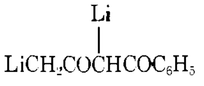
The SRN1 Mechanism in Heteroaromatic Nucleophilic Substitution. Photostimulation and Entrainment of the Reaction of Lithioacetone with 2-Chloroquinoline

James V. Hay, Tomas Hudlicky, and James F. Wolfe*

Contribution from the Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061. *Received May 2, 1974*

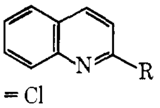
Abstract: Displacement of chloride from 2-chloroquinoline by lithioacetone occurs relatively slowly in liquid ammonia at −33°, even in the presence of excess lithium amide. However, rapid substitution takes place under near-ultraviolet irradiation or in the presence of 10 mol % of dilithiobenzoylacetone. Irradiation presumably enhances the electron-donating capacity of acetone lithium enolate, making it an efficient initiator of a radical-chain (SRN1) mechanism involving combination of 2-quinolyl radicals with lithioacetone. Catalysis by the dilithio salt of benzoylacetone is attributed to its ability to act as an entraining agent, which initiates the SRN1 process.

Although radical-chain mechanisms for nucleophilic substitution at aliphatic[1] and carboaromatic[2] centers have been demonstrated on a number of occasions, only two reports implicating similar mechanisms in heteroaromatic nucleophilic substitution have appeared to date. Most recently, Zoltewicz and Oestreich[3] found that reaction of thiophenoxide with 4-bromoisoquinoline in methanol was changed from an addition-elimination (SNAr2)[4] to a radical-anion (SRN1)[2a] mechanism upon addition of sodium methoxide. Earlier,[5] we presented evidence that the reaction of dilithiobenzoylacetone (1) with 2-choloroquinoline (2) in liquid ammonia gave diketone 3 *via* the sequence of reactions illustrated in Scheme I, where dianion 1 initiates a chain process by transferring an electron to 2.



$\mathrm{LiCH_2CO\overset{\overset{\displaystyle Li}{|}}{C}HCOC_6H_5}$

1



2, R = Cl

3, R = $CH_2COCH_2COC_6H_5$

Scheme I

$$(1)\quad \text{2-ClQ} + \text{BAc}^{2-} \longrightarrow \text{2-ClQ}^{\cdot -} + \text{BAc}^{\cdot -}$$

$$(2)\quad \text{2-ClQ}^{\cdot -} \longrightarrow \text{Q}\cdot + \text{Cl}^{-}$$

$$(3)\quad \text{Q}\cdot + \text{BAc}^{2-} \longrightarrow \text{QBAc}^{\cdot 2-}$$

$$(4)\quad \text{QBAc}^{\cdot 2-} + \text{2-ClQ} \longrightarrow \text{QBAc}^{-} + \text{2-ClQ}^{\cdot -}$$

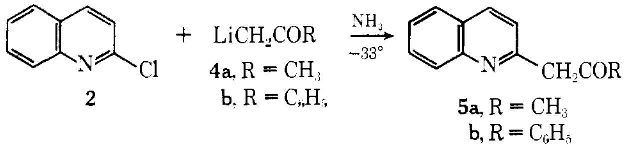
[a] 2-ClQ = 2-chloroquinoline; BAc^{2-} = dilithiobenzoylacetone.

The susceptibility of 2 to radical-chain substitution with dianion 1 in liquid ammonia prompted us to utilize this substrate and solvent system to test the mechanistic features of displacement reactions involving various nucleophiles including monoenolate ions. Surprisingly, reactions of 2 with simple ketone enolates have not been reported, although displacement reactions involving 2 and alkali salts of certain active methylene compounds[6] and phosphoranes[7] have been investigated as have reactions of monoketone enolates with several other halogenated heterocycles.[8] In none of these cases was there presented evidence for a radical-chain mechanism. With the exception of one instance where 3,4-didehydropyridine was implicated as an intermediate,[8a] all reactions were tacitly assumed to proceed by an SNAr2 mechanism.[8b-f] Moreover, many reactions of ketone enolates and other carbanions with halogenated heteroaromatics have been characterized by low yields and poor material balances.[6,8]

We now report on the mechanistic characteristics associated with reactions of two monoketone enolates with **2** in liquid ammonia. We have found that the reaction of lithioacetone (**4a**) with **2** in liquid ammonia is subject to photostimulation[9] and entrainment.[1d] Occurrence of these phenomena, which are consistent with a radical-chain substitution mechanism, has apparently gone unrecognized in heteroaromatic nucleophilic substitution.

