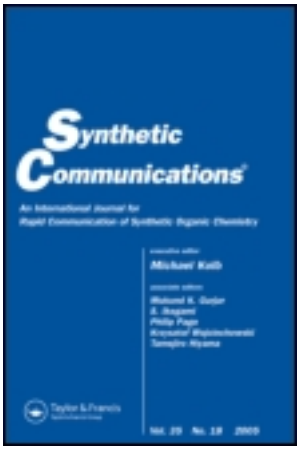

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A STUDY ON THE FRIEDEL-CRAFTS TYPE REACTION OF NINHYDRIN WITH ARENES

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Abstract : The reactions of ninhydrin (**1**, 1,2,3-indantrione) with arenes in the presence of concentrated sulfuric acid afforded mono- or di-substituted ninhydrin derivatives at the 2-position in reasonable yields.

The reactions of ninhydrin, which has a vicinal tricarbonyl functionality, with various kinds of nucleophiles have been studied. They include arylamines, phenols, ketones, β-dicarbonyl compounds, enaminoketones, and heterocyclic compounds.[1] Although the reactions of ninhydrin with arylamines and phenols have been examined extensively, simple aromatic compounds have received little attention.[2] In the course of our studies on the reactivity of 1,2,3-triketone moiety and on development of lead compounds of pesticides,[3] we intended to study on the reaction of ninhydrin with arenes. As shown in **Scheme 1** the reaction of ninhydrin (**1**) with arenes **2** in the presence of concentrated sulfuric acid affoded mono- or di-substituted ninhydrin derivatives **3** and **4** in reasonable combined yields. As shown in **Table 1**, the reaction of benzene or *p*-xylene gave mixtures of products. With arenes that have chloro, fluoro, or methoxy substituents, di-substituted derivatives **4** were obtained exclusively in high yields.

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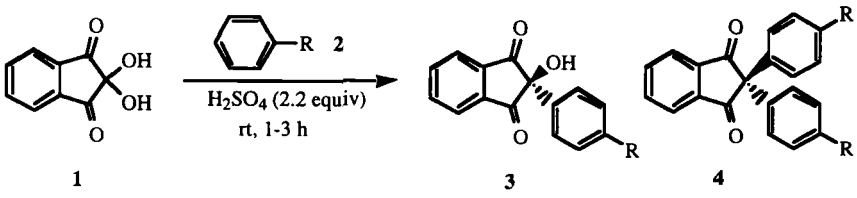
The results might be due to the increased solubility of the protonated ninhydrin complex in these more polar solvents. The reaction of *N*-methylpyrrole afforded mono-substituted derivative in 65% isolated yield with trace amounts of di-substituted compound. The reaction of nitrobenzene with ninhydrin resulted in no reaction after prolonged heating.



1 3 4

Scheme 1

Table 1. The reactions of ninhydrin (1) with some arenes 2.

entry	arenes **2**	time (h)	**3** (%)	**4** (%)	**3** + **4** (%)
a	benzene	1	55	23	78
b	*p*-xylene	3	24	22	46
c	chlorobenzene	2	trace	93[a]	93
d	fluorobenzene	2	trace	84[a]	84
e	anisole	2	trace	68[a]	68
f	*N*-methylpyrrole	2	65[b]	trace	65
g	nitrobenzene	24	-	-	-

[a]The corresponding ortho-isomer was not detected unexpectedly on TLC or in ^{1}H NMR, ^{13}C NMR spectra in appreciable amounts. [b]Substitution was occurred at the 2-position of *N*-methylpyrrole.

In the reactions acid catalyst was needed in slight amount excess (2.2 eqiuv). Boron trifluoride etherate, nitric acid, hydrochloric acid, and glacial acetic acid were not effective in the reaction. Trifluoromethanesulfonic acid showed fast and clean reaction, however, in this case decomposition was observed of the generated

2,2-diphenyl compound **4a** to benzophenone and other unidentified compounds at elevated temperatures. Anhydrous aluminium chloride showed similar results with that of sulfuric acid, however, more side products were observed on thin layer chromatography. It is interesting to note that the reaction of benzene under the influence of aluminium chloride instead of using sulfuric acid resulted the formation of **4a** (80%) and unusual 1,2-disubstituted compound (15%).[4] From the above reaction we could isolate only trace amounts of mono-substituted derivative **3a**. The structure of the compounds could be characterized clearly from their ^{1}H and ^{13}C NMR spectra. The position of substitution is clear from the number of carbon atoms in ^{13}C NMR spectra (see Experimental section and reference 4). The reactions of ninhydrin with polymethylated arenes showed somewhat interesting and unusual results, and these results will be reported separately.

EXPERIMENTAL

Typical procedure for the reaction of ninhydrin and benzene.

