Nature of the Reactions Involving 4-Haloisoquinolines and Amide Ion in Ammonia. Remarkable Competition between $S_{RN}1$ Substitution and σ Complex Formation

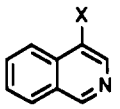
John A. Zoltewicz* and Terence M. Oestreich

Department of Chemistry, University of Florida, Gainesville, Florida 32611-2046

Received September 24, 1990

4-Bromo- (1) or 4-chloroisoquinoline (3) in refluxing liquid ammonia containing amide and thiomethoxide ions reacts preferentially with the thiolate ion to give 4-(methylthio)isoquinoline (2) in high yield. The bromo substrate was shown to require amide ion in order to react with thiomethoxide ion, no reaction taking place in its absence. Substitution product is believed to form from both halides by an $S_{RN}1$ mechanism. By contrast, 3-chloroisoquinoline under the same conditions of mixed anions gives 3-aminoisoquinoline. The role of amide ion and its addition to give σ complexes in these and other reactions of 4-halogenated isoquinolines in ammonia is discussed.

For some 50 years, the nature of the interaction between 4-bromoisoquinoline (1) and amide ion in liquid ammonia has been a puzzle, the product being described as a "tar".[1] More recently, the structures of at least six products have been determined.[2] Curiously, while 4-iodoisoquinoline and amide ion give product mixtures similar to those produced by 1, 4-fluoro- and 4-chloroisoquinoline (3) and amide ion form a single product in high yield. In these latter two cases, amination does take place but the halogen atom is retained in the 1-amino-4-haloisoquinoline product.[2]



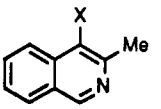
1, X = Br
2, X = CH_3S
3, X = Cl
5, X = H

We now report that 1 and 3 in liquid ammonia in the presence of thiomethoxide ion give rise to 4-(methylthio)isoquinoline (2) in very high yield.[3] The substitution reaction requires amide ion as a catalyst, a significant and remarkable feature of the conversion.

Recent advances concerning electron transfer and radical anion substitution reactions ($S_{RN}1$)[4-6] and the discovery of the facile and quantitative formation of amide ion adducts of isoquinolines in ammonia[2,7] now make possible a unified but preliminary interpretation of the peculiar and highly complex chemistry of 4-haloisoquinolines in ammonia.

Results

Table I summarizes the outcome of reactions in refluxing liquid ammonia involving primarily 1 but also 3, as well as 4-bromo-3-methyl- (4) and 3-chloroisoquinoline. In this table, the term "concentrations" simply refers to the



4, X = Br
6, X = CH_3S

amount of material that would be in solution had all of it dissolved. Sodium amide is only partially soluble under the usual reaction conditions (0.2 M) and is made even more insoluble by the presence of a large concentration of common ion from sodium thiomethoxide. Controls show sodium thiomethoxide and 1 when present alone are soluble at the 1.2 M and 0.1 M levels generally employed. They give clear solutions.

The first entry in Table I reveals in a crucial experiment that 1.2 M thiomethoxide ion by itself does not react with 1 in refluxing ammonia; 94% of 1 is isolated unchanged after 8 h of exposure. But when amide ion is present, thiomethoxydebromination product 2 is isolated in 80% average yield (entry 2). Clearly, amine ion acts as a catalyst for this conversion.

4-Chloro compound 3 also undergoes thiomethoxydehalogenation in the presence of amide ion (entry 3). Significantly, in this case a considerable amount (23%) of unreacted starting material remains. Because product separation and isolation led to lower mass balances, the yield data for this entry in Table I are based on analysis by proton NMR of the product mixture prior to separation. These higher yields provide a more accurate description of the outcome. Many other yields in Table I also are based on NMR analysis of raw product mixtures and a few on isolation (see footnotes).

Entry 4 shows that anilide ion, a weaker base than amide ion, also promotes substitution of 1 by thiomethoxide ion, but only poorly. Much starting material remains; some 2 is formed along with a new product, isoquinoline 5. Sodium metal present as the limiting reagent, entry 5, also promotes the formation of 2 from 1 along with 5, but much starting material remains unchanged again.

All reaction mixtures contain some tar. Thin-layer chromatography (TLC) on silica gel indicated this dark material consists of several components. No attempt at identification was made.

