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The Newborn Surface of Dull Metals in Organic Synthesis. Bismuth-Mediated Solvent-Free One-Step Conversion of Nitroarenes to Azoxy- and Azoarenes

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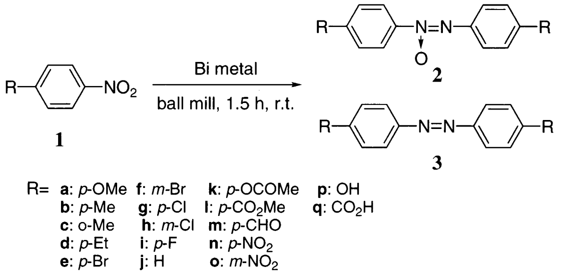
Received June 3, 2002

Abstract: When milled together with bismuth shots, nitroarenes are readily converted to azoxy- and/or azoarenes depending on substrates and conditions employed. Simple extraction with organic solvent followed by evaporation of the resulting dark pasty solid gave the product in good yield.

When a metal is mechanically crushed, the newborn metal surface should be highly activated and immediately react with atmospheric oxygen and moisture to form a thin film of metal oxide/hydroxide, which protects the metal from further oxidative degradation. With the decrease of metallic nature, however, such protective action will be moderated and the activated metal surface could survive for a short while enough to react with a neighboring molecular species other than those of atmospheric origin. With this idea in mind, we have examined the reaction of in situ pulverized metals with a series of organic compounds under completely dry conditions. Chemical activation of metals has been extensively studied and widely employed in organic synthesis.[1] However, mechanical activation of metals has been investigated mainly from physicochemical point of view,[2] and only few attempts have so far been made to exploit it in organic transformations.[3] In this paper, we wish to report a solvent-free one-step conversion of aromatic nitro compounds **1** to azoxy ones **2** (Scheme 1) based on the nascent surface of dull metals such as bismuth and lead. Numerous papers have been published on the solid-phase reactions that involve the supported reagents, solid acid/base catalysts, immobilized enzymes or imprinted solid materials, but all of these deal with the *cold and static* solid surface. The present results are concerned with the *hot and newborn* solid surface and should provide a novel aspect of solvent-free organic reactions.

SCHEME 1



Among several metals of moderate hardness or brittleness that are available commercially in the form of shots or grains, bismuth and lead have been found to exhibit a unique ability to deoxygenate nitroarenes **1** to azoxyarenes **2** and/or azoarenes **3** in good yield. Both metals are cheap and easy to handle. Lead is toxic, but bismuth is not. Some bismuth salts are orally taken as medicines for intestinal disorders.[4] A black slurry in situ generated from bismuth chloride and zinc[5] or sodium borohydride[6] in organic solvent was previously used for the reduction of nitroarenes to azoxyarenes. The active species involved therein was taken as free bismuth by the authors, but possible involvement of low valent bismuth, bismuthane (BiH_3), borane, nascent hydrogen, or electrochemical process on a binary metal system cannot be excluded.

Aromatic azoxy compounds are key materials for electronic devices based on their liquid crystalline properties, while azo compounds are important as the backbone for a variety of dyestuffs. Azoxyarenes **2** are obtained directly from nitroarenes **1** by heating with alcoholic KOH,[7] sodium alkoxide,[8] or zinc/NaOH,[9] reduction with sodium borohydride,[10] lithium aluminum hydride[11] or sodium arsenite,[12] treatment with magnesium,[13] samarium,[14] or thallium metal[15] in alcohol, catalytic reduction over palladium,[16] alkaline reduction with phosphine[17] or glucose,[18] and electrochemical reduction.[19] Aromatic azo compounds **3** are directly obtainable from nitro compounds **1** by reduction with zinc/NaOH,[20] lithium aluminum hydride[21] or dicobalt octacarbonyl,[22]

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10.1021/jo0203645 CCC: $22.00

