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THE REACTION OF NINHYDRIN WITH TRIMETHYLBENZENES UNDER FRIEDEL-CRAFTS REACTION CONDITIONS

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Abstract : The reaction of ninhydrin with 1,2,3- and 1,2,4-trimethylbenzene in the presence of H_2SO_4 or $AlCl_3$ afforded 2-monoaryl and 2,2-diaryl-1,3-indanedione derivatives as the major products. With 1,3,5-trimethylbenzene as the arene nucleophile, either a reduction product or an indenoindanone derivative was obtained depending upon the catalyst employed in the reaction.

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]

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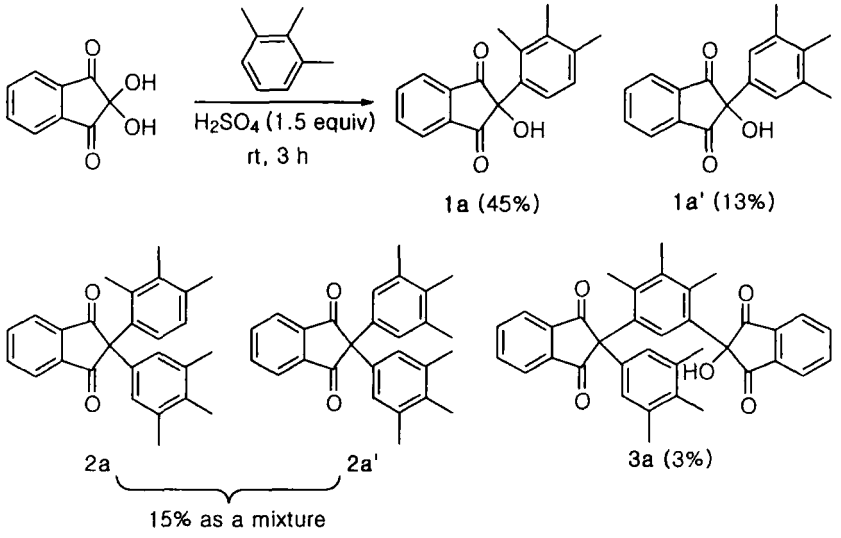
In previous studies we showed that the reaction of ninhydrin (1,2,3-indantrione) and arenes in the presence of concentrated sulfuric acid afforded 2-monoaryl and 2,2-diaryl-1,3-indanedione derivatives in moderate yields depending on the arenes.[1c] In a continuation of this work we examined the reaction of ninhydrin and 1,3,5-trimethylbenzene and observed the formation of unusual compounds (*vide infra*). Thus in this report we wish to describe the reaction of ninhydrin with various trimethylbenzenes.

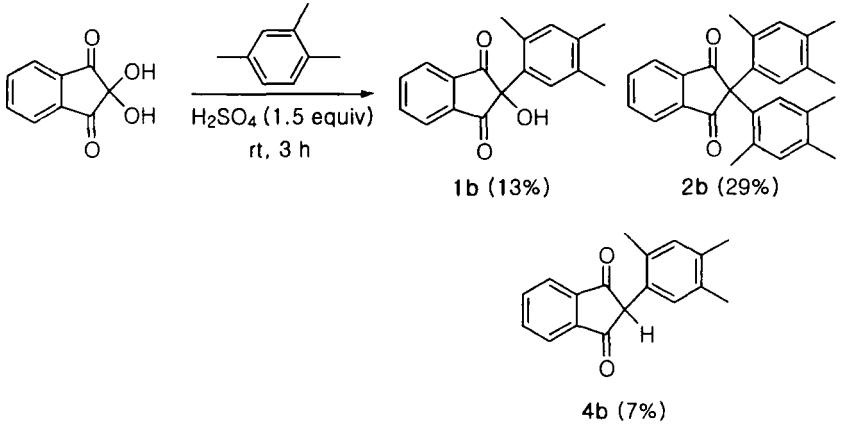
The reaction of ninhydrin and 1,2,3-trimethylbenzene in the presence of sulfuric acid (1.5 equiv) gave mono-arylated derivatives (**1a** and **1a'**) and di-arylated derivatives (**2a** and **2a'**) as the major products as expected from our previous report.[1c] The two mono-arylated products **1a** and **1a'** can be easily separated, and identified from their ^{1}H and ^{13}C NMR spectra (see Experimental section). For the diarylated derivatives isomeric mixtures were observed and separation of **2a** and **2a'** could not be achieved. Further reaction of **2a** with ninhydrin afforded **3a** in 3% isolated yield (**Scheme 1**).

