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Direct synthesis of 1,3-dithiane substituted nitroarenes via vicarious nucleophilic substitution with 2-phenylthio-1,3-dithiane

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Abstract

2-Phenylthio-1,3-dithiane underwent VNS with various nitroarenes to provide *para*-dithianyl nitroarenes regiospecifically in good to excellent yields. The resulting nitroaryl dithianes were readily unmasked to the corresponding aldehydes. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: vicarious nucleophilic substitution; nitroarenes; formylation; S_NAr, 1,3-dithiane.

Vicarious nucleophilic substitution (VNS) of hydrogen in nitroarenes is a valuable synthetic tool in introducing various substituents into the ring.[1–6] It is particularly so since ordinary electrophilic substitutions are not applicable to such electron-deficient aromatic compounds. Formylations of nitroarenes have been successfully executed with VNS of the formyl equivalents, followed by hydrolysis. Those formyl equivalents are trisphenylthiomethane[3] and haloforms,[4] both developed by Makosza et al. and more recently tris(benzotriazol-1-yl)methane[5] by Katritzky et al.

For our ongoing study directed towards synthesis of complex biaryls, we needed nitroaryl aldehydes masked with 1,3-dithiane. They could be synthesized in three steps, through a VNS of nitroarenes with one of the above formyl equivalents, followed by hydrolysis, and subsequent masking with 1,3-propanedithiol. Direct addition of 1,3-dithiane anion with some nitroarenes was reported in which the initial addition products were subsequently treated with DDQ to give the dithianylated nitroarenes as mixtures of regioisomers in low yields.[7] Realizing there is no regiospecific single step synthesis available, we figured that we could elaborate 1,3-dithiane in a way to be suited for VNS reaction with nitroarenes. A brief literature survey revealed several 1,3-dithiane candidates with a leaving group at 2 position. We first studied 2-chloro-1,3-dithiane,[8] which, we found, underwent VNS reaction with nitrobenzene, in the presence of base, to *p*-(1,3-dithian-2-yl)-nitrobenzene in a reasonable yield. The reaction was extremely capricious, though,

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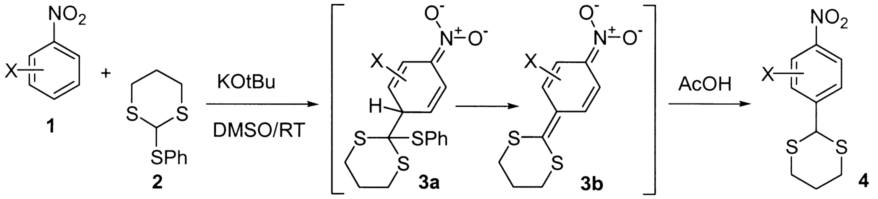
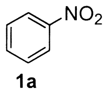
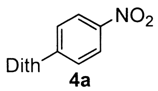
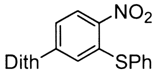
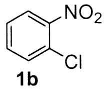
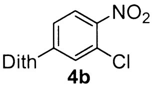
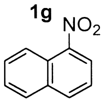
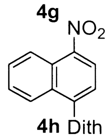
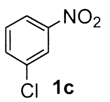
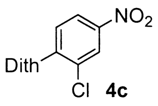
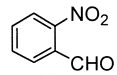
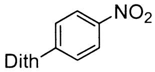
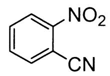
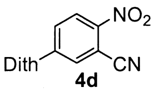
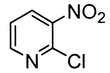
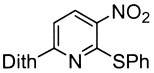
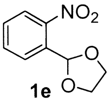
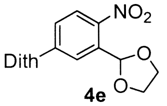
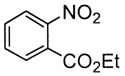
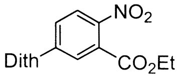
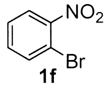
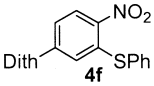
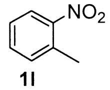
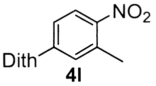
presumably due to the intrinsic instability of the reagent, 2-chloro-1,3-dithiane. The chlorine would certainly be too reactive leaving group, thus it needed to be replaced with less reactive ones. Thiophenol substituted 1,3-dithiane[9] was thought to be a good candidate, which indeed was found to be effective in introducing 1,3-dithiane group into the nitroarenes,[10] exclusively at the position *para*.



