Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Sep 2007.

To cite this article: Hyun Nam Song , Hong Jung Lee , Hyoung Rae Kim , Eung K. Ryu & Jae Nyoung Kim (1999) Friedel-Crafts Type Reactions of Some Activated Cyclic Ketones with Phenol Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:19, 3303-3311

To link to this article: http://dx.doi.org/10.1080/00397919908085958

SYNTHETIC COMMUNICATIONS, 29(19), 3303-3311 (1999)

FRIEDEL-CRAFTS TYPE REACTIONS OF SOME ACTIVATED CYCLIC KETONES WITH PHENOL DERIVATIVES

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Abstract : Friedel-Crafts type reactions of phenol derivatives with some cyclic ketones such as ninhydrin (**1**), alloxan (**2**), isatin (**3**), and parabanic acid (**4**) were examined. 2-Monoaryl- and 2,2-diaryl-1,3-indanedione derivatives were obtained depending on the acid catalyst in the cases of ninhydrin and alloxan. In the case of isatin, the corresponding diarylated derivative was obtained as the sole product in high yields. Parabanic acid was unreactive under the reaction conditions.

Friedel-Crafts type reactions of ninhydrin (**1**) have been examined by us and other groups.[1-2] Ninhydrin has an activated ketone functional group at the 2-position toward weak nucleophile such as arenes in the Friedel-Crafts reaction conditions. Such activated cyclic ketone systems have been found in many other systems such as alloxan (**2**) and isatin (**3**). Diarylated derivatives of these heterocyclic compounds have shown many interesting biological activities such as antibacterial, antiprotozoal, anti-inflammatory, anticonvulsant, anticancer, laxative, diuretic activities.[3-6] Recently,

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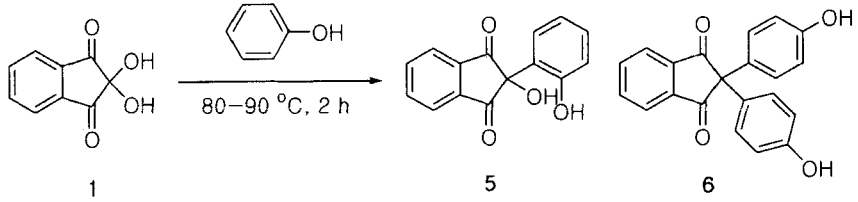
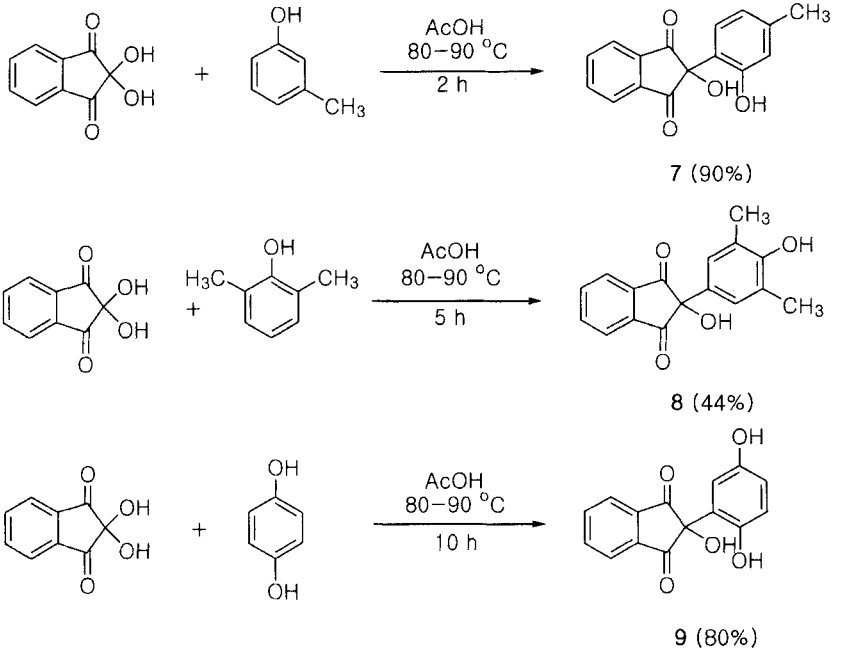
Friedel-Crafts type reaction of isatin derivatives have been studied by Olah et al., which generates 3,3-diaryloxindole derivatives in excellent yields in CF_3SO_3H.[7]

