Brønsted Acid-Promoted Cascade Alkylation/Cyclization of Pyrroles with N,N-Dimethylaminomethylene glutaric Acid Dinitrile: A Concise Route to Cyclopenta[b]pyrroles

Kaikai Wu, Ping Wu, Jiping Chen, Chenglin Sun, and Zhengkun Yu

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, Liaoning 116023, People’s Republic of China
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People’s Republic of China
Fax: (+86)-411-8437-9227; e-mail: zkyu@dicp.ac.cn

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Abstract: A Brønsted acid (p-TsOH·H₂O) promoted alkylation/cyclization cascade reaction of pyrroles with N,N-dimethylaminomethylene glutaric acid dinitrile was efficiently realized to afford functionalized cyclopenta[b]pyrroles with excellent diastereoselectivity. Deamination of the corresponding ammonium salts of the cyclopenta[b]pyrroles with methyl iodide led to dihydrocyclopenta[c]pyrroles. The cascade reaction pathway was confirmed by isolation and transformation of the reaction intermediate, i.e., the 2-alkylated pyrrole.

Keywords: Brønsted acid; cyclization; cyclopenta[b]pyrroles; N,N-dimethylaminomethylene glutaric acid dinitrile; pyrroles

Fused heterocyclic compounds containing a cyclopenta[b]pyrrole motif are present in many biologically active natural products and medicinally important compounds,[1] such as, krill fluorescent substance F[2] which is a component of the phorbine chromophore present in all types of chlorophylls, roseophilin,[1c,3] and an inhibitor of ε-amino oxidase[4] (Figure 1). Consequently, much effort has recently been devoted to the synthesis of cyclopenta[b]pyrrole derivatives. The acid-mediated Nazarov cyclization is a useful method for the construction of five-membered carbocycles,[5] which has usually been employed as a straightforward route to access cyclopentenone-fused pyrroles.[5] Transition metal-catalyzed cyclization/ring expansion of functionalized alkynes,[6] hydroformylation of 1,4-dienes followed by condensation with primary amines,[7] and other reactions[8] have also been applied for the synthesis of cyclopenta[b]pyrrole derivatives.

Brønsted or Lewis acid-promoted Friedel–Crafts cyclization has been considered as a powerful method to prepare heterocyclic compounds.[6] A pyrrole ring can thus be used as the “template”-like structure to establish another ring onto it for the construction of polycyclic compounds,[11] in which annulation of pre-functionalized alkynes or olefins to a pyrrole core is usually involved. After screening of the relevant known synthetic methods, we reasoned that a diene might be utilized to replace the pre-functionalized alkynes or olefins for the same purpose. The polarized diene, N,N-dimethylaminomethylene glutaric acid dinitrile,[12] which is structurally endowed with an electron-donating NMe₂ moiety and two electron-attracting cyano groups attached at its two C=C bonds, has been used as a C₃ building block to synthesize carbocyclic compounds.[13] Recently, we found that Brønsted acids could promote Friedel–Crafts alkylation of indoles with N,N-dimethylaminomethy-
leneglutamic acid dinitrile (2) to form 3-alkylated or 3-alkenylated indole derivatives under mild conditions (Scheme 1a). Herein, we report the synthesis of cyclopenta[b]pyrroles by Brønsted acid (p-toluene-sulfonic acid hydrate, p-TsOH·H₂O)-promoted Friedel–Crafts alkylation/cyclization cascade reactions of pyrroles with N,N-dimethylaminomethylene glutaric acid dinitrile (Scheme 1b).

Initially, the reaction of N-methylpyrrole (1a) with N,N-dimethylaminomethylene glutaric acid dinitrile (2) was employed to screen the reaction conditions. To our delight, a 1:1 molar ratio reaction occurred in the presence of 50 mol% p-TsOH·H₂O as the promoter in dichloromethane at ambient temperature, forming the target product 3a in 32% yield with excellent diastereoselectivity (dr > 20:1) (Table 1, entry 1). Increasing the Brønsted acid loading to 2 equiv. led to 3a in 81% yield with a reaction time shortening to 2 h (Table 1, entries 2–6). Further increasing the acid amount to 3 equiv. slightly reduced the reaction efficiency, giving 3a in 79% yield (Table 1, entry 7).

