

## **S<sub>RN</sub>1 REACTIONS OF ARYL HALIDES WITH CARBANIONS INITIATED BY SODIUM AMALGAM IN LIQUID AMMONIA**

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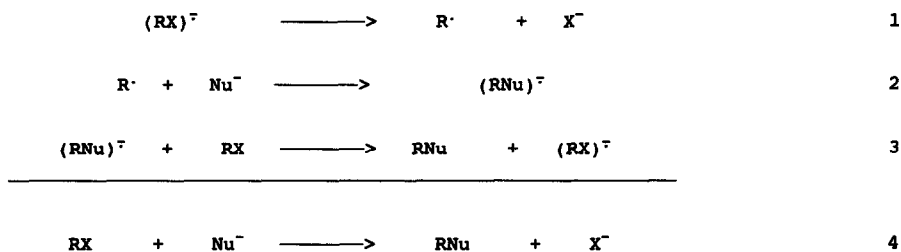
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**Abstract-** The reaction of 1-chloronaphthalene with acetone (2a) and acetophenone (2b) enolate ions was initiated by sodium amalgam [Na(Hg)] in liquid ammonia giving good yields of the substitution products 3a and 3b respectively. 2-Chloroquinoline and 2-chloropyridine gave good yields of substitution product with 2b, and moderate to good yields with 2a. 4-Bromobenzophenone and 2a gave 78% of the substitution product 5. With aryl halides whose radical anions fragment fast and consequently close to the Na(Hg) surface, such as bromobenzene and *p*-bromoanisole, only dehalogenation products were observed. However, when benzonitrile was used as a redox catalyst, about 50% of the substitution product 6 was obtained with *p*-bromoanisole and 2a. However, with the more reactive carbanionic nucleophile, such as anthrone anion 4, good yields of the substitution product 7 were obtained with bromobenzene. In all these reactions neither reduction of the aromatic moiety nor the ketone functionality was observed. It is therefore suggested that Na(Hg) amalgam initiates these S<sub>RN</sub>1 reactions.

The aromatic radical nucleophilic substitution, or S<sub>RN</sub>1, has been shown to be an excellent means of affecting the nucleophilic substitution of unactivated aromatic compounds possessing suitable leaving groups. The mechanism of the reaction is a chain process, and the propagation steps are shown in Scheme I.<sup>2</sup>

Scheme I depicts a nucleophilic substitution in which radicals and radical anions are intermediates. However, this chain process requires an initiation step. In a few systems, spontaneous electron transfer (ET) from the nucleophile to the substrate has been observed.<sup>3</sup> When ET does not occur spontaneously, it can be induced by light,<sup>4</sup> by solvated electrons in liquid ammonia,<sup>5</sup> by cathodically generated electrons,<sup>6</sup> or by certain inorganic salts.<sup>7</sup>

SCHEME I

We recently found that sodium amalgam [Na(Hg)] reacts with aryl halides in liquid ammonia<sup>8</sup>, and also it is a suitable reagent to initiate  $S_{\text{RN}}1$  reactions of aryl halides and diphenylphosphide ions in liquid ammonia.<sup>9a</sup>

Although certain carbanions have been found to be efficient nucleophiles in  $S_{\text{RN}}1$  reactions with aryl halides,<sup>2</sup> stabilized carbanions such as the enolate ions of acetophenone<sup>10</sup> or the anions of  $\alpha$ - $\beta$  unsaturated ketones<sup>11</sup> were found to be unreactive toward halobenzenes under photostimulation in liquid ammonia. The acetophenone enolate ion was shown to react with iodobenzene in liquid ammonia only under very drastic irradiation conditions to give 67% yield of  $\alpha$ -phenylacetophenone.<sup>12</sup> On the other hand, 2-naphthylmethylketone<sup>13</sup> and acetophenone<sup>14-18</sup> enolate ions react in liquid ammonia with more electrophilic substrates.

Recently<sup>19</sup> we have found that there are differences of reactivities among carbanions in the photostimulated initiation step and in the coupling reaction (eq. 2) of the propagation steps. Thus, the rate of the photostimulated ET from carbanions to iodobenzene in DMSO increases as the pKa of the ketones increases, but the rate of the coupling reactions decreases as the pKa increases. Thus, the lack of reactivity of acetophenone and other related stabilized carbanions in photostimulated reactions with haloarenes in liquid ammonia could be due to the lack of photostimulated initiation steps. We then undertook the study of the reaction of carbanions with haloarenes initiated by Na/Hg in liquid ammonia.

