# **Reaction of** *o***-Iodoaniline with Aromatic Ketones in DMSO:** Synthesis of 2-Aryl or 2-Hetarylindoles

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**Abstract:** The reactions of *o*-iodoaniline (1) with the enolate anions from acetone (2), acetophenone (4), 2-acetylnaphthalene (6), 2-acetyl-1-methylpyrrole (8a) and 2-acetylthiophene (8b) in DMSO give respectively the corresponding 2-substituted indoles in 63, 88, 73, 93 and 82% yields. These reactions are proposed to take place by an  $S_{RN}$ 1 mechanism. Depending on the ketone enolate ion involved, the reactions can occur under light or Fe(II) salts initiation.

Key words:  $S_{RN}1$  reactions, 2-arylindoles, 2-hetarylindoles, photostimulation, FeBr<sub>2</sub> induced reaction, heterocycles, enols, carbanions

The indole ring belongs to an important class of compounds due to their pharmacological activity.<sup>1</sup> The discovery of many new structures from natural products, including marine natural products, has increased the range of the family of indole alkaloids.<sup>2</sup>

Of the many procedures developed for indoles synthesis, the oldest and most widely used one is the Fisher method.<sup>3</sup> This procedure has recently been improved by the palladium-catalyzed synthesis of *N*-aryl hydrazones.<sup>4</sup> Another route, the Bischler method, has been recently modified by the NH insertion of anilines with rhodium carbenoids.<sup>5</sup>

The development of synthetic methods for the construction of the indole nucleus, particularly under non-acidic conditions is an area of current interest. Recently, the preparation of indoles from *o*-haloanilines by the palladium cross-coupling reaction followed by Rh-catalyzed hydroformylation of Heck adducts has been reported.<sup>6</sup>

The  $S_{RN}1$  mechanism is an important route to achieve the formation of a new C–C bond by the reaction of aromatic substrates with carbanions.<sup>7</sup> Good percentages of substitution are usually obtained in these reactions with the enolate ions of aliphatic ketones. These anions react with aromatic substrates under photostimulation in liquid ammonia or in DMSO at room temperature.

Aromatic ketones behave somewhat differently. For example, the enolate ion of acetophenone reacts sluggishly with halobenzenes or halonaphthalenes in liquid ammonia, under photostimulation. Heteroarylation of the anion can be achieved in this solvent either under irradiation or even in the dark with highly electrophilic substrates.<sup>8,9</sup> On the other hand, phenylation as well as heteroarylation of the anion is possible in DMSO under photostimulation.<sup>10,11</sup> A similar behavior has been observed with the enolate ions of 2-acetylnaphthalene<sup>12</sup> and other aromatic ketones such as 2-acetylfuran,<sup>11,8b</sup> and 2-acetylthio-

phene.<sup>13</sup> The latter carbanion has been reported to afford the substitution product by reaction with phenyl azosulfides,<sup>13</sup> which are very good electron acceptors that react spontaneously or under laboratory light with different nucleophiles.

The difference in reactivity between enolate anions of aromatic and aliphatic ketones toward phenyl halides in liquid ammonia has been attributed to the lower efficiency of the former in the photoinitiation step of the proposed mechanism (Scheme 1).<sup>7</sup> This situation can be overcome by employing other methods of initiation like solvated electrons from alkali metals; electrochemically; favoring the initial ET at higher temperatures (DMSO, r.t.) or performing the reaction in the presence of added nucleophiles that are less reactive than the enolate anion of the aromatic ketone toward phenyl radicals (Scheme 1, eq. 3), but are better electron donors to initiate the chain (Scheme 1, eq. 1) (entrainment reaction).

Initiation  $ArX + Nu^{-} \xrightarrow{hv} (ArX)^{-}$  (1)

Propagation  $(ArX)^{-\bullet} \longrightarrow Ar^{\bullet} + X^{-}$ 

 $Ar^{\bullet} + Nu^{-} \longrightarrow (ArNu)^{-\bullet}$  (3)

$$(ArNu)^{-} + ArX \longrightarrow ArNu + (ArX)^{-}$$
 (4)

$$ArX + Nu^{-} \longrightarrow ArNu + X^{-}$$
 (2,4)