Results and Discussion

Exposure of **2** to enolate **4a,** prepared from 3 mol equiv of acetone and 4 mol equiv of lithium amide in liquid ammonia, gave 2-acetonylquinoline (**5a**)[10] in 16.6% yield after 1 hr in the absence of light at −33° (Table I). In addition, quinoline and 2-aminoquinoline were produced in yields of 2 and 5%, respectively, while unaltered **2** was recovered in 68.2% yield. The formation of quinoline from **2**, under these conditions, implied involvement, to some extent, of a reaction mechanism, other than the addition-elimination (SNAr2) mechanism normally representative of nucleophilic substitution reactions of quinoline derivatives possessing a nucleofugic substituent at the 2 position. Repetition of this reaction in the presence of 10 mol % of *p*-dinitrobenzene (DNB) afforded **5a** in only 1.4% yield (92.7% recovery of **2**). The marked reduction in yield of ketone **5a** by catalytic amounts of DNB indicates that the radical-chain mechanism shown in Scheme *II* is operating in the reaction of **4a** with **2.**[11]



Scheme II

$$(1)\quad \text{2-ClQ} + {}^{-}\text{CH}_2\text{COR} \longrightarrow \text{2-ClQ}^{\cdot -} + \cdot\text{CH}_2\text{COR}$$

$$(2)\quad \text{2-ClQ}^{\cdot -} \longrightarrow \text{Q}\cdot + \text{Cl}^{-}$$

$$(3)\quad \text{Q}\cdot + {}^{-}\text{CH}_2\text{COR} \longrightarrow \text{QCH}_2\text{COR}^{\cdot -}$$

$$(4)\quad \text{QCH}_2\text{COR}^{\cdot -} + \text{2-ClQ} \longrightarrow \text{QCH}_2\text{COR} + \text{2-ClQ}^{\cdot -}$$

Although the reaction of **4a** with **2** appears to be largely a radical-chain process, it is relatively sluggish, as evidenced by the observation that reaction times up to 5 hr did not appreciably increase the yields of **5a.** Even though it has been observed[9] that reluctant reactions of halogenated benzenes with potassioacetone can be accelerated by near-ultraviolet radiation, illumination of a reaction mixture containing **4a** and **2** with a 250-W tungsten lamp failed to significantly alter the rate of production of **5a** from that ob-

Table I. Reactions of Lithio Salts **4a** and **4b** with 2-Chloroquinoline (**2**) in Liquid Ammonia[a]

2, mmol	—RCOCH$_2$Li— Compd	mmol	LiNH$_2$, mmol[b]	——Product—— Compd	Yield, %	2-Chloroquinoline, %
16	**4a**	48	64	**5a**	16.6	68.2
16	**4a**	48	64	**5a**	1.4[c]	92.7
16	**4a**	48	64	**5a**	15.9[d]	60.3
19.75	**4a**	80	121	**5a**	47.5[d]	18.1
9.88	**4a**	41.3	115	**5a**	62.2[d]	*f*
16	**4a**	48	192	**5a**	11.2	58.4
9.88	**4a**	41.3	121	**5a**	14.1	*f*
9.88	**4a**	41.3	115	**5a**	<1[c,d]	*f*
19.75	**4a**	80	244	**5a**	59.4[e]	27.8
16	**4a**	48	64	**5a**	6.8[e]	88.2
16	**4a**	64	192	**5a**	1.5[c,e]	40.8
16	**4b**	48	64	**5b**	18.0	78.2
16	**4b**	48	64	**5b**	<1[c]	*f*
16	**4b**	48	64	**5b**	82.3[d]	*f*

[a] Reactions were carried out in 500 ml of refluxing liquid ammonia under nitrogen for 1 hr in a flask wrapped in aluminum foil, unless otherwise noted. All yields are of isolated material. [b] Total, including that required to generate the enolate. [c] DNB (10 mol %, based on **2**) added. [d] Reaction mixture irradiated with near-uv light for 1 hr. [e] Benzoylacetone (10 mol %) added. [f] Not determined.

served in the dark reaction; ketone **5a** was formed in 15.9% yield, and 60.3% of unreacted **2** was recovered.