Among the tested solvents (dichloromethane, 1,2-dichloroethane, acetonitrile, toluene and THF), both dichloromethane and 1,2-dichloroethane were found to provide suitable reaction media, in contrast, the reaction hardly proceeded in THF (Table 1, entries 5 and 8–11). Elevating the reaction temperature to 40–60 °C lowered the formation of 3a (Table 1, entries 12 and 13). It should be noted that the reaction did not occur in the absence of the acid promoter. Thus, the reaction conditions were optimized as those shown for entry 5 in Table 1.

Under these optimal conditions, the substrate scope of pyrroles was explored (Table 2) and the reactions of 2 with a variety of N-protected pyrroles 1 were investigated. When increasing the steric hindrance of the NR¹ moiety in 1 from methyl to 2-furfuryl, the yields of cyclopenta[b]pyrroles 3a–3d varied from 81% to 60%, while introduction of a phenyl substituent remarkably reduced the yield of 3e to 23%. Notably, all the 2- and/or 3-monosubstituted or disubstituted N-methylpyrroles efficiently reacted with 2 to afford 3f–3r (72–81%) where the 2- and 3-substituents could be methyl, ethyl and phenyl groups. With 2-aryl-N-methylpyrroles as the substrate, the reactions gave the target products 3f–3r in 70–81% yields. Substituents such as methyl, methoxy, chloro, fluoro, tri-
fluoromethyl, and nitro were tolerated on the aryl moiety, exhibiting no obvious steric and electronic effects on the reaction efficiency. When 4-acetyl or 4-CONMe was the substituent on the aryl group, the yields for 3s (53%) and 3t (61%) were obviously lessened. Placing a bulky 1-naphthyl on the C-2 position of N-methylpyrrole did not affect the efficient formation of 3u (72%). However, in the case of using 2-thienyl as the substituent, the target product 3v was only formed in 32% yield. It is noteworthy that the reactions of 2 with N-unprotected pyrroles such as pyrrole, 2-methylpyrrole, 2-phenylpyrrole, and 2-acetylpyrrole were complicated, given no desired products in acceptable yields under the same conditions, which is presumably attributed to the susceptibility of these free NH-pyrroles to strong Brønsted acids, undergoing decomposition and/or self-polymerization. The molecular structures of cyclopenta[b]pyrroles 3 were further affirmed by an X-ray crystallographic determination of 3a (Figure 2).[15]

Next, 2,5-disubstituted pyrroles 4 were applied as the substrates to further explore the protocol general-
Unexpectedly, N-unprotected 2,5-dimethylpyrrole underwent the reaction with 2 to form 5a in 66% yield. The increased steric hindrance from the 2- and 5-methyl groups may protect the corresponding NH-pyrrole substrate from undergoing decomposition and side reactions. The reactions of 2 with other N-protected 2,5-dimethyl-substituted pyrroles also efficiently proceeded to afford the target products 5b–5d (80–83%). However, 2,5-diphenyl-N-methylpyrrole only exhibited a poor reactivity to form 5e in a low yield (22%). Interestingly, 1,3-phenylene-supported bispyrrole 6 reacted with 2 to yield the corresponding product 7 (55%) when using 2 equiv. of 2 and 3 equiv. of p-TsOH·H₂O [Eq. (1)].

In order to probe the mechanism of the reaction of pyrroles 1 with diene 2, the 1:1 molar ratio reaction of N-methylpyrrole (1a) with 2 was performed in the presence of the mild Brønsted acid Cl₂CHCOOH at ambient temperature (Scheme 2). Fortunately, reaction intermediate 8, generated from the Friedel–Crafts alkylation of 1a with 2, was isolated (40%) along with the target product 3a (18%). With p-TsOH·H₂O as the promoter, compound 8 was efficiently converted to the corresponding target product 3a (92%). It should be noted that 8 could not be directly isolated from the reaction of 1a with 2 in the presence of p-TsOH·H₂O under the stated conditions. Thus, the reaction of 1 and 2 can be considered to occur through a cascade pathway. The structure of compound 8 was further confirmed by an X-ray crystallographic determination (Figure 3)\[^{[15]}\].

