

He inlet pressure of 32 psi. Column B was a 7 ft \times 0.125 in. stainless steel column packed with Apiezon L (15%) on Chromosorb W operated at 210° with a N₂ inlet pressure of 15 psi. Column C was a 5 ft \times 0.125 in. stainless steel column packed with SE-30 (5%) on Chromosorb W operated at 167° with a N₂ inlet pressure of 15 psi. Column D was a 10 ft \times 0.25 in. copper

column packed with Apiezon L (25%) on Chromosorb W operated at 195° with a He inlet pressure of 40 psi.

Determination of product yields was made by comparing peak areas with that of an internal standard. Adjustment was made for differences in thermal conductivity and applied to correct the observed areas.

Notes

Aprotic Diazotization of Aniline in the Presence of Iodine^{1,2}

LESTER FRIEDMAN AND JAN F. CHLEBOWSKI³

Department of Chemistry, Case Western Reserve University,
Cleveland, Ohio 44106




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The reaction of arylamines with amyl nitrite in aromatic solvents has been conclusively demonstrated to generate aryl radicals.⁴ The presence of a radical intermediate in this reaction suggested the use of iodine, which might serve as the radical trap,⁵ to give a facile method for the formation of aryl iodides. When aniline was treated with amyl nitrite in benzene in the presence of an equivalent of iodine,⁶ iodobenzene was formed in 50% yield with small amounts of biphenyl. However, in addition to the expected products, a significant amount of *p*-diiodobenzene was found.⁷

To investigate the source of the diiodinated product, the relative amounts of aniline, iodine, and amyl nitrite were varied (Table I). When aniline is present in excess relative to amyl nitrite, the product composition is insensitive to excess iodine. When amyl nitrite is in excess the expected increase in diiodinated product with increasing iodine concentration is observed. Biphenyl formation does not become significant until less than an equivalent of iodine is present. Iodine acts as a more effective radical trap than benzene by a factor of $\sim 2 \times 10^3$.

These results do not, however, uncover the source of *p*-diiodobenzene. Addition of iodobenzene to an aprotic diazotization reaction had no effect on the yield of diiodinated product. Diazotization of aniline hydroiodide and decomposition of *N*-nitrosoacetanilide and benzenediazonium chloride under conditions similar to those employed in the reaction system gave no *p*-diiodobenzene (Table II). Since these compounds are analogous to either suggested intermediates or transient oxidation states in the diazotization se-

TABLE I
PRODUCT COMPOSITION AS A FUNCTION OF REAGENT RATIOS

| Relative concn of reagents | | | % yield | % product compn | | |
|---|-------|--|---------|---|---|---|
| C ₆ H ₅ NH ₂ | AmONO | ¹ / ₂ I ₂ | |  |  |  |
| 2 | 1 | 2 | 56 | 89 | 10 | 1 |
| 2 | 1 | 1 | 47 | 86 | 11 | 3 |
| 1 | 1 | 1 | 60 | 78 | 21 | 1 |
| 1 | 3 | 1 | 77 | 85 | 13 | 2 |
| 1 | 1.2 | 3 | 63 | 57 | 39 | 4 |
| 1 | 1.2 | 2 | 60 | 64 | 33 | 3 |
| 1 | 1.2 | 1 | 60 | 82 | 16 | 2 |
| 1 | 1.2 | 0.7 | 38 | 77 | 14 | 9 |
| 1 | 1.2 | 0.5 | 41 | 77 | 2 | 21 |

quence, the iodination process must occur prior to the diazotization reaction. Thus, *p*-iodoaniline is postulated as the precursor of *p*-diiodobenzene. When the isomeric iodoanilines are diazotized under reaction conditions, high yields of the respective diiodobenzenes are formed without side products within the limits of detection (glpc). Isolation of *p*-iodoaniline from reactions where an excess of aniline relative to amyl nitrite was employed conclusively demonstrates the intermediacy of this species as precursor of *p*-diiodobenzene.