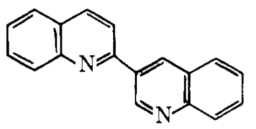
Interestingly, when the amounts of acetone and lithium amide were increased to 4 and 6 equiv, respectively, photostimulation became more effective, and **5a** was obtained in 47.5% yield. An increase in lithium amide to 12 mol equiv, with 4 mol equiv of acetone, effected an increase in formation of **5a** to 62.2% upon irradiation for 1 hr. The enhanced rates of substitution in these reactions were shown not to be a function of excess amide alone since reaction of **2** with acetone and excess lithium amide in the dark gave **5a** in only 11.2% yield.[12] Such results also rule out operation of a hetaryne mechanism in these reactions since an elimination–addition would be expected to proceed equally as well in the dark as when illuminated, to be unaffected by radical anion scavengers such as DNB,[2a] and also possibly to give rise to isomeric products, which were never observed. That breaking of the C–Cl bond in **2** resulted from initial electron transfer rather than from photolytic cleavage was supported by the finding that **2** was recovered in essentially quantitative yield following exposure to the light source for 1 hr in liquid ammonia.

Although the exact role of excess lithium amide in the photostimulated reaction has yet to be determined,[13] there would seem to be little doubt that such reactions are radical-chain processes since they are dramatically inhibited by catalytic amounts of DNB. Thus, irradiation of a reaction mixture composed of **2**, 4 mol equiv of acetone, 12 mol equiv of lithium amide, and 10 mol % of DNB afforded **5a** in less than 1% yield.

Since reaction of **4a** with **2** was strongly influenced by photostimulation, it seemed possible that substitution might also be enhanced by the presence of a electron donor more efficient than enolate **4a**. Because of the facility with which dianion **1** acts as an electron donor toward **2**,[5] it appeared that small amounts of **1** in the presence of excess enolate **4a** might serve to initiate the radical-chain process more effectively than **4a**, thereby serving to catalyze the substitution process shown in Scheme II. This was indeed observed; however, excess lithium amide was again found to be a prerequisite for formation of **5a** in yields exceeding those obtained in uncatalyzed reactions. For example, the dark reaction of **2** with 3 equiv of acetone, 4 equiv of lithium amide, and 0.1 equiv of dienolate **1** afforded ketone **5a** in 6.8% yield and a 88.2% recovery of **2**. When the acetone and lithium amide were increased to 4 and 12 equiv, respectively (0.1 equiv of **1**), **5a** was formed in 59.4% yield, while only 27.8% of unreacted **2** was recovered. The latter reaction undoubtedly follows the mechanism outlined in Scheme II, as it was strongly inhibited by DNB; ketone **5a** was formed in only 1.5% yield when 10 mol % of DNB was present in the reaction mixture.

Catalysis by dianion **1** is analogous to the entrainment reactions observed by Kornblum involving interaction of certain carbanions with *p*-nitrocumyl chloride and *α,p*-dinitrocumene.[1d] Dilithio salt **1**, with its superiority y to acetone enolate as an electron donor, apparently serves to initiate the chain process of Scheme II. Monoenolate **4a** can then combine with the chain-carrying 2-quinolyl radical to yield the radical anion intermediate shown in step 3. This radical anion then presumably transfers an electron to 2-chloroquinoline, thereby perpetuating the chain process. Thus, dianion **1** serves to entrain enolate **4a**.

