The Reaction of Ninhydrin with Polymethylbenzenes in the Presence of Acid Catalyst: Formation of 2-Aryl-1,3-indanedione and Indenoindanone Derivatives

Hyun Nam Song, Hong Jung Lee, Tae Yi Kim, and Jae Nyoung Kim*

Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea
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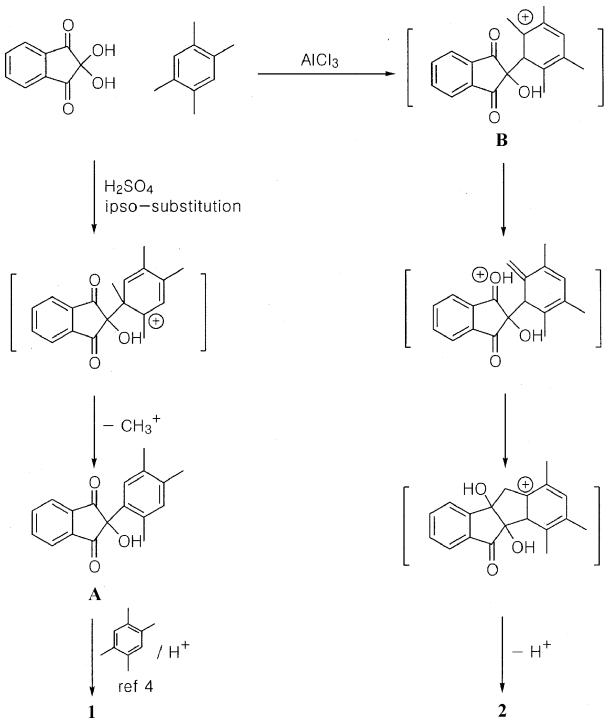
Recently, Friedel-Crafts type reactions of some cyclic ketone systems such as ninhydrin, alloxan, isatin, and parabanic acid have been examined extensively.[1] Diarylated derivatives of these heterocyclic compounds have shown many interesting biological activities such as antibacterial, antiprotozoal, anti-inflammatory, anticonvulsant, anticancer, laxative and diuretic activities.[2]

In these respects, Friedel-Crafts type reaction of ninhydrin with aromatic compounds have been examined recently in our group.[3,4] From the reactions of common aromatic compounds such as benzene, *p*-xylene, chlorobenzene, anisole, there were obtained 2-monoaryl and 2,2-diaryl derivatives in reasonable combined yields depending on the used arenes.[3a] However, as steric hindrance on the arene moiety increases as in trimethylbenzenes, somewhat unusual reaction products have emerged.[4] They include 2-aryl-1,3-indanediones,[5] isocoumarin derivatives,[6] and indenoindanone derivatives. Thus, we investigated the reaction of ninhydrin and tetra- or pentamethylbenzene and report herein the preliminary results. As shown in Scheme 1 the reaction of ninhydrin and 1,2,4,5-tetramethylbenzene in the presence of sulfuric acid afforded the corresponding 2-aryl-1,3-indanedione derivative **1** as the only isolable product in 11% isolated yield. The same reaction in the presence of aluminum chloride gave indenoindanone derivative **2** in 20% yield.

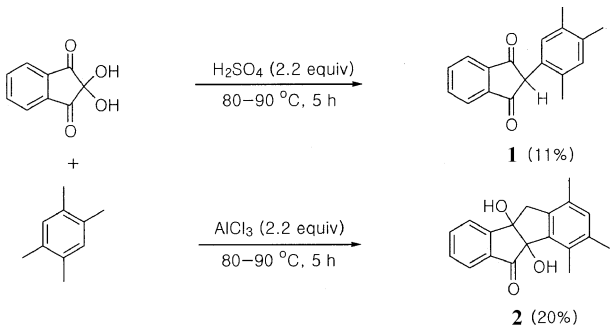
The reaction showed many spots on tlc and consequently the yields of the obtained products are low. However, the mechanism for the formation of **1**-**2** seemed quite unusual. The proposed mechanism for these compounds is represented in Scheme 2. Sulfuric acid catalyzed Friedel-Crafts type reaction of ninhydrin and 1,2,4,5-tetramethylbenzene gave **A** *via ipso*-substitution.[7] **A** was reduced to the product **1** in the reaction conditions as already we have proposed in our previous paper.[4] In the case of using aluminum chloride, intermediate **B** was formed. **B** was transformed into the tetracyclic indenoindanone derivative **2** as shown in Scheme 2 and in our previous report[4] in the reaction conditions.



