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Manganese(III) acetate-mediated oxidative coupling of phenylhydrazines with furan and thiophene: a novel method for hetero biaryl coupling

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Abstract—A convenient new method for the arylation of furan and thiophene with arylhydrazine and manganese(III) acetate is described. Oxidation of arylhydrazines with Mn(III) acetate in furan or thiophene affords the corresponding 2-aryl-substituted furans and thiophenes in good yield using commercially available materials; access to 2-substituted heterobiaryls works selectively, and coupling occurs with loss of the hydrazine moiety.

1. Introduction

Aryl-substituted aromatic heterocycles are interesting compounds as precursors to biologically and physiologically active compounds. They also exist in naturally occurring compounds such as pterofuran,[1] 2-phenyl-5-propynylthiophene,[2] and 3,4,5-tribromo-2-(3,5-dibromo-2-hydroxyphenyl)pyrrole.[3] Usually arylfurans, thiophenes and C-arylpyrroles are prepared by ring synthesis. Pd(II) salts are known to dimerize arenes[4] and aromatic heterocycles such as furans,[5a,b] thiophenes,[5b,c] and *N*-benzoyl pyrroles.[6] This Pd(II) salt methodology has been applied to the oxidative cross-coupling of aromatic heterocycles and arenes that employ stoichiometric amounts of $Pd(OAc)_2$ in the presence of excess arene in acetic acid solution.[7] It has been shown that the conditions applied furnished both 2- and 3-aryl-substituted aromatic heterocycles as well as other side products. Another method utilizes Rh(I) or Ag(I) catalysts, in which allenyl ketones can be selectively rearranged into furans under mild conditions. This very useful method yields 2-arylfurans when aryl ketones are used.[8] Catalytic-coupling reactions are now the routine means of access to biaryls. In these catalytic-coupling methods, the course of the reaction is determined by the position of the functional group specific to the method employed so that regioselective coupling is possible.[9a] There are some studies utilizing these catalytic-coupling reactions for the synthesis of aryl-substituted furans and thiophenes.[9b–d] These methods allow the synthesis of 2- or 3-substituted heterocycles just by using the appropriately substituted coupling partners.

Another method is the decomposition of arenediazonium salts in a large excess of furans or thiophenes, which furnishes 2-aryl-substituted furans and thiophenes, respectively.[10] Methods related to the decomposition of arenediazonium salts involve the generation of aryl radicals in the presence of furans or thiophenes. It has been shown that the reaction of derivatives of diazoaminobenzene and isoamyl nitrite in solvent furan affords 2-aryl furans in 30–50% yield.[11] Irradiation (in benzene solution) of 5-iodo and 5-bromo-thiophene(furan)-2-carbaldehyde or the corresponding methyl ketones furnishes the corresponding 5-phenyl derivatives in very good yields.[12]

The generation of aryl radicals and the formation of biaryls from arylhydrazines by various oxidizing agents have been reported. The earliest example is the oxidation of phenylhydrazine by mercury(II) oxide in which aniline and biphenyl are the isolated oxidation products.[13] Several oxidants for the oxidation of arylhydrazines have been reported so far, such as Pb(IV),[14] Pd or Pd–Hg,[15] barium ferrate monohydrate,[16] and manganese dioxide.[17] All of these oxidants either gave poor yields of biaryls when used in the presence of benzene or other side products like azobenzene or corresponding arenes.

Recently, we showed Mn(III) acetate to be a versatile reagent for the generation of aryl radicals from arylhydrazines and their subsequent capture by solvent benzene for the synthesis of biaryls substituted from a single phenyl ring.[18] In the same study, we showed that manganese(III) acetate was the reagent of choice among the oxidants

Keywords: arylcoupling; thiophene; furan; manganese(III) acetate.

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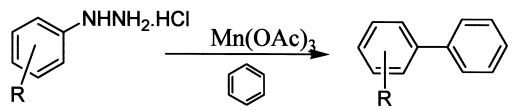


Scheme 1.