The direct reaction of aniline and molecular iodine cannot account for the formation of *p*-iodoaniline in this system. When an aniline-benzene mixture was refluxed for 3 hr with an equivalent amount of iodine, iodination of aniline did occur. However, the yield was low, and a mixture of isomers (20% *ortho*, 80% *para*) was obtained. This is not consistent with the relatively high yields and isomer distribution of diiodobenzenes (*ortho* < 1%, *para* > 99%) obtained from the diazotization reaction. Iodination of aniline in aqueous bicarbonate solution,⁸ involving hypoiodous acid as the iodinating agent,⁹ gives almost exclusively the *para* isomer (4% *ortho*) in high yield. Other examples of electrophilic iodination have also shown great *para* selectivity.^{10,11} Thus, a cationic species is postulated as the iodinating agent in this system. An attractive mechanism for the generation of such a species is the oxidation of iodine by alkoxy or hydroxyl radical. These oxidizing agents are generated in the diazotization process and could react with iodine to

(1) Aprotic refers to solvents that are not proton donors. Other examples of such diazotizations are summarized by D. Y. Curtin, J. A. Kampeier, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 863 (1965).

(2) Financial support (Grant No. GP 3976) from the National Science Foundation is gratefully acknowledged.

(3) National Science Foundation Graduate Trainee.

(4) L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1633 (1968).

(5) G. S. Hammond, *J. Amer. Chem. Soc.*, **72**, 3737 (1950).

(6) 1 equiv of iodine = ¹/₂I₂ (127 g).

(7) Small (<1%) amounts of *o*-diiodobenzene were also detected.



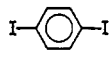
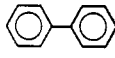
(8) R. Q. Brewster, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 347.

(9) R. M. Hann and J. Berliner, *J. Amer. Chem. Soc.*, **47**, 1710 (1925).

(10) O. Orazi, R. Corral, and H. Bertello, *J. Org. Chem.*, **29**, 1101 (1964).

(11) E. Berliner, *J. Amer. Chem. Soc.*, **72**, 4003 (1950).

TABLE II
 PRODUCTS FROM THE REACTION OF POSSIBLE PRECURSORS OF *p*-DIODOBENZENE WITH IODINE

| Precursor ^a | % yield | % product compn | | | |
|---|---------|---|--|---|---|
| | |  |  |  |  |
| C ₆ H ₅ N(NO)COCH ₃ | 18.3 | | 96.2 | 0.0 | 3.8 |
| C ₆ H ₅ N ₂ ⁺ Cl ⁻ /H ₂ O | 66.2 | 26.2 | 61.0 | 0.0 | 12.8 |
| C ₆ H ₅ NH ₃ ⁺ I ⁻ /AmONO ^b | 64.0 | | 97.6 | 0.0 | 2.3 |
| <i>p</i> -IC ₆ H ₄ NH ₂ /AmONO | 63.9 | | 0.0 | 100.0 | 0.0 |

^a In the presence of ¹/₂I₂ in excess benzene. ^b No I₂ present.