The reaction of ninhydrin and 1,2,4-trimethylbenzene gave **1b** (13%) and **2b** (29%) as the major products. However, an unusual reduction product, **4b**, was obtained in 7% isolated yield (**Scheme 2**). The formation of **4b** could be explained as shown in **Scheme 3**. Mono-arylated compound **1b** in the reaction mixture could react further with 1,2,4-trimethylbenzene to give either the diarylated derivative **2b** or the reduction product **4b** depending on the reaction pathway. Further experiments in order to clarify the reaction mechanism were performed: The reaction of isolated **1b** in 1,2,4-trimethylbenzene in the presence of sulfuric acid (1.5 equiv) gave **4b** in 5% yield together with **2b** in 26% isolated yield. The formation of the diarylmethane derivative[3] was confirmed by GCMS analysis of the nonpolar components of the reaction mixture.

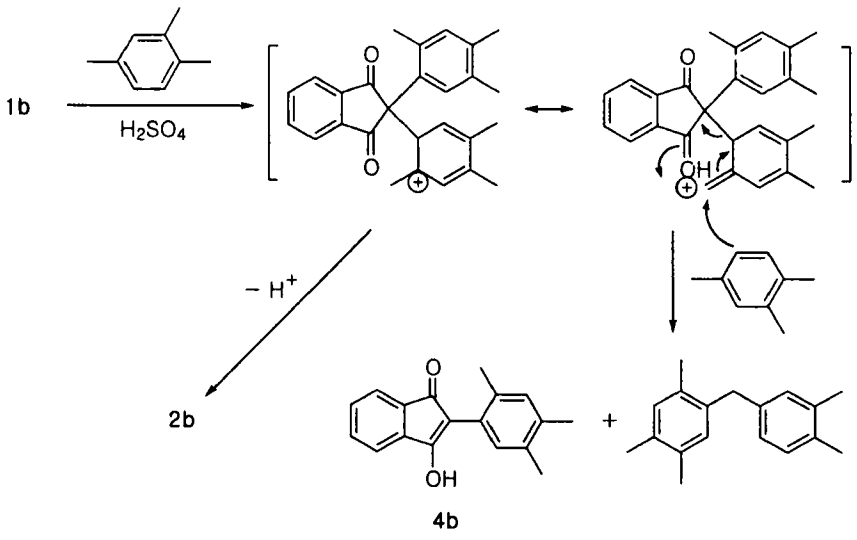
The reaction of ninhydrin and 1,3,5-trimethylbenzene did not afford the generally expected mono- and diarylated derivatives. From the reaction mixture we isolated the reduction product **4c** and the isocoumarin derivative **5c**,[4] unexpectedly (**Scheme 4**). TLC analysis



