Notes

Application of the Isoamyl Nitrite–Diiodomethane Route to Aryl Iodides

William B. Smith* and Oliver Chenpu Ho

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

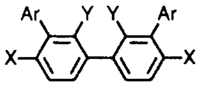
Received May 9, 1989

Introduction

A recent review has summarized the available preparative methods and unique reactions of aryl iodides.[1] The point is made there that organic syntheses with aryl iodides suffer from the absence of simple and reliable methods for preparing these compounds. The original procedure of Griess[2] in which diazonium ions are treated with iodide has not proven entirely satisfactory. As an example, the formation of 2,2′-diiodobiphenyl occurs in trivial yield from the corresponding diamine; the formation of diphenyliodonium iodide (56%) being the dominant reaction.[3]

To overcome this difficulty, Cornforth et al.[4] converted the 2,2′-bis(diazo)biphenyl to a complex with potassium iodomercurate, which was subsequently decomposed (pyrolysis) to give the diiodobiphenyl in 50% yield.

A potentially attractive alternative to the conventional diazonium procedures was offered by the observations of Cadogan, Roy, and Smith[5] using "pentyl" nitrite as the diazotizing reagent and bromoform as both solvent and halogen source. They showed that bromotrichloromethane, chloroform, and carbon tetrachloride were synthetically less satisfactory in serving the latter purpose. Subsequently, Nair and Richardson[6] have carried out the conversion of several aminopurines to their respective halo analogues using this method. With diiodomethane as the solvent, yields of the appropriate iodides were in the range of 20–70%. More recently, Cornforth, Kumar, and Stuart[7] utilized the same conditions to convert the diamine **1a** to the corresponding diiodide. Since we have an interest in preparing compounds of type **1b**, a more detailed examination of the reaction in diiodomethane seemed warranted.



1a: X = NH_2, Y = NO_2, Ar = 3-methyl-5-*tert*-butylphenyl
b: X = $OCH(CH_3)_2$, Y = NH_2

Results and Discussion

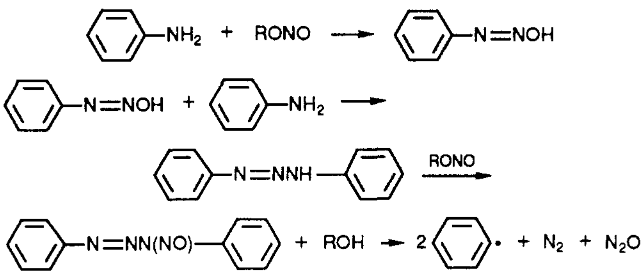
Table I records the yields produced from the reaction of a variety of amines with isoamyl nitrite in diiodomethane. The reported yield for iodobenzene via the diazotization–aqueous potassium iodide route is 75%.[2] While the isoamyl nitrite reaction is convenient to run, it suffers in this one instance in that it is hard to separate the product from excess diiodomethane. In all other cases, this separation was readily effected by simple vacuum distillation. The yield of 2,2′-diiodobiphenyl and the convenience of the method suggest that this is the method of choice for preparing this compound. As evidenced in Table I, increasing steric hindrance about the reaction site decreases the yield of product. The reactions of two compounds with the structure of **1b** (Ar = 3,5-dichloro-4-methoxyphenyl and Ar = 6-methoxy-2-naphthyl) were carried out with completely negative results. The synthesis of these diamines will be described elsewhere.

Table I. Yields of the Iodoaryls from Arylamines, Isoamyl Nitrite, and Diiodomethane at 80 °C

amine	% yield
aniline	70
2-nitroaniline	65
4-nitroaniline	90
4-methoxyaniline	78
2,2′-diaminobiphenyl	60
2,6-dinitroaniline	36[a]
o-phenylenediamine	nil[b]

[a] Temperature 105 °C. [b] Only benzotriazole was formed at either 80 or 110 °C.

