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Reactions of 2- and 3-Acetyl-1-methylpyrrole Enolate Ions with Iodoarenes and Neopentyl Iodides by the $S_{RN}1$ Mechanism

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There are several methods for synthesizing aromatic or heteroaromatic ketones. Friedel−Crafts acylations catalyzed by Lewis acids have the drawback that some substituents are incompatible with the catalyst and the reaction is often accompanied by rearrangement.[1] The regiochemistry depends on the presence of substituents or the nature of the heteroaromatic compounds; often a mixture of isomers is formed. The palladium-catalyzed coupling of organotin compounds with acyl chlorides gives the ketones with variable yields.[2] Few examples of the reactions of *N*-methylpyrrolyltrialkylstannanes with acyl chlorides are known; they afford ketones in yields of 65−72%.[3]

Another approach is the reaction of alkyl and aryl halides with enolate ions of ketones by different procedures including catalysis by Pd[4,5] or the $S_{RN}1$ reaction.[6] Many substituents are compatible with the $S_{RN}1$ mechanism, such as OR, OAr, SAr, CF_3, CO_2R, NH_2, NHCOR, NHBoc, SO_2R, CN, COAr, NR_2, and F. Even though the reaction is not inhibited by the presence of negatively charged carboxylate ions, other charged groups such as oxyanions hinder the process.[6] Substituents such as NO_2 are not suitable, except with arylazo phenyl sulfide as substrates.[7] The mechanism is a chain process, whose main steps are presented in Scheme 1.

Few systems are known to react through a thermal (or spontaneous) $S_{RN}1$ reaction. Most systems need to be initiated by other means. Photostimulation is the most frequently used technique. However, other methods such as initiation by Fe^{2+} salts have also been reported.[8]

Scheme 1

Initiation
$$\mathrm{ArX} + \mathrm{Nu}^- \xrightarrow{h\nu} (\mathrm{ArX})^{-\bullet} \tag{1}$$

Propagation
$$(\mathrm{ArX})^{-\bullet} \longrightarrow \mathrm{Ar}^{\bullet} + \mathrm{X}^- \tag{2}$$

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

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

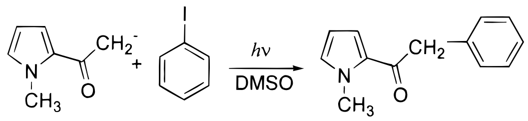
$$\mathrm{ArX} + \mathrm{Nu}^- \longrightarrow \mathrm{ArNu} + \mathrm{X}^- \tag{2,4}$$

Carbanions are among the nucleophiles more widely utilized in $S_{RN}1$ reactions. Haloarenes, haloheteroarenes, and alkyl halides (neopentyl, 1-adamantyl, and norcaranyl iodides) react with enolate ions of aromatic ketones in DMSO under irradiation. Ferrous ion (usually $FeSO_4$ in liquid ammonia or $FeCl_2$ or $FeBr_2$ in DMSO) can provide an alternative and efficient method to initiate reactions of carbanions with iodobenzene and other aryl halides to give α-substituted ketones.[6,8,9] The enolate ions of 2-acetylfuran and 2-acetylthiophene did not react with iodobenzene under irradiation[10] but reacted with highly electrophilic substrates.[11] The difference in reactivity is due to their low efficiency in the photoinitiation step. This situation can be overcome by performing the reaction in the presence of added nucleophiles that are better electron donors or by addition of $FeBr_2$ in the dark.[8] Under these conditions and by competition experiments, 2-acetylfuran enolate ion was determined to be ca. 0.8 times as reactive as acetophenone enolate ion toward iodobenzene whereas 2-acetylthiophene is ca. 0.5 as reactive.[10]

To obtain α-substituted acetylpyrroles, we studied the reactions of enolate ions of 2-acetyl (**1**) and 3-acetyl (**6**) 1-methylpyrroles with some aryl and alkyl iodides under different reaction conditions; this is the first report on the reactivity of these nucleophiles in $S_{RN}1$ reactions.

Results

Enolate Ions of 2-Acetyl (1) and 3-Acetyl (6) 1-Methylpyrroles. The photostimulated reaction of the enolate ion of 2-acetyl-1-methylpyrrole **(1)** with iodobenzene yields 98% of substitution product **2**[12] (eq 5).