TABLE 1. Reaction of *p*-Nitroanisole 1a and Bismuth Shots under Different Conditions

run	conditions	product ratio[a] **2a**/**3a**	conversion (%)	yield[b] (%)
1	under air	78/22	~100	~100
2	under air[c]	100/0	7[d]	~100
3	under N_2	17/83	~100	~100
4	under O_2	100/0	~100	~100
5	1 drop of hexane added	100/0	91[d]	~100
6	1 drop of benzene added	100/0	~100	~100

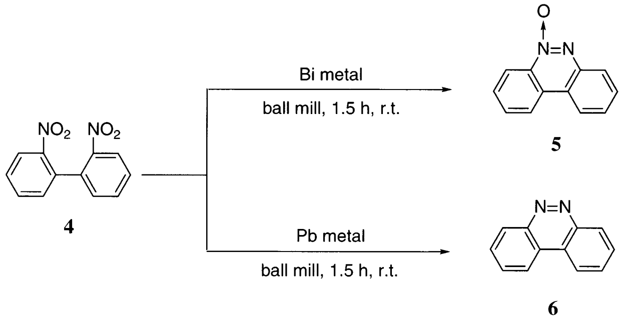
[a] Determined by ^{1}H NMR. [b] Based on conversion. [c] Powdery bismuth (~100 mesh) was used. [d] Isolated yield.

and by high-temperature reaction with ethanolamines.[23] Heating aromatic nitro compound and aniline at high temperature in the presence of powdered alkali also leads to azo compound.[24] A variety of multistep indirect routes are available for aromatic azo compounds, which include diazonium coupling, condensation of nitrosoarene with aromatic amine or azide, mild oxidation of aromatic amines, etc.[25] However, all known preparative methods involve the wet process based on solution chemistry.

4-Nitroanisole **1a**, commercial bismuth shots (Kishida, ca. 1 mm) and small stainless balls were placed in a stainless steel cylinder (1.2 × 4 cm) with a screw cap and gently shaken on a laboratory ball-mill apparatus at a rate of 30 Hz/s for 1.5 h at room temperature. The resulting dark gray to near black powder or pasty solid was extracted with ethyl acetate by trituration. The extract was filtered on a thin bed of a Celite and evaporated to leave a mixture of 4,4′-dimethoxyazoxybenzne **2a** and 4,4′-dimethoxyazobenzene **3a** in a 78:22 ratio in almost 100% combined yield (Table 1, run 1). The insoluble black powder was a mixture of bismuth and bismuth oxide which, thanks to the low reduction potential of bismuth, can be readily converted to the original metal simply by heating under an atmosphere of such reducing gases as hydrogen, carbon monoxide, and methane.[26]

The reaction vessel was not airtight and so, with an intention to exclude the influence of atmospheric oxygen, the milling was carried out under an atmosphere of nitrogen. As expected, the product composition shifted considerably toward the azo compound at the expense of the azoxy compound (**2a**/**3a** = 17:83). To our surprise, however, the addition of a drop of an inert organic solvent such as hexane or benzene to the nitroarene-bismuth mixture prior to milling led to the complete reversal of this ratio in favor of azoxyarene **2a** (Table 1, runs 5 and 6). When the bismuth shot was replaced by a commercial powdery bismuth (Ishizu; −100 mesh, 99.99% purity), the reaction came to a halt at low conversion and most of the starting material was recovered intact (run 2). These observations demonstrate a crucial role of the nascent bismuth surface in the reductive dimerization of nitroarene **1a** to azoxy- and azoarenes **2a** and **3a**.

