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Microwave-assisted Expeditious and Efficient Synthesis of Cyclopentene Ring-fused Tetrahydroquinoline Derivatives Using Three-component Povarov Reaction

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Abstract

We report here an efficient and expeditious microwave-assisted synthesis of cyclopentadiene ring-fused tetrahydroquinolines using the three-component Povarov reaction catalyzed by indium (III) chloride. This method has an advantage of shorter reaction time (10 – 15 min) with high and reproducible yields (up to 90%) and is suitable for parallel library synthesis. The optimization process is reported and the results from the microwave route are compared with those of the conventional synthetic route. In almost all cases, the microwave acceleration consistently provided improved yields favoring the *cis*-diastereomer.

Keywords

Tetrahydroquinolines; Cyclopentene ring-fused tetrahydroquinolines; Microwave-assisted synthesis; Parallel synthesis; Povarov reaction

1. Introduction

The tetrahydroquinoline derivatives have attracted considerable attention because of their important biological activities and occurrence in natural products.[1] Those containing fused cyclopentene ring have been found to exhibit a variety of pharmacological activities like agonism at BKCa receptor (**1**),[2] GPR30 estrogen receptor (**2**)[3,4] and allosteric modulation at the α7 nicotinic acetylcholine receptors (nAChRs)[5–7] as well as antitubercular activity against *M. tuberculosis* (Figure 1).[8] One such representative tetrahydroquinoline derivative is TQS (**3**; 4-(1-naphthyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[c]quinoline-8-sulfonamide), a potent type II positive allosteric modulator (PAM) of α7 nAChRs.[7,9,5,10] Such type II PAMs have been preclinically shown to be useful in improving memory, cognition and in treating neuropathic pain. Therefore, synthesis of new tetrahydroquinolines still holds great interest.[11,1] A variety of synthetic methods have been developed for constructing such tetrahydroquinolines and among them the three-component Povarov reaction has been most empowering and versatile.[12,11,1,13] This reaction which is also known as aza-Diels Alder

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reaction can be carried out in a one-pot fashion using an aniline, an aldehyde and an electron-rich dienophile in the presence of various Brønsted as well as Lewis acids.[11,14] Although the original Povarov reaction was carried out with cyclopentadiene as a dienophile, most of the later optimization and scope expansion of this reaction was focused on shelf-stable dienophiles such as pyran, furan etc.[14,11] Synthesis of cyclopentene ring-fused tetrahydroquinolines has been relatively low yielding[7,6,14,11] due to thermal instability of cyclopentadiene leading to its spontaneous dimerization at room temperature and gradual polymerization even at low temperature.[15] Various Brønsted and Lewis acids have been utilized to accelerate and improve reaction times, but have led to only limited success.[16–21,2,22,23] Microwave-assisted organic synthesis has become an important tool in organic synthesis for rate enhancement, improving reaction yields, and reducing thermal degradation byproducts.[24] To the best of our knowledge use of microwave acceleration for the Povarov reaction has been limited to thermally-stable N-vinylpyrrolidin-2-one[25], pyran[26], furan[26], 2-methoxyacrylate[27] and acrylamides[27] dienophiles. In view of this, we report here a microwave-assisted synthesis of cyclopentene ring-fused tetrahydroquinolines using $InCl_3$ as a Lewis acid, which provides excellent results in terms of yield, reaction time and diasteroselectivity.

2. Chemistry and Discussion

As significant pharmacological work has been done around the α7 nAChR allosteric modulator TQS (**3**), we selected it's synthesis as a model reaction. To date, it has been synthesized in a maximum of 22% yield with a reaction time of 24 hrs at room temperature and using 20 mol% $InCl_3$ as the catalyst.[6]

With an objective of improving this reaction yield and reducing reaction time, we carried out optimization under microwave irradiation by evaluating four different aspects of this reaction: a. reaction temperature; b. reaction time (Table 1); c. catalyst loading and d. cyclopentadiene loading (Table 2). We preferred $InCl_3$ as a Lewis acid for our optimization because compared to the conventional Lewis acids, it has some advantages including its compatibility with both organic and aqueous media, recyclability, operational simplicity and a strong tolerance to oxygen- and nitrogen- containing substrates and functional groups.[28,29] Additionally, it is a preferred catalyst in multicomponent reactions providing better regio- and diastero-selectivities.[28]