To a stirred suspension of ninhydrin (500 mg, 2.8 mmol) in benzene (30 mL) was added concentrated sulfuric acid (610 mg, 6.2 mmol) and stirred vigourously at room temperature for 1 h. The reaction mixture was poured into cold water (100 mL) and diluted with ether (100 mL). The organic layers were washed with brine, dried ($MgSO_4$), and evaporated to dryness. After column chromatography, we could obtain **3a** and **4a** in 55% (365 mg) and 23% (192 mg) isolated yields respectively as white solids. Other compounds **3b**, **3f**, and **4b-e** were synthesized according to the above typical procedure, and their melting points and the spectroscopic data were written below.

3a : mp 111-113 °C; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 1H), 7.22-7.44 (m, 5H), 7.90-8.20 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 79.45, 124.30, 126.19, 128.86, 128.98, 136.52,

136.68, 141.10, 197.79; Mass (70 eV) *m/z* (rel intensity) 52 (44), 77 (99), 105 (100), 181 (60), 238 (M^+, 100), 239 (26).

4a : mp 128-130 °C; ^1H NMR ($CDCl_3$) δ 7.20-7.40 (m, 10H), 7.88-8.14 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 67.53, 124.01, 127.99, 128.54, 128.74, 136.15, 137.99, 141.52, 199.90; Mass (70 eV) *m/z* (rel intensity) 165 (43), 239 (30), 241 (30), 298 (M^+, 100).

3b : mp 144-145 °C; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.22 (s, 3H), 3.41 (s, 1H), 6.94 (s, 2H), 7.04 (s, 1H), 7.80-8.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.97, 21.03, 80.17, 124.21, 128.28, 129.55, 132.23, 133.73, 133.95, 135.43, 136.57, 140.85, 198.28; Mass (70 eV) *m/z* (rel intensity) 77 (40), 103 (59), 104 (77), 105 (45), 132 (52), 133 (47), 223 (53), 266 (M^+, 100).

4b : mp 195-196 °C; ^1H NMR ($CDCl_3$) δ 2.05 (s, 6H), 2.18 (s, 6H), 6.79 (s, 2H), 6.95-7.08 (m, 4H), 7.80-8.10 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.99, 21.60, 70.11, 124.02, 128.43, 129.82 (2 C), 132.59, 135.32, 135.39, 135.92, 141.53, 199.99; Mass (70 eV) *m/z* (rel intensity) 133 (19), 206 (17), 293 (20), 321 (28), 353 (24), 354 (M^+, 100), 355 (31).

4c : mp 164-165 °C; ^1H NMR ($CDCl_3$) δ 7.17 (dd, J = 26.1 and 8.7 Hz, 8H), 7.80-8.05 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 66.10, 124.24, 128.86, 130.03, 134.11, 136.14, 136.53, 141.26, 198.83; Mass (70 eV) *m/z* (rel intensity) 76 (37), 119 (29), 120 (24), 163 (33), 199 (26), 239 (91), 268 (34), 275 (39), 365 (61), 366 (M^+, 100), 368 (67).

4d : mp 169-171 °C; ^1H NMR ($CDCl_3$) δ 6.90-7.20 (m, 8H), 7.80-8.10 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 65.95, 115.50, 115.79, 124.24, 130.42, 130.52, 133.66, 133.71, 136.46, 141.35, 160.65, 163.94, 199.39; Mass (70 eV) *m/z* (rel intensity) 76 (19), 183 (21), 201 (22), 277 (54), 334 (M^+, 100).

4e : mp 144-145 °C; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 6H), 7.01 (dd, J = 293.0 and 9.0 Hz, 8H), 7.85-8.12 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 55.22, 66.28, 113.99, 124.04, 129.87, 130.26, 136.07, 141.52, 159.03, 200.23; Mass (70 eV) *m/z* (rel intensity) 76 (12), 215 (15), 271 (22), 358 (M^+, 100).

3f : mp 168-169 °C; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 1H), 3.99 (s, 3H), 5.75-5.78 (m, 1H), 5.91-5.93 (m, 1H), 6.61-6.63 (m, 1H), 7.85-8.02 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 36.23, 77.36, 107.34, 111. 60, 124.20, 125.03, 126.96, 136.46, 140.03, 196.45; Mass (70 eV) *m/z* (rel intensity) 54 (39), 76 (26), 81 (100), 104 (33), 108 (79), 241 (M^+, 87), 242 (21).

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4. 2,3-Dihydroxy-2,3-diphenyl-1-indanone : mp 175-177 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 1H), 4.38 (s, 1H), 6.75-8.10 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 82.96, 85.83, 123.92, 126.80, 126.91, 127.16, 127.20, 127.26, 127.42, 127.51, 130.13, 135.68, 136.41, 138.59, 140.14, 155.16, 204.11; Mass (20 eV) *m/z* (rel intensity) 77 (17), 105 (100), 132 (43), 133 (65), 209 (30), 210 (49), 221 (51), 298 (100), 299 (100), 316 (M^+, 8).

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