1 **2**

(5)

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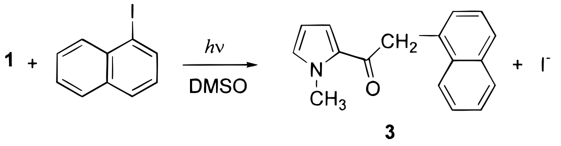
Table 1. Reaction of Aryl and Neopentyl Iodides with the Enolate Ions 1 and 6 in DMSO[a]

expt	nucleophile (M × 10^3)	substrate (M × 10^3)	t-BuOK (M × 10^3)	X^-[b]	substn product (%)[c]
1	**1**, 83.7	PhI, 27	98	100	**2**, 98
2[d,e]	**1**, 62.2	PhI, 27	107	<7	
3[e,f]	**1**, 73.8	PhI, 27	104	<5	
4[g]	**1**, 76.8	PhI, 22.5	41		**2**, 53
5	**1**, 69.1	1-$IC_{10}H_7$, 27.4	41	106	**3**, 78
6[g]	**1**, 90.8	1-$IC_{10}H_7$, 27.4	69		**3**, 17[h]
7[f]	**1**, 79.0	1-$IC_{10}H_7$, 22.9	81	15	**3**, 7
8	**1**, 76.6	$(CH_3)_3CCH_2I$, 42.5	125	100	**4**, 85
9	**1**, 76.6	$PhCH_2(CH_3)_2CCH_2I$, 30.2	125	82	**5**, 45
10	**6**, 84.3	PhI, 27	80	99	**7**, 89
11[d]	**6**, 84.3	PhI, 27	67	26	**7**, 23
12[f]	**6**, 84.3	PhI, 27	90	46	**7**, 34
13[f,d]	**6**, 84.3	PhI, 27	99	23	**7**, 18
14[g]	**6**, 84.3	PhI, 27	92		**7**, 14

[a] Photostimulated reactions (unless indicated) carried out under nitrogen at 40 °C in 20 mL of DMSO with an excess of t-BuOK to avoid condensation products. Irradiation time: 180 min. [b] Determined potentiometrically. [c] Quantified by GLC and the internal standard method. [d] p-Dinitrobenzene (30 mol %) was added. [e] More than 90% of substrate was recovered. [f] Dark reaction. [g] Dark reaction in the presence of $FeBr_2$ (90 mol %). Reaction time 30 min, 25 °C. [h] Naphthalene was quantified (<5%).

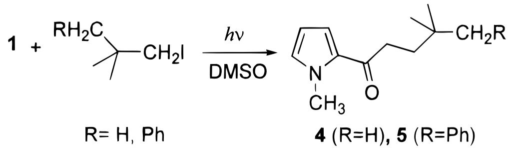
The reaction was inhibited by p-dinitrobenzene (p-DNB), a good radical anion scavenger.[6] No substitution product was formed in the absence of light stimulation. The dark reaction in the presence of $FeBr_2$ gives 53% of product (Table 1, experiments 1−4).

The reaction of **1** with 1-iodonaphthalene yields 78% of substitution product **3** under irradiation (eq 6). The reaction is sluggish in the dark, even in the presence of $FeBr_2$ (Table 1, experiments 5−7).



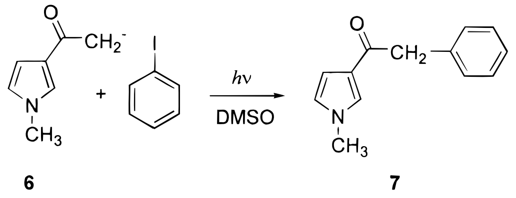
(6)

Neopentyl iodide reacts with acetophenone enolate ion under irradiation in DMSO but is unable to react with acetone enolate ion; instead reduction mainly occurs.[13] On the other hand, the photostimulated reactions of neopentyl iodide and a related substrate, 2,2-dimethyl-1-iodo-3-phenylpropane, with the anion **1** afford 85% and 45% of substitution products **4** and **5**, respectively (eq 7) (Table 1, experiments 8−9).



