An Expedient Synthesis of Arene-fused Phthalimides from Morita–Baylis–Hillman Carbonates

Beom Kyu Min, Jin Woo Lim, Hwa Jung Roh, and Jae Nyoung Kim*

*Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea. *E-mail: kimjn@chonnam.ac.kr*

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Recently, we reported synthesis of 3,4-diarylidene-*N*-phenylpyrrolidine-2,5-dione derivatives from Morita–Baylis–Hillman (MBH) carbonates.[1] The compounds have been synthesized from MBH carbonates via the formation of MBH ylides, reaction with phenyl isocyanate to form amide ylides, and a subsequent acid-catalyzed stereoselective Wittig reaction with various aldehydes.[1] More recently, aminonaphthalene has been synthesized from the amide ylide **2a** via 6π-electrocyclic ring closure of the ketenimine intermediate, as shown in Scheme 1.[2] As a continuing study, we reasoned out that 6π-electrocyclization reaction of 3,4-diarylidene-*N*-phenylpyrrolidine-2,5-dione **I** and a subsequent aerobic oxidation of intermediate **II** would produce furan-fused phthalimide derivative **4a**, as also shown in Scheme 1. Various arene-fused phthalimides have been synthesized[3,4] and found their usefulness in the areas of dual fluorescent dyes as a probe for ratiometric detection of DNA,[4a] organic light-emitting devices,[4b] and for the synthesis of conjugated polymers.[4c]

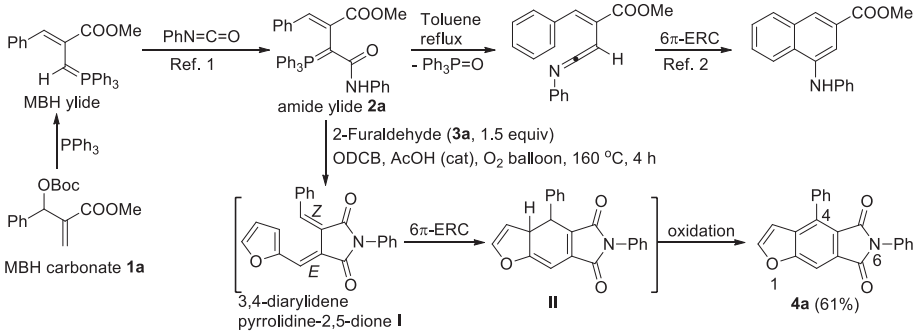
Thermal 6π-electrocyclization reaction of conjugated triene has been studied extensively.[5,6] Double bond of aromatic compounds could also be involved in 6π-electrocyclization reactions. Recently, we also reported 6π-electrocyclization reactions of conjugated trienes bearing an aromatic double bond.[6a–d] The electrocyclization could be conducted at relatively lower temperature when the resonance energy of the arene ring is small, such as furan, thiophene, or naphthalene.[7]

Thus, at the outset of our experiment, the reaction of **2a** and 2-furaldehyde (**3a**) was carried out in refluxing toluene in the presence of a catalytic amount of AcOH under O_2 balloon atmosphere. However, 4,6-diphenyl-1-oxa-6-azaindacene-5,7-dione (**4a**) was not formed at all. Instead, the formation of diarylidene intermediate **I** was observed, as in our previous paper.[1] When the reaction was conducted at higher temperature (160°C) in 1,2-dichlorobenzene (ODCB) for 4 h, **4a** was obtained in good yield (61%) to our delight. Compound **4a** might be formed via an acid-catalyzed cyclization of **2a** to form imide ring, a subsequent Wittig reaction with **3a** to form **I**,[1] thermal 6π-electrocyclization to **II**, and a final aerobic oxidation to **4a**.[8,9]

Encouraged by the successful result, the reactions of **2a** with various aromatic aldehydes were examined. We selected five-membered heteroaromatic aldehydes and naphthaldehydes that have small resonance energy,[7] in order to overcome the high activation energy during the 6π-electrocyclization. The results are summarized in Table 1. The reaction of **2a** with 2-thiophenecarboxaldehyde (**3b**) afforded **4b** in a similar yield (59%). The reactions with 5-methylfurfural (**3c**) and 5-methyl-2-thiophenecarboxaldehyde (**3d**) afforded **4c** and **4d**, respectively, in moderate yields (59 and 57%). The reaction of 3-furaldehyde (**3e**) gave **4e** in a similar yield (62%). 1-Naphthaldehyde (**3f**) and 2-naphthaldehyde (**3g**) also afforded **4f** and **4g** in moderate yields (56 and 57%), respectively. In addition, other amide ylides **2b** and **2c** were prepared according to the reported method,[1] and the reactions were also examined. The reactions of 4-chlorophenyl derivative **2b** with **3c** and **3d** also afforded **4h** (57%) and **4i** (59%) in moderate yields, respectively.

