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# Brønsted acid-catalyzed Nazarov cyclization of pyrrole derivatives accelerated by microwave irradiation

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ABSTRACT

The Brønsted acid-catalyzed Nazarov cyclization of pyrrole derivatives was developed. Microwave irradiation accelerated the Nazarov cyclization significantly at 40 °C to give cyclopenta[*b*]pyrrole derivatives in excellent yields with high trans selectivity.



In recent years, the construction of cyclopentanones via electrocyclic reactions has played an important role in synthetic organic chemistry because of the widespread occurrence of the structural features in many natural products.[1] Along this line, roseophilin **1**,[2] yuehchukene **2**,[3] and paspaline **3**[4] are representative cyclopentanones that are not only medicinally relevant but also architecturally intriguing, as depicted in Figure 1. Roseophilin **1**, which was isolated from *Streptomyces griseoviridis*, is a potent cytotoxic agent against K562 cells (chronic myeloid leukemia model; $IC_{50}$, 0.34 μM) and KB cells (nasopharyngeal carcinoma model; $IC_{50}$, 0.88 μM). Yuehchukene **2**, which was isolated from the roots of *Murraya paniculata*, exhibits estrogenic and antiestrogenic activities as well as potent anti-implantation activity. Paspaline **3**, which was isolated from *Claviceps paspali*, shows potent tremorgenic activity.

The Nazarov cyclization[5,6] is a very versatile process for the synthesis of cyclopentanones, and it is well known that Lewis[7] or Brønsted acids[8] promote this reaction. Microwave-assisted expedient synthesis has also attracted considerable interest in recent years.[9] The advantages of the microwave-assisted organic synthesis (MAOS) include short reaction time, diminished side reactions, increased yields, and improved reproducibility. MAOS has been applied to the synthesis of several natural products, including peptides and carbohydrates.[10]

Surprisingly, very few reports are available on the Nazarov cyclization of pyrrole derivatives.[7f,i,8e] Given the significance of the biological aspect of cyclopenta[*b*]pyrrole **4** derivatives, combined with our continuing interest in Brønsted acid-catalyzed reac-

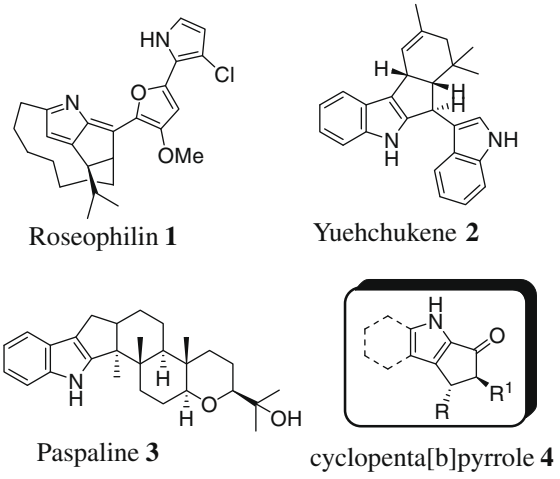


**Figure 1.** Cyclopenta[*b*]pyrrole based natural products and core structure **4**.

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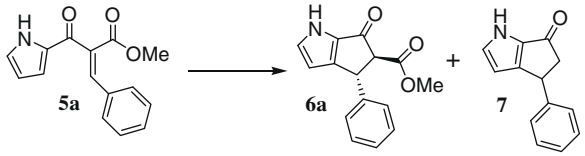
**Table 1**
Optimization of Nazarov cyclization




