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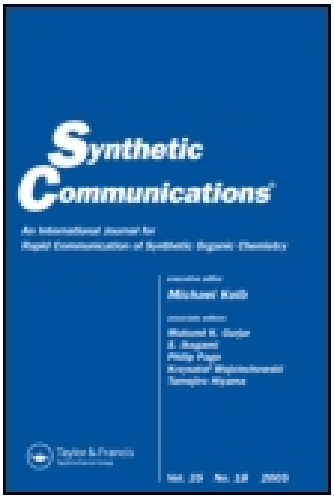

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Formation of 4-N-Arylamino-1-butanol Derivatives from Aromatic Nitro Compounds via a Novel Palladium-Catalyzed Tetrahydrofuran Ring-Opening Reaction

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FORMATION OF 4-*N*-ARYLAMINO-1-BUTANOL DERIVATIVES FROM AROMATIC NITRO COMPOUNDS VIA A NOVEL PALLADIUM-CATALYZED TETRAHYDROFURAN RING-OPENING REACTION

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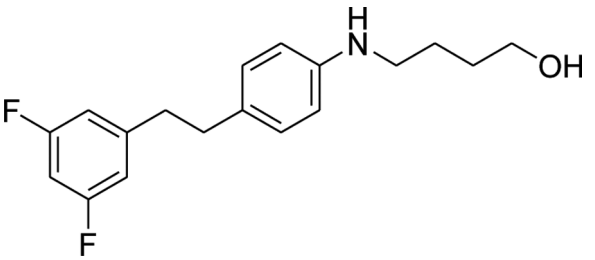
GRAPHICAL ABSTRACT



Abstract *4-N-Arylamino-1-butanol derivatives are produced via a palladium-catalyzed tetrahydrofuran ring-opening reaction. This reaction occurs during the reduction of aromatic nitro groups with polymethylhydrosiloxane (PMHS) and potassium fluoride in the presence of hydrogen peroxide. This represents a novel route for the synthesis of 4-N-arylamino-1-butanols.*

Keywords 4-Amino-1-butanol; nitro; palladium-catalyzed; reduction; ring opening; siloxane; tetrahydrofuran

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INTRODUCTION

The synthesis of *N*-substituted 4-amino-1-butanols has been reported by various methods.[1–4] Many procedures require a two- or three-step synthesis; however, a one-step method has recently been reported by high-pressure hydrogenation of primary aromatic amines. This procedure employs palladium on carbon, requires 24–36 h, and has been demonstrated on a series of amines as starting material.[5] In this laboratory, fluorinated amino analogs of the natural phytoalexin resveratrol were prepared generate stilbenes with improved biological activity.[6] Reduction of the nitro group of (*E*)-3,5-difluoro-4′-nitrostilbene (**1a**) via a palladium-catalyzed

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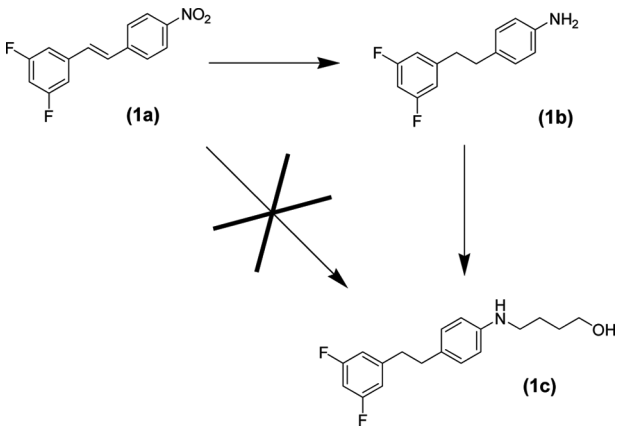

Figure 1. Synthesis of 4-{4′-(3,5-difluorophenylethyl)phenylamino}butan-1-ol (**1c**). $Pd(OAc)_2$, anhydrous THF, KF, PMHS, 0 °C to rt (4 h).