4-Bromo-3-methylisoquinoline (4) demonstrates a reactivity pattern similar to that of 1. While 4 does not react with thiomethoxide ion alone (entry 6), it does give some thiomethoxy substitution product 6 (18%) in the presence of amide ion (entry 7). But a reduction product, 3-methylisoquinoline, is present as well. In order to promote

(1) Bergstrom, F. W.; Rodda, J. H. *J. Am. Chem. Soc.* **1940**, *62*, 3030.
(2) Sanders, G. M.; van Dijk, M.; den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 273.
(3) 4-(Phenylthio)isoquinoline, mp 60-61 °C, can be formed from 1 and $NaNH_2$ and $NaSC_6H_5$ in ammonia. Although NMR analysis suggested this product was formed in high yield, isolation of pure product proved difficult. Further experiments therefore were not undertaken. Anal. Calcd for $C_{15}H_{11}NS$: C, 75.91; H, 4.68; N, 5.90. Found: C, 76.05; H, 4.59; N, 5.78.
(4) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
(5) Saveant, J.-M. *Acc. Chem. Res.* **1980**, *13*, 323.
(6) Russell, G. A. *Adv. Phys. Org. Chem.* **1987**, *23*, 271.
(7) Zoltewicz, J. A.; Helmick, L. S.; Oestreich, T. M.; King, R. W.; Kandetzki, P. *J. Org. Chem.* **1973**, *38*, 1947.

0022-3263/91/1956-2805$02.50/0

Table I. Conditions and Results of the Reactions of 0.1 M Halogenated Isoquinolines with 1.2 M Sodium Thiomethoxide in Refluxing Liquid Ammonia with and without Amide Ion for 4 h[a]

entry	haloisoquinoline	[$NaNH_2$], M	additive	% sulfide product	% start compd	% isoq
1	4-Br[b]				94[c]	
2	4-Br	0.2		80 ± 4[c]		
3	4-Cl	0.2		66	23	
4	4-Br[d]	*e*	5% EtOEt	5	70	10
5	4-Br		0.023 M Na	26	63	8
6	4-Br-3-Me[f]		23% EtOEt		94[g]	
7	4-Br-3-Me	0.2	17% EtOEt	18	41	11[h]
8	3-Cl				99	
9	3-Cl	0.2				(52)[i]
10	3-Cl	0.2[j]				(63)[i]

[a] Yields based on NMR analysis of recovered material unless indicated to the contrary. [b] Reaction time 8 h. [c] Yield of isolated material. [d] 0.05 M. [e] Contains 0.3 M $NaSCH_3$, 0.05 M $C_6H_5NH_2$, and 0.05 M C_6H_5NHNa in place of amide ion. [f] 7.5-h reaction time. [g] 87% by isolation. [h] 3-Methylisoquinoline. [i] 3-Aminoisoquinoline product; yield by isolation. [j] No $NaSCH_3$ present.

the solubility of 4, it was necessary to employ a large amount of ether cosolvent, a potential hydrogen atom donor.

Similarly, 3-chloroisoquinoline does not react in the presence of thiomethioxide ion (entry 8) until amide ion is added (entry 9). But now the substitution product is 3-amino- and not 3-(methylthio)isoquinoline. As expected from these observations, removing sulfide ion nucleophile has no bearing on the reaction with amide ion alone (entry 10). Again, the amination product is formed.

Most reactions were carried out arbitrarily to 4 h; the occasional presence among substitution product of unreacted starting material suggested a long reaction time was appropriate. But this observation is misleading. When near the end of our investigation a reaction mixture was sampled by removing aliquots after only a few minutes, the reaction was discovered to be over and additional time produced no significant change! Thus, by use of the typical concentrations in Table I, a reaction with sodium amide was 80% complete within 12 min and a similar reaction mixture with the more soluble potassium amide (0.2 M) showed 95% conversion to 2 in just 5 min. Remarkably, even when equivalent amounts of thiomethoxide ion and 1 (both 0.8 M) were used along with 1.6 M potassium amide, 2 was formed in ~90% yield within 15 min. Shorter contact times were not explored.

