

Lewis Acid-mediated ArS_E Aroylation of Naphthalene Derivative: Distinct Second Aroylation Behavior of α -Naphthyl Ketone

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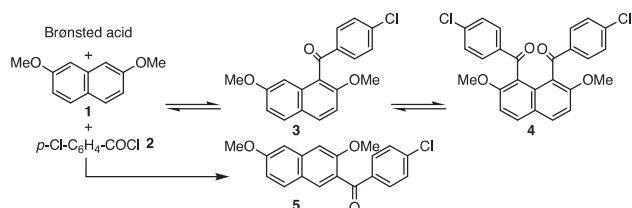
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Dual ArS_E aroylation of 2,7-dimethoxynaphthalene proceeds with distinct susceptibility and regioselectivity depending on the Lewis acid. The TiCl₄-mediated reaction readily affords 1,8-diaroylated product. In the AlCl₃-mediated reaction, monoaroylation essentially proceeds with partial ether cleavage and under some specific conditions 1,6-diaroylation proceeds in preference to 1,8-diaroylation.

The Friedel–Crafts aroylation,¹ a well-known protocol for aromatic ketone preparation,² has several different reaction features from the analogous reaction of Friedel–Crafts alkylation. The intervening aroylium species are substantially stabilized by resonance, and the reactivity and regioselectivity strongly depend on electronic conditions of aroyl-acceptant aromatic compounds. Furthermore, the aroylium species are more stable than alkanoylium species, and the achievement of electrophilic aromatic substitution (ArS_E) aroylation is ordinarily more difficult than the corresponding ArS_E alkanoylation. In this course, the difficult polyaroylation is generally attributable to the electronic deactivation of the aromatic ring by the initially introduced electron-withdrawing aroyl group. On the other hand, the authors' group has investigated acid-promoted highly reactive and consecutive ArS_E aroylation and applied it to synthesis of wholly aromatic polyketones.³ In the course of these studies, effective dual ArS_E aroylation, and unique reversible behavior of dearoylation have been found recently (Scheme 1).⁴

2,7-Dimethoxynaphthalene (**1**) reacts with 4-chlorobenzoyl chloride (**2**) in the presence of Brønsted acid to give diaroylated naphthalene **4** and monoaroylated **3** and **5**. Single-crystal X-ray studies of **3**⁵ and **4**⁶ have revealed that the aroyl groups at 1,8(*peri*)-positions are attached almost perpendicularly to the naphthalene ring and oriented in the opposite directions for **4**. The non-coplanar alignment of the aromatic rings reminds the authors of insufficient π -conjugation among the aromatic rings in these molecules. In addition, the rotation ability of aroyl- α -naphthyl bond together with steric bulkiness of aroyl group has been considered to govern the Brønsted acid-promoted dearoylation.⁴

In this letter, the authors report distinct behavior in Lewis acid-mediated ArS_E aroylation of **1**, which reflects the structural characteristics of α -naphthyl ketone molecules produced in the first aroylation and the nature of employed Lewis acid.



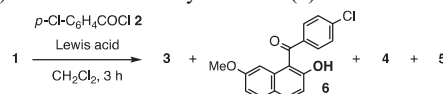
Scheme 1.

Table 1 shows the results of ArS_E aroylation of **1** undertaken with several kinds of Lewis acids. No reaction proceeded with ZnCl₂ (Entry 1). Both TiCl₄ and SnCl₄ afforded 1-mono- and 1,8-diaroylated naphthalenes **3** and **4** with 3-monoaroylated substrate **5** (Entries 2 and 4). By employment of AlCl₃ at rt, demethylated derivatives of **3**, i.e., 1-(4-chlorobenzoyl)-2-hydroxy-7-methoxynaphthalene (**6**)⁷ and its ester were yielded in addition to **3** (Entry 5). When the reaction temperature was lowered from ambient temperature to 0 °C, **3** was solely obtained in a moderate yield (Entry 6). TiCl₄ sufficiently promoted aroylation giving **3** and **4** at 0 °C (Entry 3).

The satisfactory reactivity of the monoaroylnaphthalene molecule against acceptance of aroylium electrophile species is interpreted as attributable to the non-coplanar linkage of aroyl group to the naphthalene ring that should avoid severe defects of electron density. These results also indicate that ZnCl₂ is too weak to promote aroylation and that AlCl₃ has some inhibition factors for aroylation. Contrarily, moderately strong Lewis acid such as TiCl₄ and SnCl₄ achieves smooth *peri*-aroylation.