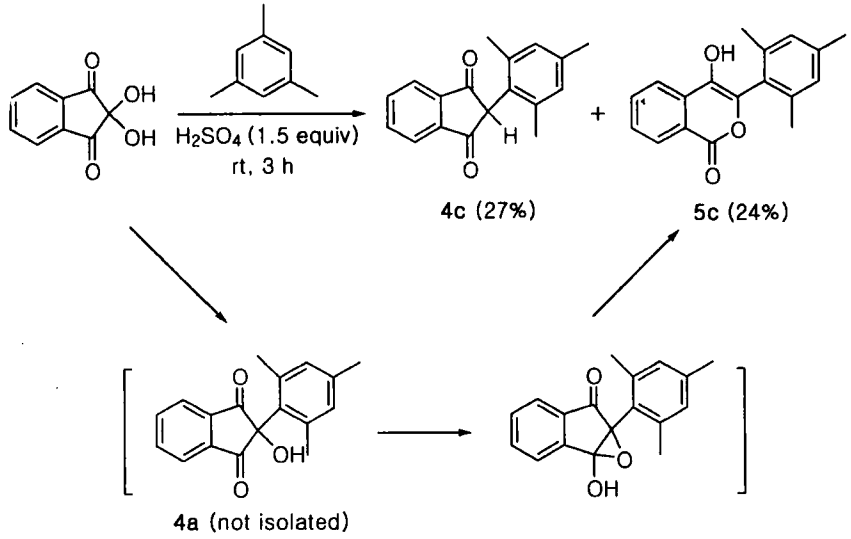
Scheme 1



Scheme 2



Scheme 3



Scheme 4

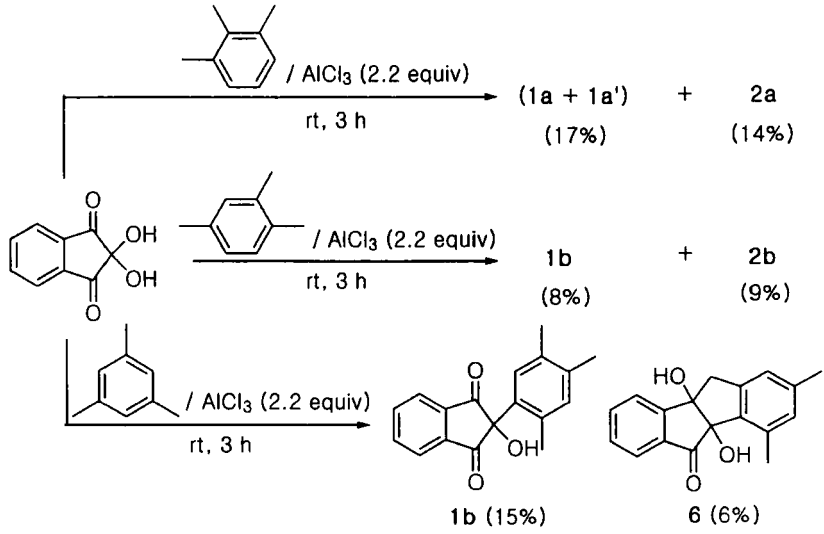
of the reaction mixture showed the presence of some unidentified compounds, however, we could not isolate them. The formation of **4c** can be rationalized as in the case of **4b** in **Scheme 3**. The formation of **5c** is noteworthy. As shown in **Scheme 4** product **4a**, generated initially, undergoes acid catalyzed intramolecular epoxidation followed by ring opening to give isocoumarin derivative **5c**. In the ^{1}H NMR spectrum of **5c**, broad singlets around 2.00 and 6.71 ppm corresponding to the ortho dimethyl and the two aromatic protons of the 1,3,5-trimethylphenyl moiety indicate that free rotation of 1,3,5-trimethylphenyl group is somewhat hampered by steric hindrance.

Changing the catalyst from sulfuric acid to aluminium chloride generates more complex product mixtures and results in lower yields of the isolated products. As shown in **Scheme 5** similar results, to the sulfuric acid catalyzed reactions, were observed in the cases of 1,2,3- and 1,2,4-trimethylbenzene. Low yields of **1** (17%, **1a** and **1a'** as a mixture) and **2a** (14%) were obtained with 1,2,3-trimethylbenzene and low yields of **1b** and **2b** were obtained from 1,2,4-trimethylbenzene. In the reaction of ninhydrin and 1,3,5-trimethylbenzene in the presence of $AlCl_3$ (2.2 equiv), we could isolate **1b** and the unexpected indenoindanone derivative **6**. **Scheme 6** rationalizes the formation of **1b** and **6**. The structure of **6** was confirmed further by converting to its acetonide **7**. The formation of **1b** results from the Lewis acid catalyzed methyl group migration[5] in order to lessen the steric hindrance of the two ortho methyl groups.

