

Manganese(III) acetate-mediated oxidative coupling of phenylhydrazines with benzene: a novel method for biaryl coupling

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The reaction of phenylhydrazines with benzene in the presence of manganese(III) acetate affords biaryls in good yields. The same reaction was carried out with similar oxidants, such as Co^{III} , Ce^{IV} and Pb^{IV} ; among these oxidants Mn^{III} acetate shows higher efficiency and selectivity.

Introduction

C–C Bond-forming reactions leading to biaryls are very important because this approach is the key step in the synthesis of many natural and unnatural biaryls. There are various biaryl coupling methods, and the applications of these methods are reviewed comprehensively in the literature.¹ Of these methods, the Pschorr reaction and the GBH reaction (Gomberg–Bachmann–Hey) utilize diazonium salts treated with copper salts to effect coupling. In the classical Ullmann reaction, aryl halides are treated with copper, forming the corresponding biaryls. The original Ullmann reaction employs high temperatures and is greatly affected by the nature of the substituents and the steric environment. An ambient-temperature variant of this reaction was developed and has been used by many researchers.² Catalytic coupling reactions are also well known in biaryl synthesis, the four most commonly used being the Kharasch, Negishi, Stille and Suzuki reactions.³ Today catalytic coupling reactions are routine means of access to biaryls in the laboratory. In these catalytic coupling methods, the course of reaction is determined by the position of the functional group specific to the method employed so that regioselective coupling is possible. Thus, the selectivity of the coupling site is now reduced to the introduction of that functional group into the desired coupling position.

The synthesis of biaryls from arylhydrazines by various oxidizing agents has been reported. The earliest one is the oxidation of phenylhydrazine by mercuric [mercury(II)] oxide in which aniline and biphenyl are isolated oxidation products.⁴ The oxidation of phenylhydrazine with Pb^{IV} acetate in aromatic solvents such as benzene, chlorobenzene, nitrobenzene and in dichloromethane has been reported.⁵ At low temperatures in dichloromethane the benzenediazonium ion was formed. At room temperature, benzene, azobenzene, biphenyl and, where aromatic solvents were used, biaryls were isolated products. Reaction in benzene yields 37% biphenyl, 6% azobenzene and trace amounts of phenyl acetate. Moreover, the same reaction in nitrobenzene yields 30% benzene and 36% nitrobiphenyl as well as trace amounts of azobenzene and phenyl acetate. Similar results were reported when using chlorobenzene as solvent. In another study, haloarenes were coupled with arylhydrazines in methanol by either Pd or Pd–Hg catalyst.⁶ It was reported that oxidized palladium was recovered by its reaction with phenylhydrazine. The reaction yields biaryls resulting from self-coupling of haloarenes as well as from cross-coupling with arylhydrazines. The catalyst was formed *in situ* by action of arylhydrazine on palladium chloride and mercury(II) chloride. Barium ferrate monohydrate was offered as an alternative

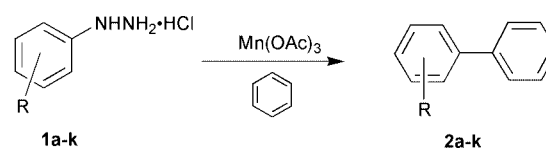
versatile reagent for oxidation of various types of organic substrates.⁷ The oxidation of phenylhydrazine with barium ferrate monohydrate in benzene yields biphenyl in 70% yield. However, oxidation of *p*-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine produced nitrobenzene and *m*-dinitrobenzene, respectively, in good yields. Manganese dioxide was reported to give *m*-nitrobenzene from 2,4-dinitrophenylhydrazine in 50% yield.⁸ Formation of aryl radicals from arylhydrazines by Cu^{II} salts and their subsequent reaction with alkenes were reported where the reaction yields varying amounts of the corresponding arenes and haloarenes.⁹ As a result, oxidation of arylhydrazines by a variety of oxidizing agents is well known to provide arenes, biaryls and azoarenes in varying amounts, depending on reaction conditions. Despite the straightforward procedure and easily available starting materials, oxidation of arylhydrazines by the oxidants mentioned above cannot be an alternative to the catalytic coupling reactions unless the yields are improved and the reaction is free of side products.