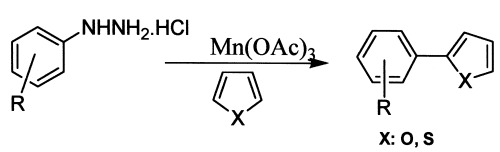
bearing similarities, with respect to a given substrate class, such as the one electron oxidants Co(III) acetylacetonate, and cerium(IV) ammonium nitrate. Reactions with manganese(III) acetate not only gave high yields (68–83%), but also were advantageous in terms of product isolation (Scheme 1).

In light of these observations, we applied this reaction to the synthesis of aryl-substituted heterocycles. Herein, we report the formation of 2-arylfurans and 2-arylthiophenes via oxidation of arylhydrazines by manganese(III) acetate (Scheme 2).

2. Result and discussion

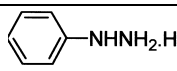
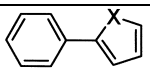
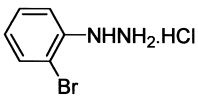
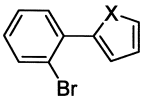
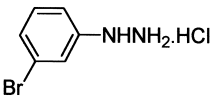
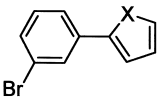
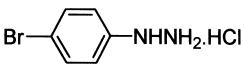
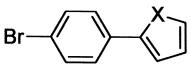
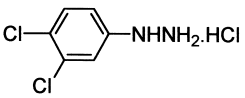
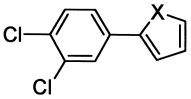
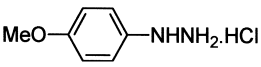
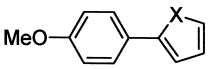
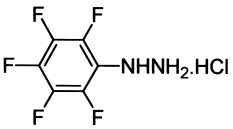
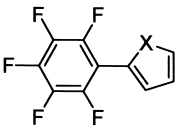
In our previous report, we showed that the oxidation of arylhydrazines is applicable to both free arylhydrazines and their salts without any complication. First, we examined the oxidation of phenylhydrazine and its salt by manganese(III) acetate in furan or thiophene. The reaction of free phenylhydrazine was sluggish and furnished a complex mixture of products as well as the desired 2-phenyl furan **2a**. However, phenylhydrazinium chloride **1a** smoothly afforded the desired products **2a** and **2b** both in furan and thiophene as shown in Table 1. This observation is advantageous since most commercially available arylhydrazines are available as their HCl salts. Moreover, free hydrazines can easily be converted into their salts by passing dry HCl through their ether solutions. Another issue, apart from the optimum reaction conditions, is the regioselectivity of the reaction. Analysis of samples taken from the reaction mixture by GC–MS always showed the presence of one isomer, identified as 2-substituted furan or thiophene by NMR spectroscopy. This was expected since it is known that a reaction at the 3-position of furan or thiophene is not easy to achieve and frontier orbitals favor this type of reactivity.[19]

After examination of the formation of 2-phenylfuran and 2-phenylthiopene 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 gave the corresponding 2-substituted furan or thiophene without isomerization as observed by GC–MS and NMR spectroscopy, and this observation was in agreement with our



Scheme 2.

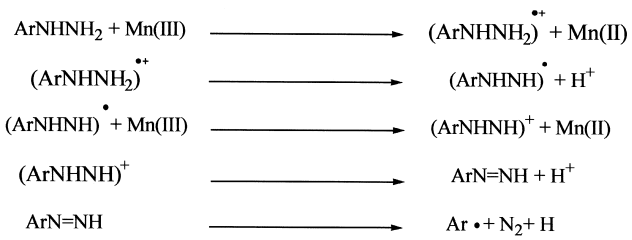
Table 1. The synthesis of 2-aryl furan and thiophene

	1	2	X	Yield (%)
a			O	60
b			S	70
c			O	53
d			S	65
e			O	60
f			S	68
g			O	65
h			S	54
i			O	64
j			S	52
k			O	30
l			S	62
m			O	22
n			S	60

All products were identified by spectroscopic methods (NMR, IR, GC–MS) and data were in agreement with the published values.[20]

previous work related to the synthesis of biaryls under the same reaction conditions. Moreover, products are easily purified just by filtration of the crude mixture through a pad of silica using hexane or petroleum ether as eluent. This method afforded analytically pure heterobiaryls in most cases. The results are summarized in Table 1.