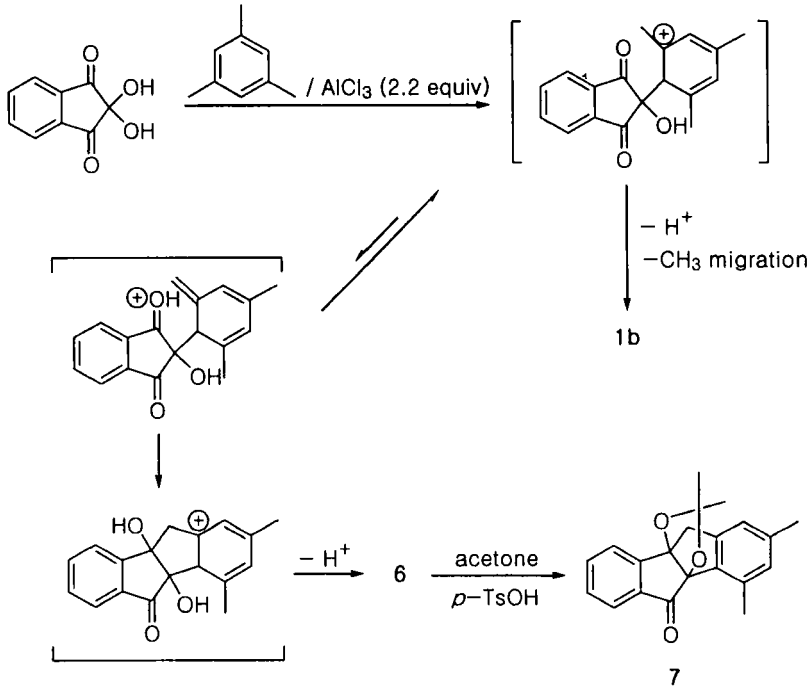
Further studies on the reaction mechanism for the formation of **4**, **5**, and **6** are currently underway. Extension of the reaction with tetra- and pentamethylbenzene derivatives are also currently ongoing, and the results of this work will be published in due course.

EXPERIMENTAL

General procedure for the reaction of ninhydrin and trimethylbenzenes in the presence of sulfuric acid.



Scheme 5



Scheme 6

To a stirred suspension of ninhydrin (1.0 g, 5.6 mmol) in the corresponding trimethylbenzene (10 mL) was added concentrated sulfuric acid (840 mg, 8.5 mmol) and the mixture stirred vigourously at room temperature for 3 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.

1a : 706 mg (45%); mp 186-187 °C; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.24 (s, 3H), 2.39 (s, 3H), 3.41 (brs, 1H), 6.89-6.97 (m, 2H), 7.80-8.06 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.82, 18.06, 20.81, 81.27, 124.20, 125.18, 127.28, 132.09, 136.37 (2C), 137.45, 137.53, 140.81, 198.19; Mass (70 eV) *m/z* (rel intensity) 104 (67), 120 (33), 236 (48), 132 (51), 147 (50), 280 (M^+, 100); HRMS Calcd. for $C_{18}H_{16}O_3$ 280.1100, Found 280.1105.

1a' : 204 mg (13%); mp 159-160 °C; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.21 (s, 6H), 7.03 (s, 2H), 7.85-8.08 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.20, 20.61, 79.44, 124.22, 125.30, 133.16, 136.48 (2C), 137.26, 141.09, 197.93; Mass (70 eV) *m/z* (rel intensity) 77 (42), 91 (41), 104 (100), 105 (38), 120 (40), 147 (43), 237 (58), 280 (M^+, 93); HRMS Calcd. for $C_{18}H_{16}O_3$ 280.1100, Found 280.1112.