Attempts were made to inhibit with additives the reaction of 1. These additives already had been shown to inhibit electron transfer reactions of 1 in methanol. However, azobenzene[8] and 1,1-diphenylethylene[9] were without significant effect in ammonia. Thus, after 5 min an aliquot from 0.1 M 1, 0.4 M KNH_2, 0.8 M $KSCH_3$, and 1.0 M azobenzene showed the reaction to be ~80% complete with the ratio of 2 to 1 being 2.9. We are reluctant to attribute the presence of some unreacted 1 to inhibition even in the presence of a large amount of potential inhibitor.

In an attempt to slow down the reaction and to explore the possibility of inhibition, the mixture first was cooled to ~−65 °C. Thus, 0.02 M 1, 0.1 M KNH_2, 0.6 M $KSCH_3$, and 0.01 M 1,1-diphenylethylene when quenched after 1 h showed 87% 2 and 9% 1. Repetition, but without inhibitor, gave after 10 min 68% 2 and 29% 1. More starting material was present in the run without the potential inhibitor; this may simply reflect a shorter reaction time and the difficulty of reproducing conditions[10] on such systems, especially at low temperatures. These collective data do not provide compelling evidence for inhibition.

A control consisting of 0.05 M authentic 4-aminoisoquinoline and 0.09 M sodium amide in ammonia gave back 75% of starting material, showing sufficient stability of the amine under typical reaction conditions. Its presence in reaction mixtures should therefore be detectable. None was found even by TLC, but "tar" also was present. 3-Aminoisoquinoline was not found when 4-haloisoquinolines were treated with amide ion.

Discussion

Hetaryne Is Not an Intermediate. Dehydrohalogenation to form arynes and hetarynes is known to occur by the action of amide ion under the conditions employed here.[11] Thiolate ions serve as efficient trapping agents for these reactive intermediates.[12,13] Such at first would seem to be the mechanism of reaction of 1 and 3, but a hetaryne mechanism to produce 3,4-isoquinolyne (3,4-didehydroisoquinoline) is incompatible with entries 1, 2, 6, and 7, which show that 4 and 1 both have the same reaction characteristics. Due to the presence of the 3-methyl group, substrate 4 cannot form 3,4-isoquinolyne and so this intermediate may be dismissed. No isomeric 3-methylthio product is found from 1 as might be expected if the didehydro intermediate did form. Moreover, a ring nitrogen atom adjacent to such unsaturation is known to be largely destabilizing of hetarynes, making their formation difficult.[11] Indeed, the substitution reaction must take place by a different route.

Known Complex Product Mixtures. The nature and number of products formed from 4-haloisoquinolines under conditions where amide ion is a reactant is critically dependent on the identity of the reacting halogen atom, an important clue to the mechanism.[14] Thus, both 4-fluoro- and 4-chloroisoquinoline (3) with excess potassium amide in refluxing ammonia each give one major product after 24 h, 1-amino-4-haloisoquinoline in 93 and 86% yields, respectively.[2] These are classical Chichibabin amination products.[15,16] In marked contrast, under the same conditions and after only 10 and 30 min, respectively, 4-bromo-(1) and 4-iodoisoquinoline yield at least six products. The product of apparent direct substitution, 4-aminoisoquinoline, is found only in trace amount.[2] Our control experiment shows this material to be stable under the reaction conditions and would therefore be detectable if present.

Among the multiple products are those that clearly arise by a redox process. Included are isoquinoline, 1-amino-4-haloisoquinoline, and 4,4′-biisoquinolines. The 4-chloro substrate also gives rise to small amounts of the same products.[2] Thus, bromide 1 and chloride 3 give very different product compositions and ratios in the presence of amide ion alone, unlike the results we report for amide–thiomethoxide ion mixtures.