In the oxidation of monoarylhydrazines with several oxidizing agents, the observed products have been explained in terms of generated phenyldiimide and its subsequent breakdown. A mechanism similar to that proposed for lead(IV) acetate and Cu(II) is probably in effect during the reaction, which is outlined in Scheme 3.[14,21] This radical mechanism is also consistent with our previous results in which the use of substituted benzenes as solvent furnished an isomeric mixture without an apparent selectivity, characteristic of reactions of radicals with substituted



Scheme 3.

benzenes. Theoretically 2 equiv. of manganese (III) acetate are needed for oxidation but the best results are obtained using 3 equiv. of manganese(III) acetate. This is in agreement with our previous work with this oxidant where excess oxidant was sometimes necessary for better yields.[22] There are two possible reasons for this observation. First, the third equivalent of the oxidant is necessary to oxidize the intermediate radical formed by attack of the aryl radical on furan or thiophene. Second, since Mn(III) acetate is a hydrate of unspecified composition and forms manganese oxide hydrate with water,[22d] the exact content of the Mn(III) is uncertain. The manganese(III) acetate used in this study was commercial and dried over P_2O_5 prior to use. Alternatively it can be synthesized from manganese(II) nitrate and acetic anhydride.[22a]

In conclusion, we have shown that it is possible to oxidize arylhydrazines with Mn(III) acetate in furan or thiophene to form the corresponding 2-aryl-substituted furans and thiophenes in good yield with commercially available materials; access to 2-substituted heterobiaryls works selectively, and coupling occurs with loss of the hydrazine. This method is a useful alternative to the published methods.

3. Experimental

NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: δ=7.26) and $CDCl_3$ (^{13}C: δ=77.0) as internal standard. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (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 program (oven): $T_{0\ min}$=60°C, $T_{3\ min}$=60°C, $T_{14\ min}$=280°C (heating rate 20°C min^{-1}), $T_{19\ min}$=280°C, $T_{25\ min}$=280°C, MS: Thermo Quest Finnigan multi Mass (EI, 70 eV). Mps were measured on a capillary tube apparatus and are uncorrected.

3.1. Typical procedure

To a mixture of manganese(III) acetate (563 mg, 2.1 mmol $Mn(OAc)_3{\cdot}2H_2O$) in 10 mL furan or thiophene, phenylhydraziniumchloride (100 mg, 0.7 mmol) was added and the resulting mixture refluxed for 5–10 h (formation of the products was monitored by TLC using *n*-hexane/silica gel). After completion of the reaction, the mixture was filtrated through a pad of silica using hexane or petroleum ether as eluent. Concentration under reduced pressure furnished 2-phenylfuran (**2a**) (50 mg, 60%, colorless oil, (lit.[20a]) and 2-phenylthiophene (**2b**) (77 mg, 70%, mp 35–36°C (lit.,[20b] 34–36°C, white crystals), as confirmed by NMR, IR, and GC–MS.