2a and **2a'** as a mixture : 320 mg (15%); ^{1}H NMR ($CDCl_3$) δ 2.11, 2.12, 2.13, 2.14, 2.20, 2.21, and 2.24 (seven peaks corresponding to seven different methyl groups), 6.42-8.08 (complicated aromatic peaks); ^{13}C NMR ($CDCl_3$) δ 15.13, 16.14, 19.27, 19.52, 20.67, 20.72, 20.83, 67.40, 70.30, 123.94, 124.04, 126.99, 127.40, 127.80, 127.85, 129.24, 132.55, 133.93, 134.56, 134.77, 135.18, 135.53, 135.59, 135.85, 136.43, 136.66, 137.31, 141.17, 141.77, 199.85, 200.38; Mass (70 eV) *m/z* (rel intensity) 77 (14), 133 (13), 191 (9), 349 (15), 380 (21), 381 (11), 382 (M^+, 100), 383 (24); HRMS Calcd. for $C_{27}H_{26}O_2$ 382.1934, Found 382.1943.

3a : 91 mg (3%); mp 277-278 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 1.72 (s, 3H), 2.09 (s, 3H), 2.12 (s, 6H), 2.16 (s, 3H), 2.35 (s, 3H), 6.21 (s, 1H), 6.63 (s, 1H), 6.86 (s, 1H), 7.67-8.10 (m, 8H); ^{13}C NMR

($CDCl_3$ + DMSO-d_6) δ 15.10, 16.30, 18.10, 19.11, 20.59, 69.76, 81.10, 123.46, 123.96, 126.92, 129.65, 131.63, 132.41, 134.47, 134.85, 135.15, 136.23, 136.58, 136.74, 137.12, 139.10, 139.98, 140.29, 198.80, 199.15; Mass (70 eV) *m/z* (rel intensity) 77 (32), 103 (28), 104 (43), 105 (26), 251 (25), 382 (32), 542 (M^+, 100), 543 (30); HRMS Calcd. for $C_{36}H_{30}O_5$ 542.2094, Found 542.2104.

1b : 205 mg (13%); mp 131-132 °C; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3H), 2.09 (s, 3H), 2.25 (s, 3H), 3.20 (brs, 1H), 6.85 (s, 1H), 6.94 (s, 1H), 7.80-8.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.12, 19.25, 20.81, 80.29, 124.17, 128.91, 131.46, 133.82, 133.95, 134.25, 136.48, 137.31, 140.87, 198.41; Mass (70 eV) *m/z* (rel intensity) 43 (29), 51 (20), 52 (23), 77 (48), 103 (66), 104 (100), 120 (43), 132 (45), 147 (44), 237 (61), 280 (M^+, 65); HRMS Calcd. for $C_{18}H_{16}O_3$ 280.1100, Found 280.1103.

2b : 620 mg (29%); mp 188-190 °C; ^1H NMR ($CDCl_3$) δ 1.95 (s, 6H), 2.01 (s, 6H), 2.09 (s, 6H), 6.65 (s, 2H), 6.85 (s, 2H), 7.74-8.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.11, 19.29, 21.48, 69.68, 123.96, 130.44, 132.88, 133.85, 134.05, 135.59, 135.77, 135.88, 141.55, 200.26; Mass (70 eV) *m/z* (rel intensity) 133 (40), 146 (35), 234 (23), 349 (22), 368 (24), 382 (M^+, 100), 383 (32); HRMS Calcd. for $C_{27}H_{26}O_2$ 382.1934, Found 382.1939.

4b : 104 mg (7%); mp 142-144 °C; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.18 (s, 3H), 2.20 (s, 3H), 4.42 (s, 1H), 6.62 (s, 1H), 6.98 (s, 1H), 7.85-8.07 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.15, 19.30, 19.69, 58.87, 123.56, 129.59, 130.49, 132.34, 134.41, 134.45, 135.79, 136.45, 142.45, 199.10; Mass (70 eV) *m/z* (rel intensity) 50 (25), 63 (25), 76 (38), 77 (30), 91 (25), 103 (25), 104 (33), 119 (26), 146 (29), 147 (100), 264 (M^+, 39); HRMS Calcd. for $C_{18}H_{16}O_2$ 264.1151, Found 264.1162.