Table 2 displays the results of ArS_E aroylation carried out in various ratios of **1**, **2**, and Lewis acid (TiCl₄ or AlCl₃). In order to prevent contamination of further reaction products of the hydrolyzed derivative **6**, the results of the reaction undertaken at 0 °C are tabulated. When the ratio of **1**, **2**, and AlCl₃ was fixed as 1:1.1:1.1 or 1:1.1:3.3, **3** was satisfactorily obtained (Entries 1 and 2). Further aroylation proceeded at 6- and 8-positions when the ratio was 1:2.2:2.2 (Entry 3). Use of extra amounts of AlCl₃ disturbed the aroylation of the 8-position (Entry 4). Further addition of AlCl₃ decreased the aroylation of the 6-position, and finally, no second aroylation of **3** proceeded in the ratio of 1:2.2:6.6 (Entry 5). The 1,6-diaroylated product **7** was formed most efficiently together with

Table 1. Lewis acid-mediated ArS_E aroylation of 2,7-dimethoxynaphthalene (**1**) with 4-chlorobenzoyl chloride (**2**)^a



| Entry | LA | Temp /°C | Product distribution/% ^b | | | | |
|-------|-------------------|----------|-------------------------------------|----------|-----------------|----------|----------|
| | | | 1 | 3 | 6 | 4 | 5 |
| 1 | ZnCl ₂ | rt | 100 | 0 | 0 | 0 | 0 |
| 2 | TiCl ₄ | rt | 4 | 46 (35) | 0 | 47 (45) | 3 |
| 3 | TiCl ₄ | 0 | 4 | 58 (56) | 0 | 34 (33) | 4 |
| 4 | SnCl ₄ | rt | 11 | 73 (58) | 0 | 12 (15) | 4 |
| 5 | AlCl ₃ | rt | 40 | 12 (11) | 48 ^c | 0 | 0 |
| 6 | AlCl ₃ | 0 | 67 | 33 (30) | 0 | 0 | 0 |

^aReaction conditions: 2,7-dimethoxynaphthalene (**1**, 0.2 mmol), 4-chlorobenzoyl chloride (**2**, 0.44 mmol), Lewis acid (1.32 mmol), CH₂Cl₂ (0.5 mL), N₂ atmosphere, 3 h.¹⁴ ^bCalculated on the basis of ¹H NMR spectra. Isolated yields are given in parentheses. ^c1,8-Bis-(4-chlorobenzoyl)-2-(4-chlorobenzoyloxy)-7-methoxynaphthalene was included. The ratio of **6**:the ester was 87:13.

Table 2. ArS_E arylation of 2,7-dimethoxynaphthalene (**1**) with 4-chlorobenzoyl chloride (**2**) in various molar ratios^a

$$1 \xrightarrow[\text{CH}_2\text{Cl}_2, 3 \text{ h}]{\text{Lewis acid, } p\text{-Cl-C}_6\text{H}_4\text{COCl } 2} 3 + 6 + 4 + 7 + 5$$

| Entry | LA | Molar ratio 1:2:LA | Product distribution/% ^b | | | | | |
|-----------------|-------------------|-----------------------|-------------------------------------|---------|-----------------|---------|---------|---|
| | | | 1 | 3 | 6 | 4 | 7 | 5 |
| 1 | AlCl ₃ | 1:1.1:1.1 | 22 | 78 (61) | 0 | 0 | 0 | 0 |
| 2 | AlCl ₃ | 1:1.1:3.3 | 32 | 68 (49) | 0 | 0 | 0 | 0 |
| 3 | AlCl ₃ | 1:2.2:2.2 | 0 | 66 (65) | 0 | 10 (9) | 21 (16) | 3 |
| 4 | AlCl ₃ | 1:2.2:3.3 | 5 | 72 (60) | 0 | 3 | 19 (11) | 1 |
| 5 | AlCl ₃ | 1:2.2:6.6 | 67 | 33 (30) | 0 | 0 | 0 | 0 |
| 6 | AlCl ₃ | 1:3.3:3.3 | 2 | 36 (31) | 0 | 20 (13) | 42 (37) | 0 |
| 7 | AlCl ₃ | 1:3.3:9.9 | 76 | 21 (19) | 0 | 1 | 2 | 0 |
| 8 ^c | AlCl ₃ | 1:3.3:9.9 | 27 | 25 (21) | 48 ^d | 0 | 0 | 0 |
| 9 | TiCl ₄ | 1:1.1:1.1 | 9 | 81 (64) | 0 | 5 (3) | 0 | 5 |
| 10 | TiCl ₄ | 1:1.1:3.3 | 24 | 65 (53) | 0 | 5 (2) | 0 | 6 |
| 11 | TiCl ₄ | 1:2.2:2.2 | 3 | 87 (73) | 0 | 9 (7) | 0 | 1 |
| 12 | TiCl ₄ | 1:2.2:3.3 | 7 | 75 (67) | 0 | 12 (8) | 0 | 6 |
| 13 | TiCl ₄ | 1:2.2:6.6 | 4 | 58 (56) | 0 | 33 (29) | 0 | 5 |
| 14 | TiCl ₄ | 1:3.3:3.3 | 6 | 70 (54) | 0 | 17 (10) | 0 | 7 |
| 15 | TiCl ₄ | 1:3.3:9.9 | 9 | 42 (38) | 0 | 44 (37) | 0 | 5 |
| 16 ^c | TiCl ₄ | 1:3.3:9.9 | 12 | 4 | 0 | 78 (69) | 0 | 6 |