 TABLE III
 APROTIC DIAZOTIZATION OF AROMATIC AMINES WITH IODINE PRESENT^a

| R of RC ₆ H ₄ NH ₂ | Solvent | % yield | % product compn | | | | |
|---|-------------------------------|---------|----------------------------------|--------------------------------|-----------------------------------|--|---|
| | | | RC ₆ H ₄ I | RC ₆ H ₅ | RC ₆ H ₄ Cl | RC ₆ H ₃ C ₆ H ₅ | RC ₆ H ₄ I ₂ |
| H | CCl ₄ | 60.7 | 81 | 0 | 4 | | 15 ^b |
| H | C ₆ H ₆ | 58.4 | 84 | | | 2 | 14 ^b |
| <i>m</i> -CH ₃ | CCl ₄ | 19.7 | 43 | Trace | 20 | | 37 ^c |
| <i>m</i> -CH ₃ | C ₆ H ₆ | 49.5 | 74 | 3 | | 2 | 21 ^c |
| <i>p</i> -CH ₃ | CCl ₄ | 48.6 | 83 | 1 | 5 | | 11 ^d |
| <i>p</i> -CH ₃ | C ₆ H ₆ | 59.8 | 93 | 1 | | 0 | 6 ^d |
| <i>p</i> -I | CCl ₄ | 49.8 | 80 | 6 | 14 | | 0 |
| <i>p</i> -I | C ₆ H ₆ | 63.9 | 100 | 0 | | 0 | 0 |

^a RC₆H₄NH₂/AmONO/¹/₂I₂ = 1:1.2:1. ^b *p*-Diiodobenzene. ^c Mixture of 2,3- and 2,5-diiodotoluene. ^d 2,4-Diiodotoluene.

give alkyl hypoiodite or hypoiodous acid. Alternative and/or additional processes are possible.¹²

Iodobenzene may also be formed by hydrogen abstraction by *p*-iodophenyl radical. However, the reaction of aniline, *m*-toluidine, and *p*-iodoaniline with amyl nitrite and iodine in benzene or carbon tetrachloride yielded only small amounts of reduction product (Table III). At best, less than 1% of the iodobenzene formed can be accounted for by this scheme.

The above results are consistent with Scheme I. Amyl nitrite and an electrophilic iodinating agent compete for available aniline. The first process, a relatively fast reaction, ultimately gives phenyl radical which can react further with either iodine or benzene

to form either iodobenzene or biphenyl, respectively.¹³ Reaction of aniline with the iodinating agent, the generation of which may be dependent on the reaction of aniline and amyl nitrite, is a relatively slow process. *p*-Iodoaniline, generated *in situ* from this reaction undergoes diazotization with amyl nitrite to then yield *p*-iodophenyl radical. *p*-Diiodobenzene is formed on reaction of this species with iodine.¹⁴

The use of this reaction in the preparation of aryl iodides is only slightly limited by the competing side reaction. The desired product, obtainable in a 50% yield, can be easily separated from other materials by steam or vacuum distillation. In addition, the reaction of the iodoanilines and toluidines suggests that substituted amines may not be subject to this complication. The facility with which the reaction is accomplished indicates that it is an attractive alternative to the classical aqueous diazotization method.¹⁵

Experimental Section

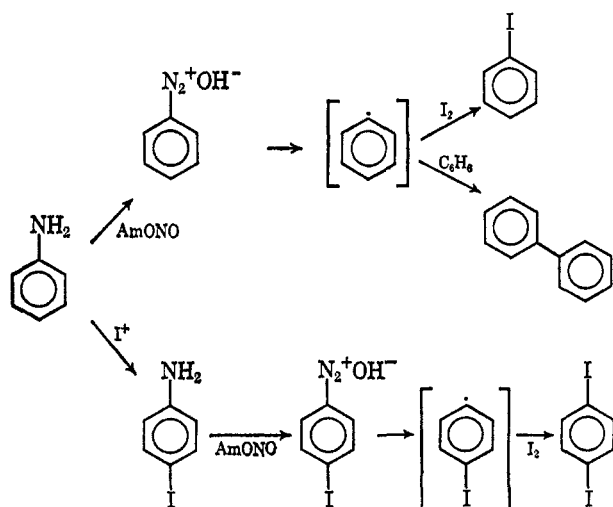
Reagents.—N. F. grade Mallinckrodt "amyl" (isopentyl) nitrite was used without purification.