| Entry | Acid (mol %) | Solvent | Temp | Time (h) | Yield of **6a**[a] (%) |
|---|---|---|---|---|---|
| 1 | TsOH[e] (20%) | Toluene | 80 | 24 | 33[i] |
| 2 | CSA[f] (20%) | Toluene | 80 | 24 | No reaction |
| 3 | TfOH[g] (20%) | MeCN[c] | 60 | 34 | 46[j] |
| 4 | $Tf_2NH$[h] (20%) | MeCN | rt | 135 | 32 |
| 5 | $Tf_2NH$ (30%) | MeCN | rt | 37 | 55 |
| 6 | $Tf_2NH$ (30%) | MeCN | 35 | 12 | 50 |
| 7 | $Tf_2NH$ (30%) | MeCN | 40, MW[d] | 6 | 72 |
| 8 | $Tf_2NH$ (30%) | MeCN | 40, MW | 9 | 78 |
| 9 | $Tf_2NH$ (30%) | Toluene | 40 | 6 | 25 |
| 10 | $Tf_2NH$ (30%) | Toluene | 40, MW | 6 | 69 |
| 11 | $Tf_2NH$ (30%) | DCE[b] | 40 | 12 | 62 |
| 12 | $Tf_2NH$ (30%) | DCE | 40, MW | 6 | 81 |

[a] Isolated yield.
[b] DCE = dichloroethane.
[c] MeCN = acetonitrile.
[d] MW = microwave.
[e] TsOH = 4-toluenesulfonic acid.
[f] CSA = camphorsulfonic acid.
[g] TfOH = trifluoromethanesulfonic acid.
[h] $Tf_2NH$ = trifluoromethanesulfonimide.
[i] 1:0.4 mixture of **6a** and **7**.
[j] 1:0.5 mixture of **6a** and **7**.

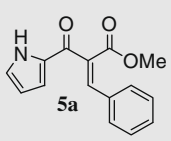
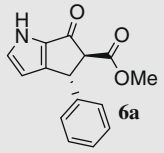
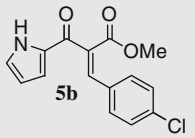
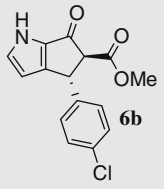
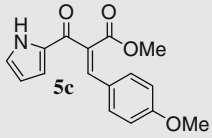
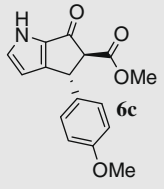
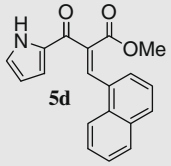
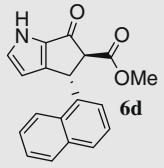
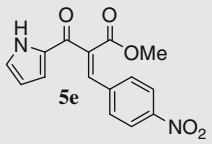
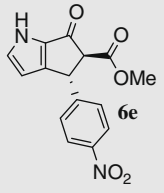
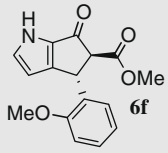
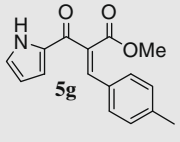
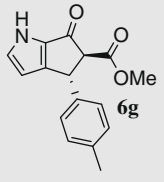
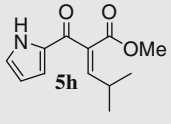
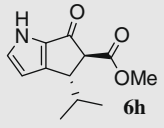
tions,[11,12] we turned our attention to the development of a simple and flexible method that is viable for producing closely related cyclopenta[*b*]pyrrole derivatives. We herein report our preliminary studies on the microwave-assisted Brønsted acid-catalyzed Nazarov cyclization of polarized pyrrole derivatives.

At the outset, we selected dienone **5a** as the model substrate and screened the Brønsted acid for the Nazarov cyclization. The results are shown in Table 1. Upon treatment of **5a** with 20 mol % TsOH at 80 °C, the enone underwent Nazarov cyclization to furnish **6a** in a low yield (entry 1). No reaction was observed with 20 mol % CSA at 80 °C (entry 2). Use of 30 mol % $Tf_2NH$[13] (entry 5) turned out to be more promising than that of TfOH (entry 3) even though it again resulted in incomplete conversion. It is noted that the reaction at higher temperature with extended hours of heating resulted in the formation of a significant amount of decarboxylated compound of 4-phenyl-4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one **7**[14] accompanied by the cyclized product of **6a**. Hence, it is vital to firstly maintain the reaction temperature below 60 °C and secondly, shorten the reaction time to obtain **6a** in good yield.