Scheme I



Aniline was found to react very rapidly with isoamyl nitrite to form diazoaminobenzene, a fact initially recorded in 1875.[8] This offers a convenient method of preparation (yield 67%) for small amounts of this substance. At room temperature, nitrogen evolution begins slowly and only when additional nitrite is present. Diazoaminobenzene is stable in diiodomethane at 80 °C. Addition of a second equivalent to isoamyl nitrite at that temperature leads to the rapid formation of iodobenzene, which is the only observable product by NMR or GC detection. In the case of *o*-phenylenediamine, only benzotriazole is formed, this particular triazene being stable to isoamyl nitrite even at 110 °C. The mechanistic proposal depicted in Scheme I builds on those suggested by earlier workers[5,6,9] but includes the formation of diazoaminobenzene as a necessary portion of the pathway.

Recently, Ku and Barrio[10] have shown that 3,3-dialkyl-1-aryltriazenes can be decomposed by trimethylsilyl iodide, forming the corresponding aryl iodides in yields comparable with those in Table I. The proposed mechanism involves the formation of the 3-trimethylsilyl deriv-

---

[1] Merkushev, E. B. *Synthesis* **1988**, 923.
[2] Griess, P., *Ann. Chem. Pharm.* **1866**, *127*, 76.
[3] Lothrop, W. C. *J. Am. Chem. Soc.* **1941**, *63*, 1187.
[4] Cornforth, J.; Ridley, D. D.; Sierakowski, A. F.; Ugen, D.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2317.
[5] Cadogan, J. I. G.; Roy, D. A.; Smith, D. M. *J. Chem. Soc. C* **1966**, 1249.
[6] Nair, V.; Richardson, S. G. *Synthesis* **1982**, 670; *J. Organomet. Chem.* **1980**, *45*, 3969.
[7] Cornforth, J.; Kumar, A.; Stuart, A. S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 859.
[8] Meyer, V.; Ambuhl, G. *Ber. Dtsch. Chem. Ges.* **1875**, *8*, 1073.
[9] Friedman, L.; Chlebowski, J. F. *J. Org. Chem.* **1968**, *33*, 1633.
[10] Ku, H.; Barrio, J. R. *J. Org. Chem.* **1981**, *46*, 5239.

0022-3263/90/1955-2543$02.50/0

ative, which then undergoes a displacement by iodide at the aryl point of attachment. As a comparison, diazoaminobenzene was treated with trimethylsilyl iodide in acetonitrilie, yielding iodobenzene in ca. 20% yield. In contrast, the treatment of 3,3-diethyl-1-phenyltriazene with isoamyl nitrite in diiodomethane gave a 44% yield of iodobenzene, confirming the generalization above that triazenes and isoamyl nitrite may be used to generate aryl radicals. The dialkylaryltriazenes in their study were produced by the reaction of the appropriate diazonium ion with the secondary amine under alkaline conditions. As a possible approach to enhancing yields, several unsuccessful attempts were made to prepare the diethylphenyltriazene directly from aniline, diethylamine, and isoamyl nitrite. It was apparent that the undesired reaction of the dialkylamine with the nitrite was very much the faster reaction. It is mentioned parenthetically that treatment of acetanilide with isoamyl nitrite in diiodomethane did not produce yields of iodobenzene comparable to those obtained when aniline was used.

The reaction of 2,6-dinitroaniline with isoamyl nitrite at 80 °C returned only unreacted starting material. When the nitrite was added in portions to the amine in diiodomethane at 105 °C, a 36% yield of the iodo compound was obtained. No doubt steric hindrance prevents the facile formation of the triazene. Of course, in this instance, an intermediate diazonium compound may directly decompose to free radicals.

In summary, the reactions of aryl amines with isoamyl nitrite in an excess of diiodomethane often forms aryl iodides cleanly and in good yields. It is clear from the results in Table I that increasing steric hindrance about the amine group decreases the yield.

Experimental Section

Melting points were taken on a Thomas-Hoover or on a Koefler Heizbank instrument and are uncorrected. All NMR spectra were taken in deuteriochloroform with internal TMS as the standard. Proton and carbon spectra were taken on a Varian XL-300 instrument operating at 300 MHz for protons and 75 MHz for carbon. Mass spectra were determined on a Finnigan Model 1020 instrument.