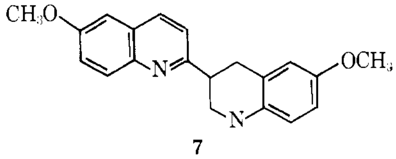
The use of alkali metals as a source of solvated electrons has been shown to promote the reaction of alkali enolates with halogenated benzenes.[2b] In the present study, attempted promotion of the SRN1 reaction of lithioacetone with 2-chloroquinoline by lithium metal resulted in severe competing reactions. For example, addition of 1 equiv of lithium metal to a reaction mixture of **2**, 3 equiv of acetone, and 4 equiv of lithium amide in liquid ammonia produced a complex mixture of products consisting of 17.9% recovered **2**, 18.0% quinoline, 15.2% **5a**, 17.5% 2,3′-biquinoline (**6**),[14] and 7.9% 2-aminoquinoline. The structure of **6** was substantiated by its pmr spectrum. The highly deshielded 2′ and 4′ protons each appeared as a one proton doublet (J = 2.0 Hz) at 9.80 and 8.88 ppm, respectively.[15]



6

Unlike the photostimulated and dianion entrained reactions of **4a** with **2**, the lithium-promoted reactions appeared to be insensitive to the concentration of lithium amide. Thus, addition of 0.5 equiv of lithium metal to a reaction mixture containing 4 equiv of acetone and 12 equiv of lithium amide per equiv of **2** afforded 21.8% **2**, 14% quinoline, 14.2% **5a**, 13.7% **6**, and 8.3% 2-aminoquinoline.

The formation of **6** in the presence of lithium metal is somewhat surprising, as 2,2′-biquinoline is the dimer which would be expected to arise by the coupling of 2-quinolyl radicals. There is, however, precedent for formation of dimers related to **6** under reaction conditions approximating those used in this study. For example, lithium–ammonia reduction of 6-methoxyquinoline gave, among other reduced products, the tetrahydro-2,3′-biquinoline **7**.[16]



7

Evidence now in hand demonstrates that reactions of lithioacetophenone (**4b**) with 2-chloroquinoline in liquid ammonia also proceed by a radical-chain process. Exposure of **2** to **4b**, prepared from 3 equiv of acetophenone and 4 equiv of lithium amide, afforded **5b**[10] in 18.0% yield after 1 hr at −33° in the dark. Repetition of this reaction in the presence of 10 mol % of DNB lowered the yield of **5b** to less than 1%.

In contrast to the photostimulated reactions of **4a**, irradiation of reaction mixtures of **4b** and **2** resulted in marked acceleration of the desired substitution without excess lithium amide. Thus, irradiation of a liquid ammonia solution of **2** and **4b**, prepared from 3 equiv of acetophenone and 4 equiv of lithium amide, increased the yield of **5b** from 18 to 82.3% after a reaction time of 1 hr.

The present study reveals some heretofore unknown characteristics of heteroaromatic nucleophilic substitution. Recognition of radical-chain character in such reactions raises numerous synthetic possibilities which we currently have under investigation.

Experimental Section

General. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Proton magnetic resonance (pmr) spectra were recorded on a JEOL JMN-PS-100 instrument employing tetramethylsilane as internal standard. Thin-layer chromatography (tlc) analyses were performed on Eastman Chromagram (Type 6060) silica gel sheets with fluorescent indicator, employing ether–hexane (6:4) as the developing solvent; components were detected with ultraviolet light. Analytical gas chromatography (glpc) was carried out on a Varian Aerograph Model 90-P chromatograph using a 5 ft × 0.25 in. 6.3% Carbowax 20M on Gas Chrom Z column at 235°. 2-Chloroquinoline and hexane were distilled prior to use; all other chemicals were commercial reagent grade and were used without further purification.

