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Reactions of N-Thioacetylmorpholine Anion with Iodoarenes and 1-Iodoadamantane by the $S_{RN}1$ Mechanism

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Abstract: The anion of N-acetylthiomorpholine **2** was studied in photostimulated reactions with iodobenzene **1a** and 1-iodonaphthalene **1b** in DMSO, giving good yields of the substitution products **3a** and **3b** by the $S_{RN}1$ mechanism. The reaction of **1a** with **2** is also induced with $FeBr_2$. 1-Iodoadamantane **4** did not react with the anion of N-acetylmorpholine, but reacted with **2** to give the substitution product **5** under irradiation. By competition experiments, acetophenone enolate ions are 1.4 times more reactive than **2** toward **1a** and 3.3 times toward **4**. © 1997 Elsevier Science Ltd. All rights reserved.

The radical nucleophilic substitution, or $S_{RN}1$ reaction, is a process through which a nucleophilic substitution is obtained. The scope of the process has considerably increased and nowadays it constitutes an important synthetic possibility to achieve substitution with different substrates.[1] Several nucleophiles can be used, such as carbanions and anions from compounds bearing heteroatoms, which react to form a new C-C or C-heteroatom bond in good yields. The mechanism is a chain process, whose main steps are presented in Scheme I.

Scheme I

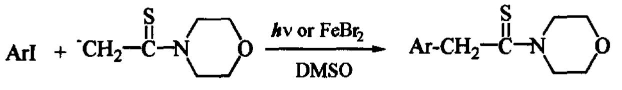
$$\begin{array}{lcll}
(ArX)^{\cdot -} & \longrightarrow & Ar^{\cdot} + X^{-} & (1) \\
Ar^{\cdot} + Nu^{-} & \longrightarrow & (ArNu)^{\cdot -} & (2) \\
(ArNu)^{\cdot -} + ArX & \longrightarrow & (ArX)^{\cdot -} + ArNu & (3) \\
\hline
ArX + Nu^{-} & \longrightarrow & ArNu + X^{-} & (1\text{-}3)
\end{array}$$

Few systems are known to react by the $S_{RN}1$ mechanism by a thermal (or spontaneous) reaction. Most of the systems need to be initiated by different means. Photostimulation or reaction stimulated by alkali metals in liquid ammonia,[1] or electrons from a cathode[2] are the most frequently used techniques. However, other methods to initiate the reactions, such as Fe^{+2} have been reported.[3]

Carbanions are the more widely studied nucleophiles within the $S_{RN}1$ mechanism. It has been shown by competition experiments that the reactivity of carbanions on the propagation steps of the $S_{RN}1$ cycle depends on the pKa of the conjugated acid and on the energy difference (ΔE_π) of the HOMO of the carbanion and the SOMO of the radical anion formed in the coupling of the aromatic radical and the carbanion. Thus, the relative reactivity found is acetone enolate anion: 1.00, acetophenone enolate anion: 7.5 and anthrone anion: 16.5 toward iodobenzene in DMSO.[4]

It was our interest to know if changing the carbonyl group to a thiocarbonyl functionality in the carbanions would increase their reactivity of radicals in the $S_{RN}1$ mechanism. The N,N-dialkylacetamide anions react with halobenzenes giving good yields of substitution products,[3c,5] so we chose N-acetylthiomorpholine anion **2** as a model nucleophile with the C=S functionality.[6] Apart from their wide use as intermediates in organic synthesis,[7] thioamides have also attracted attention in the field of peptide chemistry,[8] as well as in their synthesis.[9] The reaction of this type of nucleophile with aryl or alkyl halides would give an alternative route to α-substituted thioacetamide derivatives.

The photostimulated reaction (1.5 h) of iodobenzene (**1a**) with **2** (prepared by the acid base reaction of N-acetylthiomorpholine with *t*-BuOK in DMSO) gave 60% yield of the substitution product **3a**[10] (eq. 4). This reaction does not occur in the dark. However, when the reaction was carried out in the presence of $FeBr_2$, a high yield (87%) of **3a** was found. These results then suggest that **1a** reacts with **2** by the $S_{RN}1$ mechanism (Table I).



(4)

1a: Ar = Ph
1b: Ar = 1-naphthyl

2

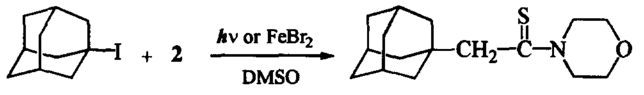
3a: Ar = Ph
3b: Ar = 1-naphthyl

There is no photostimulated (1.5 h) reaction of bromobenzene with **2**. 1-Iodonaphthalene does not react in the dark in 15 min, but under irradiation (15 min) it gives 67% of the substitution product **3b**.[11] The yield of **3b** in the photostimulated reaction (1 h) was 70% (Table I).

Acetophenone enolate ion is more reactive than acetone enolate ion toward **1a**, and probably N,N-dialkylacetamide ions are even less reactive than acetone enolate ions. By competition experiments[4,12] with **1a**, the relative reactivity of acetophenone enolate ions is similar to **2** (it is only 1.4 times more reactive, Table II).

The same trend of the reactivity of carbanions is observed in the competition experiments with 1-iodoadamantane **4** in DMSO, and the relative reactivity found is acetone enolate anion: 1.00, acetophenone enolate anion: 11, anion of nitromethane: 32, and anthrone anion: 80.[13] The photostimulated reaction of **4** with acetone enolate anions is sluggish (20% of substitution product). High yields of substitution products are obtained with more stabilized carbanions, such as acetophenone enolate anion, induced by light[13] or $FeBr_2$.[3d]

There is no substitution product in the photostimulated reaction of the anion of N-acetylmorpholine with **4** in 1 h. However, the photostimulated reaction of **4** with **2** gives 60% of the substitution product **5**.[14] The reaction induced with $FeBr_2$ gives 65% yield of **5** (Table I) (eq. 5).