With the exception of the reactions of aniline forming iodobenzene, it was convenient to work up the reaction mixtures by a standard procedure that involved distilling off the excess diiodomethane at ca. 1 mm in a Kugelrohr apparatus with gentle heating. The weight, NMR parameters, and often a melting point of the crude product were obtained. If the material was very dark, it was purified by passage through a plug of alumina with a benzene-methylene dichloride solvent, 1:1.

Diazoaminobenzene. This material was prepared by a modification of the method of Meyer and Ambuhl.[8] A solution of 1.86 g (20 mmol) of aniline in 30 mL of 1.1 ethanol–water was reacted at room temperature with 3 mL of isoamyl nitrite overnight. The long, golden needles of product were collected and dried: 1.97 g (67%); mp 95–96 °C (lit.[13] mp 98 °C); ^{1}H NMR 7.16 (2 H, t), 7.34–7.44 (8 H, m); ^{13}C NMR with gated decoupling with a 5-s delay, 117.9 (4 C), 125.2 (2 C), 129.2 (4 C), and a quaternary C at 145.1. Note: one quaternary C was never found and may be overlapped in the spectrum.

In one experiment, 0.93 g (10 mmol) of aniline in 10 mL of deuteriochloroform was reacted at room temperature with 1.17 g (10 mmol) of isoamyl nitrite. After 10 min, the NMR spectrum in the aromatic region showed only diazoaminobenzene. The NMR spectrum of a sample of diazoaminobenzene in diiodomethane remained unchanged after heating at 80 °C for 2.5 h.

Reactions with Aniline. a. Preparation of Iodobenzene. A mixture of 0.5 g (5.3 mmol) of aniline, 1.17 g (10 mmol) of isoamyl nitrite, and 10 mL of diiodomethane was stirred at room temperature for 0.5 h and then heated under nitrogen at 80 °C for 2 h. The separation of iodobenzene from excess diiodomethane was effected by addition of the reaction mixture at room temperature to a solution of piperidine (25 mL) and acetonitrile (25 mL). A vigorous exothermic reaction ensued, following which excess volatile reagents were removed by rotary evaporation at 80 °C and water-pump pressure. The residue was washed with 10% hydrochloric acid, and the iodobenzene layer was separated and dried over anhydrous magnesium sulfate. Separated by filtration, and product (0.77 g, 70%) was identified as iodobenzene by direct comparison of the NMR spectra with those of an authentic sample: ^{1}H NMR 7.08 (2 H, t), 7.31 (1 H, t), 7.66 (2 H, d, J = 8.1 Hz); ^{13}C NMR 94.5 (C-1), 136.9 (C-2,6), 129.9 (C-3,5), 127.0 (C-4).

b. In a second reaction, 0.93 g (10 mmol) of aniline in 3 mL of methylene diiodide was reacted at room temperature with 2.34 g (20 mmol) of isoamyl nitrite. After 10 min, a small sample was drawn off and added to deuteriochloroform. Both the proton and carbon NMR spectra showed only diazoaminobenzene in the aromatic region.

After standing for 1.5 h, gas evolution from the mixture was noted. The mixture was heated to 80 °C for 1.5 h. Examination by NMR showed the isoamyl nitrite to be gone. The aromatic region indicated only the presence of iodobenzene by comparison with the spectra of an authentic sample of that material.

Preparation of 2-Nitroiodobenzene. A solution of 1.38 g (10 mmol) of 2-nitroaniline in 10 mL of diiodomethane was stirred at room temperature. Isoamyl nitrite (3.6 g (30 mmol)) was added over a period of 30 min. The evolution of gas was monitored over a period of 4 h. At this time, gas evolution had ceased, the reaction mixture had taken on a golden color, and solid had deposited around the walls of the flask.

The standard workup gave, after washing through an alumina plug, a reddish amorphous mass (1.63 g, 65%), which gave proton and carbon spectra identical with those of an authentic sample of 2-nitroiodobenzene: mp 47–49 °C (lit.[12] mp 49.5 °C); ^{1}H NMR 7.27 (1 H, t), 7.50 (1 H, t), 7.85 (1 H, d), 8.04 (1 H, d); ^{13}C NMR 86.1 (C-1), 153.0 (C-2), 125.4 (C-3), 129.1 (C-4), 133.4 (C-5), 141.9 (C-6).