We were pleased to discover that even though the reaction did not proceed to completion after 12 h (entry 6) with a sub-stoichiometric amount of $Tf_2NH$ in acetonitrile alone, the reaction rate was improved significantly by microwave irradiation (entries 7 and 8). Having secured an efficient approach to the cyclization of **5** in 30 mol % $Tf_2NH$ in acetonitrile under microwave irradiation, we focused our subsequent efforts on the solvent system. We conducted the reaction in toluene and dichloroethane (entries 9–12). Dichloroethane was found to be the optimal solvent under standard microwave irradiation at 40 °C for 6 h, affording **6a** in 81% yield. When this reaction was conducted thermally at 40 °C for 12 h, 62% of **6a** was obtained.

With the optimized reaction conditions in hand, we set out to define the scope of the Nazarov cyclization of a range of pyrrole derivatives **5** (Table 2).[15] The cyclization of polarized reactants **5c**, **5f**, and **5g** bearing electron-donating components at the β-posi-

**Table 2**
$Tf_2NH$-catalyzed Nazarov cyclization[a]

| Entry | Substrate | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  **5a** | 6 |  **6a** | 81 |
| 2 |  **5b** | 14 |  **6b** | 82 |
| 3 |  **5c** | 9 |  **6c** | 95 |
| 4 |  **5d** | 9 |  **6d** | 89 |
| 5 |  **5e** | 14 |  **6e** | 83 |
| 6 |  **5f** | 8 |  **6f** | 94 |
| 7 |  **5g** | 13 |  **6g** | 80 |
| 8 |  **5h** | 15 |  **6h** | 70 |

[a] Reaction conditions: 1 mmol of dienone, 30 mol % of $Tf_2NH$, DCE, 40 °C, MW.
[b] Isolated yields.

tion proceeded smoothly to give the corresponding products in excellent isolated yields (entries 3, 6, and 7). In the presence of electron-withdrawing components of **5b** and **5e**, the reaction rate was slightly reduced (entries 2 and 5) although the desired product was also obtained in excellent isolated yields. On the other hand, **5d** that had an additional aromatic ring system gave a slightly higher yield than **5a** (entries 4 and 1). Finally, **5h** bearing a β-alkyl group gave cyclized product **6h** in moderate yield with a low reaction rate (entry 8). Only one diastereomer with a trans relationship between an α-methoxycarbonyl group and a β-phenyl or alkyl group was obtained after column chromatography in all the cases examined. This 3,4-trans relative stereochemistry was supported by previous results.[7f]

In conclusion, we have developed a simple, efficient, and cost-effective cyclization of polarized pyrrole derivatives using $Tf_2NH$ (30 mol %) in dichloroethane at 40 °C under microwave irradiation. Studies directed towards the synthesis of bioactive natural products and explorative works on asymmetric Nazarov cyclization using this methodology are ongoing.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.04.109.

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13. For recent example of the $Tf_2NH$-catalyzed reactions, see: (a) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2001**, 1851; (b) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45; (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204; (d) Takasu, K.; Nagao, S.; Ihara, M. *Adv. Synth. Catal.* **2006**, *348*, 2376; (e) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48; (f) Figueroa, R.; Hsung, R. P.; Guevarra, C. C. *Org. Lett.* **2007**, *9*, 4857; (g) Jung, M. E.; Chu, H. V. *Org. Lett.* **2008**, *10*, 3647.
14. Identified by $^1H$ NMR, isolated as a mixture of **6a** and **7**.
15. *General procedure for the Nazarov cyclization.* A mixture of dienone (1.0 mmol) and $Tf_2NH$ (0.3 mmol) in dichloroethane (1.5 mL) in glass vial was flushed with argon for 1 min and sealed with cap. The resulting mixture was stirred at 40 °C in microwave reactor (Biotage Initiator™, Focused microwave heating system) for the time shown in Table 2. When the reaction was complete (as indicated by TLC analysis) the organic solvent was removed under reduced pressure and the residue was purified by either flash column chromatography or preparative thin layer chromatography using hexane–ethyl acetate as eluent to yield the corresponding cyclized product.