K_2CO_3 MW, 180 °C, *o*-xylene, K_2CO_3[c]	2.5 h 5 min 1 min	74 97 94
5	 **11**	 **12**	Δ, 140 °C, *o*-xylene, K_2CO_3, de > 99% Δ, 140 °C, *o*-xylene MW, 140 °C, *o*-xylene, K_2CO_3, de > 99% MW, 140 °C, *o*-xylene	5 days — 13 h —	73 —[b] 74 —[b]
6	 **13**	 **14**	Δ, 140 °C, *o*-xylene, K_2CO_3, de > 99% [Ref. 10] Δ, 140 °C, *o*-xylene MW, 140 °C, *o*-xylene, K_2CO_3, de > 99% MW, 140 °C, *o*-xylene	5 days — 13 h —	75 —[b] 80 —[b]

(*continued on next page*)

Table 2 (*continued*)

Entry	Starting material	Product	Conditions	Time	Yield[a] (%)
7	 **15**	 **16**	Δ, 180 °C, *o*-xylene, sealed tube, K_2CO_3, de ≈ 0% MW, 180 °C, *o*-xylene, K_2CO_3, de ≈ 0%[c] MW, 180 °C, *o*-xylene, de ≈ 0%[c]	12 h 30 min 12 h	26 52 8
8	 **17**	 **18**	Δ, 180 °C, *o*-xylene, sealed tube, K_2CO_3, de = 20% MW, 180 °C, *o*-xylene, K_2CO_3, de = 19%[c] MW, 180 °C, *o*-xylene, de = 18%[c]	12 h 30 min 1 h	31 68 15
9	 **19**	 **20**	Δ, 200 °C, xylene, sealed tube, de = 82% [Ref. 11] MW, 180 °C, *o*-xylene, K_2CO_3, de = 80%[c]	2 h 15 min	95 91
10	 **21**, R = Et	 **23**, R = Et	**21**: Δ, 140 °C, *o*-xylene, de = 10% [Ref. 12] MW, 140 °C, *o*-xylene, K_2CO_3, de = 14% MW, 200 °C, *o*-xylene, K_2CO_3, de = 12%[c]	24 h 2 h 5 min	75 80 80
11	**22**, R = *i*-Pr	**24**, R = *i*-Pr	**22**: Δ, 140 °C, *o*-xylene, de = 10% [Ref. 12] MW, 140 °C, *o*-xylene, K_2CO_3, de = 12% MW, 200 °C, *o*-xylene, K_2CO_3, de = 13%[c]	24 h 2 h 5 min	69 71 68

[a] Isolated yield.

[b] In the absence of K_2CO_3 only decomposition products were observed.[13]

[c] MW experiments were performed in the presence of a heating bar, Weflon, Milestone.

rearranged products was observed using sealed vessel microwave irradiation conditions with an additional small improvement in the observed stereoselectivity. The acceleration of the rearrangement of allylic imidates to amides (8–30-fold) and of allylic thiocyanates to isothiocyanates (24–80-fold) in comparison with thermal reactions carried out at the reflux temperature of the solvent has been described.

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6. Microwave experiments were conducted using a focused microwave system (CEM Discover). *Typical procedure* (Table 2, entries 1–11): The imidate was weighed in a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. *o*-Xylene (5 mL) and powdered anhydrous K_2CO_3 (10 mg) were added. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for the time given in Table 2. The reaction mixture was purified by flash chromatography on silica gel.
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14. All new compounds gave satisfactory analytical and spectral data in accordance with their structures. Selected data for compound **12**: white crystals; mp 75–76 °C; $[\alpha]_D^{25}$ +55.3 (c 0.25; $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.15 (3H, s, CH_3), 0.17 (3H, s, CH_3), 0.92 (9H, s, $3 \times CH_3$), 1.35 (3H, br s, CH_3), 1.54 (3H, br s, CH_3), 3.85 (1H, d, $J_{5,4} = 2.9$ Hz, H_4), 4.02 (1H, d, $J_{5,5} = 12.5$ Hz, H_5), 4.15 (1H, dd, $J_{5,5} = 12.5$ Hz, $J_{5,4} = 2.9$ Hz, H_5), 5.00 (1H, d, $J_{2,1} = 3.6$ Hz, H_2), 5.35 (1H, dd, $J_{7trans,6} = 17.6$ Hz, $J_{7trans,7cis} = 0.7$ Hz, H_{7trans}), 5.39 (1H, dd, $J_{7cis,6} = 10.9$ Hz, $J_{7trans,7cis} = 0.7$ Hz, H_{7cis}), 5.88 (1H, d, $J_{2,1} = 3.6$ Hz, H_1), 6.08 (1H, dd, $J_{7trans,6} = 17.6$ Hz, $J_{7cis,6} = 10.9$ Hz, H_6), 9.21 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4, −4.8, 19.0, 26.0 (3×C), 26.2, 26.6, 59.6, 70.0, 82.6, 92.9, 104.3, 112.4, 116.8, 130.5, 161.4. Anal. Calcd for $C_{18}H_{30}Cl_3NO_5Si$ (474.88): C, 45.53; H, 6.37; N, 2.95. Found C, 45.54; H, 6.67; N, 2.74.