Preparation of 4-Iodoanisole. A mixture of *p*-anisidine (0.2 g, 1.62 mmol), isoamyl nitrite (1.17 g, 10 mmol), and 10 mL of diiodomethane was stirred at room temperature for 1 h and then heated under nitrogen at 65 °C for 2 h. The product was recovered by the standard procedure, yielding 0.30 g of NMR-pure-4-iodoanisole (78%): mp 50–51 °C (lit.[13] mp 51–52 °C); ^{1}H NMR 6.65 (2 H, d), 7.52 (2 H, d); ^{13}C NMR 159.3 (C-1), 116.3 (C-2,6), 138.0 (C-3,5), 82.7 (C-4), 55.2 (methoxy).

Preparation of 4-Nitroiodobenzene. A mixture of 0.14 g (1 mmol) of 4-nitroaniline, 0.59 g (5 mmol) of isoamyl nitrite, and 7 mL of diiodomethane was stirred at room temperature for 1 h. The mixture was then heated and stirred for 2 h at 80 °C. The standard workup gave 0.23 g (90%) of NMR-pure 4-iodonitrobenzene: mp 169–171 °C (lit.[14] mp 172 °C); ^{1}H NMR 7.93 (br); ^{13}C NMR 147.7 (C-1), 124.8 (C-2,6), 138.6 (C-3,5), 102.6 (C-4).

Preparation of 2,2′-Diiodobiphenyl. A mixture of 0.184 g (1 mmol) of 2,2′-diaminobiphenyl, 1.17 g (10 mmol) of isoamyl nitrite, and 10 mL of diiodomethane was stirred at room temperature for 1 h. It was then heated under nitrogen at 80 °C for 3 h. The standard workup gave crude material, which showed the presence of carbazole. It was taken up in 20 mL of benzene and washed with concentrated sulfuric acid followed by a wash with 3 M sodium hydroxide. The benzene solution was dried over magnesium sulfate and filtered and the benzene removed under vacuum on a rotary evaporator, yielding a residue of NMR-pure 2,2′-diiodobiphenyl (0.24 g, 60%): mp 106–109 °C (lit.[15] mp 106–108 °C); ^{1}H NMR 7.08 (2 H, td), 7.18 (2 H, dd), 7.41 (2 H, td), 7.93 (2 H, dd); ^{13}C NMR 148.8 (C-1), 99.6 (C-2), 138.8 (C-3), 129.8 (C-4), 127.9 (C-5), 129.3 (C-6).

Preparation of 2,6-Dinitroiodobenzene. A mixture of 0.18 g (1 mmol) of 2,6-dinitroaniline, 0.59 g (5 mmol) of isoamyl nitrite, and 6 mL of diiodomethane was stirred for 1 h at room tem-

---

(11) Fischer, B. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 641.

(12) Ullmann, F. *Ibid.* **1896**, *29*, 1880.

(13) Reverdin, F. *Ibid.* **1896**, *29*, 997.

(14) Mayes, H. A.; Turner, E. E. *J. Chem. Soc.* **1929**, 500.

(15) Mascarelli, L. *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **1908**, *17* II, 580.

perature and then heated for 2 h at 80 °C. The volatile materials were removed by gentle heating at ca. 1 mm. Examination of the product by NMR showed only unreacted starting material.

Subsequently, the reaction was repeated at 105 °C with 2 mmol of the aniline. The standard workup gave 0.21 g (36%) of yellow crystalline NMR-pure 2,6-dinitroiodobenzene: mp 113 °C (lit.[16] mp 113 °C).

Reaction of *o*-Phenylenediamine. A mixture of *o*-phenylenediamine (0.216 g, 2 mmol), isoamyl nitrite (1.2 g, 10 mmol), and 5 mL of diiodomethane was heated with stirring at 80 °C for 2 h. The standard workup produced a dark residue (0.27 g), which upon ^{1}H and ^{13}C NMR examination proved to be benztriazole by comparison with the spectra of an authentic sample. An entirely similar result was obtained when the reaction was carried out at 110 °C.