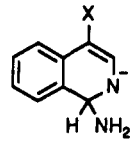
Proposed Interpretation. The seemingly unrelated and complex chemistry of 4-haloisoquinolines in ammonia containing amide ion now can be interpreted broadly

(8) Zoltewicz, J. A.; Oestreich, T. M. *J. Am. Chem. Soc.* **1973**, *95*, 6863.
(9) Zoltewicz, J. A.; Oestreich, T. M.; Sale, A. A. *J. Am. Chem. Soc.* **1975**, *97*, 5889.
(10) Bunnett, J. F.; Mitchel, E.; Galli, C. *Tetrahedron* **1985**, *41*, 4119.
(11) Reineke, M. *Tetrahedron* **1982**, *38*, 427.
(12) Bunnett, J. F.; Brotherton, T. K. *J. Org. Chem.* **1958**, *23*, 904.
(13) Scardiglia, F.; Roberts, J. D. *Tetrahedron* **1958**, *3*, 197.
(14) Amatore, C.; Pinson, J.; Saveant, J. M.; Thiebault, A. *J. Am. Chem. Soc.* **1981**, *103*, 6930.
(15) McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 2.
(16) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Tetrahedron* **1988**, *44*, 1.

within a single complex reaction scheme involving two different types of competing reactions: amide ion addition to position 1 of starting material to give an anionic σ complex[2,7] and electron-transfer reactions[6] probably initiated by this complex. Several facts support this interpretation.

Compelling evidence has already been presented to demonstrate that 1 can react with a thiolate ion by the $S_{RN}1$ mechanism involving chain electron transfer. Nucleophilic substitution takes place by this route in heated methanol with benzenethiolate ion.[8] In the absence of this nucleophile, reductive debromination to isoquinoline occurs,[1,9] again by a radical chain mechanism.

Isoquinoline and many other nitrogen-containing heteroaromatic molecules are known to react on mixing with amide ion in ammonia to give anionic σ adducts,[17] position 1 being favored for isoquinolines. Numerous NMR spectra have been reported as direct evidence, including those for 7 and isoquinoline in ammonia.[7]



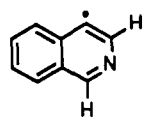
7, X = CH_3S
8, X = Cl
9, X = Br

Particularly pertinent is the report that the NMR spectrum of 4-chloro adduct 8 may be observed for at least 30 min at −34 °C in ammonia. Only slowly is it converted to 1-amino-4-chloroisoquinoline[2] Chichibabin amination product by an unknown oxidation mechanism.[15,16]

The lifetime of typical radical anions of aryl and hetaryl halides increases in the order I < Br < Cl < F. For example, radical anions from 2-haloquinolines expel chloro, bromo, and iodo nucleofuges in a 1:7.6:175 order at −40 °C in ammonia.[18] Moreover, the ease of such rings accepting an electron is expected to decrease in the same sequence.[14]

Because chloride ion is anticipated to be a poorer leaving group than bromide ion and the chloro substrate is less likely to accept an electron to form a radical anion than the bromo analogue, the chlorine atom reduces the rate of the radical ion process, hence the domination of the amino product from σ complex formation with the chloro substrate in the absence of thiolate ion. The same is true for 4-fluoroisoquinoline, which gives rise to the 1-amino-4-fluoro amination product in high yield. By contrast, the more easily reducible bromo and iodo substrates with their better nucleofuges allow the electron-transfer route to compete and even to dominate.

We propose that an electron-transfer pathway generates a radical anion of starting material. This radical anion than expels halide ion to give the 4-isoquinolyl σ radical 10 as a key intermediate.



10

A major odd feature of the old chemistry is the absence of abundant amounts of 4-aminoisoquinoline. According to the proposed electron-transfer scheme amide, a known radical trapping agent,[19] is expected to capture the 4-isoquinolyl radical to give substitution product. Only traces are detected.

This curious anomaly is not unprecedented. Lithium amide in ammonia had little influence on the complex chemistry of the 2-quinolyl radical, for example.[20]

Thiomethoxydehalogenation and Its Mechanism. In marked contrast to the very different outcomes observed for 1 and 3 in ammonia containing only amide ion, we find that both 1 and 3 in the presence of both amide and thiomethoxide ions give the same thiomethoxydehalogenation product 2 in high yield. The formation of 2 from 1 requires amide ion, with no reaction taking place in its absence (Table I). Although a control was not run to show that 3 also does not react with thiomethoxide ion in the absence of amide ion, it seems most likely that it too is essentially inert under our conditions. The reactivities of bromo and chloro substrates in aromatic nucleophilic substitution by the S_NAr mechanism[21] often are quite similar. Moreover, neither 4-bromo-3-methyl- nor 3-chloroisoquinoline react with thiomethoxide ion in the absence of amide ion (Table I).