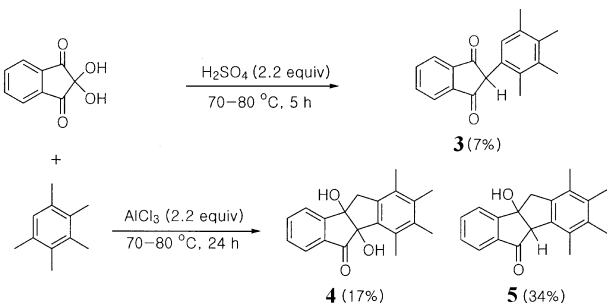
Scheme 2

In the case of pentamethylbenzene with the aid of sulfuric acid, we could isolate the corresponding 2-aryl-1,3-indanedione derivative **3** in 7% yield. As in the case of tetramethylbenzene, indenoindanone derivatives **4** and **5** were isolated in 17% and 34% respectively with aluminum chloride.

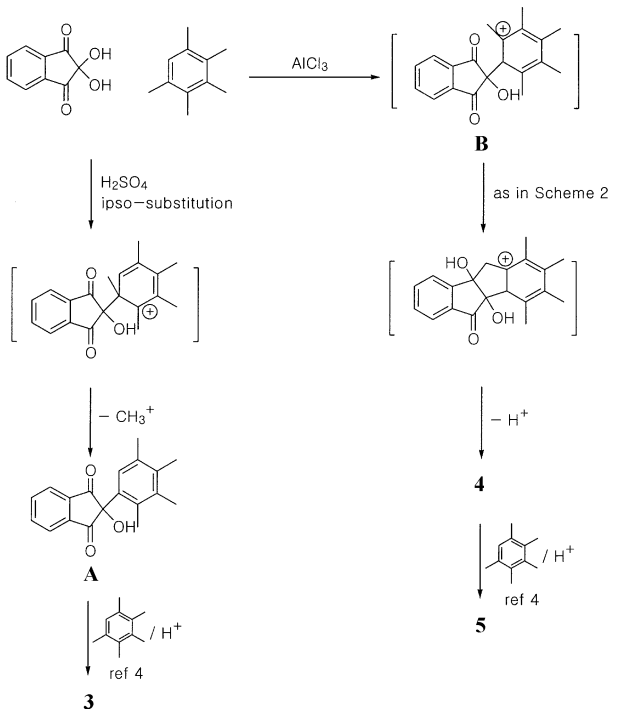
The same mechanism for the formation of **3** and **4** could be proposed as shown in Scheme 4. Another compound **5**



Scheme 1



Scheme 3



Scheme 4

was obtained in this case from **4** by further reduction in the reaction conditions.[4]

In conclusion in this report, the reaction of ninhydrin with polymethylbenzenes in the presence of sulfuric acid gave 2-aryl-1,3-indanedione *via ipso*-substitution, whereas in the presence of aluminum chloride we could obtain tetracyclic indenoindanone derivatives.

The difference in major pathway depending on the acid catalyst, H_2SO_4 or $AlCl_3$, is not clear until now. Further studies on the reaction mechanism are in progress.

