Nucleophilic Aromatic tele-Substitution of Hydrogen of 9-Nitroanthracene with 2-Naphthols and Phloroglucinol

Su Yeon Kim, Jin Woo Lim, Kye Chun Nam, and Jae Nyoung Kim*

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

Received May 20, 2016, Accepted June 21, 2016, Published online August 31, 2016

Keywords: tele-Substitution, 9-Nitroanthracene, 2-Naphthols, Phloroglucinol

Nucleophilic substitution reaction of hydrogen atom in electron-deficient arenes has been extensively studied.1-3 An addition of nucleophile to electron-deficient arenes such as nitroarene proceeds readily at the positions occupied by hydrogen atom to form σH-adducts. Usually, the σH-adducts can be converted to products either via a vicarious nucleophilic substitution (VNS)1b,c or an oxidative nucleophilic substitution of hydrogen (ONSH).1d Many oxidants have been used for the oxidation of σH-adducts including an aerobic oxidation process with molecular oxygen.2,4 Recently, Kumar et al. reported β-arylation of indole under an aerobic oxidation condition, as shown in Scheme 1.3a Very recently, we also reported an aerobic ONSH reaction of nitroarenes with 2-arylindoles or uracil.3b In addition, the aerobic ONSH reaction was extended to the intramolecular version of nitroarene bearing a nitroalkane tether by us, as also shown in Scheme 1.3c

Although the ONSH reaction has been studied extensively with various nitroarenes, the reaction of 9-nitroanthracene (1) has not been studied much.4 During our studies on ONSH reaction,3b,c an aerobic ONSH reaction of 1 with indole (2a) was examined in the presence of Cs2CO3 in DMSO under O2 balloon atmosphere, as shown in Scheme 2. However, the yield of 3a (32%) was low presumably due to steric hindrance caused by the peri hydrogen atoms at 4- and 5-positions of 1. Thus, we examined the reaction of 1 with 2-naphthol (2b) under the same reaction conditions, because the C1-position of 2-naphthol has been proved to be highly nucleophilic in many reactions.5 A successful C–C bond formation was observed; however, the result was quite surprising. Generally expected ONSH product 3b was obtained in low yield (22%) along with an unusual tele-substitution product 4b (63%) as a major product.6,7

In a tele-substitution reaction, the nucleophile is attached to the position located by more than one atom from the atom to which the leaving group is attached.6 In order to further reduce the amount of ONSH product 3b, the reaction was examined in DMF under N2 balloon atmosphere. However, the yields of both 3b (9%) and 4b (55%) decreased. The reaction of 1 and 2b in DMSO in an open flask showed a similar result (see, entry 1 in Table 1) to that of the reaction carried out under O2 balloon atmosphere (Scheme 2).

Thus, we examined the reactions of 1 with 2-naphthol derivatives 2c–2f in DMSO in an open flask. The results are summarized in Table 1. The reaction of naphthalene-2,7-diol (2c, entry 2) afforded the corresponding tele-substitution products 4c (68%) as a major product along with a low yield of 3c (19%). In the reaction, the formation of 1,8-dianthracenyl derivative was not observed. A second introduction of anthracene moiety to 4c was not observed even in the presence of an excess amount of 1 presumably due to steric reason. The reaction with 7-methoxynaphthalene-2-ol (2d, entry 3) produced 4d in good yield (70%) along with 3d (9%). The reaction of 6-methoxynaphthalene-2-ol (2e, entry 4) produced 3e (35%) and 4e (45%). The reason for the formation of 3e in a relatively larger amount than other entries is not clear at this stage. The reaction of 3-methoxynaphthalene-2-ol (2f, entry 5) afforded 4f in good yield (71%) along with a low yield of 3f (8%, vide infra).

A plausible reaction mechanism for the formation of 4b is shown in Scheme 3. A formal 1,6-conjugate addition of naphthol anion to 1 and keto-enol tautomerization would produce I.8 As reported in aerobic ONSH reactions, I could be converted to 3b via the hydroperoxide intermediate II.3 A proton transfer of acidic phenolic proton to the C-9 position would produce III4b,9 and a following 1,4-elimination of nitrous acid could provide 4b.
A similar trend was also observed in the reactions with 1,3-cyclohexanedione (2g) or 5,5-dimethyl-1,3-cyclohexanedione (dimedone, 2h), as shown in Scheme 4. The reaction of 2g produced a tele-substitution product 4g (71%) as a major product along with a low yield of 3g (10%). The reaction of dimedone also afforded 4h (79%) in good yield along with 3h (9%).

The most striking selectivity between ONSH and tele-substitution was observed in the reaction of 1,3,5-trihydroxybenzene (phloroglucinol, 2i), as shown in Scheme 5. The reaction of 1 and 2i afforded only tele-substitution products 4i (22%) and 2,4-(dianthracen-9-yl)benzene-1,3,5-triol 5 (49%) under the typical reaction condition (2i:1 = 1:1, 1.5 equiv of Cs₂CO₃, rt, 3 h). When we used 2i in a three-fold excess amount (2i:1 = 3:1, 2.5 equiv of Cs₂CO₃, rt, 3 h), the yield of 4i increased up to 68%. The formation of a symmetrical 1:3 adduct 6 was not observed. In addition, compound 6 was not formed in any trace amount even in the reaction of 5 and 1. A third introduction of anthracene moiety at the 6-position of 5 might be sterically restricted due to the presence of two anthracene moieties at 2- and 4-positions.