Reaction of Lithioacetone (4a) with 2-Chloroquinoline (2) in the Dark. To a suspension of lithium amide (64 mmol), prepared from 0.44 g (64 mg-atoms) of lithium wire in 500 ml of anhydrous liquid ammonia under a nitrogen atmosphere, was added a solution of acetone (2.78 g, 48 mmol) in 25 ml of anhydrous ether. The reaction flask was enclosed in aluminum foil, and the light gray reaction mixture of enolate **4a** was stirred for 15 min prior to the addition of a solution of 2.62 g (16 mmol) of **2** in 75 ml of ether. The reaction mixture was stirred for 1 hr before being quenched with excess solid ammonium chloride (100 mmol). The ammonia was evaporated (hot-air gun) while being replaced with 500 ml of ether. Water (200 ml) was added, and the ethereal phase was separated. The aqueous phase was extracted with two 100-ml portions of ether; the combined organic solution was dried ($MgSO_4$) and concentrated. Glpc analysis of the residue indicated quinoline, 2-acetonylquinoline (**5a**), and 2-aminoquinoline as reaction products in approximate yields of 2, 15, and 5%, respectively. Chromatography of the brown oil on silica gel, eluting with hexane, afforded 1.79 g (68.2% recovery) of **2**. Elution with hexane–ether (9:1) gave 0.49 g (16.6%) of 2-acetonylquinoline (**5a**) as a yellow-orange solid, mp 71–74° (lit.[10] mp 76–77°). Spectral characteristics of this material were identical with those of an authentic sample of **5a**.

A similar reaction employing 16 mmol of **2**, 48 mmol of acetone, and 192 mmol of lithium amide afforded 0.33 g (11.2%) of **5a**, while a reaction using 9.88 mmol of **2**, 41.3 mmol of acetone, and 121 mmol of lithium amide gave 0.26 g (14.1%) of **5a**.

Reaction of 4a with 2 in the Presence of *p*-Dinitrobenzene (DNB). To **4a** (48 mmol), prepared as in the preceding experiment, in 500 ml of liquid ammonia was added 0.27 g (1.6 mmol) of DNB followed by 2.62 g (16 mmol) of **2** in 75 ml of ether. The reaction mixture was stirred for 1 hr in the dark before being quenched with excess solid ammonium chloride. The reaction mixture was processed in the usual manner, and the crude product was chromatographed on silica gel to give 2.41 g (92.7% recovery) of **2** and 0.041 g (1.4%) of **5a**.

Photostimulation of the Reaction of 4a with 2. Acetone (2.39 g, 41.3 mmol) in 25 ml of ether was added to a suspension of lithium amide (115 mmol) in 500 ml of liquid ammonia under a nitrogen atmosphere in a flask equipped with a Dry Ice–acetone condenser, and the resulting mixture was stirred for 15 min. Irradiation of this reaction mixture by a 250-W tungsten lamp was begun, and **2** (1.62 g, 9.88 mmol) in 50 ml of ether was added. After being stirred for 1 hr, the reaction mixture was quenched with excess solid ammonium chloride and was processed in the normal manner. Chromatography of the reaction product on silica gel afforded 1.14 g (62.2%) of **5a**.

A similar photostimulated reaction employing 19.75 mmol of **2**, 80 mmol of acetone, and 121 mmol of lithium amide gave 1.74 g (47.5%) of **5a** and 0.58 g (18.1% recovery) of **2**, while photostimulation of a reaction using 16 mmol of **2**, 48 mmol of acetone, and 64 mmol of lithium amide afforded a 60.3% recovery (1.58 g) of **2** and only 15.9% (0.47 g) of **5a**.

Attempted Photostimulation of the Reaction of 4a with 2 in the Presence of DNB. To a reaction mixture of enolate **4a** (41.3 mmol), prepared from 41.3 mmol of acetone and 115 mmol of lithium amide, in 500 ml of liquid ammonia, 0.166 g (0.988 mmol) of DNB was added. Irradiation was begun, and **2** (9.88 mmol) in 50 ml of ether was added. After 1 hr, the reaction mixture was quenched with excess solid ammonium chloride and then processed in the normal manner. Chromatography of the reaction product on silica gel afforded less than 1% of **5a**.

DNB inhibition of a photostimulated reaction employing 16 mmol of **2**, 48 mmol of acetone, and 64 mmol of lithium amide gave 2.23 g (85.1% recovery) of **2** and 0.074 g (2.5%) of **5a**.