We began our optimization by executing the TQS synthesis (Scheme 1) under microwave irradiation at 100°C and utilizing 20 mol% of $InCl_3$ and 3 equivalents of cyclopentadiene in acetonitrile as a solvent. The reaction was complete within 15 minutes, giving TQS in 60% yield (Table 1). The reaction was very clean and no chromatographic purification was required as the product was obtained in greater than 99% purity (by HPLC and ^{1}H-NMR). TQS has three chiral centers with the cyclopentene and 1- naphthyl rings oriented *cis*-to each other. We observed that these reaction conditions favored the formation of the *cis*-diastereomer. The relative orientation of cyclopentene ring and 1-naphthyl ring was *cis* as determined from the coupling constants and NOE measurements (Figure 2). In the ^{1}H NMR spectra of compound **3**, the two doublets at δ 5.45 and 4.25 were attributed to protons H-4 and H-9b respectively. The coupling constants between protons H-3a and H-4 ($J_{3a,4}$ = 3.5Hz) in ^{1}H NMR confirmed the cis- relationship of these protons.

Although the above experiment gave the desired product in good yield, in order to find optimal reaction conditions, we executed this reaction under conditions vary ing in temperature and time (Table 1). We got similar yields (i.e. 60%) for a shorter period of time (10 min) and at a lower temperature (75 °C). Temperatures and reaction times higher or lower than this did not improve reaction yields. In subsequent experiments, the amounts of

$InCl_3$ and cyclopentadiene were varied only to confirm that any reduction in these quantities led to reduced yields (entries 1, 2, 5 and 6; Table 2). Also increasing the quantities of $InCl_3$ and cyclopentadiene did not improve reaction yields. Thus, in our hands, 3 equivalents of cyclopentadiene with 20 mol% of $InCl_3$ at 75°C for 10 minutes in a Biotage Microwave Synthesizer was the most efficient procedure for the synthesis of TQS.[30] We then extended the scope of this reaction to various substituted aldehydes and anilines and compared their yields with those reported under standard conditions (Table 3). As seen, microwave-assisted reaction conditions provided significantly improved reaction yields for almost all analogs synthesized compared to those obtained under standard conditions. In all cases, except for compound **8**, we observed formation of only the *cis*-diastereomer under our reaction conditions. Compound **8** was obtained as a 72:28 mixture of *cis: trans* diastereomers.

In summary, we have developed a microwave-assisted, rapid and high yielding one-pot Povarov reaction for the synthesis of cyclopentene ring-fused tetrahydroquinoline derivatives. In general, the reactions for various substrates were rapid, clean and in most cases no chromatographic purification was necessary, produced superior yields with high diastereoselectivities and could be scaled up to gram quantities.