Experimental Section

General procedure for the reaction of ninhydrin and polymethylbenzenes in the presence of sulfuric acid. To a stirred suspension of ninhydrin (1.0 g, 5.6 mmol) in the corresponding polymethylbenzene (10 mL) was added concentrated sulfuric acid (1.2 g, 12.2 mmol) and stirred vigourously at 70-90 °C for 5 h. The reaction mixture was poured into cold water (50 mL) and diluted with ether (100 mL). The organic layer was washed with brine, dried with $MgSO_4$, and evaporated to dryness. After flash column chromatography (hexane/ethyl acetate, 9/1), the corresponding products were obtained. Their spectroscopic data are as follows.

1: The structure of **1** was identical in all respects with the compound obtained from the reaction of ninhydrin and 1,2,4-trimethylbenzene (see reference 4).

3: ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.17 (s, 3H), 2.19 (s, 3H), 2.22 (s, 3H), 4.49 (s, 1H), 6.59 (s, 1H), 7.88-8.09 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.16, 16.67, 17.34, 20.67, 60.05, 123.58, 128.82, 129.07, 132.93, 134.04, 135.23, 135.74, 136.10, 142.25, 199.18; Mass (70 eV) *m/z* (rel intensity) 77 (12), 91 (12), 115 (12), 124 (16), 133 (30), 191 (18), 192 (18), 278 (M^+, 100), 279 (20).

General procedure for the reaction of ninhydrin and polymethylbenzenes in the presence of aluminium chloride. To a stirred suspension of ninhydrin (1.0 g, 5.6 mmol) in corresponding polymethylbenzene (10 mL) was added aluminum chloride (1.65 g, 12.3 mmol) and stirred vigorously at 70-90 °C for 5-24 h. The reaction mixture was poured into cold water (50 mL) and diluted with ether (100 mL). The organic layers were washed with brine, dried with $MgSO_4$, and evaporated to dryness. After flash column chromatography (hexane/ethyl acetate, 9/1), the corresponding products were obtained. Their melting points and spectroscopic data are as follows.

2: mp. 60-62 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.21 (s, 3H), 2.68 (s, 3H), 2.85 (d, J = 17.7 Hz, 1H), 3.00 (d, J = 17.7 Hz, 1H), 6.86 (s, 1H), 7.38-7.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.77, 18.06, 19.63, 39.51, 87.30, 88.32, 124.62, 126.61, 129.87, 130.88, 131.56, 132.03, 133.33, 135.29, 136.44, 137.44, 139.74, 152.64, 204.27; Mass (70 eV) *m/z* (rel intensity) 73 (56), 149 (30), 261 (40), 276 (54), 294 (M^+, 24).

4: mp. 79-80 °C (dec); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.18 (s, 3H), 2.24 (s, 3H), 2.80 (s, 3H), 2.97 (d, J = 17.7 Hz, 1H), 3.13 (d, J = 17.7 Hz, 1H), 3.74 (brs, 1H), 3.84 (brs, 1H), 7.43-7.82 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.97, 16.02, 16.26, 16.86, 40.35, 86.91, 88.38, 124.57, 126.53, 129.76, 130.19, 130.68, 133.20, 135.00, 135.97, 136.41, 136.49, 137.00, 152.74, 204.51; Mass (70 eV) *m/z* (rel intensity) 115 (17), 123 (11), 203 (12), 275 (100), 276 (31), 290 (55), 308 (M^+, 45).

5: mp. 215-216 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 2.17 (s, 3H), 2.56 (s, 3H), 2.60 (s, 3H), 3.09 (d, J = 17.7 Hz, 1H), 3.19 (d, J = 17.7 Hz, 1H), 3.20 (brs, 1H), 4.79 (s, 1H), 7.36-7.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.06, 16.20, 16.56, 18.87, 43.78, 58.52, 88.21, 124.57, 126.31, 128.19, 129.13, 130.28, 133.36, 134.78, 135.03, 136.17, 136.36, 137.77, 152.34, 205.82; Mass (70 eV) *m/z* (rel intensity) 107 (16), 115 (16), 220 (14), 259 (100), 274 (35), 292 (M^+, 47).

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