Manganese triacetate is a one-electron oxidant, largely used as a radical generator. Since the pioneering work of Heiba and Bush in 1968,¹⁰ Mn^{III} -mediated oxidations have been extensively studied. Fristad showed that the rate of radical generation with $\text{Mn}(\text{OAc})_3$ with bridging acetates correlates with the enolizability and CH acidity of the substrates.¹¹ Thus it is this reagent's ability to generate radicals in such systems that leads to highly efficient C–C bond-forming reactions, especially for the construction of cyclic systems, a topic reviewed by Snider.¹² Previously, we published several papers in the area of manganese triacetate-mediated oxidation of ketones to form C–O bonds.¹³

Since it is possible to form biaryls by the generation of aryl radicals from arylhydrazines, we began investigating their oxidation by manganese triacetate. Herein we report the formation of biaryls *via* oxidation of hydrazines by manganese triacetate.

Results and discussion

At first, we examined the oxidation of phenylhydrazine in benzene with manganese(III) acetate at room temperature as shown in Scheme 1. A mixture of manganese(III) acetate and phenyl-



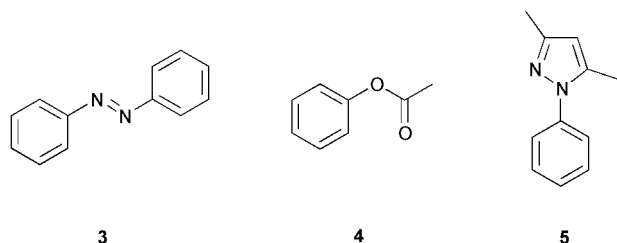
Scheme 1

hydrazine in benzene was stirred at room temperature and the reaction was monitored by GC-MS. After 4 hours, 45% conversion of phenylhydrazine to biphenyl was observed. Refluxing of the same reaction mixture for one hour using a Dean–Stark trap furnished biphenyl in 73% yield as the sole product without any purification. No product formation was observed using phenylhydrazinium chloride at RT. Refluxing was necessary to obtain biphenyl from phenylhydrazinium chloride in 75% yield. Consequently, the reaction is applicable for both arylhydrazines and their salts without any complication. The highest yield was obtained by using three equivalent of manganese(III) acetate. We noticed that a slight excess of the oxidant secures the highest yields. The yield of the reaction was satisfactory and, contrary to the other reported oxidizing agents, was free from azobenzene and other side products.

After examination of the formation of biphenyl from phenylhydrazinium chloride, other commercially available hydrazines were treated under the same reaction conditions. Of these hydrazines, *o*-, *m*- and *p*-bromophenylhydrazine were used to test the reaction's applicability to different isomers. These hydrazines have been shown to give the corresponding biphenyl product without isomerization as observed by GC-MS and NMR of crude products. Thus it is evident from these results that the coupling occurs from the position where the hydrazine moiety was originally substituted. Reactions with free hydrazines (**1h**, **j** and **k**) were complete in shorter times. Also examined were phenylhydrazines having electron-withdrawing and electron-releasing groups at different positions. The results are summarized in Table 1. The yields are affected by the position of substitution. While *p*-bromophenylhydrazine gives an 81% yield, the *ortho* isomer gives a 70% yield, and the highest yields were attained with a strong electron-releasing group at the *para* position.

When the oxidations were carried out in substituted benzene solvents such as toluene and bromobenzene the corresponding biaryls were obtained in good yields but no apparent selectivity was observed for the formation of biaryls. As shown in Table 2 *ortho*- and *para*-products are obtained as major products.