We suggest that substrate 1 is rapidly converted on mixing with amide ion into anion 9. This σ complex is a poor election acceptor and so does not undergo nucleophilic substitution either by the classical S_NAr route or by the $S_{RN}1$ process. On workup involving the addition of ammonium ion acid, it is readily converted back to starting material, which then is recovered. Recovery therefore does not suggest the presence of an unreactive starting material, rather, the formation of σ adduct.

σ Complex 9, a π anion, may have another role to play: it may be an electron donor to uncomplexed starting material,[6,22] thereby serving as an initiator to give radical 11 and the radical anion of 1 (eq 1), which then undergoes

11

$$1 + 9 \rightarrow 1^{\bullet-} + 11 \quad (1)$$

$$1^{\bullet-} \rightarrow 10 + Br^- \quad (2)$$

$$10 + CH_3S^- \rightarrow 2^{\bullet-} \quad (3)$$

$$2^{\bullet-} + 1 \rightarrow 2 + 1^{\bullet-} \quad (4)$$

fragmentation to σ radical 10 and halide ion (eq 2). An important feature of this scheme is that both σ complex 9 and unreacted starting halide are required. If the electron-transfer process is too slow, then adduct formation will dominate the outcome.

The thiolate ion, by being a very efficient radical trapping agent,[23-25] drastically changes the course of the reaction and outcome in the case of substrates 1 and 3. In the presence of this efficient trapping agent for σ radicals, 10 is captured (eq 3) to give the radical anion of observed

(17) Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* **1983**, *34*, 306.
(18) Amatore, C.; Chaussard, J.; Pinson, J.; Saveant, J. M.; Thiebault, A. *J. Am. Chem. Soc.* **1979**, *101*, 6012.
(19) Tremelling, M. J.; Bunnett, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7375.
(20) Hay, J. V.; Hudlicky, T.; Wolfe, J. F. *J. Am. Chem. Soc.* **1975**, *97*, 374.
(21) Bunnett, J. F.; Garbisch, E. W., Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385.
(22) Russell, G. A.; Jansen, E. G.; Stom, E. T. *J. Am. Chem. Soc.* **1964**, *86*, 1807.
(23) Amatore, C.; Oturan, M. A.; Pinson, J.; Saveant, J. M.; Thiebault, A. *J. Am. Chem. Soc.* **1985**, *107*, 3451.
(24) Thiomethoxide ion is 145 times less reactive than thiophenoxide ion toward 4-benzoylphenyl σ radical in acetonitrile.[25]
(25) Amatore, C.; Pinson, J.; Saveant, J. M.; Thiebault, A. *J. Am. Chem. Soc.* **1982**, *104*, 817.

product.[26,27] Subsequent transfer of an electron from this radical anion to 1 (eq 4) continues the chain. This rapid chain reaction accelerates substitution and thereby changes the outcome, especially for 3, and supresses Chichibabin amination.

Radical trapping by thiolate ions can be extremely efficient. Benzenethiolate ion reacts with 3- and 4-quinolyl radicals in ammonia at −38 °C only about a factor of 10 slower than that for a diffusion-limited process.[23]

Reductive dehalogenation products also are observed. These in the case of 1 may form by electron transfer to radical 10 to generate the 4-isoquinolyl anion, which then abstracts a proton from solvent to give 5.[14] This radical may also remove a hydrogen atom from ether cosolvent to yield the same product. Both processes are unproductive in terms of the formation of substitution products; they retard substitution by removing the intermediate radical from chain propagation.[14] Perhaps this is why methyl substrate 4 in the presence of ether gives back so much starting material and 3-methylisoquinoline, a reductive dehalogenation product.

Consistent with the $S_{RN}1$ interpretation is entry 5 of Table I, showing that substitution can be promoted by electrons from dissolving sodium metal.[4,14] On the assumption that both substitution product 2 and reduction product 5 are radical derived, their combined yield on the basis of the metal as a limiting reagent is 145%, consistent with a chain mechanism.[28] We cannot eliminate the possibility that some small amount of amide ion was formed on addition of the metal and it served as an initiator in place of solvated electrons. Nevertheless, initiation is indicated.