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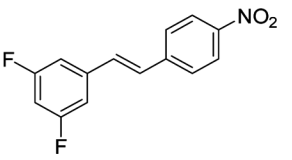
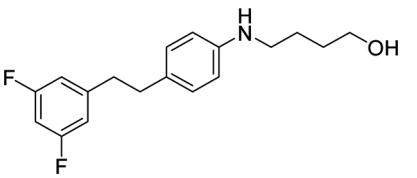
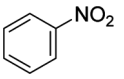
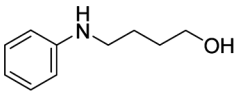
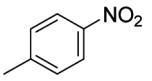
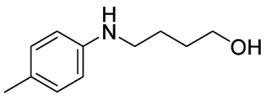
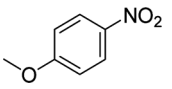
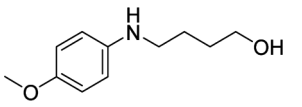
siloxane (PMHS) aqueous potassium fluoride procedure,[7] yielded the amino compound **1b** and an unexpected by-product. The by-product was identified by spectroscopic analysis as 4-{4′-(3,5-difluorophenylethyl)phenylamino}butan-1-ol **1c** (Fig. 1). The scope of this palladium-catalyzed siloxane reduction reaction is now reported using various aromatic and aliphatic nitro and amino compounds (**1**–**8**).

RESULTS AND DISCUSSION

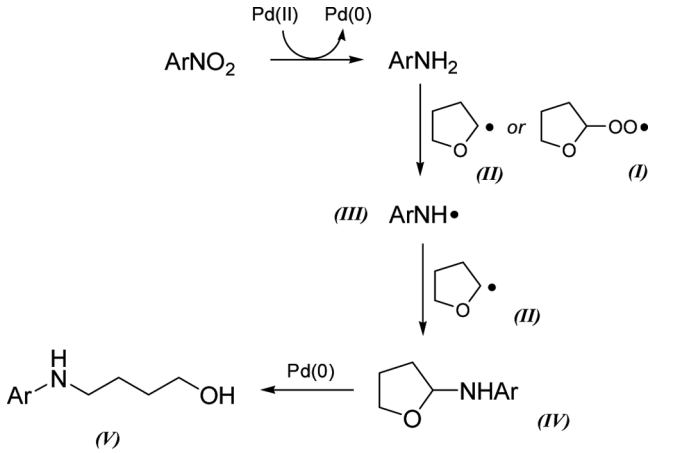
This palladium-catalyzed siloxane reduction reaction was initially investigated on a series of nitro compounds (**1a**–**4a**), which were reduced to form both the amine (**b**) and the amino-butanol species (**c**) respectively. All the reactions went to completion with quantitative yields, and the ratio of amine to amino-butanol is presented in Table 1. The preparations of compounds **2c**,[8] **3c**,[9] and **4c**[10] have been reported previously, but by different methods than those employed here. This novel one-step approach for the synthesis of amino-butanols requires approximately 4 h as opposed to the previously reported reaction, which requires 24–36 h and appears to be selective for nitro compounds. Potassium fluoride may be used as a reagent because of the ability of fluoride to activate the PMHS, and it has been reported that PMHS and $Pd(OAc)_2$ form highly active palladium nanoparticles.[7] Although the ring opening of tetrahydrofuran (THF) by amines has been reported, it normally involves the complexing of the THF with cationic metal compounds such as uranium amide compounds[11] and zirconium complexes.[12]

A free-radical-based mechanism for the palladium-mediated tetrahydrofuran ring opening has been reported.[5] This mechanism was based on the use of unstabilized THF, allowing for a potential build up of THF hydroperoxide. With the addition of hydrogen peroxide as a reagent, the formation of hydroperoxides is enhanced. This can result in cleavage of the hydrogen-oxygen bond of the hydroperoxide forming a