Results and Discussion

It has been shown that Na(Hg) (3% w/w) in liquid ammonia forms a heterogeneous mixture, and no solvated electrons are present in the solution.<sup>9a-b</sup> No reaction of 1-chloro-naphthalene (1) with acetone enolate ion (2a) has been observed in the dark or under irradiation in liquid ammonia;<sup>10b</sup> however, in the presence of Na(Hg), a 98% yield of the substitution product 3a was obtained (eq. 4). No reduction on the naphthyl moiety was observed, as has been found in the reaction initiated with potassium metal in liquid ammonia<sup>10b</sup> (Table 1, experiment 1).

Substrate 1 reacted neither in the dark nor under irradiation (only 8% of reaction after 3 h of irradiation) with acetophenone enolate ion (2b) in liquid ammonia.<sup>10b</sup> However, in the presence of Na(Hg), a very good yield of substitution product 3b was obtained (eq. 4) (Table 1, experiment 2) and also no reduction products were observed.



**TABLE 1:** Reaction of Aryl Halide with Carbanions Induced by Sodium Amalgam in Liquid Ammonia.<sup>a</sup>

Expt.	ArX <sup>b</sup> (mmol)	Nucleophile (mmol)	Na(Hg) (mmol)	ArH %	Substitution Product (%) <sup>c</sup>
1	1-ClNaph (4.0)	2a (16.0)	12.0	d	3a (98)
2	1-ClNaph (4.0)	2b (12.0)	12.0	d	3b (98) <sup>e</sup>
3	2-ClQuin (3.0)	2a (10.0)	12.0	f	4a (49) <sup>g</sup>
4	2-ClQuin (3.0)	2b (9.0)	9.0	-	4b (98)
5	4-BrBenz (3.0)	2a (6.0)	9.0	6	5 (78)
6 <sup>h</sup>	<i>p</i> -BrAn (2.5)	2a (5.0)	7.5	25	6 (45)
7 <sup>h</sup>	<i>p</i> -BrAn (2.5)	2a (10.0)	7.5	21	6 (57)
8 <sup>i</sup>	PhBr (2.0)	4 (4.0)	6.0	d	7 (70)
9	2-ClPyr (3.0)	2a (10.0)	8.0	10 <sup>j</sup>	8a (15)
10	2-ClPyr (3.0)	2b (10.0)	8.0	5	8b (75)

<sup>a</sup>Reactions carried out in ca. 200 mL of liquid ammonia. <sup>b</sup>1-ClNaph = 1-chloro-naphthalene; 2-ClQuin = 2-chloroquinoline; 4-BrBenz = 4-bromobenzophenone; *p*-BrAn = *p*-bromoanisole; 2-ClPyr = 2-Chloropyridine. <sup>c</sup>Quantified by GLC, unless otherwise indicated. <sup>d</sup>Detected, but not quantified. <sup>e</sup>70% yield of pure isolated product. <sup>f</sup>The reduction product quinoline was not detected, but ca. 50% of the dimeric product biquinolyl was found. <sup>g</sup>Duplicate run. <sup>h</sup>PhCN was added as a redox catalyst (300 mmol%). <sup>i</sup>PhCN was added as a redox catalyst (800 mmol%). <sup>j</sup>The dimer bipyridyl was formed in ca. 55%.

In the reaction of *p*-bromoanisole and 2a stimulated with Na(Hg) in the presence of benzonitrile as redox catalysts, 45% yield of the substitution product *p*-anisylacetone 6 was obtained. Increasing twice the concentration of 2a, there was only a slight increase of the substitution product (Table 1, experiments 6-7).

It is interesting to note that the reaction of *p*-bromoanisole and 2a stimulated with K metal in liquid ammonia gave 36% yield of *p*-anisylacetone and 10% yield of the reduction product 1-(*p*-anisyl)-2-propanol.<sup>20</sup> In the reaction stimulated with Na(Hg), only the substitution product was obtained, and no reduction product was detected.