Acknowledgments

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30. *Experimental procedure for the synthesis of TQS (3) :* In a microwave vial, cyclopentadiene (254 mg, 3.84 mmol, 3 equiv.) was added to a suspension of 1-naphthaldehyde (200 mg, 1.28 mmol), 4-aminosulfonamide (220 mg, 1.28 mmol) and indium (III) chloride (55.6 mg, 0.256 mmol, 0.2 equiv.) in acetonitrile (5 mL). The reaction vial was placed in a Biotage Initiator microwave synthesizer and heated to 100°C for 15 min. The contents were added to 10% aqueous Na_2CO_3 solution (0.1 M; 10 mL) and extracted with chloroform (3×20 mL). The combined organic layer was washed with brine (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was treated with hexane/dichloromethane to precipitate out compound **3** as an off white solid (290 mg; yield 60%).[7] Compounds 7, 8, 10, 11, 13, and 14 were purified by column chromatography (EtOAc/Hexane = 10/90 → 50/50) to yield the desired product. The rest were crystallized from dichloromethane/hexane. All compounds were >95% pure by HPLC and ^{1}H NMR.Compound **9**: ^{1}H NMR (500 MHz, DMSO-d6) δ 7.34 (d, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.89 (s, 2H), 6.80 (d, *J* = 9.0 Hz, 1H), 5.87 – 5.81 (m, 1H), 5.70 – 5.65 (m, 1H), 5.62 (s, 1H), 3.89 (d, *J* = 9.0 Hz, 1H), 3.02 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 2.33 – 2.23 (m, 1H), 2.22 – 2,14 (m,2H), 1.88 – 1.60 (m, 4H), 1.34 – 1.10 (m, 4H), 1.16 – 0.88 (m, 2H); m/z = 333.79 [M +H]+. Compound **10**: ^{1}H NMR (500 MHz, CDCl3) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.44 (m, 3H), 7.27 (d, *J* = 7.5 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 5.99 (s, 1H), 5.84 – 5.79 (m, 1H), 5.65 – 5.59 (m, 1H), 5.52 (d, *J* = 3.0 Hz, 1H), 4.90 (s, 2H), 4.28 (d, *J* = 9.0 Hz, 1H), 3.33 (dq, *J* = 9.0 Hz, 2.0 Hz, 1H), 2.56 (ddd, *J* = 14.5 Hz, 9.0 Hz, 2.0 Hz, 1H), 1.66 (ddd, *J* = 15.5 Hz, 9.0 Hz, 1.5 Hz, 1H); m/z = 377.84 [M+H]+. Compound **12**: ^{1}H NMR (500 MHz, DMSO-d6) δ 7.69 (brs, 1H), 7.66 (dd as t, *J* = 1.5 Hz, 1H), 7.42 (d, *J* = 1.5 Hz, 1H), 7.32 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.95 (s, 2H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 1.5 Hz, 1H), 6.20 (s, 1H), 5.88 – 5.82 (m, 1H), 5.67 – 5.63 (m, 1H), 4.51 (d, *J* = 2.0 Hz, 1H), 4.04 (d, *J* = 9.0 Hz, 1H), 2.99 (dq, *J* = 8.5 Hz, 3.5 Hz, 1H), 2.38 (ddd, *J* = 16.5 Hz, 9.5 Hz, 2.5 Hz, 1H), 1.98 (dd, *J* = 16 Hz, 9 Hz, 1H); m/z = 317.64 [M+H]+. Compound **13**: ^{1}H NMR (500 MHz, CDCl3) δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.90 (dd, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.57 – 7.46 (m, 3H), 6.72 (s, 1H), 6.64 (d, *J* = 1.5 Hz, 2H), 5.86 – 5.79 (m, 1H), 5.68 – 5.60 (m, 1H), 5.35 (d, *J* = 3.0 Hz, 1H), 4.25 – 4.18 (m, 1H), 3.78 (s, 3H), 3.54 (s, 1H), 3.30 (dq, *J* = 9.0 Hz, 2.5 Hz, 1H), 2.66 (qdd, *J* = 17.0 Hz, 9.0 Hz, 2.5 Hz, 1H), 1.64 (tdd, *J* = 16.5 Hz, 9.0 Hz, 2.0 Hz, 1H); m/z = 328.36 [M+H]+. Compound **14**: ^{1}H NMR (500 MHz, CDCl3) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H) 7.81 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 6.5 Hz, 1H), 7.58–7.48 (m, 3H), 7.23 (dd, *J* = 2.5 Hz, 1.0 Hz, 1H), 7.10 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 5.82 – 5.79 (m, 1H), 5.68 – 5.62 (m, 1H), 5.40 (d, *J* = 3.0 Hz, 1H), 4.20 (d, *J* = 9.0 Hz, 1H), 3.75 (s, 1H), 3.30 (dq, *J* = 8.5 Hz, 3.0 Hz, 1H), 2.62 (qdd, *J* = 17.0 Hz, 9.5 Hz, 2.5 Hz, 1H), 1.64 (qdd, *J* = 16.0 Hz, 8.5 Hz, 1.5 Hz, 1H); m/z = 377.16 [M+H]+. Compound **15**: ^{1}H NMR (500 MHz, DMSO-d6) δ 7.51 (d, *J* = 1.5 Hz, 1H), 7.32 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.91 (s, 2H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.31 (d, *J* = 1.5 Hz, 1H), 5.82 – 5.76 (m, 1H), 5.74 – 5.68 (m, 1H), 3.82 (s, 1H), 3.12 – 3.02 (m, 1H), 2.70 – 2.54 (m, 3H), 2.09 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H); m/z = 250.99 [M+H]+. Compound **16**: ^{1}H NMR (500 MHz, DMSO-d6) δ 12.21 (s, 1H), 7.66 (s, 1H), 7.65 (d, *J* = 10.0 Hz, 1H), 7.52 (dt, *J* = 8.0 Hz, 2.0 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.39 (s, 1H), 5.98 – 5.90 (m, 1H), 5.64 – 5.56 (m, 1H), 4.89 (d, *J* = 2.5