3.1.1. 2-(2-Bromophenyl)-furan (2c). Yield 53%, colorless oil, ν_{max}(neat) 2932, 2855, 1475, 1008, 756, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (dd, *J*=3.4, 1.9 Hz, 1H), 7.02 (td, *J*=7.6, 1.6 Hz, 1H), 7.08 (dd, *J*=3.4, 0.7 Hz, 1H), 7.38 (td, *J*=7.7, 1.3 Hz, 1H), 7.42 (dd, *J*=1.8, 0.8 Hz, 1H), 7.56 (dd, *J*=7.9, 1.7 Hz, 1H), 7.72 (dd, *J*=7.9, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.9, 111.7, 120.0, 127.6, 128.6, 129.1, 131.6, 134.4, 142.3, 151.6. Anal. calcd for $C_{10}H_7BrO$ (223.07): C, 53.84; H, 3.16; found: C, 53.71; H, 3.38.

3.1.2. 2-(2-Bromophenyl)-thiophene (2d). Yield 65%, colorless oil, data consistent with the literature.[20c]

3.1.3. 2-(3-Bromophenyl)-furan (2e). Yield 60%, colorless oil, data consistent with the literature.[8]

3.1.4. 2-(3-Bromophenyl)-thiophene (2f). Yield 68%, colorless oil, ν_{max}(neat) 2923, 1610, 1586, 1490, 800, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (m, 1H), 7.11–7.20 (m, 3H), 7.28 (m, 1H), 7.42 (m, 1H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.4, 124.1, 124.8, 125.3, 125.8, 128.3, 129.2, 130.6, 136.8, 143.0. Anal. calcd for $C_{10}H_7BrS$ (239.13): C, 50.23; H, 2.95; found: C, 50.41; H, 3.12.

3.1.5. 2-(4-Bromophenyl)-furan (2g). Yield 65%, white crystals, mp 80–82°C (lit.,[20d] 80–83°C), data consistent with the literature.

3.1.6. 2-(4-Bromophenyl)-thiophene (2h). Yield 54%, white crystals, mp 100–101°C (lit.,[20e] 100°C), data consistent with the literature.

3.1.7. 2-(3,4-dichlorophenyl)-furan (2i). Yield 64%, white crystals, mp 51–52°C (lit.,[11] 51–52°C); ν_{max}(KBr) 2920, 1596, 1575, 1496, 1013, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (m, 1H), 6.51 (m, 1H), 7.29–7.33 (m, 3H), 7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 106.6, 112.2, 123.2, 125.9, 130.9, 131.0, 131.4, 133.4, 143.0, 152.0. Anal. calcd for $C_{10}H_6Cl_2O$ (213.06): C, 56.37; H, 2.84; found: C, 56.21; H, 2.98.

3.1.8. 2-(3,4-dichlorophenyl)-thiophene (2j). Yield 52%, white crystals, mp 61–62°C; ν_{max}(KBr) 3104, 2925, 1468, 1132, 1025, 857, 826, 714, 536 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.0 (dd, *J*=6.9, 3.7 Hz, 1H), 7.20 (dd, *J*=3.6, 0.9 Hz, 1H), 7.23 (dd, *J*=5.1, 0.9 Hz, 1H), 7.35 (m, 2H), 7.60 (d, *J*=1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.4, 125.3, 126.1, 127.9, 128.5, 131.0, 131.7, 133.5, 134.8, 142.0. Anal. calcd for $C_{10}H_6Cl_2S$ (229.13): C, 52.42; H, 2.64; found: C, 52.25; H, 2.88.

3.1.9. 2-(4-Methoxyphenyl)-furan (2k). Yield 30%, white crystals, mp 36–37°C (lit.,[20a] 37–38°C), data consistent with the literature.

3.1.10. 2-(4-Methoxyphenyl)-thiophene (2l). Yield 62%, white crystals, mp 105–107°C (lit.,[9d] 106–107°C), data consistent with the literature.

3.1.11. 2-(Pentafluorophenyl)-furan (2m). Yield 22%, white crystals, mp 36–37°C (lit.,[20f] 37–38°C), data consistent with the literature.

3.1.12. 2-(Pentafluorophenyl)-thiophene (2n). Yield 60%, colorless oil, data consistent with the literature.[20g]

Acknowledgements

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