Dilithiobenzoylacetone (1) Entrained Reaction of 4a with 2. To a suspension of lithium amide (244 mmol) in 500 ml of liquid ammonia under a nitrogen atmosphere was added a solution of 4.64 g (80 mmol) of acetone in 25 ml of ether. The reaction mixture was stirred for 15 min, and 0.33 g (1.975 mmol) of benzoylacetone was added as a solid. After an additional 15 min, 3.23 g (19.75 mmol) of **2** in 100 ml of ether was added. After stirring for 1 hr in the "dark," the deep red reaction mixture was quenched with excess solid ammonium chloride and then processed in the usual manner to give a brown oil. Chromatography on silica gel afforded 0.89 g (27.8 recover) of **2** and 2.13 g (59.4%) of **5a**.

Entrainment of the reaction of 16 mmol of **2**, 48 mmol of acetone, and 64 mmol of lithium amide with 1.6 mmol of dilithiobenzoylacetone gave 0.20 g (6.8%) of **5a** and 2.31 g (88.2% recovery) of **2**.

Dilithiobenzoylacetone (1) Entrained Reaction of 4a with 2 in the Presence of DNB. To a suspension of lithium amide (192 mmol) in 500 ml of liquid ammonia under a nitrogen atmosphere was added 3.71 g (64 mmol) of acetone in 25 ml of ether. After 15 min, 0.26 g (1.6 mmol) of benzoylacetone was added. After the mixture was stirred an additional 15 min, 0.27 g (1.6 mmol) of DNB was added, followed by 2.62 g (16 mmol) of **2** in 75 ml of ether. The reaction mixture was stirred in the "dark" for 1 hr, quenched with excess solid ammonium chloride, and then processed in the normal manner. Chromatography of the crude product on silica gel gave 1.07 g (40.8% recovery) of **2** and 0.043 g (1.5%) of **5a**.

Reaction of 4a with 2 in the Presence of Lithium Metal. A solution of acetone (3.71 g, 64 mmol) in 25 ml of ether was added to a suspension of lithium amide (192 mmol) in 500 ml of liquid ammonia under a nitrogen atmosphere. The resulting mixture was stirred for 15 min, and a solution of **2** (2.62 g, 16 mmol) in 75 ml of ether was added, followed immediately by 0.06 g (8 mmol) of lithium metal. The reaction mixture was stirred in the "dark" for 1 hr, quenched with excess solid ammonium chloride, and then processed in the normal manner. Chromatography of the crude product on silica gel, eluting with hexane, gave initially 0.57 g (21.8% recovery) of **2** followed by 0.28 g (14.0%) of quinoline, identified by comparison of spectral characteristics to those of authentic material. Elution with hexane containing increasing amounts of ether afforded 0.42 g (14.2%) of **5a**, followed by 0.28 g (13.7%) of 2,3′-biquinoline (**6**), mp 175–177.5° after recrystallization from acetone–hexane (lit.[14] mp 175°): mass spectrum (*m/e*) 256 (M^+); pmr ($CDCl_3$) δ 7.44–8.08 (m, 7 H), 8.16–8.40 (m, 3 H), 8.88 (d, 1 H, $J = 2.0$ Hz), and 9.80 (d, 1 H, $J = 2.0$ Hz) ppm.[15]

Continued elution with ether–hexane gave 0.19 g (8.3%) of 2-aminoquinoline, mp 120–127° (lit.[17] mp 129°).

A similar reaction was carried out using 16 mmol of **2**, 48 mmol of acetone, 64 mmol of lithium amide, and 16 mmol of lithium metal. Chromatography of the reaction product on silica gel afforded 0.47 g (17.9% recovery) of **2**, 0.39 g (18.0%) of quinoline, 0.45 g (15.2%) of **5a**, 0.36 g (17.5%) of **6**, and 0.16 g (7.9%) of 2-aminoquinoline.