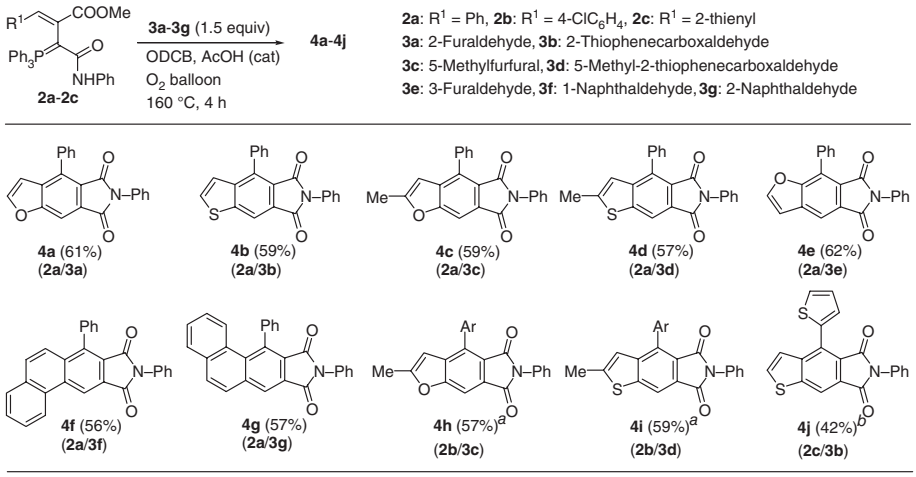
However, the reaction of amide ylide **2c**, bearing a 2-thienyl moiety, showed somewhat different result. The reaction of **2c** and **3b** afforded the desired product **4j** in low yield (42%) along with benzo[*b*]thiophene **5**[2] in appreciable amount (14%), as shown in Scheme 2. A dipolar interaction between the sulfur atom and phosphorous atom in **2c** might facilitate an abstraction of amide proton and subsequent elimination of $Ph_3P{=}O$ to form a ketenimine intermediate. The ketenimine underwent 6π-electrocyclization reaction to produce **5**, as already reported in our previous report.[2]

It is also interesting to note that the reaction of **2c** and **3a** afforded a mixture of **4k** and **4k′** (1:2, 35%) along with **5** (8%), as shown in Scheme 3. Although the stereochemistry of both double bonds of 3,4-diarylidene-*N*-phenylpyrrolidine-2,5-dione intermediate **I** (see Scheme 1) could be controlled under mild conditions (benzene, 80°C, 30 min) in our previous paper,[1] the double bonds might be isomerized in part under the drastic conditions (ODCB, 160°C, 4 h), as shown in Scheme 3.[10] Thus, both double bonds of furan and thiophene could be involved in a following 6π-electrocyclization reaction to produce **4k** and **4k′**.



Scheme 1. Synthetic rationale of furan-fused phthalimide **4a**.

Table 1. Synthesis of arene-fused phthalimides.

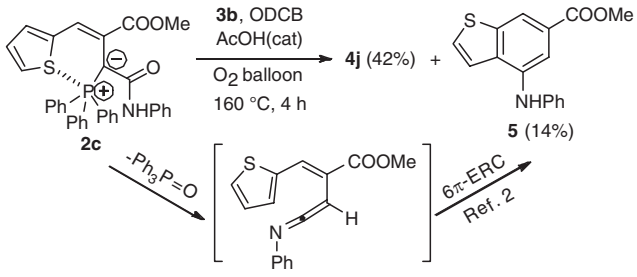


[a]Ar is 4-ClC_6H_4–.
[b]Benzo[*b*]thiophene **5** (14%) was isolated (see Scheme 2).

Unfortunately, the separation of **4k** and **4k′** was impossible and the ratio was determined based on its ^{1}H NMR spectrum (see, Supporting information). When we used benzaldehyde (**3h**) in the reaction of **2c**, compound **4b** was obtained in low yield (38%) along with **5** (11%). Compound **4b′** was not formed in an appreciable amount. The result clearly stated that the double bond of thiophene, that has small resonance energy as compared to that of benzene,[7] was used preferentially in a 6π-electrocyclization reaction.

As a next trial, the reaction of **2a** and benzaldehyde (**3h**) was also examined. The resonance energy of benzene ring is larger than that of the above heteroaromatic rings (**3a–3e**) or naphthalene ring (**3f** and **3g**);[7] however, the reaction afforded **4l**[3f] in a reasonable yield (38%) under the typical reaction condition (160°C, 4 h). The yield of **4l** was improved slightly to 44% under refluxing ODCB (180°C, 4h) condition, as shown in Scheme 4.

In summary, various arene-fused phthalimides were synthesized via one-pot reaction of amide ylides and aromatic aldehydes in the presence of AcOH in ODCB at 160°C. The reaction involved 6π-electrocyclization reaction

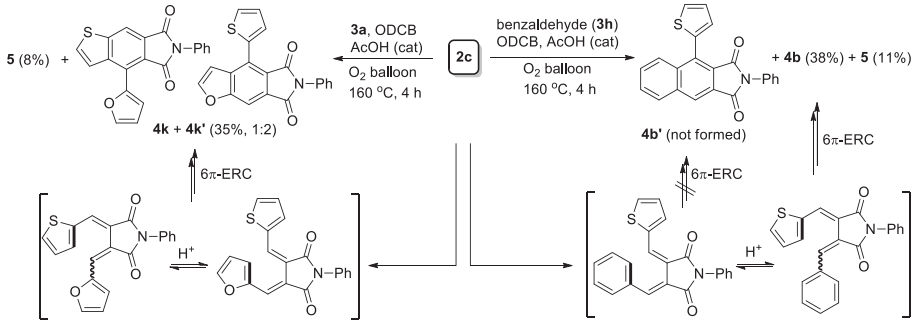


Scheme 2. Competitive formation benzo[*b*]thiophene **5**.

