Acid-catalyzed rearrangement of morphinans using microwave heating

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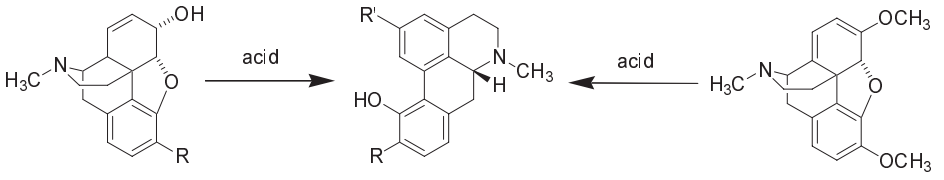
Összefoglaló

Morfinszármazékok savkatalizált átrendeződése mikrohullámú aktiválással. A morfin, kodein és tebain savkatalizált átrendeződési reakcióját vizsgáltuk mikrohullámú aktiválással. A hagyományos melegítési technikákkal összehasonlítva minden esetben sikerült az átrendeződés hozamán jelentősen javítani. A gyógyászati szempontból is jelentős, dopamin agonista hatású R(-)-apomorfin szintézisét 75%-os hozammal sikerült megvalósítanunk morfinból kiindulva.

A key step in the synthesis of many aporphines is the acid-catalyzed rearrangement of the corresponding morphinan. It is well known, that morphine **(1)** and its congeners rearrange with concentrated acids to aporphines[1-4] (Scheme 1.). However the yields of the conversion of morphine **(1)** to apomorphine **(4)**[1,2] and codeine **(2)** to apocodeine **(5)**[3] are low, using a variety of acids. Granchelli et al.[4] investigated the acid-catalyzed rearrangement of thebaine **(3)** with methanesulfonic acid, resulting in the formation of 2,10-dimethoxy-11-hydroxy-aporphine **(6)** in 60% yield. The yield of this rearrangement can be improved[5] by carrying out the rearrangement with methanesulfonic acid, in the presence of methanol. Recently we reported the investigation of the acid catalyzed rearrangement of a series of morphinans[6] using conventional thermal techniques. The results of our study on the microwave-assisted acid-catalyzed rearrangement of a series of morphinans are reported here.



	R			R	R'	
1	OH	morphine	**4**	OH	H	apomorphine
2	OCH_3	codeine	**5**	OCH_3	H	apocodeine
			6	OCH_3	OCH_3	
			7	OCH_3	OH	morphothebaine

3 thebaine

Scheme 1.

Automated and focused microwave flash heating has recently proven to be very effective in accelerating organic transformations and has been widely applied in parallel syntheses and in drug discovery processes. Numerous successful reactions with great efficiency and dramatically enhanced reaction rates have been described[7, 8, 9].

The conditions of the microwave-promoted rearrangements with methanesulfonic acid and hydrochloric acid were optimized in the case of the morphine **(1)** to apomorphine **(4)** rearrangement (Table 1.).

Table 1.

*Optimization of the microwave-assisted rearrangement reaction of morphine **(1)***

Acid	Time (min)	T (°C)	Yield (%)[a]
99% CH_3SO_2OH	5	60	50
99% CH_3SO_2OH	10	60	52
99% CH_3SO_2OH	5	90	75
99% CH_3SO_2OH	2	150	64
37% HCl	5	150	70
37% HCl	10	150	60
[a]Isolated yield			

The change in temperature and microwave power did not affect the yield of the microwave assisted rearrangement. The optimal conditions were found to be in the case of the rearrangement with methanesulfonic acid at 90°C, with 5 min stirring. In the case of the rearrangement with hydrochloric acid at 150°C, with 5 min stirring, under pressure. Methanesulfonic acid was shown to be an excellent solvent to mediate microwave energy, thus lower microwave power was sufficient to achieve full conversion.

In the course of our study we found a significant improvement in the yields in the acid-catalyzed rearrangements of morphinans using microwave heating, compared to the conventional heating techniques (Table 2.). Another advantage

to the use of microwave heating was, the shorter reaction time required, thus the products obtained did not need any further purification.