Scheme 1

The  $S_{RN}1$  mechanism has been shown to be a valuable reaction to the synthesis of heterocycles, 2-alkyl substituted indoles being one of them. The discovery that the photostimulated reactions of *o*-bromo- and *o*- iodoanilines with aliphatic ketone enolate ions in liquid ammonia afford 2alkylindoles from spontaneous ring closure of the substitution product in very good yields, has opened an important synthetic route to substituted indoles in non-acidic conditions (Scheme 2).<sup>14,15</sup>

With the enolate ion of aldehydes, unsubstituted or 3-substituted indoles are obtained.<sup>16</sup> Good yields of 2-alkylindoles are also obtained in the photostimulated reaction of enolate ions of ketones with methyl substituted *o*-bromoanilines and with *o*-chloroanilines substituted at position

(2)



#### Scheme 2

5 with Ph, MeO, or  $\text{CO}_2^{-.14,17}$  Even *o*-chloroaniline reacts with acetone enolate ion in the presence of Fe<sup>+2</sup> in liquid ammonia to afford 2-methylindole (51%).<sup>18</sup> The reaction of *o*-iodoaniline with ketone or acetaldehyde enolate ions induced by electrodes also affords very good yields of indoles.<sup>19</sup> Benzoindoles can be obtained in the photostimulated reaction of 1-bromo-2-amino- or 1-amino-2bromonaphthalenes with aliphatic ketone enolate ions.<sup>20</sup> 2-Substituted azaindoles are obtained under irradiation in the reaction of different *o*-iodoaminopyridines.<sup>21</sup> 3-Amino-2-chloropyridine also affords the azaindole in good yields (Scheme 3).<sup>14,19,22</sup>



# Scheme 3

All these syntheses were carried out in liquid ammonia. The reactions afforded poor results with aromatic ketones in this solvent. Thus the photostimulated reaction of 3-amino-2-chloropyridine with the enolate ions of propiophenone and 2-acetylpyridine gave respectively only 30 and 21% yields of the azaindoles.<sup>19</sup> As we found that the enolate ions of aromatic ketones react readily with iodoarenes to give good yields of substitution products in DMSO,<sup>10</sup> we decided to study the synthesis of 2-aryl or 2-hetarylindoles through the S<sub>RN</sub>1 mechanism in this solvent in order to increase its synthetic scope.

*o*-Iodoaniline (1) does not react with acetone enolate ion (2) in DMSO (1.5 h). Under irradiation (1.5 h) 2-methylindole (3)<sup>14</sup> was obtained in 10% yield (Scheme 4). Also low yield of 3 is obtained (17%) in the reaction induced by FeBr<sub>2</sub> (Table, Entries 1, 2, 5).



## Scheme 4

This is an unexpected result because it is well known that the photostimulated reaction of iodobenzene with 2 in

DMSO under the same experimental conditions gives the substitution product in ca. 90% yields.<sup>10, 23, 24</sup> We performed the reactions with an excess of t-BuOK to avoid condensation products of the ketones.<sup>7</sup> The pKa of acetone and t-BuOH in DMSO are 26.5 and 32.2 respective- $1y^{25}$  If the pKa of **1** (at NH) is similar to that of *t*-BuOH, the substrate could be ionized in the reaction media, conditions under which it could be inhibited to react by the S<sub>RN</sub>1 mechanism.<sup>26</sup> When we performed the photostimulated reaction (1.5 h) without excess t-BuOK, 3 was obtained in 63% yield (isolated product). This reaction is inhibited by p-DNB, a good radical anion scavenger (Table, Entries 3, 4).<sup>7</sup> Also good yield of **3** is obtained when the reaction is induced by FeBr<sub>2</sub> (Table, Entry 6). Substrate 1 does not react with the enolate anion of acetophenone 4 in the dark, but it reacts under irradiation to afford 88% yield of indole  $5^{27}$  (Scheme 5). When the reaction is induced by FeBr<sub>2</sub>, 5 is formed in 83% yield (Table, Entries 7–9).





The photostimulated reaction of **1** with the enolate ions of 2-acetylnaphthalene **6** affords 73% yield of indole  $7^{28}$  (Scheme 6). Lower yields of indole **7** (43%) were obtained in the presence of excess *t*-BuOK. The reaction induced by FeBr<sub>2</sub> gave 66% yields of **7** (Table, Entries 10–13).



