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Preparation of β-phenylnitroethanes having electron-donating aryl substitution☆

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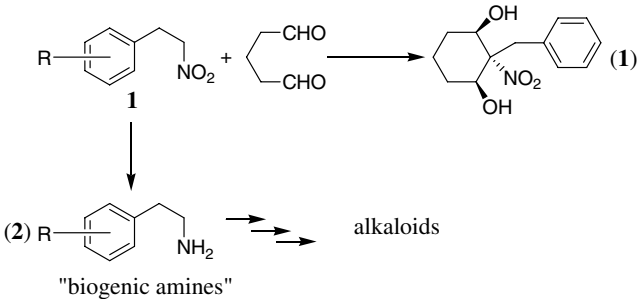
Abstract—β-Phenyl-β-hydroxynitroethanes having activating aryl substituents are treated with triethylsilane/trifluoroacetic acid under solventless conditions to give the corresponding phenylnitroethanes. Substrates having no aryl substituents or substituents that are only mildly activating or deactivating do not result in appreciable conversion to the title compounds.

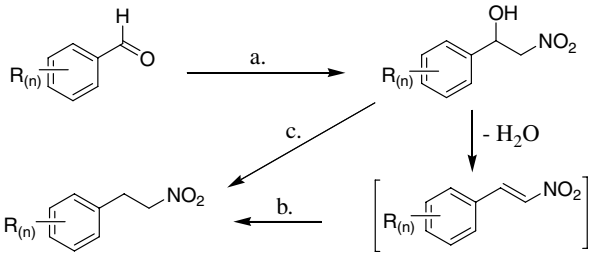
1. Introduction

Alkylnitro compounds are valuable starting materials and intermediates in all phases of organic synthesis whether a complex multistep campaign or a simple starting material preparation.[2] The saturated C-nitro functionality can serve as a precursor to other functional groups such as amines,[3a] ketones,[3b] aldehydes[3c] and carboxylic acids[3d] and the nitro group itself is an excellent carbon activator for making carbon–carbon bonds through the many variants of the nitroaldol reaction or the nitronate Michael addition.[4,5] Within the broad class of alkylnitro compounds are the 2-arylnitroethanes, compounds which can serve as precursors to a diverse array of β-arylethylamines, and with elaboration, structurally complex alkaloids (Scheme 1).[6] We have demonstrated the usefulness of phenyl-substituted 2-phenylnitroethanes **1** when reacted with glutaraldehyde in the so-called 'double Henry' reaction. On catalysis with *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG), the double nitroaldol thereby provides the *meso* or the enantiomeric 2-benzyl-2-nitro-1,3-cyclohexanediols depending on the reaction conditions (Scheme 1). In turn, the resultant *meso* cyclohexanediols make excellent substrates for enzymatic desymmetrization.[7a,b] Typically, the present routes to 2-arylnitroethanes entail a nitroaldol (Henry reaction) of the appropriate substituted benzaldehyde and nitromethane with promotion by base. Usually, the intermediate nitroalcohol dehydrates



Scheme 1. Synthetic utility of phenylnitroethanes: Eq. 1, 'double Henry' reaction of phenylnitroethanes **1** with glutaraldehyde giving a *meso* nitrodiol; Eq. 2, reduction of **1** to biogenic amines-precursors to several alkaloid families.

under more vigorous Henry conditions and ultimately provides the nitroolefin as the overall product (Scheme 2). The nitroolefin, in turn, can be partially reduced,



Scheme 2. Preparation of β-arylnitroethane intermediates via the Henry reaction and dehydration/reduction: (a) base, nitromethane; (b) $NaBH_4$-mediated reagent systems; (c) direct benzylic deoxygenation.

☆ See Ref. 1.

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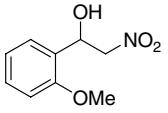
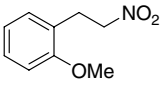
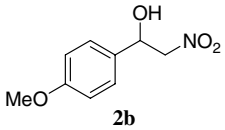
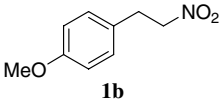
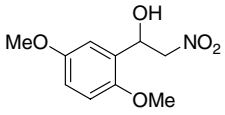
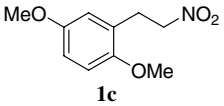
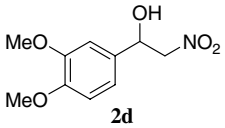
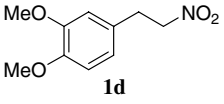
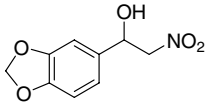
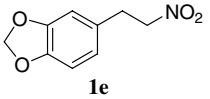
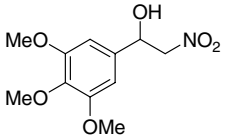
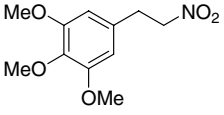
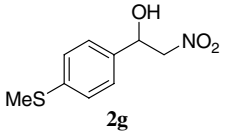
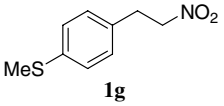
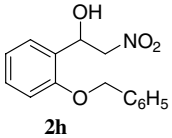
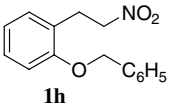
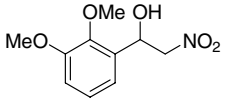
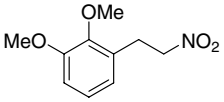
under carefully controlled conditions, to the β-arylnitroethyl product,[7c] or with the use of more robust conditions, directly to the β-arylethylamine.