In the course of our recent studies on the alkylation of 2-(2-hydroxyphenyl)-2-hydroxy-1,3-indanedione (**5**), we have found unusual phenomena, *transfer of nucleophilicity*.[8] Thus, we presumed to study further on the reaction, consequently we have to prepare various 2-(2-hydroxyaryl)-2-hydroxy-1,3-indanediones and related compounds. The reaction of ninhydrin (**1**) with phenol derivatives in acetic acid have been reported in our previous paper.[8] As described previously, the reaction could be conducted in acetic acid at 80-90 °C and gave good to moderate yields of mono-arylated products **5**, **7**, and **8**. The reaction of **1** and hydroquinone in acetic acid afforded **9** in 80% isolated yield. As shown in **Scheme 1**, ortho-hydroxyaryl derivatives **5**, **7**, and **9** were obtained as the sole products in acetic acid. The corresponding para-substituted derivatives were not found, presumably due to stabilization of the ortho isomer by the intramolecular hydrogen bonding between the ketone functionality and ortho-hydroxyl group. In the case of 2,6-dimethylphenol, para-isomer **8** was obtained in moderate yield. We could not observe the formation of diarylated compounds in the reaction mixtures using acetic acid. It is interesting to note that the reaction of phenol and ninhydrin in acetic acid in the presence of $AlCl_3$ (2.0 equiv) gave **5** (53%) and 2,2-disubstituted para-isomer **6** in 42% yield. The formation of disubstituted ortho, ortho or ortho, para isomer was not found. The reaction of phenol and ninhydrin in acetic acid in the presence of H_2SO_4 (2.0 equiv) gave **5** (18%) and **6** (76%). In other words, the amounts of diarylated compound **6** increased according to the acidity of the reaction medium.

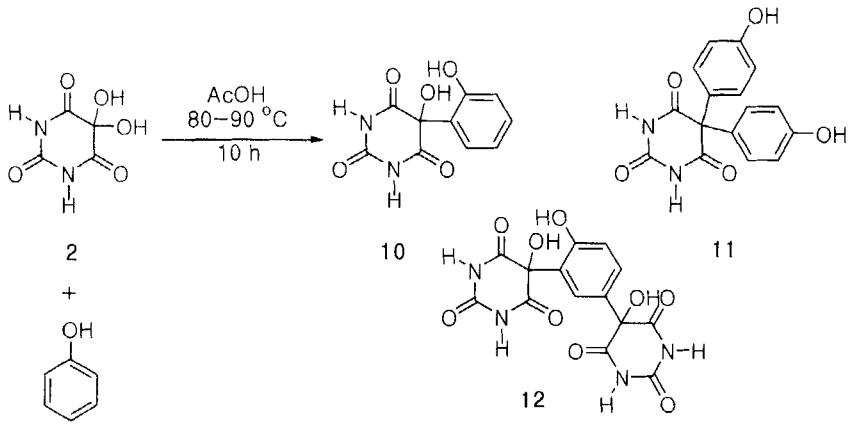
The reaction of alloxan (**2**) and some phenols in acetic acid gave the same results with those of ninhydrin as shown in **Scheme 2**. The reaction of **2** and phenol afforded mono-arylated ortho derivative **10** in 27% together with ortho-para disubstituted compound **12** in 31% isolated yield. By adding aluminium chloride (2 equiv) to the reaction medium we could obtain **10** in 48% yield,



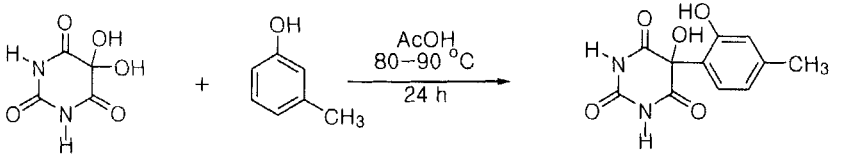
condition	yield (%)	
AcOH	67	–
AcOH / $AlCl_3$ (2 equiv)	53	42
AcOH / H_2SO_4 (2 equiv)	18	76



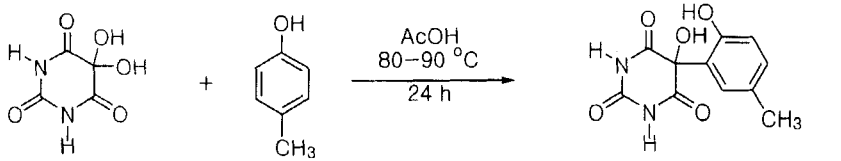
Scheme 1



condition	yield (%)		
	10	11	12
AcOH	27	–	31
AcOH / $AlCl_3$ (2 equiv)	48	trace	–
AcOH / H_2SO_4 (2 equiv)	trace	85	–