By competition experiments, Ph<sub>2</sub>P<sup>-</sup> ions are about 6 times more reactive than pinacolone enolate ion in liquid ammonia,<sup>21</sup> and it is expected that the reactivity of 2a should not be different from these values. Because Ph<sub>2</sub>P<sup>-</sup> ions are more reactive than 2a, the reaction of Ph<sub>2</sub>P<sup>-</sup> ions and *p*-bromoanisole and Na(Hg) and benzonitrile is more effective than the reaction with 2a as nucleophile.

In order to see if more reactive carbanionic nucleophiles are able to react in this condition, and as anthrone anion is 16.5 times more reactive than 2a in the coupling reaction with phenyl radicals,<sup>19</sup> we studied the reaction of this nucleophile in this experimental condition. In the reaction of bromobenzene and anthrone ion 4 in the presence of benzonitrile and catalyzed by Na(Hg), 70% yield of the substitution product 10-phenylanthrone 7 was obtained (Table 1, experiment 8).

In the reaction of 2-chloropyridine and 2a with Na(Hg), a low yield of 2-pyridylacetone 8a was obtained, and 10% yield of pyridine together with a substantial amount of the dimeric product bipyridyl (Table 1, experiment 9), indicating a slow rate of coupling of 2-pyridyl radicals with 2a. However, with a more reactive carbanionic nucleophile as 2b, good yields of substitution product 8b were obtained (Table 1, experiment 10).

**Conclusions:** All these results suggest that Na(Hg) amalgam is an efficient reactive to initiate S<sub>RN</sub>1 reactions of aryl halides and carbanions in liquid ammonia, and no reduction products derived from the ketone functionality or the aromatic moieties are found. In the case of aryl halides, where their radical anions fragment very fast and close to the Na(Hg) surface, they are reduced to arenes. In this case, a redox catalyst, such as benzonitrile must be used, and moderate to good yields are obtained, especially with nucleophiles very reactive toward aryl radicals. When the radical anions derived from the aryl halides did not fragment close to the Na(Hg) surface, and diffused to the bulk solution, a very good yield of substitution products was obtained.

## EXPERIMENTAL SECTION

**General Method.**  $^1\text{H}$  NMR spectra of  $\text{CD}_2\text{Cl}_2$  solutions were recorded with a Varian T-60 and with a Bruker 200 nuclear magnetic resonance spectrometers. The positions of the signals are reported in parts per million relative to  $\text{Me}_4\text{Si}$  (5). Mass spectra were recorded with a Finnigan 3300 f-100 mass spectrometer. Gas chromatographic analyses were performed with either a Shimadzu GC8A gas chromatograph equipped with a Shimadzu CR-3A data system or a Spectra Physics SP-2400 gas chromatograph equipped with a flame ionization detector. A 3 mm x 1.5 m column packed with 5% OV 17 on Chromosorb P was used. Quantitative analysis was done by the internal standard method. The potentiometric titration of halide ions was performed with a pHmeter (Seybold Wien) equipped with a  $\text{Ag}/\text{Ag}^+$  electrode and  $\text{AgNO}_3$  standard. Melting points were measured with a Büchi 510 apparatus and are uncorrected.

**Materials:** p-Bromoanisole (Fluka), 1-chloronaphthalene (Fluka), 2-chloroquinoline (Fluka), 2-chloropyridine (MCB), bromobenzene (Aldrich), 4-bromobenzophenone (Janssen), acetophenone (Carlo Erba), anthrone (Carlo Erba) and benzonitrile (BDH) were commercially available and were used as received. Na(Hg) amalgam (3% w/w) was prepared and its concentration was determined as reported.<sup>9a</sup>