N-Nitrosoacetanilide was prepared from acetanilide and nitrosyl chloride using the method described by DeTar.¹⁶

Benzenediazonium chloride hydrate was prepared from aniline hydrochloride by diazotization with amyl nitrite in ethanol. This is a modification of the Knoevenagel preparation of diazonium ion salts.¹⁷

Procedure.—Reactions were carried out in the following manner. Amyl nitrite (1.4 g, 0.012 mol) was added to a stirred mixture of aniline (0.93 g, 0.01 mol), iodine (1.26 g, 0.005 mol), and 30 ml of benzene (or other aromatic solvent) in a 50-ml, round-bottom flask equipped with a reflux condenser and gas

SCHEME I



(12) Refluxing equivalent amounts of amyl nitrite and iodine in excess benzene produces no iodobenzene. With an equivalent of acetic acid added to this system, only trace (<0.5%) amounts of iodobenzene were detected. No product formation occurred when sodium nitrite was substituted for the alkyl nitrite. Thus, generation of an iodinating agent by reaction of iodine with amyl nitrite does not occur.

(13) An additional source of iodobenzene can be aniline hydroiodide formed *in situ* as a reaction by-product. On reaction with amyl nitrite, this material yields iodobenzene almost exclusively (Table II).

(14) *p*-Iodobiphenyl is not observed. If the competition for *p*-iodophenyl radical between benzene and iodine is similar to that observed for phenyl radical, only trace amounts of *p*-iodobiphenyl would be formed and would not be detected with the analytical method used.

(15) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 143, p 351.

(16) D. F. DeTar, *J. Amer. Chem. Soc.*, **73**, 1448 (1951).

(17) E. Knoevenagel, *Ber.*, **23**, 2995 (1890).

bubbler. The flask was then placed in an oil bath and gradually heated to solvent reflux. The temperature of the oil bath was maintained at 100°. Reaction was allowed to continue until gas evolution ceased. The mixture was then allowed to cool to room temperature, internal standard was added, and analysis was performed.

Analysis.—The products of these reactions were analyzed by gas chromatography. Compounds were identified by comparison of their retention times to those of authentic materials. In some cases further authentication was made by collecting samples *via* glpc and comparing the infrared spectra and melting points.

Analyses were carried out on a gas chromatography instrument constructed at Case Western Reserve equipped with a 5 ft × 0.25 in. copper column packed with GE-SF-96 (20%) on Chromosorb P operated at 210° with a He inlet pressure of 32 psi.

Determination of product yields was made by comparing peak areas with that of an internal standard, *p*-chlorobiphenyl, adjusting for molar thermal conductivity difference.

Synthetic Application.—*p*-Iodotoluene was prepared in 40% yield by a modification of the procedure described above. Iodine (150 g, 1.18 equiv) and amyl nitrite (140 g, 1.2 mol) were added to 1 l. of benzene in a 2-l., three-necked flask equipped with a mechanical stirrer and reflux condenser. *p*-Toluidine (107 g, 1.0 mol), dissolved in ~200 ml of benzene, was added dropwise over a 2-hr period. The reaction is sufficiently exothermic to bring the solution to reflux temperature without external heating; caution must be exercised in the rate of addition. The rate of nitrogen evolution is dependent on the amine and is accelerated in the presence of iodine and may become excessively vigorous. After allowing the reaction to reflux for an additional 2 hr, the mixture was washed with 700-ml portions of 5% sodium bisulfite solution, water, 5% potassium hydroxide solution, and water. Solvent was removed on a rotary evaporator and the remainder was steam distilled. The organic layer was extracted with petroleum ether (30–60°) and distilled under a vacuum to yield white plates, mp 34–35° (lit.¹⁸ mp 35°), in 40% yield of >99% purity (glpc).

(18) A. Edinger and P. Goldberg, *Ann.*, **167**, 347 (1871).