13 (86%)



14 (52%)

Scheme 2

whereas diarylated **11** was obtained in 85% yield by using sulfuric acid in acetic acid. The reaction of **2** with *m*-cresol and *p*-cresol in acetic acid at 80-90 °C afforded the mono-arylated ortho-isomers **13** and **14** in moderate yields. As a representative example, we determine the regiochemistry of **13** by NOE experiment. As shown in **Figure 1**, irradiation of methyl group of **13** showed NOE increasement of the two ortho proton H_a and H_b. If the structure were **13'**, H_a only would show NOE.

The reaction of phenol and isatin (**3**) in acetic acid did not afford any products. However, by increasing the acidity we could obtain the corresponding 3,3-diarylated oxindole derivative **15** in high yields as shown in **Scheme 3**. We could not obtain the mono-arylated derivatives, and these results were well coincidence with Olah's results.[7]

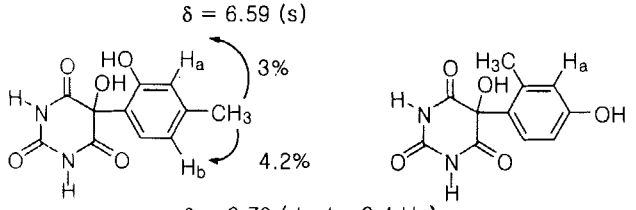
The reaction of parabanic acid (**4**) as the representative example of non-activated cyclic ketone was examined. As expected the reaction of **4** and phenol did not gave any isolable products. The carbonyl group in **4** is amide carbonyl group and has diminished electrophilicity. Addition of aluminium chloride or sulfuric acid did not change the results.

The studies on alkylation and acyaltion of these compounds are undergoing. The biological activities of these compounds are under evaluation and will be published in due course.

EXPERIMENTAL

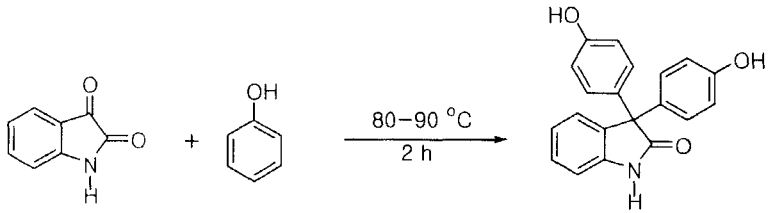
Synthesis of 5 and 6 as a typical example.

To a stirred suspension of ninhydrin (1.8 g, 10 mmol) and phenol (1.9 g, 20 mmol) in glacial acetic acid (10 mL) was added aluminium chloride (2.7 g, 20 mmol), and stirred vigorously at 80-90 °C for 2 h. To the cooled reaction mixture was added water (50 mL) and extracted with chloroform (50 mL x 3). The organic layers were dried ($MgSO_4$), evaporated, and separated by silica gel column chromatography to give the desired products **5** (1.35 g, 53%) and **6** (1.39 g, 42%). The compounds thus prepared were characterized by their mp, ^1H, ^{13}C, and mass spectra.



13 13'

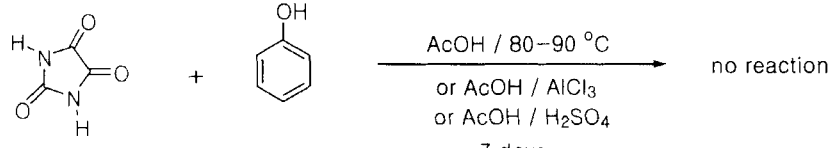
Figure 1. Observed NOE's and chemical shifts.



3 15

condition	yield (%)
AcOH	no reaction
CF_3COOH	70
AcOH / $AlCl_3$ (2 equiv)	89
AcOH / H_2SO_4 (2 equiv)	86

Scheme 3



4

Scheme 4

For compounds **5**, **7**, and **8**, see reference 8.

6: mp 228-229 °C; ^{1}H NMR ($CDCl_3$) δ 6.76 (d, J = 9.0 Hz, 4H), 7.06 (d, J = 9.0 Hz, 4H), 7.84-8.06 (m, 4H), 8.68 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 66.19, 115.37, 123.67, 128.75, 129.62, 135.76, 141.31, 156.49, 200.34; Mass (70 eV) *m/z* (rel intensity) 113 (9), 181 (8), 257 (14), 273 (27), 330 (M^+, 100), 331 (25); Anal. Calcd for $C_{21}H_{14}O_4$: C, 76.36; H, 4.27. Found: C, 76.16; H, 4.32.