The absence of significant inhibition by additives that did retard the $S_{RN}1$ reaction of 1 in methanol is not evidence against the $S_{RN}1$ mechanism in ammonia. Substantial amounts of σ complex always are present, either as the halo compound[2] or as the methylthio substitution product 7 in ammonia[7] but not in methanol. These can serve to initiate electron transfer. The reactions are so fast that any delay associated with inhibition is difficult to detect.

Conclusion

There is a novel and remarkable feature to the proposed competition between amide ion addition to 4-halogenated isoquinolines and subsequent electron transfer from the resultant σ complex to starting material. For only a very short time on mixing does a "window" exist during which the $S_{RN}1$ pathway is possible. If this σ complex transfers an electron to starting substrate not yet complexed and the resultant radical anion eliminates halide ion, then $S_{RN}1$ substitution becomes a possibility. But if this redox process and the following propagation steps leading to substitution product are slow and the chain process is inefficient, then adduct formation dominates, retarding nucleophilic substitution. The identity of the halogen atom and its ability to promote reduction and to act as a leaving group play a critical role in determining the outcome of the competition. The contrasting outcome (thiomethoxydehalogenation) pertaining to 1 and 3 having the halide group in the 4 position and that (aminodehalogenation) for 3-chloroisoquinoline in the presence of a mixture of thiomethoxide and amide ions points to another interesting feature: the result of the competition is sensitive to the position of the leaving group. In the case of the 3-chloro substrate in aqueous ammonia[29] and also the 3-bromo analogue in liquid ammonia,[30] the 3-aminoisoquinoline product arises, at least in part, by rearrangement of the amino σ complex, a ring-opening scheme designated S_N(ANRORC).[31] Thus, it does not suffice to have a substrate that can form a σ complex and contains a potential halide ion leaving group; the position of the nucleofuge is important. Even the presence of an efficient radical trapping agent such as thiomethoxide ion, which can bring about a chain $S_{RN}1$ process, does not ensure that the radical ion scheme will prevail. Much remains to be done to provide a detailed understanding of this complex chemistry.

Experimental Section

Chemicals. 4-Bromoisoquinoline (1) (Aldrich) was recrystallized from ether or hexane to remove isoquinoline impurity. 4-Chloroisoquinoline (3), mp 27–29 °C (lit.[32] mp 28.5–29.5 °C), was prepared by chlorinating isoquinoline that first had been converted to 2-cyano-1,2-dihydro-1-hydroxyisoquinoline.[33] 3-Chloroisoquinoline, mp 41–45 °C (lit.[34] mp 46.5–47.5 °C), was prepared from 1,3-dichloroisoquinoline.[35] 4-Aminoisoquinoline, mp 107–108 °C (lit.[2] mp 108 °C), was synthesized from 4-bromoisoquinoline.[36] Proton NMR spectra were recorded at 60 MHz to confirm structures. Methyl mercaptan was used as received and was distilled from the pressure cylinder into ammonia. Solid sodium methylmercaptide was made by adding 1 equiv of sodium metal to methyl mercaptan suspended in liquid ammonia followed by evaporation of the solvent under a stream of nitrogen. The same method was employed for the preparation of sodium thiophenoxide, starting with thiophenol.

4-(Methylthio)isoquinoline (2). A mixture of 1.4 g (19 mmol) of sodium thiomethoxide and 1.0 g (4.8 mmol) of 4-bromoisoquinoline in 10 mL of reagent grade *N,N*-dimethylformamide was heated at 100 °C for 2 h with stirring. After the mixture was diluted with 100 mL of water, the precipitate (0.40 g, 2.2 mmol), mp 50–53 °C, was collected. Recrystallization from hexane yielded 0.20 g (1.1 mmol, 24%) of light yellow needles, mp 65–66 °C: H NMR (CCl_4) δ 2.54 (s, 3 H), 7.23–8.23 (m, 4 H), 8.37 (s, 1 H), 8.93 (s, 1 H). Anal. Calcd for $C_{10}H_9NS$: C, 68.51; H, 5.17; N, 7.99. Found: C, 68.88; H, 5.14; N, 7.89.