(5)

4 **5**

By competition experiments we found that the relative reactivity of acetophenone enolate ion is only 3.3 more reactive than **2** toward 1-adamantyl radicals (Table II).

The fact that **4** does not react with the oxo homolog, but reacts with **2**, and that **2** has a similar reactivity to acetophenone enolate ion, leads to the conclusion that **2** is a powerful nucleophile in $S_{RN}1$ reactions with iodoarenes and **4**. Reactions of this type of nucleophile with aryl or alkyl halides would give an alternative route to α-substituted thioacetamide derivatives. Further work is in progress to examine the reaction conditions and to extend the scope of the reaction by using different nucleophiles with the C=S functionality.

Table I: Reactions of **1a**, **1b** and **4** with **2** in DMSO.[a]

Expt.	**Substrate (mmol)**	**2 , mmol**	**Conditions**	**I^-, %**	**Substitution Product, (Yield %)[b]**
1	**1a** (0.53)	2.98	dark, 1.5 h	< 10	--
2	**1a** (0.53)	2.98	*hv*, 1.5 h	100	**3a** (60)
3	**1a** (0.53)	2.90	$FeBr_2$, 50°C[c]	nq	**3a** (87)
4	**1a** (0.50)[d]	2.91	*hv*, 1.5 h	< 10	---
5	**1b** (0.40)	3.00	dark, 15 min	< 10	---
6	**1b** (0.51)	2.92	*hv*, 15 min	100	**3b** (67)[e]
7	**1b** (0.51)	3.00	*hv*, 1 h	100	**3b** (70)[f]
8	**4** (0.52)	3.00[g]	*hv*, 1 h	< 10	----
9	**4** (0.44)	2.40	dark, 1 h	< 10	---
10[h]	**4** (0.55)	2.81	*hv*, 1 h	95	**5** (60)[i]
11	**4** (0.52)	2.94	$FeBr_2$, 50°C[c]	nq	**5** (65)[j]

[a]The irradiation was carried out with two 400 W high pressure Hg lamps, in 12 mL of DMSO under nitrogen atmosphere. [b]Determined by glc with the internal standard method. [c]$FeBr_2$ (0.53 mmol) was added. [d]The substrate was PhBr. [e]Isolated yield. [f]Naphthalene (14%). [g] The nucleophile was the anion of N-acetylmorpholine. [h] Duplicate experiments. [i]Adamantane (24 %) .[j]Adamantane (19 %).

Table II: Competition Experiments of **1a** and **4** toward Acetophenone Enolate Ion and **2**.[a]

Expts	**R-I (mmol)**	**Nu_1^- (mmol)[b]**	**Nu_2^- (mmol)[c]**	**R-Nu_1 (%)**	**R-Nu_2 (%)**	**Relative Reactivity**
1	**1a** (0.53)	1.71	1.50	42[d]	32[e]	1.3
2	**1a** (0.53)	1.71	1.56	43[d]	32[e]	1.3
3	**1a** (0.53)	1.71	1.64	47[d]	31[e]	1.5
					Average	1.4 ± 0.1
4	**4** (0.55)	1.71	1.57	42[f]	13[g]	3.2
5	**4** (0.56)	1.71	1.57	43[f]	13[g]	3.3
					Average	3.3 ± 0.1

[a]Photostimulated reaction (1 h) in 12 mL of DMSO. [b]Acetophenone enolate ions. [c] Nucleophile **2**. [d]α-Phenylacetophenone. [e]Product **3a**. [f]α-(1-Adamantyl)acetophenone. [g]Product **5**.

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11. (a) **3b**: mp 140-141°C (lit.[11b] 141°C); IR (cm^{-1}) 800.0, 1038.6, 1122.8, 1270.1, 1452.0, 1487.7; ^{1}H-NMR (200 MHz, ($CDCl_3$) δ 3.30-4.00 (m, 6H), 4.46 (m, 2H), 4.78 (s, 2H), 7.21-8.03 (m, 7 H); ^{13}C-NMR ($CDCl_3$) δ 47.22, 49.92, 50.74, 66.14, 66.39, 122.38, 124.47, 125.57, 125.97, 126.50, 127.75, 129.00, 131.01, 131.52, 133.78, 200.53; MS, m/e (rel. intensity) 271 (61, M$^+$), 238 (10), 184 (25), 152 (21), 141 (36), 130 (100), 115 (22), 112 (50), 86 (58). (b) Siemons, M.M. J-L, Vignau, M. *Bull. Soc. Chim. Fr.* **1951**, 90.

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14. **5**: mp 148-149°C; IR (cm^{-1}) 1025.2, 1117.4, 1275.3, 1426.7, 1485.9, 2848.3, 2907.5; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.59-1.80 (m, 12H), 1.85-2.12 (m, 3H), 2..85 (s, 2H), 3.66-3.90 (m, 6H), 4.32-4.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.77, 34.89, 36.64, 43.15, 50.12, 51.56, 55.85, 66.31, 66.56, 200.54; MS, m/e (rel. intensity) 279 (53, M$^+$), 246 (19), 144 (100), 135 (59), 110 (33), 86 (57). Anal. calcl. for $C_{16}H_{25}NOS$, C 69.00, H 8.94, N 5.00, S 11.43. Found: C 68.77, H 9.02, N 5.01, S 11.47.

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