Reaction of Lithioacetophenone (4b) with 2 in the Dark. To a suspension of lithium amide (64 mmol) in 500 ml of liquid ammonia under a nitrogen atmosphere was added a solution of acetophenone

(5.77 g, 48 mmol) in 25 ml of ether. The reaction mixture was stirred for 15 min, and **2** (2.62 g, 16 mmol) in 75 ml of ether was added. The reaction was stirred for 1 hr in the "dark," quenched with excess ammonium chloride, and then processed in the normal manner. Unreacted acetophenone was removed by vacuum distillation. The residue from the distillation was chromatographed on silica gel to give 2.05 g (78.2% recovery) of **2** and 0.71 g (18%) of 2-phenacylquinoline (**5b**), mp 110–113° (lit.[10] mp 114–116°). Spectral characteristics of this material were identical with those of an authentic sample of **5b.**

Reaction of 4b with 2 in the Presence of DNB. To **4b** (48 mmol), prepared as in the preceding experiment from lithium amide (64 mmol) and acetophenone (48 mmol), 0.27 g (1.6 mmol) of DNB was added followed by 2.62 g (16 mmol) of **2** in 75 ml of ether. The reaction mixture was stirred for 1 hr, quenched with excess solid ammonium chloride, and then processed in the usual manner. Glpc analysis of the residual oil indicated that ketone **5b** was produced in less than 1% yield.

Photostimulation of the Reaction of 4b with 2. Just prior to the addition of **2** (2.62 g, 16 mmol) in 75 ml of ether to 48 mmol of **4b** in 500 ml of liquid ammonia under a nitrogen atmosphere, irradiation from a 250-W tungsten lamp was begun. After being stirred for 1 hr, the reaction mixture was quenched with excess solid ammonium chloride and then processed in the usual manner. Chromatography of the residue on silica gel afforded 3.25 g (82.8%) of **5b.**

Acknowledgment. This work was generously supported by the National Institute of Neurological Diseases and Stroke under Grant No. NS 10197. We are indebted to Dr. J. G. Mason for helpful discussions.

References and Notes

(1) For reviews, see (a) N. L. Holy and J. D. Marcum, *Angew. Chem., Int. Ed. Engl.*, **10**, 115 (1971); (b) G. A. Russell, *Chem. Soc., Spec. Publ.*, **No. 24**, 271 (1970). For examples of aliphatic radical–anion substitutions see (c) N. Kornblum and F. W. Stuchal, *J. Amer. Chem. Soc.*, **92**, 1804 (1970); (d) N. Kornblum, R. T. Swiger, G. W. Earl, H. W. Pinnick, and F. W. Stuchal, *ibid.*, **92**, 5513 (1970); (e) N. Kornblum, S. D. Boyd, and F. W. Stuchal, *ibid.*, **92**, 5783 (1970); (f) N. Kornblum and S. D. Boyd, *ibid.*, **92**, 5784 (1970); (g) G. A. Russell, R. K. Norris, and A. R. Metcalf, *ibid.*, **94**, 4959 (1972); (h) S. Limatibul and J. W. Watson, *J. Org. Chem.*, **37**, 4491 (1972); (i) M. Barreau and M. Julia, *Tetrahedron Lett.*, 1537 (1973).

(2) For examples of radical–anion substitutions at carboaromatic centers, see (a) J. K. Kim and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 7463 (1970); (b) *ibid.* **92**, 7464 (1970); (c) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 3020 (1973), and references cited therein; (d) *J. Amer. Chem. Soc.*, **96**, 112 (1974); (e) F. Pietra, M. Bartolozzi, and F. Del Cima, *Chem. Commun.*, 1232 (1971).

(3) J. A. Zoltewicz and T. M. Oestreich, *J. Amer. Chem. Soc.*, **95**, 6863 (1973).

(4) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969).

(5) J. F. Wolfe, J. C. Greene, T. Hudlicky, *J. Org. Chem.*, **37**, 3199 (1972).

(6) Y. Mizuno, K. Adachi, and K. Ikeda, *Chem. Pharm. Bull.*, **2**, 225 (1954).

(7) E. C. Taylor and S. F. Martin, *J. Amer. Chem. Soc.*, **94**, 2874 (1972).

(8) For examples, see (a) R. Levine and W. W. Leake, *Science*, **121**, 780 (1955); (b) T. Higashino, *Chem. Pharm. Bull.*, **10**, 1048 (1962); (c) H. Boer and H. J. den Hertog, *Tetrahedron Lett.*, 1943 (1969); (d) E. Oishi, *Yakugaku Zasshi*, **89**, 959 (1969); (e) T. Higashino, Y. Tamura, K. Nakayama, and E. Hayashi, *Chem. Pharm. Bull.*, **18**, 1262 (1970); (f) T. Higashino and E. Hayashi, *ibid.*, **18**, 1457 (1970).