4c : 400 mg (27%); mp 217-218 °C; ^1H NMR ($CDCl_3$) δ 1.77 (s, 3H), 2.27 (s, 3H), 2.40 (s, 3H), 4.75 (s, 1H), 6.79 (s, 1H), 6.96 (s, 1H), 7.85-8.06 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.87, 21.09, 58.25, 123.23, 127.72, 129.22, 129.66, 135.64, 135.89, 137.65, 138.67, 141.39, 198.93; Mass (70 eV) *m/z* (rel intensity) 43 (34), 52 (31), 77 (30), 119 (47), 146 (44), 147 (43), 149 (71), 178 (47), 231 (99), 246 (94), 264 (M^+, 100); HRMS Calcd. for $C_{18}H_{16}O_2$ 264.1151, Found 264.1149.

5c : 376 mg (24%); mp 139-140 °C; ^1H NMR ($CDCl_3$) δ 2.00 (brs, 6H), 2.20 (s, 3H), 5.43 (brs, 1H), 6.71 (s, 2H), 7.57-7.79 (m, 4H); ^1H

NMR (DMSO-d_6) δ 2.00 (brs, 6H), 2.24 (s, 3H), 6.87 (s, 2H), 7.70-7.94 (m, 4H), 9.07 (brs, 1H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ 19.89, 20.98, 103.92, 124.10, 125.66, 127.48, 128.44, 128.69, 131.52, 131.97, 134.31, 139.69, 144.58, 167.25, 203.46; Mass (70 eV) *m/z* (rel intensity) 65 (20), 91 (21), 119 (28), 146 (84), 147 (100), no M^+; Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.33; H, 5.69.

General procedure for the reaction of ninhydrin and trimethylbenzenes in the presence of aluminium chloride.

To a stirred suspension of ninhydrin (1.0 g, 5.6 mmol) in corresponding trimethylbenzene (10 mL) was added aluminium chloride (1.65 g, 12.3 mmol) and stirred vigorously at room temperature for 3 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.

6 : 95 mg (6%); ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.81 (s, 3H), 3.11 (s, 2H), 3.40 (brs, 2H), 6.80 (s, 1H), 6.97 (s, 1H), 7.47-7.85 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.02, 21.18, 40.66, 87.69, 87.84, 123.48, 124.68, 126.56, 129.91, 131.20, 133.36, 135.02, 136.35, 137.17, 139.45, 139.55, 152.44, 203.87; Mass (70 eV) *m/z* (rel intensity) 105 (45), 206 (68), 238 (68), 147 (51), 247 (65), 262 (84), 280 (M^+, 100); HRMS Calcd. for $C_{18}H_{16}O_3$ 280.1100, Found 280.1099.

7 : mp 162-164 °C; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.32 (s, 3H), 2.30 (s, 3H), 2.78 (s, 3H), 3.13 (d, J = 18 Hz, 1H), 3.40 (d, J = 18 Hz, 1H), 6.84 (s, 1H), 6.99 (s, 1H), 7.48-7.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.55, 21.22, 28.28, 28.81, 37.54, 96.70, 97.97, 117.76, 123.92, 125.17, 126.42, 130.11, 130.84, 134.80, 134.94, 136.48, 136.89, 139.84, 141.19, 151.05, 202.70; Mass (70 eV) *m/z* (rel intensity) 189 (29), 206 (54), 247 (45), 263 (100), 305 (64), 320 (M^+, 9); HRMS Calcd. for $C_{21}H_{20}O_3$ 320.1413, Found 320.1417.

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3. From the nonpolar hydrocarbon components of the reaction mixtures, we could identify the expected diarylmethane derivative: MS (70 eV) *m/z* (rel intensity) 91 (11), 117 (14), 132 (100), 133 (16), 237 (40), 238 (M^+, 11).
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