9: mp 227-229 °C; ^{1}H NMR (acetone-d_6) δ 5.77 (s, 1H, D_2O exchangeable), 6.56 (s, 1H, D_2O exchangeable), 6.60-8.04 (m, 7H), 8.07 (s, 1H, D_2O exchangeable); Mass (70 eV) *m/z* (rel intensity) 77 (26), 104 (59), 137 (100), 224 (21), 252 (27), 270 (M^+, 46); Anal. Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73. Found: C, 66.60; H, 3.79.

10: mp 193-194 °C; ^{1}H NMR ($CDCl_3$) δ 6.58-7.50 (m, 4H), 10.64 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 73.08, 114.90, 118.94, 124.47, 126.72, 129.19, 149.89, 153.11, 170.68; Mass (70 eV) *m/z* (rel intensity) 65 (37), 76 (28), 150 (66), 121 (100), 122 (53), 236 (M^+, 56); Anal. Calcd for $C_{10}H_8N_2O_5$: C, 50.85; H, 3.41; N, 11.86. Found: C, 50.82; H, 3.53; N, 11.82.

11: mp 292-293 °C; ^{1}H NMR (acetone-d_6) δ 6.83 (d, J = 9.0 Hz, 4H), 7.08 (d, J = 9.0 Hz, 4H), 8.57 (s, 2H), 10.38 (brs, 2H); ^{13}C NMR (acetone-d_6) δ 66.37, 115.86, 129.96, 131.23, 149.89, 158.06, 171.88; Mass (70 eV) *m/z* (rel intensity) 76 (23), 84 (21), 99 (52), 181 (23), 197 (57), 198 (85), 226 (42), 255 (22), 312 (M^+, 100); Anal. Calcd for $C_{16}H_{12}N_2O_5$: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.65; H, 3.98; N, 8.95.

12: mp 96 °C (decomp); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 6.69 (d, J = 8.6 Hz, 1H), 7.30 (dd, J = 8.6 and 2.5 Hz, 1H), 7.72 (d, J = 2.5 Hz, 1H), 11.20 (brs, 4H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 72.32, 76.39, 114.42, 124.57, 126.05, 126.59, 128.37, 149.84, 150.27, 153.63, 170.59, 170.98; Anal. Calcd for $C_{14}H_{10}N_4O_9$: C, 44.46; H, 2.66; N, 14.81. Found: C, 44.50; H, 2.91; N, 14.76.

13: mp 192-194 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 2.23 (s, 3H), 6.59 (s, 1H), 6.70 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 9.15 (brs, 1H), 10.59 (s, 2H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 20.84, 73.62, 116.16, 120.24, 121.19, 126.55, 139.92, 150.08, 153.29, 170.87; Mass (70

eV) *m/z* (rel intensity) 77 (25), 89 (14), 134 (12), 135 (100), 136 (47), 164 (40), 250 (M^+, 41); Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.90; H, 4.33; N, 11.07.

14: mp 208-209 °C; ^1H NMR (acetone-d_6) δ 2.27 (s, 3H), 6.22 (s, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 8.84 (s, 1H), 10.19 (brs, 2H); ^{13}C NMR (acetone-d_6) δ 20.74, 74.15, 115.31, 115.39, 126.32, 128.66, 129.13, 130.58, 150.36, 151.80, 170.92; Mass (70 eV) *m/z* (rel intensity) 77 (37), 89 (18), 107 (22), 135 (100), 136 (51), 164 (77), 250 (M^+, 60); Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.95; H, 4.13; N, 11.20.

15: mp 188-191 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 6.72 (d, *J* = 8.7 Hz, 4H), 6.91-7.00 (m, 2H), 7.05 (d, *J* = 8.7 Hz, 4H), 7.12-7.20 (m, 2H), 9.93 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 60.69, 109.32, 114.45, 121.12, 125.12, 126.95, 128.62, 132.22, 133.89, 140.51, 155.58, 179.39; Mass (70 eV) *m/z* (rel intensity) 120 (11), 135 (9), 196 (26), 272 (13), 288 (100), 289 (27), 317 (M^+, 77), 318 (19); Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.53; H, 4.79; N, 4.39.

Acknowledgements. We wish to thank the Chonnam National University Research Foundation for financial support of this work.

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(Received in Japan 5 January 1999)