SCHEME 2



The reaction of 2,2′-dinitrobiphenyl **4** with bismuth shots was quite slow and incomplete, giving benzo[*c*]cinnoline *N*-oxide **5** in 90% yield based on conversion. However, by replacing bismuth with lead (Ishizu; 99.999% purity), nitroarene **4** readily underwent reductive cyclization to form benzo[*c*]cinnoline **6** in 95% isolated yield (Scheme 2). These polycyclic azaarenes were previously prepared by the reduction of **4** with lithium aluminum hydride,[27] sodium borohydride[28] or samarium metal,[14] oxidation of 2,2′-diaminobiphenyl with sodium perborate,[29] and photochemical cyclodehydrogenation of azobenzene **2a** in concentrated sulfuric acid.[30]

The reductive dimerization of nitroarenes by bismuth metal is highly dependent on the nature of a substituent group present in aromatic ring. When the substituent is alkyl, alkoxy, or halogen, azoxybenzenes **2a**−**i** are obtained in good isolated yield. In contrast, the electron-withdrawing substituents such as acyl, acyloxy, and nitro groups suppressed the reaction. As expected, the presence of hydroxy and carboxy functions inhibited the reaction (Table 2).

Among several other metals commercially available in the form of shots or grains, which included tin, manganese, copper, aluminum, antimony, and lead, only the last metal showed satisfactory deoxygenating ability and gave acceptable results. The oxidation−reduction potentials of these metals follow the order Al > Mn > Sn > Pb > H > Sb > Bi > Cu.[31] When the lead shots were subjected to ball-milling in the presence of **1a**, azo compound **3a** was obtained as the sole product in 96% isolated yield (Table 3, run 3). Little or no azoxy compound could be detected. This is consistent with the more reactive nature of lead as compared to bismuth, but at variance with the previous report that nitroarenes are reduced to azoxy-

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TABLE 2. Reduction of Various Nitroarenes with Bismuth Shots under a Hexane Vapor[a]

nitroarene	product ratio[b] **2**/**3**	conversion[c] (%)	yield[d] (%)
1a	100/0	91	~100
1b	100/0	86	~100
1c	100/0	~100	~100
1d	100/0	89	~100
1e	100/0	98	~100
1f	100/0	43	~100
1g	100/0	~100	~100
1h	100/0	92	~100
1i	100/0	63	~100
1j	0/100	~100	~100
1k−**q**	−	0	0

[a] For details, see the Experimental Section. [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] Based on conversion.

TABLE 3. Reduction of Nitroarenes 1a, 1g, and 1j with Different Metal Grains or Shots

run	substrate	metal	additive	product ratio[a] **2**/**3**	yield[b] (%)
1	**1a**	Bi	hexane	100/0	91
2	**1a**	Pb	hexane	60/40	89
3	**1a**	Pb		0/100	96
4	**1f**	Bi	hexane	100/0	~100
5	**1f**	Pb	hexane	95/5	71
6	**1f**	Pb		0/100	94
7	**1j**	Sb			0
8	**1a**	Sn			0
9	**1a**	Mn			0
10	**1a**	Al			0

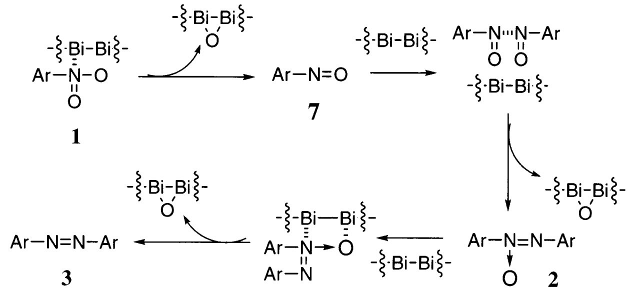
[a] Determined by ^{1}H NMR. [b] Refer to isolated compounds. Not optimized. Reaction time was 1.5 h.

arenes by heating with lead in DMF under reflux.[32] In the reaction with metallic lead, however, care should be taken when opening the reaction vessel, since the resulting black powdery mixture was liable to catch fire in contact with air. Lead was probably converted to an inflammable lower oxide or so during the reductive dimerization of nitroarene **1a**. Such spontaneous ignition was never observed with bismuth. Antimony belongs to the same family as bismuth, but it was quite reluctant to react with nitroarenes.