(9) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973).

(10) M. J. Weiss and C. R. Hauser, *J. Amer. Chem. Soc.*, **71**, 2023 (1949).

(11) For a discussion of the intervening aptitude of DNB in chain reactions involving radical–anion intermediates, see (a) R. C. Kerber, C. W. Urry, and N. Kornblum, *J. Amer. Chem. Soc.*, **87**, 4520 (1965); (b) N. Kornblum, R. E. Michel, and R. C. Kerber, *ibid.*, **88**, 5662 (1966); (c) N. Kornblum, *Proc. Int. Congr. Pure Appl. Chem., 23rd*, **4**, 81 (1971).

(12) 2-Haloquinolines are rapidly and nearly quantitatively converted into mixtures of 2-aminoquinoline, 2-methylquinazoline, and quinoline by excess potassium amide in liquid ammonia. See H. J. den Hertog and D. J. Buurman, *Recl. Trav. Chim. Pays-Bas.*, **86**, 187 (1967). However, we have found as much as a 12-fold molar escess of lithium amide consumes less than 30% of 1 equiv of **2** after 1 hr at −33° in the dark.

(13) Other investigators[3,9] have also observed that the rates of $S_{RN}1$ reactions are increased by basic reagents other than the nucleophilic reagent which eventually replaces the nucleofugic substituent of the substrate.

(14) W. H. Mills and H. G. Ordish, *J. Chem. Soc.*, 86 (1928).

(15) The chemical shifts of 2′ and 4′ protons of **6** are reported to be 9.76 and 8.86 ppm, respectively: J. C. Carey and W. H. F. Sasse, *Aust. J. Chem.*, **21**, 207 (1968).

(16) W. A. Remers, G. J. Gibs, C. Pidacks, and M. J. Weiss, *J. Org. Chem.*, **36**, 279 (1971).

(17) J. Ephraim, *Chem. Ber.*, **24**, 2819 (1891).

Imidazole-Catalyzed Hydrolysis of Anilides. Nucleophilic Catalysis or Proton-Transfer Catalysis?

Ralph M. Pollack* and Thomas C. Dumsha

Contribution from the Laboratory for Chemical Dynamics, Department of Chemistry,
University of Maryland Baltimore County, Baltimore, Maryland 21228.

Received June 17, 1974

Abstract: Imidazole is found to act as a catalyst for proton transfer and not as a nucleophile in the hydrolysis of trifluoroacetanilides.

The imidazole-catalyzed hydrolysis of esters and amides is of great current interest because of the catalytic role of the imidazole group of histidine-57 in the mechanism of action of chymotrypsin and other proteolytic enzymes.[1] Although both nucleophilic and general base pathways have been observed for ester hydrolysis,[2] buffer catalysis of amide hydrolysis has generally been interpreted as specific base–general acid catalysis.[3] Recently, however, it has been suggested that in the hydrolysis of 2,2,2-trifluoroacetanilides imidazole acts solely as a nucleophile.[4] Furthermore, it was proposed that substantial quantities of the tetrahedral intermediate formed from addition of imidazole accumulate during the reaction.

We now wish to report that the imidazole-catalyzed hydrolysis of *p*-nitro-2,2,2-trifluoroacetanilide (I) shows kinetic behavior which is inconsistent with the proposed nucleophilic mechanism. On the contrary, our results point to general base-catalyzed formation of a tetrahedral intermediate (T^-), coupled with general acid-catalyzed breakdown of this intermediate as being the *only* mechanism for this reaction. We have also reinvestigated the hydrolysis of two of the anilides originally used as a basis for the nucleophilic mechanism and find no evidence for either nucleophilic attack by imidazole or buildup of an intermediate.

Results and Discussion

The hydrolysis of I was followed spectrally at pH 6.55, 7.06, and 7.62 in imidazole buffers at 25.0° and ionic strength of 0.2 (NaCl). Excellent pseudo-first-order kinetics were observed in all cases where the reaction was fol-