Table 1. Synthesis of 4-*N*-arylamino-1-butanols from nitro compounds and THF

Entry	Nitro (a)	Amino-butanol product (c)	**b**/**c**
1			1:1
2			3:5
3			3:5
4			1:2

peroxide free radical **I**, which can then abstract a hydrogen from the 2-position of THF forming radical **II** (Scheme 1). Either radical (**I** or **II**) can then remove a hydrogen from the amine to form the aminyl radical **III** which is resonance stabilized. This in turn could couple to radical **II** to form the intermediate 2-amino–THF **IV**. Complexing of the palladium to the intermediate **IV** may occur at this point, which in turn forces ring opening via an imino alcohol. Reduction of the imine double bond can then take place to yield the final amino-butanol product **V**. This reaction mechanism is plausible for the synthesis of the 4-amino-butan-1-ol compound **1c**. The THF used in this initial reaction was of anhydrous grade and free of inhibitor/stabilizer. It was



Scheme 1. Proposed free-radical-based mechanism for the palladium-mediated tetrahydrofuran ring opening.

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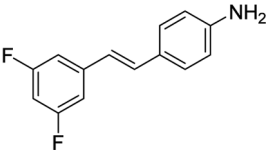
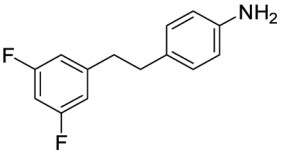
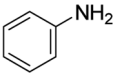
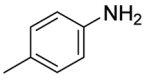
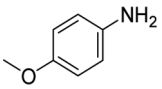
also a relatively old bottle of solvent (~1 year old), which makes the likelihood of hydroperoxide formation a real possibility. A test for peroxide was carried out on the THF solvent used in these reactions, using Quantofix peroxide test sticks (Sigma Aldrich). The result of this starch/iodide test proved positive for the presence of peroxides in the solvent. Only the amino compound was formed when a fresh bottle of anhydrous THF was used. However, the formation of the amino-butanol compounds in addition to their respective amines was observed using fresh anhydrous THF as solvent with the addition of hydrogen peroxide. Therefore, the addition of a few drops of hydrogen peroxide to the reaction was employed for all subsequent experiments.

A series of compounds were reduced to investigate this palladium–siloxane reaction in more detail. The initial results of this preliminary study employed nitro compounds and is presented in Table 1. Following this, a second series of reductions investigating the possible reaction between the respective amines and THF was carried out. These results are presented in Table 2. In all cases the amino compounds failed to be converted to the amino-butanol compounds. In an attempt to drive these amino reactions to the desired product, the quantities of reagents and reaction times were doubled. It has been noted that 0.75 molar equivalences of $Pd(OAc)_2$ represents a relatively high catalyst loading. However, it has been shown that quantities can reduced significantly without affecting the reducing potential of this reaction.[7] Further work will aim to reduce this capacity without affecting the reducing capability and more importantly the ring-opening catalyzed reaction. Also attempts to recover the catalyst on completion will be addressed.

Amino-butanols can display biological properties such as the *p*-aminobenzoate analog of 4-diethylamino-1-butanol, which has in vivo anaesthetic properties greater than those of cocaine.[13] A 4-amino-1-butanol derivative of 2-methylquinoline-5,8-dione was recently shown to be a potent antitumor agent both *in vitro* and *in vivo*. The amino-butanol analog in this case was obtained *via* a two-step sequence involving

Table 2. Attempted synthesis of 4-*N*-arylamino-1-butanols from amines and THF

Entry	Amine (a)	Product (b)
5		
6		NR[a]
7		NR[a]
8		NR[a]

[a]No reaction.

the hydrolysis of an aminoacetyldione to the aminodione, followed by the addition of a tetrahydrofuran molecule in the presence of concentrated sulfuric acid.[14]

EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich, Lennox Chemicals, or Fluorochem Limited and used as received. Commercial-grade reagents were used without further purification. Riedel-Haën silica gel was used for thin-layer and column chromatography. Melting-point determinations were carried out using a Stuart melting-point (SMP3) apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum GX Fourier transform (FT)–IR system. Ultraviolet (UV) spectra were obtained on a UV-vis-NIR Perkin-Elmer Lambda 900 spectrometer. NMR spectra were obtained on a Bruker AC 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR, 376 MHz for ^{19}F NMR, and 100 MHz for ^{13}C NMR. The ^{1}H and ^{13}C NMR chemical shifts (δ) are relative to tetramethylsilane, and the ^{19}F NMR, chemical shifts (δ) are relative to trifluoroacetic acid. All coupling constants (*J*) are in hertz (Hz).