Ancillary Experiments. 1. Reaction of Diazoaminobenzene with Trimethylsilyl Iodide. To a mixture of 0.75 g (5 mmol) of sodium iodide and 0.39 g (2 mmol) of diazoaminobenzene in 10 mL of acetonitrile was added 0.55 g (5 mmol) of trimethylsilyl chloride. The mixture turned dark, and gas evolution began immediately. The mixture was heated to 60 °C for 15 min, and the solvent was evaporated under water-pump pressure on a rotary evaporator. The ^{1}H and ^{13}C NMR spectra of the crude mixture showed a complex mix of products. It was estimated from these spectra that approximately 20% starting material remained and that a similar amount of iodobenzene had been formed. No further analysis was carried out. A duplicate reaction gave the same result.

2. Reaction of 1-Phenyl-3,3-diethyltriazene with Isoamyl Nitrite. The method of Ku and Barrio[10] was used to prepare 1-phenyl-3,3-diethyltriazene from benzenediazonium chloride. A mixture of 0.89 g (5 mmol of triazene was dissolved in 10 mL of diiodomethane, and 1.17 g (10 mmol) of isoamyl nitrite was added. The reaction mixture was allowed to stand at room temperature for 30 min and then heated to 80 °C for 2 h. A small portion of the solution was dissolved in deuteriochloroform and examined directly by ^{1}H and ^{13}C NMR. The composition of the mixture was 44% iodobenzene and 56% unreacted starting material. This could be increased to 63% iodobenzene–37% starting material by the addition of a second 10 mmol of isoamyl nitrite and a further 2 h of heating at 80 °C.

Several attempts were made to prepare the triazene directly by the reaction of isoamyl nitrite on mixtures of aniline and diethylamine in chloroform. These reactions were followed by NMR, which indicated that the isoamyl nitrite reacted much more rapidly with the diethylamine than with the aniline. Presumably *N*-nitrosodiethylamine was being formed, though this matter was not further investigated.

3. Reaction of Acetanilide with Isoamyl Nitrite. Acetanilide (0.75 g, 5 mmol) was dissolved in 10 mL of diiodomethane, and 1.17 g (10 mmol) of isoamyl nitrite was added. The mixture was heated at 80 °C for 1.5 h. An additional 1.17 g of isoamyl nitrite was added, and the heating was continued for another hour. The aromatic regions of the proton and carbon spectra showed absorptions due only to iodobenzene. An estimated yield based on both NMR and GC analysis were 30–40%.

In a similar experiment, the diacetyl derivative of 2,2′-diaminobiphenyl was reacted with an excess of isoamyl nitrite in diiodomethane. Examination of the product by NMR showed no starting material remaining after 1.5 h at 80 °C. There was no spectral evidence for the formation of 2,2′-diiodobiphenyl.

Acknowledgment. Grateful acknowledgement is hereby extended to the Robert A. Welch Foundation for the support of this work.

Registry No. PhNH$_2$, 62-53-3; *o*-NO$_2$C$_6$H$_4$NH$_2$, 88-74-4; *p*-MeOC$_6$H$_4$NH$_2$, 104-94-9; *p*-NO$_2$C$_6$H$_4$NH$_2$, 100-01-6; *o*-NH$_2$C$_6$H$_4$C$_6$H$_4$NH$_2$-*o*, 1454-80-4; *o*-NH$_2$C$_6$H$_4$NH$_2$, 95-54-5; PhNHCOCH$_3$, 103-84-4; PhI, 591-50-4; *o*-NO$_2$C$_6$H$_4$I, 609-73-4; *p*-IC$_6$H$_4$OMe, 696-62-8; *p*-NO$_2$C$_6$H$_4$I, 636-98-6; *o*-IC$_6$H$_4$C$_6$H$_4$I-*o*, 2236-52-4; 2,6-dinitroaniline, 606-22-4; 1-phenyl-3,3-diethyltriazene, 13056-98-9; diazoaminobenzene, 136-35-6; 2,6-dinitroiodobenzene, 26516-42-7; benztriazole, 95-14-7.

---

[16] Korner, W. *Jahresbericht* **1875**, 322.