A plausible mechanism for the Friedel–Crafts alkylation/cyclization cascade of pyrroles 1 and diene 2 is proposed in Scheme 3. The reaction is presumably initiated by protonation of one of the polarized C=C bonds of 2 to form cationic...
carbon atom of $A$ at the C-5 position of 1 forms species $B$, affording the reaction intermediate of type 8 by deprotonation. Protonation of the enamine group of 8 with the promoter or tautomerization of $B$ leads to iminium species $C$. The subsequent intramolecular Friedel–Crafts cyclization of $C$ gives species $D$ which undergoes deprotonation to yield cyclopenta[b]pyrrole 3.

Further transformations of cyclopenta[b]pyrroles 3 and 5 were investigated. Deamination of 3a was achieved by its reaction with methyl iodide, quantitatively forming the corresponding quaternary ammonium salt 9, followed by treatment with $t$-BuOK in MeOH at $-35^\circ$C for 1 h to afford the deaminative products 1,6-dihydrocyclopenta[b]pyrrole 10 (40%) and its isomer 1,4-dihydrocyclopenta[b]pyrrole 11 (27%), which can be used as useful synthons in organic synthesis (Scheme 4). Notably, compound 11 could be easily isomerized to 10 at ambient temperature. To our surprise, treatment of 5a–5d with MeI in a similar fashion directly afforded the target deamination products, i.e., 1,6-dihydrocyclopenta[b]pyrroles 12a–12d (64–73%) [Eq. (2)].

It should be noted that the present synthetic methodology is not applicable to indole substrates. Under the same conditions as shown in Table 2 and Table 3, the reaction of 2,3-unsubstituted N-methylindole (13) with 2 catalyzed by 2 equiv. of the Brønsted acid $p$-TsOH-H$_2$O gave a complicated mixture of products, from which the desired Friedel–Crafts alkylation/cyclization cascade product of cyclopenta[b]indole could not be isolated. However, in the case of using 1 equiv. of the Brønsted acid, the same reaction afforded 3-alkylated indole 14 which is structurally similar to compound 8 (Scheme 5). Treatment of 14 under acidic conditions led to 3-olefinated indoles ($E$) and ($Z$)-15 [Eq. (3)].
In summary, Brønsted acid (p-TsOH·H₂O)-promoted Friedel–Crafts alkylation/cyclization cascade reactions of pyroles with N,N-dimethylaminomethylene-glutaconic acid dinitrile were efficiently realized to afford cyclopenta[b]pyrrole derivatives with excellent diastereoselectivity. Deamination with MeI gave synthetically useful dihydrocyclopenta[b]pyrroles. This protocol provides a concise route to access functionalized cyclopenta[b]pyrrole derivatives under mild conditions.

**Experimental Section**

**Typical Procedure for the Synthesis of 3a**

A mixture of 1a (41 mg, 0.5 mmol), 2 (74 mg, 0.5 mmol), and p-TsOH·H₂O (190 mg, 1.0 mmol) in CH₂Cl₂ (2 mL) was stirred at ambient temperature for 2 h. After the reaction was completed by TLC monitoring, 5 mL of saturated aqueous NaHCO₃ were added and the resulting mixture was extracted with CH₂Cl₂ (3×10 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na₂SO₄, and the volatiles were removed under reduced pressure. Purification of the resulting residue by flash silica gel column chromatography (eluent: CH₂Cl₂/EtOAc = 50:1, v/v) afforded 3a as a yellow solid; yield: 92 mg (81%).

**Typical Procedure for the Synthesis of 12a**

A mixture of 5a (121 mg, 0.5 mmol) and methyl iodide (142 mg, 1.0 mmol) in acetone (2 mL) was stirred at ambient temperature for 24 h. After the reaction was completed by TLC monitoring, all the volatiles were removed under reduced pressure. Purification of the resulting residue by flash silica gel column chromatography (eluent: CH₂Cl₂/petroleum ether = 60–90°C = 2:1, v/v) afforded 12a as a yellow solid; yield: 67 mg (68%).

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**References**


[15] CCDC 1002540 and CCDC 1012221 (compounds 3a and 8, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