The formation of azoxyarene **2** from nitroarene **1** under aqueous conditions has been known to proceed via the stepwise reduction processes from **1** to nitrosoarene **7** to *N*-arylhydroxylamine, followed by the dehydrative coupling of the last two species to produce **2**.[33] Under the present completely dry conditions, however, no proton source is available. Therefore, the deoxygenative dimerization of nitroarenes on the activated bismuth surface is most likely to proceed according to the pathway illustrated in Scheme 3.

Nitroarene **1** is adsorbed and deoxygenated on the newborn bismuth surface to form nitrosoarene **7** as the initial product, which then couples with another molecule of **7** to afford azoxyarene **2**. In the presence of oxygen or some additive, part of active metal surface would be occupied or destroyed by these molecular species and further reduction will be suppressed. In the absence of these, however, the reaction goes further to produce azoarene **3**. This interpretation is substantiated by runs 3/4 in Table 1 and runs 5/6 in Table 3, where the product ratios **2**/**3** were reversed in the presence of an additive. Consistent with this Scheme, the milling of **2a** with bismuth shots readily gave a quantitative yield of **3a**. The electron-donating substituent would facilitate the nucleophilic attachment of the oxygen atom of the nitro function onto the newborn bismuth surface in a push−pull manner, but the electron-withdrawing group would disfavor such a process. Thus, *p*-dinitrobenzene **1n** does not react with bismuth shots under the conditions employed, but *p*-nitrosonitrobenzene was readily converted to 4,4′-dinitroazobenzene **3n**. Therefore, the conversion of the nitro group to the nitroso group is most likely the key step of this overall transformation. When an equimolar mixture of two different nitroarenes **1a** and **1b** was milled together with bismuth, two symmetrical and one unsymmetrical azoxyarenes were formed in an approximate ratio of 1:1:1. This observation contrasts with the previous reports that symmetrical azoxybenzenes were always obtained as the major product from the reaction of differently substituted nitrosobenzene and *N*-phenylhydroxylamine due to the rapid equilibrium between these two substrates in solution.[34] Interestingly enough, parent nitrobenzene **1j** contrasts in its behavior to substituted nitrobenzenes **1a**−**i**, producing not the expected azoxybenzene **2j** but azobenzene **3j** as the sole product. This may be taken to reflect some topological feature of the newborn solid surface, on which less bulky **1j** can settle down better to be transformed to **3j** beyond **2j**. Attempts to trap a nitrene or nitrenoid species failed, precluding its possible intermediacy in the formation of azoxy- and/or azoarenes.

SCHEME 3



The present methodology was successfully extended to the single-step synthesis of long-chain 4-alkoxyazoxyarenes **9** from the corresponding nitro compounds **8** (Table 4). Compounds **9a**−**h** are long known for their liquid crystalline property.[35] The reaction was clean and the yield based on conversion was almost quantitative. The unsatisfactory conversion observed with nitroarenes having an alkoxy chain longer than eight carbon units may be attributed to inefficient mixing, but it may also reflect some role played by the longer alkoxy chain in the reduction of nitroarenes **8** on the structured solid surface. The product was always azoxy compound irrespective of the presence or absence of an additive. Prolonged reaction

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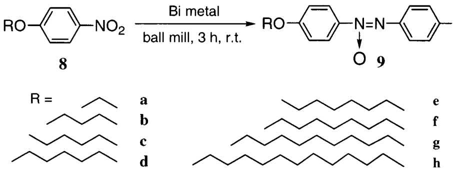
TABLE 4. Reduction of Long-Chain 4-Alkoxynitroarenes with Bismuth Shots



substrate	carbon chain length (= *n*)	conversion[a] (%)	yield[b] (%)
8a	2	79	~100
8b	4	91	~100
8c	5	82	~100
8d	6	97	~100
8e	7	87	~100
8f	8	20	~100
8g	10	44	~100
8h	12	25	~100

[a] Refer to isolated compounds. Reactions were not optimized. All products are known.[35] [b] Based on conversion.

time did not improve conversion but favored the decomposition of azoxy to azo compound. Replacement of bismuth by lead resulted in the formation of an identified third product in addition to the expected azoxy and azo compounds. The reported yields of azoxy compounds **9** are in the range 45−88%.[35] In ordinary solution chemistry, the alkyl chain length does not seem to influence much on the product yield.