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Synthesis of 4-{4′-(3,5-Difluorophenylethyl)phenylamino}butan-1-ol (1c)

3,5-Difluoro-4′-nitrostilbene **1a** (0.5 g, 1.92 mmol) and palladium(II) acetate (0.33 g, 1.44 mmol) were dissolved in anhydrous THF (20 ml) under an atmosphere of nitrogen. Aqueous potassium fluoride (0.33 g, 5.76 mmol) was added dropwise, and the solution was cooled on an ice bath prior to very slow addition of PMHS (0.69 ml, 11.52 mmol). The reaction was stirred for a further 4 h. After all stilbene starting material had been consumed, the black reaction mixture was diluted with diethyl ether and washed repeatedly with water. The organic layers were combined and stirred in celite. This mixture was passed through an alumina/celite plug to yield an orange solution. Purification by column chromatography with hexane/ethyl acetate as eluant yielded compound **1b** (0.20 g, 45%) and the title compound **1c** as a beige powder (0.29 g, 50%).

Data for 1c

Mp 68–70 °C. IR (KBr): υ 3272, 2920, 2850, 1783, 1616, 1595, 1516, 1495, 1310, 1252, 1116, 1075, 968, 853, 825, 803, 747, 680 cm^{-1}. UV (ACN): λ_{max} 254; 303 nm. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.90–6.99 (5H, m, -Ar*H* 2, 4, 6, 2′ & 6′, 6.46 (2H, d, $J = 8.4$, Hz-Ar*H* 3′ & 5′), 5.33 (1H, t, $J = 5.4$ Hz, -N*H*-), 4.40 (1H, t, $J = 5.2$ Hz, -O*H*), 3.42 (2H, q, $J = 6.2$, -CH_2 1), 2.95 (2H, q, $J = 6.6$, -CH_2 4), 2.80–2.84 (2H, m, -CH_2), 2.69–2.72 (2H, m, -CH_2), 1.45–1.58 (4H, m, -CH_2 2 & 3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3 (d, $J = 244.0$ Hz, -Ar*C*F), 162.1 (d, $J = 243.0$ Hz, -Ar*C*F), 147.3 (-Ar*C* 4′), 146.2 (t, $J = 9.4$ Hz, -Ar*C* 1), 128.7 (-Ar*C* 2′ & 6′), 127.4 (-Ar*C* 1'), 111.8 (-Ar*C* 3′ & 5′), 111.5 (d, $J = 24.0$ Hz, -Ar*C* 2 & 6), 101.1 (t, $J = 25.8$ Hz, -Ar*C* 4), 60.5 (-*C*H$_2$ 1, -VE DEPT), 42.9 (-*C*H$_2$ 4, -VE DEPT), 37.0 (-*C*H$_2$, -VE DEPT), 35.5 (-*C*H$_2$, -VE DEPT), 30.2 & 25.4 (-*C*H$_2$ 2 & 3, -VE DEPT). ^{19}F NMR (376 MHz, DMSO-d_6): δ −110.84 (2 F, t, $J = 8.0$ Hz).

CONCLUSION

In summary, a novel procedure for the one-pot conversion of aromatic nitro compounds to 4-*N*-arylamino-1-butanols in the presence of palladium and the siloxane PMHS, has been demonstrated. It has been shown that the initial nitro reduction step is essential for conversion to the amino-butanol product. A previously proposed free-radical-based mechanism for a palladium-catalysed tetrahydrofuran ring opening is highly plausible with the addition of hydrogen peroxide as a reagent. Further studies are in progress to examine the scope of this reaction. This reaction should prove useful in the synthesis of new amino alcohols.

ACKNOWLEDGMENT

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