#### Scheme 6

Recently we have found that 2-acetyl-1-methylpyrrole enolate ion **8a** gives good yields of substitution products in its photostimulated reaction with iodoarenes and neopentyl iodide in DMSO.<sup>29</sup> 2-Acetylthiophene enolate ion **8b** did not react under irradiation with iodobenzene, however, it affords good yields of substitution by FeBr<sub>2</sub> inducement or when the photostimulated reaction is performed in the presence of the enolate ion of acetone (entrainment reagent).<sup>30</sup> The photostimulated reaction (2 h) of **8a** with **1** gives the indole **9a**<sup>31</sup> in 63% yield, which increases up to 93% in the reaction induced by FeBr<sub>2</sub> (Scheme 7, Table, Entries 14–15). Carbanion **8b** does not react with **1** under irradiation, or in the presence of ace-

Table Reactions of o-Iodoanilines with Carbanions in DMSO <sup>a</sup>	Table	Reactions	of o-Iodoanilin	es with	Carbanions	in DMSO <sup>a</sup>
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Entry	1 (mmol)	Carbanion (mmol)	Conditions	<b>I</b> ⁻ (%) <sup>b</sup>	Indol	Yield <sup>c</sup> (%)
$2^{e,f}$	1.14	2 (5.00)	<i>h</i> v, 1 h	38	3	10
3 <sup>g</sup>	0.51	2 (5.45)	<i>h</i> v, 1.5 h	92	3	63 <sup>h</sup>
4 <sup>i,d</sup>	0.48	2 (5.11)	hv, 1.5 h	19	3	11
5 <sup>e</sup>	0.52	2(4.00)	FeBr <sub>2</sub> , 1 h	ن_	3	17 <sup> h</sup>
6 <sup>k</sup>	0.48	2 (5.18)	FeBr <sub>2</sub> , 1.5 h	72	3	57
7 <sup>d</sup>	0.54	4 (5.02)	dark, 1.5 h	<3	5	_
8	0.50	4 (5.14)	<i>h</i> v, 3 h	90	5	88
9	0.52	4 (3.00)	FeBr <sub>2</sub> , 1 h	Ľ.	5	83, 67 <sup>h</sup>
10 <sup>e,f</sup>	0.48	6 (5.00)	<i>h</i> v, 3 h	64	7	43
11	0.51	6 (5.00)	<i>h</i> v, 2 h	87	7	73
12	0.56	6 (4.00)	<i>h</i> v, 2 h	88	7	53 <sup>h</sup>
13	0.51	6 (5.00)	FeBr <sub>2</sub> , 1 h	ن	7	66
14 <sup>1</sup>	0.49	<b>8a</b> (2.42)	hv, 2h	84	9a	63
15 <sup>m</sup>	0.48	<b>8a</b> (2.20)	FeBr <sub>2</sub> , 1 h	100	9a	93
16 <sup>d</sup>	0.48	<b>8b</b> (4.90)	hv, 1.5 h	<3	9b	_
17 <sup>n,d</sup>	0.46	<b>8b</b> (5.02)	hv, 1.5 h	<12	9b	3
18°	0.51	<b>8b</b> (5.00)	FeBr <sub>2</sub> , 1 h	93	9b	82
19	4.44	<b>8b</b> (44.5)	$FeBr_2$ , 1h	Ľ.	9b	79 <sup>h</sup>

<sup>a</sup> Reactions carried out under  $N_2$  at 40 °C in DMSO (20 mL); *t*-BuOK used in 1–2% excess with respect to the ketone unless otherwise indicated. In the reactions induced by FeBr<sub>2</sub>, an equimolar amount of the inorganic salt and the substrate were used.

<sup>b</sup> Determined potentiometrically.

<sup>c</sup> Quantified by GC and the internal standard method (unless otherwise stated).

<sup>d</sup> *o*-Iodoaniline recovered unchanged.

<sup>e</sup>Reaction performed in the presence of excess *t*-BuOK (1.5 mmol).

<sup>f</sup> Aniline and o-iodoaniline detected, but not quantified.

<sup>g</sup> *o*-Iodoaniline (3%); aniline (13%).

<sup>h</sup> Isolated product.

<sup>i</sup> p-DNB (20 mol %) was added.

<sup>j</sup> Not quantified.

<sup>k</sup> o-Iodoaniline (16%).

<sup>1</sup> Aniline (20%).