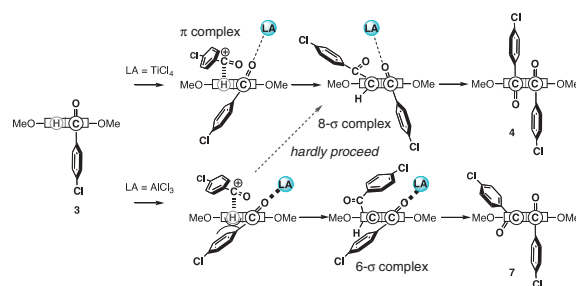
^aReaction conditions: 2,7-dimethoxynaphthalene (**1**, 0.2 mmol), 4-chlorobenzoyl chloride (**2**), Lewis acid (AlCl₃ or TiCl₄), CH₂Cl₂ (0.5 mL), 0 °C, N₂ atmosphere, 3 h.¹⁴ ^bCalculated on the basis of ¹H NMR spectra. Isolated yields are given in parentheses. ^cAt rt. ^dThe ratio of **6**:the ester in Entry 8 was 67:33.

roughly a half amount of 1,8-diaroylated naphthalene **4** when three-equimolar amounts of both **2** and AlCl₃ were employed (Entry 6). Contrarily, three-equimolar amounts of **2** and nine-equimolar amounts of AlCl₃ only afforded monoaroylated naphthalene **3** in a rather low yield (Entry 7). With large excess amounts of AlCl₃ against **2**, elevation of reaction temperature gave monohydrolyzed compound **6** in the case of employing two-equimolar amounts or more of **2** against **1** (Entry 8; Entry 5 in Table 1). On the other hand, the TiCl₄-mediating arylation at *peri*-position easily proceeded (Entries 9–16). Furthermore, the second arylation smoothly underwent only at the 8-position. The dual arylation at the *peri*-position took place more readily with increase of the ratio of TiCl₄ against **2** (Entries 12 and 13 vs. 11; Entries 15 and 16 vs. 14). The governing factors and the clear mechanistic interpretation for susceptibility and regioselectivity in the dual ArS_E arylation, however, still remain indeterminable.⁸

Conclusively, ArS_E arylation of **1** proceeds with distinct susceptibility and regioselectivity depending on the Lewis acid employed. After the first arylation at the 1-position giving 1-monoaroylated product **3**, the second arylation is strongly affected by the kind of Lewis acid employed. The TiCl₄-mediated reaction readily affords 1,8-diaroylated product **5**. The AlCl₃-mediated dual arylation proceeds rather moderately to yield 1,6-diaroylated derivative **7** as major product and 1,8-diaroylated **4** as minor product under some specific conditions. The use of excess amount of AlCl₃ promotes the cleavage of the ether linkage adjacent to the aryl group or retards the second arylation resulting in formation of mixture of monoaroylated product **3** and the ether-cleaved derivative **6**. Regioselective dual arylation controlled by Lewis acid can be applied to precise synthesis of highly congested aromatic rings-accumulated molecules. The resulting compounds^{11–13} are expected as novel candidate units for electrical- and optical functional materials.

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- The authors speculate the distinct second arylation behavior depending on Lewis acid to be as follows: AlCl₃ tightly bound to the ketonic oxygen of the α -naphthyl ketone should be situated at the same time in the vicinity of 2-methoxy oxygen. It can be also regarded as fixation by C=O...AlCl₃...OMe interaction⁹ from another viewpoint. The proximate location of AlCl₃ to the ketonic oxygen and the 2-methoxy oxygen of **3** is also supported by the regioselective demethylation of **3** at rt (Entry 5 in Table 1 and Entry 8 in Table 2). Under these circumstances, free rotation of the aryl group is presumably inhibited. Consequently the conversion of π complex to σ complex¹⁰ at the 8-position is disturbed (Scheme 2). On the other hand, the interaction of TiCl₄ with ketonic oxygen may be rather weak so that the rotation of aryl–naphthalene bond should occur to a certain extent to allow smooth interconversion between π and σ complexes leading substitution at 8-position.

**Scheme 2.**

The authors have previously reported the retardation behavior in dearylation of 1,8-diaroylated naphthalene **4** in the presence of superacid.⁴ This phenomenon is considered attributable to restricted conversion of the σ complex to the π complex by conformational fixation of aryl groups in **4** through chelation of C=O...H⁺...OMe. In this relation, the ready rotation of the aryl–arene bond in the initially formed monoaroylated arene in ArS_E arylation is assumed to be the second requisite for achievement of dual arylation in addition to the non-coplanar configuration of the aromatic ketone moiety of the intervening α -naphthyl ketone affording rather weak conjugation system.

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