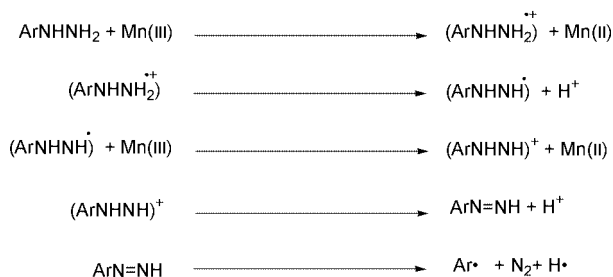
Manganese(III) acetate bears many similarities, with respect to a given substrate class, with other one-electron oxidants like Co^{III} and Ce^{IV}, and some two-electron oxidants like Pb^{IV}. For comparison, phenylhydrazine was treated with cerium(IV) ammonium nitrate (CAN), Co^{III} acetylacetonate and Pb^{IV} acetate under similar conditions. Reaction of phenylhydrazine with Pb^{IV} acetate gave two major products: biphenyl and azobenzene (5 : 1) and a trace amount of phenyl acetate. The results of this Pb^{IV} acetate reaction are comparable with previously reported literature results.⁵ The reaction of phenylhydrazine with Co(III) acetylacetonate gave two major products: biphenyl and pyrazole derivative **5** (3 : 1 respectively). Treatment of phenylhydrazine with CAN furnished a mixture of products. The major fractions were identified as biphenyl and azobenzene (3 : 2 respectively). In addition to these compounds, complex mixtures of terphenyl isomers and azobenzene derivatives of biphenyls were detected by GC-MS. As shown in Table 3, the isolated yields of products are very low. In all cases there were unidentifiable products.



The results in Tables 1 and 3 show that oxidation of phenylhydrazine with oxidants showing similar behavior towards a

given substrate class gave similar product distribution. Mn^{III} acetate is more selective and effective than Co^{III}, Ce^{IV} and Pb^{IV}. Selectivities can be attributed to the slow formation of radicals with Mn^{III} acetate. Co^{III}, Ce^{IV} and Pb^{IV} compounds are more powerful oxidants, and therefore less selective.

In the oxidation of monoarylhazines with several oxidizing agents, the observed products have been explained in terms of a generated phenyldiimide and its subsequent breakdown. A similar mechanism that is proposed for Pb^{IV} acetate and Cu^{II} is probably operating during the reaction, which is outlined in Scheme 2.^{5,9} Azoarene products might result from the oxidation



Scheme 2

of hydrazobenzene which is produced by diazonium attack on arylhydrazine to give tetrazene followed by loss of nitrogen as proposed by Aylward.⁵ Theoretically, two equivalents of manganese^{III} acetate are needed for the oxidation but the best results are obtained by using three equivalents of manganese^{III} acetate. The manganese^{III} acetate used in this study was commercial and dried over P₂O₅ prior to use. Alternatively it can be synthesized from manganese^{II} nitrate and acetic anhydride.^{13a} Since Mn^{III} acetate is a hydrate of unspecified composition and forms manganese oxide hydrate with water,^{13g} the exact content of the Mn^{III} acetate is uncertain. Hence, we arbitrarily used an excess of Mn^{III} acetate per mole substrate in our ongoing work. Interestingly, we repeatedly observed that the use of only 3 equivalents of the oxidant was the best choice. This is a truly remarkable result and warrants further experimentation.

In conclusion, we showed that it is possible to oxidize arylhydrazines with Mn^{III} acetate in benzene to form the corresponding phenyl-substituted benzene derivatives in good yield; access to biaryls works selectively, and coupling occurs where hydrazine departs. Using substituted benzenes as solvents furnishes isomeric mixtures of the corresponding biaryls. In light of these investigations, we developed a simple, selective and efficient method for the formation of biaryls starting with simple commercially available compounds. Also we showed that Mn^{III} acetate is more selective and effective than Co^{III}, Ce^{IV} and Pb^{IV}. This method offers an attractive alternative to the other published methods. Coupling of arylhydrazines in heteroaromatic solvents is under investigation.

Experimental

NMR spectra were recorded on a Bruker DPX 400. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). TLC was carried out on aluminium sheets precoated with silica gel 60F₂₅₄ (Merck), and the spots were visualized with UV light (λ = 254 nm). IR spectra were measured on a Philips model PU9700 spectrometer. GC-MS spectra were determined using a ThermoQuest (TSP) TraceGC-2000 Series equipped with phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane, 30 m, 250 μm; T_{GC}(injector) = 250 °C, T_{MS}(ion source) = 200 °C, time programme (oven): T_{0 min} = 60 °C, T_{3 min} = 60 °C, T_{14 min} = 280 °C (heating rate 20 °C min⁻¹), T_{20 min} = 280 °C, MS: ThermoQuest Finnigan multi Mass (EI, 70 eV). Mps were measured on a capillary tube apparatus and are uncorrected.