4-Bromo-3-methylisoquinoline (4). To a mixture of 72 g (0.50 mol) of 3-methylisoquinoline and 70 mL of 40% hydrobromic acid, concentrated to a slurry, was added 80 g (0.50 mol) of bromine. After the mixture was heated at reflux for 6.5 h, aqueous NaOH was added to make the mixture basic. The organic phase was separated and distilled at 120 °C (3.0 Torr) to yield 46 g (0.2 mol, 42%) of product. A second distillation gave white product, mp 30–33 °C: H NMR (CCl_4) δ 2.75 (s, 3 H), 7.03–8.05 (m, 4 H), 8.82 (s, 1 H). Anal. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.04; H, 3.79; N, 6.20.

3-Methyl-4-(methylthio)isoquinoline (6). A mixture of 4.0 g (1.8 mmol) of 4-bromo-3-methylisoquinoline and 5.0 g (0.71 mol) of sodium thiomethoxide in 30 mL of dimethyl sulfoxide was heated at 100 °C for 30 min. After the addition of 120 mL of water to the cooled mixture and three extractions with 20 mL of ether, distillation at 103 °C (0.6 Torr) gave 2.4 g (1.3 mmol, 72%) of product: H NMR (CCl_4) δ 2.28 (s, 3 H), 2.88 (s, 3 H), 7.24–7.90 (m, 3 H), 8.43 (d, 1 H, J = 9 Hz), 8.98 (s, 1 H). Anal. Calcd for $C_{11}H_{11}NS$: C, 69.79; H, 5.87; N, 7.40. Found C, 70.00; H, 5.96; N, 7.23.

General Procedure for Reactions in Ammonia. Ammonia was added to a flame-dried three-necked flask equipped with dry ice condenser, stirrer, and calcium chloride drying tube. Addition

(26) The radical anion of 6 is not likely to fragment to the methyl radical and the corresponding thiolate ion.[27]

(27) Rossi, R. A.; Palacios, S. M. *J. Org. Chem.* **1981**, *46*, 5300.
(28) Kim, K. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7464.
(29) Wahren, M. *Tetrahedron* **1968**, *24*, 441.
(30) Sanders, G. M.; van Dijk, M.; den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 198.
(31) van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462.
(32) Gadekar, S. M.; Frederick, J. L.; Semb, J.; Vaughan, J. R., Jr. *J. Org. Chem.* **1961**, *26*, 468.
(33) Johnson, M. D. *J. Chem. Soc.* **1964**, 200.
(34) Gabriel, S. *Chem. Ber.* **1886**, *19*, 1653.
(35) Haworth, R. D.; Robinson, S. *J. Chem. Soc.* **1948**, 777.
(36) Craig, J. J.; Cass, W. E. *J. Am. Chem. Soc.* **1942**, *64*, 783.

of gaseous methanethiol produced an insoluble ammonium salt. Freshly cut sodium or potassium metal, added in small pieces, reacted quickly. It was convenient to alternate the addition of thiol and metal to give a clear solution. The concentration of sodium thiomethoxide was calculated from the amount of metal consumed. Addition of a small excess of metal turned the solution blue, indicating the complete conversion of thiol. A small crystal of ferric nitrate hydrate catalyst then was added along with the appropriate quantity of metal to make amide ion. The formation of amide in the presence of thiolate ion appears to be unusually slow, requiring hours.

Substrate was added, occasionally dissolved in ether, and a deep color appeared. After the mixture was refluxed, excess NH_4Cl was added and the deep color faded immediately. Solvent was allowed to evaporate following the addition of 50 mL of ether. The resulting solid then was dissolved in water and extracted with three portions of ether and dried (sodium sulfate). Prior to analysis of the concentrated ether extracts by NMR, *tert*-butyl alcohol was added as an internal standard. Some yields were calculated from NMR data, the area of H-3 generally serving as a measure of the isoquinoline. All yield data given in Table I that use NMR as a method of analysis are based on a weighed amount of substrate as the limiting reagent. Evaporation of the ether gave product, purified by standard methods. Mixtures were not always separated, however.

Sodium anilide was generated by the addition of a known amount aniline to the thiomethoxide–amide ion mixture prior to the addition of substrate.