Table 2. Microwave-assisted rearrangement of morphinans

Acid	Yield (%)[Ref.]	Conditions
Morphine **(1)** → apomorphine **(4)**		
37% HCl	34[1]	Thermal/150°C, 30min, pressure
99% CH_3SO_2OH	23[10]	Thermal/90°C, 30min
99% CH_3SO_2OH	45[6]	Thermal/60°C, 30min
37% HCl	70	Microwave/150°C, 5min, pressure
99% CH_3SO_2OH	75	Microwave/90°C, 5min
Codeine **(2)** → apocodeine **(5)**		
99% CH_3SO_2OH	32[4]	Thermal/90°C, 30min
99% CH_3SO_2OH	65[6]	Thermal/60°C, 30min
99% CH_3SO_2OH	78	Microwave/90°C, 5min
Thebaine **(3)** → 2,10-dimethoxy-11-hydroxyaporphine **(6)**		
99% CH_3SO_2OH	60[4] (sideproduct: **7**)	Thermal/90°C, 30min
99% CH_3SO_2OH	70 (sideproduct: **7**)	Microwave/90°C, 5min
CH_3SO_2OH / 16% CH_3OH	95[5]	Thermal/90°C, 30min
CH_3SO_2OH / 16% CH_3OH	95	Microwave/90°C, 5min

The morphine **(1)** to apomorphine **(4)** rearrangement (Scheme 1.) was carried out with methanesulfonic acid in 75% yield using microwave-assisted heating at 90 °C, for 5 min. This rearrangement was also attempted in concentrated hydrochloric acid using microwave-assisted heating at 150 °C, for 5 min, under pressure. This reaction resulted in apomorphine **(4)** in 70% yield, a considerable improvement compared to the classical method using traditional heating techniques[1]. In the case of codeine **(2)** and thebaine **(3)** the optimized conditions were applied for the microwave-promoted rearrangement with methanesulfonic acid. After heating at 90 °C, for 5 min in a microwave reactor with methanesulfonic acid, codeine **(2)** afforded apocodeine **(5)** in 78% yield. 2,10-dimethoxy-11-hydroxyaporphine **(6)** was obtained from thebaine **(3)** with methanesulfonic acid in 70% yield using similar conditions. Morphothebaine **(7)** was also isolated, whose formation is the result of the water content of the methanesulfonic acid[5]. 95% yield was achieved by carrying out the microwave-assisted rearrangement of thebaine **(3)** with methanesulfonic acid, in the presence of 16% methanol. Under these conditions morphothebaine **(7)** was not isolated.

In conclusion, the microwave-promoted synthesis was successfully applied for the acid-catalyzed rearrangement of morphinans. R(-)-apomorphine **(4)** was

synthesized from morphine **(1)** with methanesulfonic acid in 75% isolated yield using microwave heating.

Experimental: Microwave irradiation was carried out with a CEM Discover microwave instrument. Melting points were measured with a Thomas Hoover Capillary Melting Point Apparatus, and are uncorrected. ^{1}H NMR spectra were obtained on Varian 300 spectrometer, chemical shifts are reported in ppm (δ) from internal TMS and coupling constants (J) are measured in Hz. Thin layer chromatography was performed on precoated Merck 5554 Silica gel 40 F_{254} foils, the spots were visualized with Dragendorff's reagent.

General procedure for the microwave-assisted rearrangement of morphinans

The morphinan (0.3mmol) was dissolved in the appropriate acid (1.5mL) in a 10mL glass tube, under nitrogen, with ice-cooling. The vessel was sealed with a septum and placed into the microwave cavity. The reaction mixture was stirred for 5 min, at 90°C in microwave reactor, then after cooling to room temperature the reaction mixture was added to ice-water (20mL). The pH was adjusted to 9 by adding ammonia, with ice-cooling. The mixture was extracted with ethyl acetate (3x10mL), the organic layer was washed with brine (20mL), dried with sodium sulfate, filtered and evaporated in vacuo to afford the appropriate aporphines.