As a next experiment, in order to obtain 3b as a major product, we examined the reaction of 1 and 2b in the presence of an oxidant KMnO₄ (2.0 equiv). The yield of 3b was increased to 91%, as expected, and 4b was formed in only a trace amount (Scheme 6). In addition, compound 3f (vide supra, entry 5 in Table 1) could also be synthesized in good yield (70%) by using KMnO₄-mediated ONSH reaction between 1 and 2f.

In summary, a selective nucleophilic aromatic tele-substitution reaction has been observed in the reaction of 9-nitroanthracene with 2-naphthols, 1,3-cyclohexanediones, and phloroglucinol. The corresponding nitroanthracene derivatives, obtained by an ONSH process, were formed in variable yields as minor products depending on the substrates.

### Experimental

**Typical Procedure for the Synthesis of 3b and 4b.** To a stirred solution of 1 (112 mg, 0.5 mmol) and 2b (72 mg, 0.5 mmol) in DMSO (1.5 mL) was added Cs₂CO₃ (245 mg, 0.75 mmol), and the reaction mixture was stirred at room temperature for 7 h. After the usual aqueous workup and column chromatographic purification process (n-hexane/EtOAc, 15:1), compounds 3b (38 mg, 21%) and 4b (104 mg, 65%) were obtained. Other compounds were synthesized similarly, and the selected spectroscopic data of 3b, 4b, 3h, 4h, and 4i are as follows.

**Compound 3b.** 21%; yellow solid, mp 80–82°C (dec.); IR (KBr) 3456, 1623, 1524, 1341 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.63 (br s, 1H), 6.76 (d, J = 8.5 Hz, 1H), 7.20 (t, J = 8.5 Hz, 1H), 7.37 (t, J = 8.5 Hz, 1H), 7.39–7.44 (m, 34H,

---

**Table 1.** The reaction of 1 and 2-naphthols 2b–2f.ᵃᵇ

<table>
<thead>
<tr>
<th>Entry</th>
<th>2 Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b 3b (21) 4b (65)</td>
</tr>
<tr>
<td>2</td>
<td>2c 3c (19) 4c (68)</td>
</tr>
<tr>
<td>3</td>
<td>2d 3d (9) 4d (70)</td>
</tr>
<tr>
<td>4</td>
<td>2e 3e (35) 4e (45)</td>
</tr>
<tr>
<td>5</td>
<td>2f 3f (8) 4f (71)</td>
</tr>
</tbody>
</table>

ᵃ Conditions: 1 (0.5 mmol), 2 (0.5 mmol), Cs₂CO₃ (1.5 equiv), DMSO, rt.
ᵇ Reaction time: 7 h (for entries 1 and 4), 4 h (for entries 2, 3 and 5).
Scheme 3. Proposed reaction mechanism.

Scheme 4. The reaction of 1,3-cyclohexanediones.

Scheme 5. The reaction of phloroglucinol.
Acknowledgments. This work was supported by the National Research Foundation of Korea (NRF) grant (NRF-2015R1A4A1041036). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

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

References


4. The ONSH reaction of 9-nitroanthracene has been reported with an enolate of acetone, methylmagnesium chloride or silyl enol ether in the presence of oxidants such as H₂O₂, Pb(OAc)₄, Br₂ or DDQ, see: (a) I. V. Blokhin, Y. M. Atroschenko, O. V. Shishkin, S. S. Gitis, E. N. Alifanova, N. I. Blokhina, A. Y. Kaminskii, Y. D. Grudtysn, V. F. Andrianov, I. V. Shakhkholdyan, Russ. J. Org. Chem. 1997, 33, 1288; (b) N. Armillotta, G. Bartoli, M. Bosco, R. Dalpuzzo, Synthesis 1982, 836; (c) T. V. RajanBabu, G. S. Reddy, T. Fukunaga, J. Am. Chem. Soc. 1985, 107, 5473.


7. The reactions of 1 with 1-naphthol or phenol were not effective to produce either ONSH or tele-substitution products. A loss of resonance energy of phenol or 1-naphthol would be larger than that of 2-naphthol during the formation of corresponding σ⁺-adducts, and this would be the major reason for the failure. Stahly has obtained the ONSH products in moderate yields only in the reactions of 1,3-dinitrobenzene and 2,6-disubstituted phenols under the influence of NaOH in DMSO, see: G. P. Stahly, Russ. Chem. Bull. 1998, 47, 3091.

8. For similar protonation of σ⁺-adduct and elimination of HNO₂, see: (a) B. H. Asghar, Monatsh. Chem. 2013, 144, 301; (b) S. Blażej, A. Kwas, M. Małkowsa, Tetrahedron Lett. 2004, 45, 3193.

9. Both 2-naphthol and DMSO could be oxidized by KMnO₄, thus we used 2b and KMnO₄ in excess amount (2.0 equiv) in a mixed solvent (THF/DMSO).