In summary, a convenient and effective one-pot procedure has been developed for the solvent-free one-step conversion of nitroarenes to azoxyarene and/or azoarenes. The reaction is clean and highly chemoselective, manipulation is simple, reaction time is short, and yield is generally good. Extension of the present methodology to other functional group transformations is under way.

Experimental Section

Reagents and metal shots were all reagent-grade commercial products and used as obtained. Long-chain alkoxy nitroarenes **8** were prepared by the reaction of *p*-nitrophenol and long-chain alkyl bromides in DMF in the presence of potassium carbonate. Ball milling was carried out in a stainless cylinder (1.2 × 4 cm; 5 mL volume) using stainless balls of 7 mm diameter on a laboratory ball milling apparatus (Retsch mixer mill, MM200; Retsch GmbH, Haan, Germany). Chromatographic purification of products were performed with Wakogel 200 (100−200 mesh) using hexanes−EtOAc (1−5:1) as the eluting solvent. All products are known and were identified by comparison of melting points and ^{1}H NMR, IR, and/or MS spectra with those of authentic samples or literature data.[35,36]

Caution: Care should be taken when the ball milling reduction of nitroarenes is carried out using lead shots. The resulting black powder and pasty solid often catch fire in contact with air.

Reduction of Nitroarenes with Bismuth Shots under Milling Conditions. Representative Procedure. 4-Nitroanisole (**1a**, 0.076 g; 0.50 mmol), bismuth shots (0.865 g, 4.13 mmol; Kishida, ca. 1 mm; 99.999% purity), and two stainless balls were placed in a stainless cylinder (5 mL volume) and a drop of hexane was added just before closing a screw cap. The reaction vessel was shaken on a ball mill apparatus at a rate of 30 Hz/s. The cylinder considerably warmed by mechanical friction. After 1.5 h, milling was stopped and the resulting gray to near black powder or pasty solid was extracted with ethyl acetate by trituration. The combined extracts were filtered on a thin Celite bed and evaporated to leave 4,4′-dimethoxyazoxybenzene **2a** (0.059 g, 91%) as yellow crystals, mp 120−122 °C (lit.[32] mp 118−119 °C).

Reduction of Nitroarenes with Lead Shots under Milling Conditions. Representative Procedure. 2,2′-Dinitrobiphenyl (**4**, 0.0288 g; 0.118 mmol), lead shots (0.172 g, 0.832 mmol; Ishizu, ca. 0.5 mm; 99.999% purity), and two stainless balls were placed in a stainless cylinder (5 mL volume) and shaken on a ball mill apparatus at a rate of 30 Hz/s. After 1.5 h, milling was stopped, and the resulting black pasty product was extracted with ethyl acetate by trituration. The combined extracts were filtered on a thin Celite bed and evaporated to leave a pale yellow solid, which was chromatographed on silica gel using a mixture of hexane/ethyl acetate (2:1) to give benzo[*c*]cinnoline **6** (0.020 g, 92%) as pale yellow needles, mp 157−158 °C (lit.[14] mp 157−158 °C).

Under the similar conditions using bismuth shots, compound **4** was converted slowly to benzo[*c*]cinnoline *N*-oxide **5**, mp 137−138 °C (lit.[14] mp 139−140 °C). The yield based on unrecovered material was around 90%.

Supporting Information Available: ^{1}H NMR data of azoxy and azo compounds obtained (**2**, **3**, **5**, and **6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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