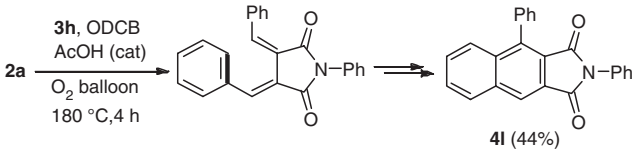
of conjugated triene bearing an aromatic double bond and a following aerobic oxidation process.

Experimental

Typical Procedure for the Synthesis of 4a. To a stirred mixture of amide ylide **2a** (278 mg, 0.5 mmol) and 2-furaldehyde (**3a**, 72 mg, 0.75 mmol) in ODCB (1.5 mL) was added two drops of AcOH, and the reaction mixture was heated to 160°C for 4 h under O_2 balloon atmosphere.



Scheme 3. Partial double bond isomerization.



Scheme 4. Synthesis of benzene-fused phthalimide.

After removal of ODCB and column chromatographic purification process (hexanes/CH_2Cl_2, 1:1) compound **4a** was obtained as a pale yellow solid, 104 mg (61%). Other compounds were synthesized similarly, and the selected spectroscopic data of **4a**, **4d**, **4e**, and **4j** are as follows.

Compound 4a. Yield 61%; pale yellow solid, mp 196–197°C; IR (KBr) 1714, 1374 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.89 (dd, J = 2.3, 0.9 Hz, 1H), 7.35–7.39 (m, 1H), 7.42–7.55 (m, 7H), 7.59–7.62 (m, 2H), 7.86 (d, J = 2.3 Hz, 1H), 8.08 (d, J = 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 107.4, 107.9, 122.0, 126.8, 128.1, 128.3, 129.1 (2C), 129.7, 129.9, 131.9, 133.5, 133.9, 136.0, 149.1, 157.3, 166.8, 167.0; ESIMS m/z 340 [M^++H]. Anal. Calcd for $C_{22}H_{13}NO_3$: C, 77.87; H, 3.86; N, 4.13. Found: C, 77.74; H, 3.98; N, 3.95.

Compound 4d. Yield 57%; pale yellow solid, mp 233–234°C; IR (KBr) 1712, 1369 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.61 (s, 3H), 7.02 (s, 1H), 7.32–7.38 (m, 1H), 7.40–7.47 (m, 4H), 7.48–7.55 (m, 5H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.7, 117.7, 122.8, 123.3, 126.8, 127.0, 127.9, 128.2, 128.7, 129.0, 129.8, 132.0, 135.0, 136.1, 144.6, 144.8, 146.7, 166.9, 167.2; ESIMS m/z 370 [M^++H]. Anal. Calcd for $C_{23}H_{15}NO_2S$: C, 74.78; H, 4.09; N, 3.79. Found: C, 74.91; H, 4.33; N, 3.92.

Compound 4e. Yield 62%; white solid, mp 217–219°C; IR (KBr) 1715, 1373 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.05 (d, J = 2.1 Hz, 1H), 7.34–7.40 (m, 1H), 7.43–7.57 (m, 7H), 7.68–7.74 (m, 2H), 7.87 (d, J = 2.1 Hz, 1H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 108.4, 116.9, 123.5, 126.6, 126.8, 128.0, 128.1, 128.2, 129.1, 129.4, 130.3, 130.6, 132.0, 132.9, 149.5, 155.9, 166.8, 167.1; ESIMS m/z 340 [M^++H]. Anal. Calcd for $C_{22}H_{13}NO_3$: C, 77.87; H, 3.86; N, 4.13. Found: C, 77.79; H, 4.04; N, 4.08.

Compound 4j. Yield 42%; pale yellow solid, mp 214–215°C; IR (KBr) 1717, 1368 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.22 (dd, J = 5.1, 3.6 Hz, 1H), 7.35–7.40 (m, 2H), 7.43–7.50 (m, 4H), 7.57 (dd, J = 5.1, 1.2 Hz, 1H), 7.62 (dd, J = 5.6, 0.8 Hz, 1H), 7.74 (d, J = 5.6 Hz, 1H), 8.47 (d, J = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 118.7, 124.3, 125.3, 126.8, 127.2, 127.7, 127.9, 128.1, 129.1, 129.88, 129.91, 131.6, 131.9, 134.3, 144.6, 144.8, 166.4, 166.8; ESIMS m/z 362 [M^++H]. Anal. Calcd for $C_{20}H_{11}NO_2S_2$: C, 66.46; H, 3.07; N, 3.88. Found: C, 66.81; H, 3.34; N, 3.69.

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Supporting Information. Additional supporting information is available in the online version of this article.

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