Our goal in preparing β-arylnitroethanes was to bypass the formation of the nitroolefin thereby excluding any process involving the reduction of the doubly conjugated double bond. Such reductions are problematic and can lead to complex mixtures of products, including dimers and carbonyl compounds, as well as the desired saturated nitro compounds.[8] Hence, starting with a β-aryl-β-hydroxynitroethyl compound, one is only faced

Table 1. Preparation of β-arylnitroethyl derivatives **1a–i** by reaction of β-arylnitroalkanols **2a–i** with triethylsilane (TES) and trifluoroacetic acid (TFA)

Nitroalkanol	Product	Conditions[b] (h)	Yield[a] (%)	Ref.
 **2a**	 **1a**	3	64	13
 **2b**	 **1b**	1	90	13
 **2c**	 **1c**	3	70	18
 **2d**	 **1d**	3.5	76	14
 **2e**	 **1e**	1.75	85	14
 **2f**	 **1f**	16	62	15
 **2g**	 **1g**	16	89	18
 **2h**	 **1h**	16	47	16
 **2i**	 **1i**	5	62[c]	17

[a] Isolated yields of chromatographically homogeneous product unless otherwise specified.
[b] All reactions were run at room temperature.
[c] Isolated as a chromatographically inseparable 4:1 mixture of desired product/dehydration product.

with a straightforward deoxygenation of the benzylic position to a benzylic methine or methylene. A number of methods are available for the direct deoxygenation of benzylic alcohols with varied selectivity and include hydrogenolysis,[9a] triethylsilane and Lewis[9b] or Brønsted acid,[9c] borane-dimethyl sulfide,[9d] samarium diiodide/H_2O.[9e] The direct schemes are exclusive of two step methods such as radical deoxygenation of preformed xanthate derivatives or halogenation–reduction.[10]

2. Results and discussion

The protocol for deoxygenation of the aryl-substituted nitroalcohol substrates to the nitroalkanes is rapid, simple and straightforward (Eq. 3).

(3)

R=electron donating groups

After preparation of the Henry products,[11] the procedure entails the direct treatment of these intermediates with triethylsilane and concentrated trifluoroacetic acid under solventless conditions (Table 1). The crude reaction mixtures are then directly submitted to flash-chromatography or distillation after reagent removal with high vacuum or extractive workup. The reactions are easily monitored by thin layer chromatography and usually require 1–16 h of reaction time under nitrogen at room temperature (20–25 °C). Running the reaction under solventless conditions is dictated more by necessity than by choice. The employment of chlorinated solvents retard the reaction while the use of solvents such as toluene or benzene at higher temperatures contribute to dehydration, which yields the nitroolefin. The results listed in Table 1 demonstrate that substrates, which yield product, are those bearing one or more electron releasing groups, for example, the methoxy or the methylenedioxy group. In cases where the phenyl group in the nitroalcohol is unsubstituted (**2j**, Fig. 1) or has only mildly activating or deactivating groups (**2k**–**n**, Fig. 1), no desired product is recovered and the reaction mixture only affords unreacted starting material or dehydration product. The only exception is the *ortho*-methyl-substituted substrate **2m** (Fig. 1), which gave a 12% yield of the corresponding phenylnitroethane.[19] Furthermore, at least one activating substituent (even in the case of multiple substitution) should be at the *ortho* or *para* positions in the substrates for the reagent system to be effective. Such substrate selectivity is evidenced by **2o** (Fig. 1), which has the methoxy group in the *meta* position and afforded only unreacted starting material and no product. Substrates, which bear protecting groups on the phenolic hydroxyls, give variable results depending on the reactivity of the protecting group. Substrates such as **2h** give appreciable conversion to the expected product **1h** (Table 1) while a similar analogue having the more sensitive 4-methoxybenzyl (PMB) group **2r** (Fig. 1) affords a 25% yield of deoxygenated deprotected (phenolic) product. Similar to **2h**, substrate **2s** was converted to the corresponding product **1s** having the 4-benzyloxy group intact in 58% yield.[20] Treatment of 4-*O*- and 2-*N*-acetyl-protected **2p** and **2q** (Fig. 1) under normal conditions gave complete cleavage of the acetyl group, respectively, and afforded none of the desired O- or N-derivatized product. From a mechanistic point of view, the substrates bearing electron-donating substituents yielded the expected reduced products despite the presence of the electron-withdrawing β-nitro group. Presumably, the promotion of the benzylic carbenium ion by the Brønsted acid, with further facilitation by the electron-donating substituents, is the overwhelming factor. Ionic reduction of the carbenium ion through hydride reduction from the silane then takes place thereby affording the products.[12]