<sup>m</sup> Aniline (4%).

<sup>n</sup> In the presence of 2.28 mmol of **2**.

°Aniline (10%).

tone enolate ion as entrainment reagent, but in the presence of FeBr<sub>2</sub> it gives 82% of indole  $9b^{32}$  (Scheme 7, Table, Entries 16–19).





In conclusion, all these results indicate that the reaction of 1 (under irradiation or in the presence of  $\text{FeBr}_2$ ) with aromatic and heteroaromatic ketones is a very promising route to the synthesis of 2-aryl or 2-hetarylindoles in DM-SO. The good yields obtained in the presence of  $\text{FeBr}_2$  avoids the need of a special photochemical device to achieve the synthesis here reported.

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker 200 nuclear magnetic resonance spectrometer with CDCl<sub>3</sub> as solvent. Mass spectra were obtained with a GC/MS Perkin Elmer Q-mass 910. GC analyses were performed with a Hewlett Packard 5890 series II, with a flame ionization detector and HP data system, 0.53 mm × 5m column packed with HP1 or 0.53 mm × 10 m column packed with HP50+. Column chromatography was performed on silica gel (70–270 mesh ASTM). Radial TLC was done using silica gel 60 PF-254 with calcium sulfate (E. Merck). The distillation at reduced pressure was performed in a Kugelrohr distillation apparatus. Irradiation was conducted in a reactor equipped with two 400-W lamps emitting maximally at 350 nm (Philips Model HPT, air and water refrigerated). Potentiometric titration of halide ions was performed in a pH-meter using a Ag/Ag<sup>+</sup>electrode.

*t*-BuOK was commercially available and used as received. DMSO was distilled under vacuum and stored over molecular sieves (4Å). Acetone and acetophenone were distilled and stored over molecular sieve (4Å). 2-Acetylnaphthalene was recrystallized from petroleum ether (bp 60–80°C).<sup>33</sup> *o*-Iodoaniline, 2-acetyl-1-methylpyrrole and 2-acetylthiophene were commercially available and distilled under reduced pressure in a Kugelrohr distillation apparatus.

#### Photostimulated Reaction of Acetone Enolate Ions with *o*-Iodoaniline; General Procedure

The reactions were carried out in a 50 mL three-neck round-bottomed flask equipped with a N2 inlet and a magnetic stirrer. To anhyd and degassed DMSO (20 mL) under N2 was added t-BuOK (5.5 mmol, 0.616 g) and acetone (0.316 g, 5.45 mmol). After 15 min, oiodoaniline (0.45 mmol, 0.099 g)<sup>34</sup> was added and the mixture was irradiated for 90 min. The reaction was quenched with an excess of NH<sub>4</sub>NO<sub>3</sub> and H<sub>2</sub>O (60 mL). The mixture was extracted twice with  $CH_2Cl_2$  (20 mL), the organic extract was washed with water (2 × 20 mL), dried, and quantified by GC. The iodide ions in the aqueous solution were determined potentiometrically. The solvent was removed under reduced pressure. The residue, after column chromatography on silicagel or radial TLC (eluted with petroleum ether (bp 60-80°C)/ acetone, 90:10) gave the products. The spectroscopic data and melting point of products are in agreement with that reported in the literature; 3: mp 57-60 °C (Lit.14 mp 58-60°C); 5: mp 188–190 °C (Lit.<sup>27</sup> mp 187°C); **7**: mp 199–201 °C (Lit.<sup>27b,28</sup> mp 203–204 °C); **9a**: mp 89–91 °C (Lit.<sup>31</sup>mp 91–92°C); and **9b**: mp 163-165 °C Lit.32 mp 167-168°C).

# Fe(II) Induced Reaction of Acetone Enolate Ion with *o*-Iodoaniline

The reactions were carried out in a 50 mL three-neck round-bottomed flask equipped with a N<sub>2</sub> inlet and a magnetic stirrer. To anhyd and degassed DMSO (20 mL) under N<sub>2</sub> was added t-BuOK (5.3 mmol, 0.594 g), acetone (0.302 g, 5.2 mmol) and FeBr2 (0.114 g, 0.53 mmol). After a few minutes *o*-iodoaniline (0.48 mmol, 0.105 g) was added. The reaction was quenched after 90 min and worked up as given above.

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