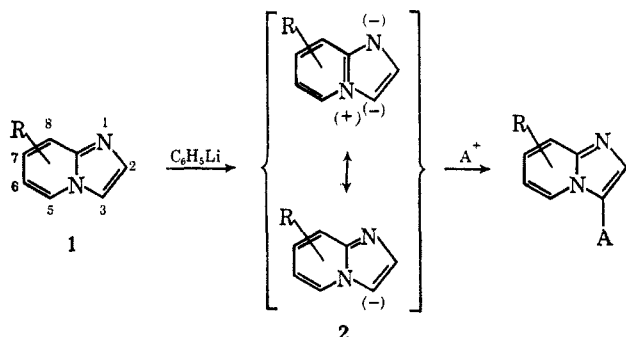
The Syntheses of Substituted Imidazo[1,2-*a*]pyridines via "Ylidelike" Intermediates

WILLIAM W. PAUDLER AND HYUN G. SHIN

Clippinger Laboratories, Department of Chemistry,
Ohio University, Athens, Ohio 45701

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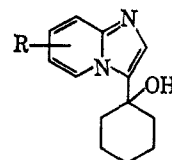
We have recently described the base-catalyzed protium–deuterium exchanges that occur in various "polyazaindenes."^{1,2} The application of these observations to the syntheses of substituted imidazo[1,2-*a*]pyridines is outlined by the reaction sequence^{3,4}



(1) W. W. Faudler and L. S. Helmick, *Chem. Comm.*, 377 (1967).

(2) W. W. Faudler and L. S. Helmick, *J. Org. Chem.*, **33**, 1087 (1968).

We now wish to report the syntheses of a number of substituted imidazo[1,2-*a*]pyridines by this method. The substances prepared by addition of cyclohexanone to compound 2 are represented by the general structure given for compounds 4–8. The addition of dimethyl-

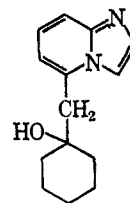


- 4, R = H
5, R = 6-CH₃
6, R = 7-CH₃
7, R = 8-CH₃
8, R = 2-CH₃

formamide and phenyl isocyanate to compound 2 (R = H) affords the imidazo[1,2-*a*]pyridine-3-carboxaldehyde and -3-carboxanilide, respectively. The structure proofs of the various compounds rest upon their nmr (see Table I) and mass (see Experimental Section) spectra and the usual elemental analyses.

The considerable deshielding effect that the substituent in the three position has upon H₅ is of some interest and also contributes considerably to the structure elucidation of these compounds.

A further point of interest is the observation that the protons of the 5-methyl group are the only protons of the various isomeric methylimidazo[1,2-*a*]pyridines that are sufficiently acidic to react with phenyllithium to yield, after treatment with cyclohexanone, compound 11.



11

The structure proof of this compound rests upon its nmr spectrum (the absence of a methyl group) and the other identifying features reported in the Experimental Section. 3-Methylimidazo[1,2-*a*]pyridine could, potentially, afford a substance analogous to 11. However, under the reaction conditions which give the products reported in this Note, *no reaction* occurs between phenyllithium and the 3-methyl compound, the latter being recovered from the reaction mixture. The reactivity of the 5-methyl group is reminiscent of that of the 2-methyl group in pyridines.⁵

Experimental Section⁶

(1-Hydroxycyclohexyl)imidazo[1,2-*a*]pyridines.—To a stirred solution of 2.6 mmol of the appropriate imidazo[1,2-*a*]pyridine

(3) During the course of this work, the reaction of pyridine *N*-oxides, under similar reaction conditions, with cyclohexanone was described and interpreted in terms of an ylide intermediate: R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

(4) A. W. Johnson ("Ylid Chemistry in Organic Chemistry, A series of monographs," Vol. 7, A. T. Blomquist, Ed., Academic Press Inc., New York, N. Y., 1966, suggests the use of the term "ylid" rather than "ylide.")

(5) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955: R. B. Woodward and E. C. Kornfeld, p 413; L. A. Walter, p 757, and elsewhere.

(6) Melting points are corrected. The nmr spectra were obtained with a Varian A-60 spectrometer and the mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E mass spectrometer.