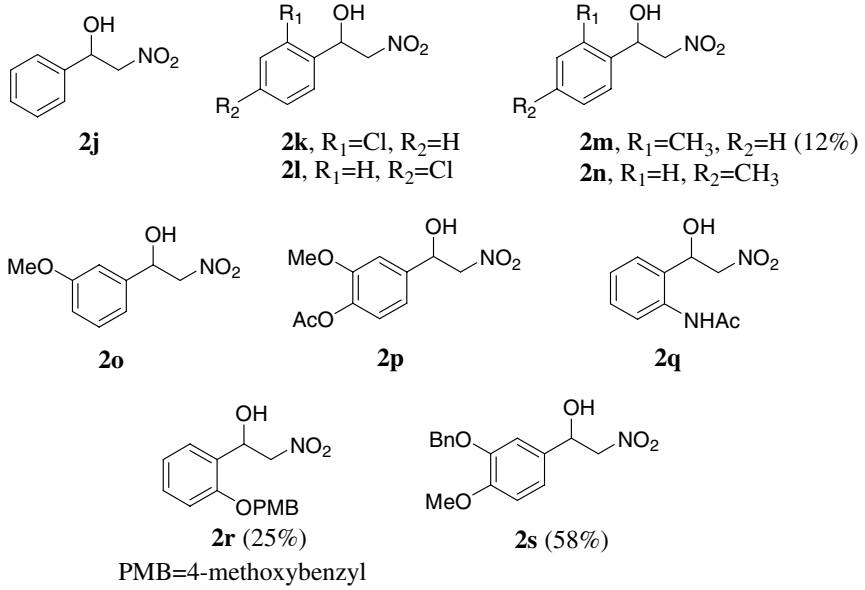


Figure 1. Selected substrate nitroalkanols treated with TES/TFA.

3. Conclusion

In summary, we have described a protocol for direct conversion of ring-activated β-aryl-β-hydroxynitro compounds to the corresponding β-arylnitroethanes. Although the direct ionic reduction of activated benzylic alcohols with TES/TFA is well-precedented, the application of this reaction to benzylic β-nitroalkanols represents a new and useful extension of this transformation and thus provides intermediates, which can be easily transformed to the corresponding amines. Though limited to aryl rings bearing electron donating substituents, the reaction is a reasonable alternative to both the nitroaldol/dehydration/reduction sequence and the Kornblum reaction, which utilizes β-arylhaloethanes and nitrite ion.

4. Experimental

4.1. Typical procedure for the TES/TFA reduction of nitroalcohols

4.1.1. 1,2,3-Trimethoxy-5-(2-nitroethyl)benzene (1f, Table 1). To a stirred suspension containing 1-(3,4,5-trimethoxy-phenyl)-2-nitroethanol (**2f**, Table 1) (32.5 mg, 0.13 mmol) and triethylsilane (200 μL, 1.25 mmol) at 0 °C, was added trifluoroacetic acid (50 μL, 0.67 mmol) dropwise. As the reaction proceeded, the suspension turned into a clear solution. The reaction mixture was stirred from 0 °C to room temperature for 16 h, after which the reaction mixture was quenched by the slow addition of saturated aqueous sodium bicarbonate (2 mL). The product was extracted with dichloromethane (3 × 2 mL) and the combined organic layers were washed with brine (2 mL), dried over sodium sulfate and concentrated. The crude oily residue was purified by flash column chromatography eluting first with hexane then followed by hexane/diethyl ether (1:1) to yield the pure arylalkylnitro compound (**1f**, Table 1) as an off-white amorphous solid (19.0 mg, 62%): R_f: 0.18 (petroleum ether/diethyl ether, 1:1); mp: 80–81 °C (lit.:[15] 82–83 °C).

Acknowledgements

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18. *Analytical data for previously unreported compounds* **2c** *and* **2g** *(Table 1)*. For **2c**: (pale pink oil) R_f 0.25 (hexane/ethyl acetate, 1:1); FTIR (KBr, cm^{-1}) 2935, 1545, 1384, 1039. ^1H NMR (500 MHz, $CDCl_3$) 3.28 (t, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 4.61 (t, 2H), 6.74–6.79 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 153.44, 151.59, 124.77, 116.98, 112.83, 111.11, 74.62, 55.67, 29.27; HRMS ($[M+Na]^+$) calcd for $C_{10}H_{13}NO_4$ ($[M+Na]^+$) 234.0742, found 234.0743. For **2g**: (yellow oil) R_f 0.51 (hexane/ethyl acetate, 2:1); FTIR (KBr, cm^{-1}) 3063, 1560, 1381; ^1H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.27 (t, 2H), 4.58 (t, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 132.6, 129.3, 127.3, 76.4, 33.1, 16.0; HRMS (FAB+Na) calcd for $C_8H_{11}NO_2S$ ($[M+Na]^+$) 220.0408, found 220.0408.
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