A Facile One-Pot Synthesis of Unsymmetrical Biaryl-2-carbonitriles by Novel Reaction of Ylidenemalononitriles with Dienamines

Bir Sain and Jagir S. Sandhu*

Regional Research Laboratory, Jorhat 785 006, India

Received August 4, 1989

Although symmetrical biaryl can be prepared by many aryl–aryl carbon bond formation reactions,[1] the known methods for the synthesis of unsymmetrical biaryls[2] are limited. The synthetic value of these methods is further diminished by poor yields of the products and the formation of an intricate mixture of the isomers which are not readily separable.

In continuation to our studies on cycloaddition reactions of dienamines,[3] herein we report a novel reaction of readily accessible ylidenemalononitriles[4] **1** with dienamines[5] **2** to afford unsymmetrical biaryl-2-carbonitriles **3** in good yields (Scheme I). This method constitutes a very convenient and facile one-pot synthesis for the preparation of unsymmetrical biaryls **3**, which are not readily obtainable by conventional aryl–aryl coupling reactions.[1,2]

Reaction of 2-thienylidenemalononitrile (**1a**) and 4-(1,3-butadienyl)morpholine (**2a**) in equimolar quantities gave bright red crystals, mp 160–161 °C. This product is assigned biaryl-2-carbonitrile structure **3a** on the basis of elemental analyses and spectral data. Reaction of 2-thienylidenemalononitrile (**1a**) with *N*,*N*-diethyl-1,3-butadienylamine **2b** also yielded biaryl **3a** in comparable yield. The versatility of this method was demonstrated by the synthesis of biaryl-2-carbonitriles **3b–g** from ylidenemalononitriles **1b–g** derived from aldehydes having electron-withdrawing as well as electron-releasing groups.

A plausible mechanism for the formation of biaryl-2-carbonitriles by this reaction could be (4 + 2) cycloaddition of ylidenemalononitriles **1** and dienamine **2** followed by concomitant elimination of HCN and amine moieties from the adduct. The formation of the adducts of type **4** and **5** which would have been the result of the addition of one molecule of ylidenemalononitrile onto the intermediate product was not observed in these reactions (Scheme I).

In conclusion this method appears to be very convenient and fairly general for the synthesis of unsymmetrical biaryl-2-carbonitriles which could be difficult to reach otherwise. The easy availability of a variety of ylidenemalononitriles and diene partners significantly extends the scope of this methodology and more particularly ylidenemalononitriles derived from polycyclic, aromatic, and hetero aromatic aldehydes are likely to afford interesting novel biaryls.

---

[1] (a) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. (b) Colon, I.; Kelsey, D. R. *J. Org. Chem.* **1986**, *51*, 2627 and references cited therein.

[2] (a) Beadle, J. R.; Korzeniowski, S. H.; Rosenberg, D. E.; Garcias-langa, B. J.; Gokel, G. W. *J. Org. Chem.* **1984**, *49*, 1594. (b) Tamura, Y.; Inoue, M. W.; Minamikawa, J. *Synthesis* **1978**, 822. (c) Bartle, M. G.; Mackie, R. K.; Tedder, J. M. *J. Chem. Soc., Chem. Commun.* **1974**, 271. (d) Goshaev, M.; Otroshchenko, O. S.; Sadykov, A. A. *Zh. Khim.* **1970**, *7Zh*, 354.

[3] (a) Davi, P.; Sandhu, J. S.; Thyagarajan, G. *J. Chem. Soc., Chem. Commun.* **1979**, 710. (b) Borah, H. N.; Devi, P.; Sandhu, J. S.; Baruah, J. N. *Tetrahedron* **1984**, *40*, 1617. (c) Devi, P.; Sandhu, J. S. *Indian J. Chem.* **1979**, *18B*, 453.

[4] For recent reviews, see: (a) Campaigne, E.; Schneller, S. W. *Synthesis* **1976**, 705. (b) Freeman, F. *Chem. Rev.* **1980**, *80*, 329. (c) Freeman, F. *Synthesis* **1981**, 925.

[5] For recent reviews on enamines and dienamines, see: (a) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (b) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 3383. (c) Hickmott, P. W. *Tetrahedron* **1984**, *40*, 2989.

0022-3263/90/1955-2545$02.50/0