(7)

The enolate ion of 3-acetylmethylpyrrole **6** reacted with iodobenzene under irradiation to afford 89% of product **7**[14] (eq 8). Lower yields were found in the presence of p-DNB or in dark conditions, with or without $FeBr_2$ (Table 1, experiments 10−14).



(8)

Competition Experiments. The relative reactivities of **1**, **6**, and the enolate ion of acetophenone (**8**) toward iodobenzene under photoinitiation were determined in competition experiments.[15] It was found that **1** is 2.6 times more reactive than **8**. On the other hand, **6** and **8** have similar reactivity (Table 2).

The present experimental evidence leads us to conclude that enolate ions **1** and **6** react with aryl and neopentyl iodides to afford good yields of substitution products by the $S_{RN}1$ mechanism. The higher reactivity of these anions under photoinitiation shows that they are able to participate in initiation in contrast to the enolate ions of the five-membered-ring analogues 2-acetylthiophene (**9)** or 2-acetylfuran (**10)**. Although all these carbanions react with iodobenzene in the presence of $FeBr_2$, only carbanions **1** and **6** react under irradiation, and even spontaneous initiation occurs with carbanion **6**.

Since the $S_{RN}1$ mechanism is a chain process, overall reactivity depends on the step under consideration. Thus while carbanion **6** seems to be a better initiator than **1**, it has a lower reactivity in the coupling reaction toward phenyl radicals, as determined by the competition experiments (Table 3).

These reactions open an alternative route to α-substituted acetylpyrroles, even by reaction with neopentyl iodides, which are largely unreactive under polar substitution reactions. They also demonstrate that carbanions **1** and **6** are efficient nucleophiles in the different steps of the reaction, giving good yields of substitution without the need of added initiators (entrainment conditions).

Experimental Section

General Methods.[10] Column chromatography was performed on silica gel (70−270 mesh ASTM). Radial TLC was performed using silica gel 60 PF-254 with calcium. Distillation at reduced pressure was performed in a Kügelrohr 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^+ electrode.

Materials. PhI, $FeBr_2$, 1-iodonaphthalene, neopentyl iodide, and t-BuOK were commercially available and used as received. DMSO was distilled under vacuum and stored under molecular sieves (4 Å). 2,2-Dimethyl-1-iodo-3-phenylpropane was synthesized as reported.[16] Acetophenone was distilled and stored with molecular sieves (4 Å). 2- and 3-acetyl-1-methylpyrroles were distilled.

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(15) The equation used in the relative reactivity determination of pairs of nucleophiles vs a radical is shown below,

$$\frac{k_1}{k_2} = \frac{\ln([\mathrm{Nu}_1]_0/[\mathrm{Nu}_1]_t)}{\ln([\mathrm{Nu}_2]_0/[\mathrm{Nu}_2]_t)}$$

where $[Nu_1]_0$ and $[Nu_2]_0$ are initial concentrations and $[Nu_1]_t$ and $[Nu_2]_t$ are concentration at time t of both nucleophiles. This equation is based on a first-order reaction of both anions with the phenyl radicals, see: Bunnett, J. F. In *Investigation of Rates and Mechanisms of Reactions*, 3rd ed.; Lewis, E. S., Ed.; Wiley-Interscience: New York, 1974; Part 1, p 159.

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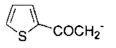
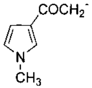
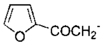
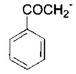
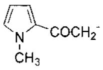
Table 2. Competition Experiments between Carbanions 1, 6, and 8 toward Iodobenzene

Nu_1 ($M \times 10^3$)	Nu_2 ($M \times 10^3$)	substitution product ($M \times 10^3$)		k_{Nu1}/k_{Nu2}
1 (0.610)	**6** (0.783)	**2** (0.132)	**7** (0.084)	k_1/k_6 2.1 ± 0.2
1 (0.578)	**6** (1.29)	**2** (0.120)	**7** (0.097)	k_1/k_6 2.9 ± 0.2
			average:	k_1/k_6 2.5 ± 0.4
1 (0.607)	**8** (0.783)	**2** (0.155)	Ph-**8**[a] (0.085)	k_1/k_8 2.6 ± 0.4[b]
6 (0.560)	**8** (1.20)	**7** (0.027)	Ph-**8**[a] (0.073)	k_6/k_8 0.79 ± 0.06
6 (0.576)	**8** (0.721)	**7** (0.034)	Ph-**8**[a] (0.063)	k_6/k_8 0.67 ± 0.06
			average:	k_6/k_8 0.73 ± 0.08

[a] α-Phenylacetophenone. [b] Duplicate run.