**Reaction of Na(Hg) with 1-Chloronaphthalene and Acetophenone Enolate Ion in Liquid Ammonia:** The following procedure is representative of these reactions. To 200 mL of distilled liquid ammonia (previously dried under nitrogen with Na metal) and under nitrogen were added 20 mmol of potassium *tert*-butoxide, 12.0 mmol of acetophenone and 4.0 mmol of 1-chloronaphthalene. The reaction vessel was wrapped with aluminum foil to exclude light, and 12 mmol of Na(Hg) was added with magnetic stirring. After 2 h the reaction was quenched by adding ammonium nitrate in excess and the ammonia was allowed to evaporate. The residue was dissolved in water and the solution was extracted with dichloromethane, and then the chloride ions were determined potentiometrically in the water solution. The dichloromethane solution was dried and quantified by GLC (internal standard method). The solvent was removed under reduced pressure. The residue, after radial chromatography on silica-gel (eluted with petroleum ether: diethyl ether 7:3) gave  $\alpha$ -(1-naphthyl)acetophenone,<sup>22</sup> mp 102-103°C,  $^1\text{H}$  NMR ( $\text{Cl}_4\text{C}$ )  $\delta$  4.73 (s, 2H); 7.3-8.1 (m, 12H); MS (70 eV)  $m/e$  (relative intensity) 246 (9,  $\text{M}^+$ ), 215 (7), 202 (15), 105 (30).

(1-Naphthyl)acetone,<sup>22</sup>  $^1\text{H}$  NMR ( $\text{Cl}_3\text{CD}$ )  $\delta$  2.10 (s, 3H); 4.1 (s, 2H); 7.3-8.0 (m, 7H).

(2-Quinolyl)acetone,<sup>23</sup> mp 74-75 °C (lit<sup>24</sup> mp 76-77°C). MS (70 eV)  $m/e$  (relative intensity) 185 (100), 170 (69), 143 (71), 142 (28), 128 (3), 115 (4), 43 (15). IR ( $\text{cm}^{-1}$ ) = 593, 731, 1152, 1183, 1334, 1414, 1556, 1643, 2978, 3056, 3185.

*p*-Anisylacetone,<sup>25</sup>  $^1\text{H}$  NMR ( $\text{Cl}_4\text{C}$ )  $\delta$  1.9 (s, 3H); 3.8 (s, 3H); 4.0 (s, 2H); 6.9 (m, 4H).

2-Pyridylacetone,<sup>26</sup>  $^1\text{H}$  NMR ( $\text{Cl}_4\text{C}$ )  $\delta$  2.22 (s, 3H); 3.91 (s, 2H); 7.09-7.76 (m, 4H); IR ( $\text{cm}^{-1}$ ) 478.92, 807.79, 1118.51, 1314.51, 1370.76, 1431.29, 1500.07. MS (70 eV)  $m/e$  (relative intensity) 135 (7,  $\text{M}^+$ ), 93 (100), 66 (12, 43 (32)).

**4-Benzoylphenylacetone.** <sup>1</sup>H NMR (Cl<sub>4</sub>C) δ 1.7 (s, 3H); 3.1 (s, 2H); 6.8-7.4 (m, 9H). MS (70 eV) m/e (relative intensity) 239 (4), 238 (3), 196 (5.4), 180 (9.6), 165 (9.1), 135 (2.5), 119 (5), 105 (100), 91 (13), 77 (59.8), 59 (26), 43 (40). <sup>13</sup>C NMR = 30.7, 52.95, 121.60, 122.72, 122.83, 123.51, 126.19, 127.78, 128.51, 129.55, 130.89, 136.26, 137.80, 152.89, 188.25, 205.29.

**α(2-Quinolyl)acetophenone.** Mp 117-118°C (Lit.<sup>27</sup> mp 119-120°C). <sup>1</sup>H NMR (Cl<sub>4</sub>C) δ 4.60 (s, 2H); 7.20-8.50 (m, 11H) IR (cm<sup>-1</sup>): 597, 643, 752, 1156, 1161, 1206, 1315, 1522, 1566, 1660, 3030, 3182.

**α-Phenylacetophenone.** Mp 54-55°C (Lit.<sup>28</sup> mp 55-56°C). <sup>1</sup>H NMR (Cl<sub>4</sub>C) δ 4.68 (s, 2H); 6.8-7.4 (m, 10H).

**α(p-Anisyl)acetophenone.** Mp 99.5-100.5°C (Lit.<sup>28</sup> mp 98-99°C) <sup>1</sup>H NMR (Cl<sub>4</sub>C) δ 3.78 (s, 3H); 4.70 (s, 2H); 7.1-7.7 (m, 9H).

**10-Phenylanthrone.** Compound pure compared with an authentic sample.<sup>19</sup>

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