Table 1 The synthesis of biaryls

	1	2^a	Yield (%) ^b	Mp (lit.)
a			75	69 (69–72 ^c)
b			70	Oil
c			73	Oil
d			81	91–92 (90–92 ^c)
e			69	60–62 (59–61 ^{14a})
f			80	49–50 (49–50 ^{14b})
g			83	89 (86–90 ^c)
h			68	37–39 (36–38 ^c)
i			75	Oil
j			74	112 (111–112 ^{14c})
k			69	Oil

^a All products were identified by spectroscopic methods (NMR, IR, GC-MS) and the data were in agreement with the published values.¹⁴ If necessary, additional purification was done by column chromatography (silica gel; 5% diethyl ether–hexane). ^b The yields indicate the loss of some material at some stage of the reaction. Loss of product during work-up or adsorption of starting material by salts during reaction might be the reason. This problem is still under investigation. ^c Commercially available material.

Table 2 Ratio of isomers obtained in the oxidation of hydrazines

Hydrazine	Solvent	Proportions of isomers		
		<i>o</i> -	<i>p</i> -	<i>m</i> - ^a
1a	Bromobenzene	47.7	29.5	22.7
1a	Toluene	70.4	21.1	8.4
1b	Bromobenzene	38.2	33.7	28.0
1f	Toluene	50.5	26.2	23.2
1g	Bromobenzene	60.1	29.6	10.3
1h	Toluene	61.2	21.4	17.3

^a Positions are based on the solvent used and are determined from the crude products by GC-MS using commercially available products as references.

Typical procedure

A mixture of manganese(III) acetate [2.79 g, 10.4 mmol Mn(OAc)₃·2H₂O] in 30 ml benzene was refluxed for 30 minutes using a Dean–Stark apparatus. Then phenylhydrazinium chloride (0.5 g, 3.47 mmol) was added and resulting mixture

was refluxed for 4 hours. After completion of the reaction, the mixture was filtered off and the residue was washed with 15 ml of Et₂O. The resulting solution was washed successively with saturated aq. NaHCO₃, NH₄Cl, and brine, and dried over MgSO₄. Concentration under reduced pressure furnished 0.4 g of biphenyl (mp 71–73 °C), confirmed by NMR, IR and GC-MS as the sole product. Reactions with Co^{III}, Ce^{IV} and Pb^{IV} were run in basically the same fashion with a 1 : 2 phenylhydrazine to oxidant mole ratio.

Acknowledgements

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Table 3 Oxidation products of phenylhydrazine with various oxidants

Oxidant	Mole ratio (hydrazine : oxidant)	Reaction time ^a (t/h)	Product (yield %) ^b
Mn(OAc) ₃	1 : 3	1	2a (75)
Pb(OAc) ₄	1 : 2	1	2a (32), 3 (6), 4 ^c
Co(acac) ₃ ^d	1 : 2	2	2a (21), 5 (7) ^e
CAN	1 : 2	1,5	2a (16), 3 (10) ^f

^a The reactions were run under reflux conditions. Carrying out reactions at room temperature gave similar results after longer reaction times, but with lower yields (24–30 h), and the reactions were monitored by TLC and GC-MS until the complete consumption of phenylhydrazine. ^b Isolated yields; products purified by column chromatography (5% diethyl ether–hexane was used as eluent for biphenyl and 1 : 7 EtOAc–hexane was used to purify azobenzene. ^c Phenyl acetate was detected by GC-MS. ^d 5–7% of Co(acac)₃ is recovered. ^e The product is purified by column chromatography and identified by spectroscopic methods. The data of the product were in agreement with those of the commercially available compound. ^f The crude product contains a mixture of terphenyl isomers and azobenzene derivatives of biphenyl isomers.

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