Hz, 1H), 4.08 (d, J = 8.5 Hz, 1H), 3.06 (ddq, J = 8.5 Hz, 3.5 Hz, 1.5 Hz, 1H), 2.36 (ddd, J = 15.5 Hz, 10.0 Hz, 2.0 Hz, 1H), 1.61 (dd, J = 15.0 Hz, 9.0 Hz, 1H); m/z = 361.23 [M+H]$^{+}$.
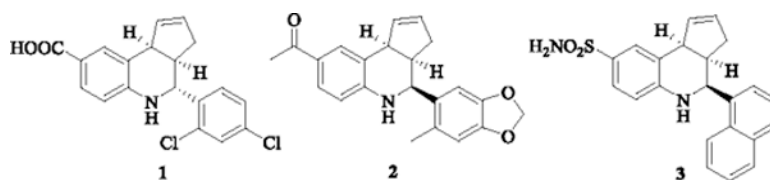
Figure 1.
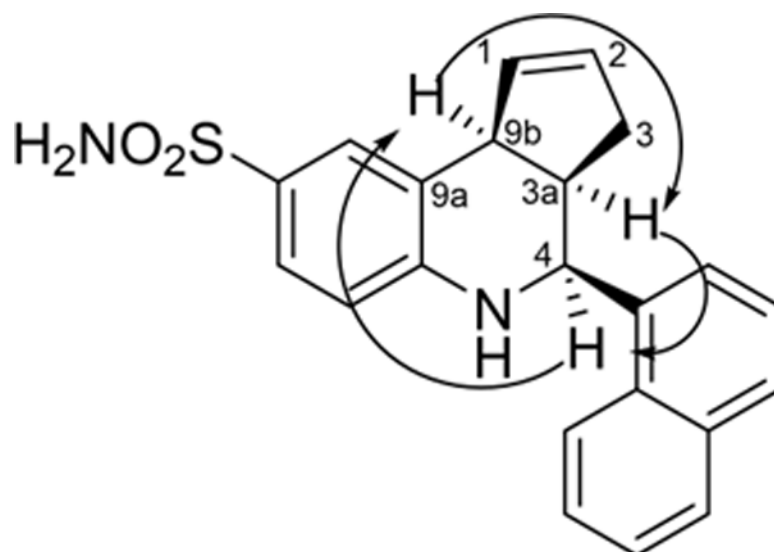Representative biologically-active cyclopentene ring-fused tetrahydroquinolines.
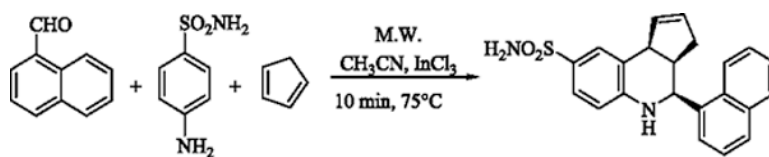
Figure 2.
Characteristic NOEs of TQS (3)

Scheme 1.
Microwave acclerated synthesis of TQS.

Table 1

Influence of reaction temperature and time

Entry	Temperature (°C)	Time (min)	Yield (%)
1	100	15	60
2	75	15	60
3	50	15	35
4	75	5	49
5	75	10	60
6	120	5	55

Table 2

Effect of catalyst and cyclopentadiene loading

Entry	InCl$_3$ (mol%)	Cyclopentadiene (equiv.)	Yield (%)
1	10	3	41
2	15	3	50
3	20	3	60
4	25	3	60
5	20	1	43
6	20	2	45

Table 3

Comparison of microwave-assisted synthesis of tetrahydroquinoline under standard reaction conditions.

Compound	R$_1$	R$_2$	Microwave Heating		Conventional heating	
			Time	Yield (%)	Time	Yield (%)
3	naphthyl	p-SO$_2$NH$_2$	10 min	60	48 h	22 (ref:7)
4	F-phenyl	p-SO$_2$NH$_2$	15 min	66	24 h	2 (ref:7)
5	NO$_2$-phenyl	p-SO$_2$NH$_2$	15 min	90	24 h	20 (ref:7)
6	naphthyl	p-SO$_2$NH$_2$	10 min	61	48 h	19 (ref:7)
7	CF$_3$-phenyl	p-SO$_2$NH$_2$	15 min	67	24 h	30 (ref:6)
8	methylphenyl	p-SO$_2$NH$_2$	15 min	66	12 h	13 (ref:7)
9	cyclohexyl	p-SO$_2$NH$_2$	15 min	67	–	–
10	naphthyl	o-SO$_2$NH$_2$	15 min	55	–	–

Compound	R₁	R₂	Microwave Heating		Conventional heating	
			Time	Yield (%)	Time	Yield (%)
11	(benzodioxole-Br)	*p*-COCH₃	15 min	74	2 h	98 (ref: 3)
12	(furan)	*p*-SO₂NH₂	15 min	40	–	–
13	(naphthalene)	*p*-OMe	10 min	58	–	–
14	(naphthalene)	*p*-Br	10 min	56	–	–
15	–H	*p*-SO₂NH₂	15 min	48	–	–
16	(dichlorophenyl)	*p*-COOH	15 min	65	–	–