R(-)-apomorphine hydrochloride (4): a) Starting from morphine hydrate (1) using methanesulfonic acid the extraction was carried out with chloroform (5x10mL) and after drying with sodium sulfate to the filtered extract HCl-ether was added to afford the hydrochloride salt. After evaporation the solid pure HCl-salt was filtered from anhydrous ether (68mg, 75%), mp: 210°C>dec. (Lit. (Merck Index 12th Edition) mp: 195 °C (dec.)), ^{1}H-NMR (CD_3OD) δ 2.75 (1H, t, C-H), 2.93-3.06 (1H, m, C-H), 3.09 (3H, s, NCH_3), 3.32-3.55 (3H, m, C-H), 3.64-3.76 (1H, m, C-H), 4.18 (1H, m, C-H), 6.73 (2H, dd, J=8Hz, H-8, H-9), 7.15 (1H, d, J=8Hz, H-3), 7.35 (1H, t, H-2), 8.42 (1H, d, J=8Hz, H-1).

b) Starting from morphine hydrate **(1)**, using concentrated hydrochloric acid, the rearrangement was carried out in microwave reactor for 5 min, at 150 °C, under pressure in a sealed vial. The work up was identical to the previously mentioned method. Yield: 63mg (70%), mp: 210°C>dec. (Lit. (Merck Index 12th Edition) mp: 195 °C (dec.)), the ^{1}H NMR spectrum was identical to the above spectrum.

R(-)-apocodeine hydrochloride (5): Starting from codeine (3) using methanesulfonic acid, the product was converted to the hydrochloride salt with HCl-ether to yield a white solid (75mg, 78%), mp: 269-270°C (dec.) (Lit.[2] mp: 260-263°C (dec.)). ^{1}H-NMR (CD_3OD) δ 2.8 (1H, t, C-H), 2.96-3.18 (1H, m, C-H), 3.2 (3H, s, NCH_3), 3.33-3.6 (3H, m, C-H), 3.77-3.86 (1H, m, C-H), 3.91

(3H, s, OCH_3), 4.33 (1H, m, C-H), 6.89 (2H, dd, J=8.5Hz, H-8, H-9), 7.19 (1H, d, J=8Hz, H-3), 7.38 (1H, t, H-2), 8.44 (1H, d, J=8Hz, H-1).

2,10-dimethoxy-11-hydroxyaporphine hydrochloride (6): a) Starting from thebaine **(3)** using methanesulfonic acid, the two component product was separated by column chromatography (Silicagel 60, chloroform:methanol=19:1).

The first eluted compound was converted into the hydrochloride with HCl-ether to give white solid crystals of **6** (73mg, 70%), mp: 87-90°C (Lit.[6] mp: 87-90°C). ^{1}H-NMR (CD_3OD) δ 2.5 (1H, m, C-H), 2.8 (1H, t, C-H), 3.1 (1H, m, C-H), 3.2 (3H, s, NCH_3), 3.3-3.6 (2H, m, C-H), 3.8 (1H, m, C-H), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.23 (1H, m, C-H), 6.76 (1H, d, J=1.5Hz, H-3), 6.88 (2H, dd, J=8Hz, H-8, H-9), 8.1 (1H, d, J=1.5Hz, H-1).

The second eluted compound was converted into the hydrochloride with HCl-ether to give white solid crystals of **7** (15mg, 15%), mp: 258-260 °C (Lit. (Merck Index 12th Edition) mp: 256-260 °C). ^{1}H-NMR (DMSO) δ 2.9-3.6 (5H, m, C-H), 3.46 (3H, s, NCH_3), 4.09 (1H, m, C-H), 4.27 (3H, s, OCH_3), 4.62 (1H, m, C-H), 6.98 (1H, s, H-3), 7.22 (1H, d, J=8Hz, H-8), 7.35 (1H, d, J=8Hz, H-9), 8.24 (1H, s, H-1).

b) Starting from thebaine **(3)** using methanesulfonic acid in the presence of 16% methanol, the pure oily product was converted into the hydrochloride with HCl-ether to give white solid crystals of **6** (99mg, 95%), mp: 87-90°C (Lit.[6] mp: 87-90°C). The ^{1}H NMR spectrum was identical with the above mentioned data.

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