Table 3. Reactivities of Aromatic Ketone Enolates toward Iodobenzene in DMSO

	 **9**	 **6**	 **10**	 **8**	 **1**
Initiation by light	No	Yes	No	Yes	Yes
Relative Reactivities	0.49	0.73	0.83	1.00	2.60

Photostimulated Reaction. The procedure was as previously reported.[10] The reaction mixture was extracted with methylene chloride and water. The methylene chloride was removed under reduced pressure. The substitution products were isolated by column chromatography on silica gel and eluted with petroleum ether/diethyl ether (90:10). The reaction of iodobenzene with carbanions **1** and **6** afforded ethanone, 1-(1-methyl-1*H*-pyrrole-2-yl)-2-phenyl (**2**)[12] and ethanone, 1-(1-methyl-1*H*-pyrrole-3-yl)-2-phenyl (**7**),[14] respectively.

Ethanone, 1-(1-Methyl-1*H*-pyrrole-2-yl)-2-(1-naphthyl) (3). Purified by radial TLC (eluted with petroleum ether/diethyl ether 95:5). MS *m/e*: 249 (9.34), 141 (7.88), 108 (100). ^{1}H NMR δ 8.05−7.94 (m, 1H), 7.89−7.70 (m, 2H), 7.53−7.35 (dd, 4H), 7.22−7.17 (dd, 1H), 6.86−6.78 (dd, 1H), 6.21−6.13 (dd, 1H), 4.54 (s, 2H), 3.89 (s, 3H). ^{13}C NMR δ 188.5 (c), 133.9 (c), 132.5 (c), 132.1 (c) 131.4, 130.4, 128.7, 128.1, 127.6, 126.2, 125.6, 125.4, 124.2, 119.4, 108.1, 43.3, 37.6. HRMS (MH$^+$) calcd 249.115364, found 249.115811.

Pentanone, 1-(1-Methyl-1*H*-pyrrole-2-yl)-4,4-dimethyl (4). Purified by radial TLC (eluted with petroleum ether/diethyl ether 95:5). MS *m/e*: 193 (9.3), 136 (11.2), 108 (100). ^{1}H NMR δ 6.91−6.99 (dd, 1H), 6.76−6.82 (dd, 1H), 6.08−6.16 (dd, 1H), 3.93 (s, 3H), 2.80−2.66 (m, 2H), 1.52−1.69 (m, 2H), 0.94 (s, 9H). ^{13}C NMR δ 192.4, 130.7, 118.8, 107.7, 105.0, 39.4, 37.7, 34.5, 30.3, 29.2. HRMS (MH$^+$) calcd 194.154489, found 194.153649.

Pentanone, 1-(1-Methyl-1*H*-pyrrole-2-yl)-4,4-dimethyl-5-phenyl (5). Isolated by radial TLC (eluted with petroleum ether/diethyl ether 90:10). The liquid isolated was distilled in the Kügelrohr. MS *m/e*: 269 (7.5), 178 (84.6), 136 (36.1), 108 (100). ^{1}H NMR δ 7.34−7.09 (m, 5H), 7.00−6.91 (dd, 1H), 6.83−6.75 (m, 1H), 6.16−6.08 (dd, 1H), 3.93 (s, 3H), 2.84−2.73 (m, 2H), 2.55 (s, 2H), 1.74−1.60 (m, 2H), 0.90 (s, 6H). ^{13}C NMR δ 192.0, 138.9, 130.8, 130.6, 127.6, 125.8, 118.8, 107.8, 43.4, 37.7, 37.4, 34.3, 34.1, 26.7. HRMS (MH$^+$) calcd 270.185790, found 270.185647.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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