Reactions requiring the removal of samples were carried out in a 50-mL three-necked flask having a stopcock attached near the bottom. Mesitylene was added to the 50-mL flask to serve as an NMR standard. Samples of the ammonia mixture were run through the stopcock into 3 × 30 cm test tubes containing ammonium chloride and cooled in a flask of acetone–dry ice. Stirring these aliquots caused the deep color to bleach. Ether then was added, the solvent was allowed to evaporate prior to analysis by NMR. A control reaction consisting of the usual contents but not amide ion showed that the mole ratio of 4-bromoisoquinoline to mesitylene determined by NMR on a recovered sample agreed to within 10% of that calculated from the weights of materials used in the ammonia mixture. The method of recovery appears to be suitably quantitative.

Unsuccessful attempts were made to observe by proton NMR reactions in liquid ammonia. A sample consisting of 0.7 M 1, 1.4 M $NaSCH_3$, and 1.4 M $NaNH_2$ was very viscous and dark brown. Spectra taken at −40 and 0 °C were poorly resolved.

The reaction flask was cooled in an acetone–dry ice bath prior to the addition of substrate for reactions at −65 °C.

Residues of reaction mixtures were spotted on silica gel plates (GF_{254}, Merck) and developed with various solvents by vertical ascension in a closed tank.

All reactions were conducted under an atmosphere of air.

Synthesis of 1,4-Keto Esters and 1,4-Diketones via Palladium-Catalyzed Acylation of Siloxycyclopropanes. Synthetic and Mechanistic Studies

Tsutomu Fujimura, Satoshi Aoki, and Eiichi Nakamura*,†

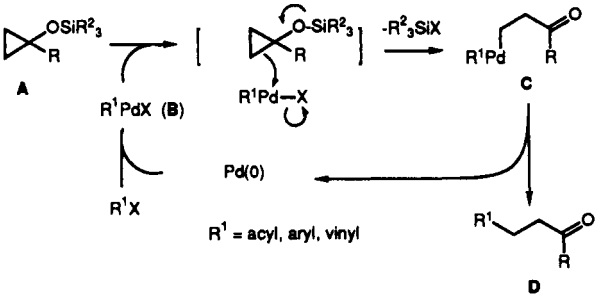
Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Received November 27, 1990

The reaction of a variety of siloxycyclopropanes with acid chlorides in the presence of a catalytic amount of a palladium/phosphine complex gives 1,4-dicarbonyl compounds to good yield. 1-Alkoxy-1-(trialkylsiloxy)-cyclopropanes react with both aromatic and aliphatic acid chlorides in chloroform to give 1,4-keto esters. Synthesis of 1,4-diketones by the acylation of 1-alkyl- or 1-aryl-1-siloxycyclopropanes has been achieved by carrying out the reaction if HMPA under 10–20 atm of carbon monoxide. Kinetics studies and product analysis revealed the unique mechanism of this reaction, which involves rate-determining cleavage of the strained cyclopropane carbon–carbon bond with a coordinatively unsaturated acylpalladium chloride complex. Ab initio calculations of hydroxylated cyclopropane model compounds showed that the unique reactivities of the siloxycyclopropanes may be correlated with the molecular orbital properties of these compounds rather than their ground-state structural properties.

Since the preparation of platinacyclobutanes by the reaction of cyclopropanes with a platinum(II) complex[1] and their subsequent characterization,[2] activation of carbon–carbon σ-bonds by homogeneous transition-metal complexes has been extensively studied in relation to the preparation of stable metal complexes[3] and metal-catalyzed rearrangement of strained molecules.[4] However, the potential of the C–C bond activation in organic synthesis, especially, with regard to its use for intermolecular C–C bond formation, has been little explored, and only a few catalytic C–C bond forming reactions between highly strained molecules and low molecular weight molecules[5] have been recorded as successful examples of such endeavors. It has thus remained a challenge for synthetic and organometallic chemists to develop metal-catalyzed reactions that effect an intermolecular C–C bond formation

Scheme I



† Adjunct professor at Institute for the Molecular Science, Okazaki National Research Institutes.

(1) Tipper, C. F. H. *J. Chem. Soc.* **1955**, 2043.

0022-3263/91/1956-2809$02.50/0