The 2-phenylthio-1,3-dithiane (**2**), readily prepared in one-pot from 1,3-dithiane according to the literature protocol,[9] can be stored on a shelf without decomposition. The VNS reactions with nitroarenes were effectuated by adding a mixture of the isolated **2** and nitroarene into the DMSO solution of KO*t*Bu or KHMDS at rt, which furnished the *p*-(1,3-dithiane-2-yl)-nitroarenes **4** in good to excellent isolated yields (Table 1).[10] Use of potassium counter ion seemed to be critical, which might be in part due to its coordination to the aromatic rings, developing negative

Table 1
Preparation of 1,3-dithiane substituted nitroarenes

SUBSTRATE	PRODUCT	YIELD^{c}	SUBSTRATE	PRODUCT	YIELD^{c}
 **1a**	 **4a**	95 %^{a}	 **1g**	 **4g**	69 %^{a}
 **1b**	 **4b**	90 %^{a}	 **1h**	 **4h**	70 %^{b}
 **1c**	 **4c**	78 %^{a}	 **1i**	 **4i**	67 %^{b}
 **1d**	 **4d**	44 %^{a}	 **1j**	 **4j**	61 %^{b}
 **1e**	 **4e**	81 %^{a}	 **1k**	 **4k**	88 %^{b}
 **1f**	 **4f**	48 %^{a}	 **1l**	 **4l**	trace^{a,b}

[a] KOtBu was used.
[b] KHMDS was used, yields were less than 5% with KOtBu.
[c] all the yields are based on isolation

charge.[11] All the new *p*-(1,3-dithiane-2-yl)-nitroarenes were fully characterized with ^{1}H, ^{13}C NMR, IR and HR-MS.

Overall, 2-phenylthio-1,3-dithiane is somewhat analogous to trisphenylthiomethane, developed by Makosza et al.[3] In their work, triphenylthiomethane underwent VNS with four distinct types of nitroarenes to give bisphenylthiomethyl nitroarenes in the yields of 15 to 65%. Our reagent is apparently more general in the reaction scope and gives higher yields (11 examples with 48 to 95% yields), although they cannot be directly compared since each reagent produces different products.

Similar to Katritzky's case,[5] the exclusive substitution of 1,3-dithiane at the position *para* to the nitro group would be due to the steric bulkiness of the anion of the reagent **2**, as further evidenced by the slower rates in the VNS with *meta*-substituted nitroarenes than with *ortho*- or unsubstituted ones. In case of **1f**, **1g** and **1j**, the liberated phenylthiolate anion came back and displaced halides, to give the doubly substituted 2-phenylthio-4-(1,3-dithianyl)-1-nitrobenzene (**4f**, **4g**, **4j**). The entries **1h** through **1k** did not provide the desired VNS products with KO*t*Bu, but did so with more basic KHMDS. In contrast, very little reaction was observed with 2-nitrotoluene (**1l**). Crude ^{1}H NMR of the reaction mixture showed no -CH_3 peak, thus we presumed that the deprotonation of the methyl group interfered the VNS. Use of less basic KOH also produced the same results. Such trend appeared to be consistent throughout the nitroarenes containing acidic protons, except the entry **1e** where the removal of the methine proton is thought to be kinetically slow. The entry **1e** is interesting in that two formyl groups were masked in two different ways, dioxolane and dithiane (**4e**). VNS with 1-nitro-naphthalene could be potentially complicated, but yet cleanly provided 4-dithianylated nitronaphthalene **4h**, regiospecifically in high yield. Entry **1j** experienced an unusual decarbonylation to give deformylated dithianyl nitrobenzene **4j** (same as **4a**). The mechanism of the deformylation is not understood, off hand, and needs further study. The dithianylated nitroarenes **4** were conveniently hydrolyzed to the aldehydes in the range of 70 to 90% yields with $AgNO_3$/NCS system.[12]

In conclusion, we were able to prepare *p*-(1,3-dithiane-2-yl)-nitroarenes, regiospecifically, in one step from nitroarenes via VNS of 2-phenylthio-1,3-dithiane. The dithianylated products can be directly hydrolyzed to the corresponding nitroaryl aldehydes without isolation, if necessary. These 1,3-dithiane substituted nitroarenes may find further uses as valuable building blocks in the synthesis of other interesting aromatic compounds.

Acknowledgements

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10. Typical experimental procedure: To a solution of KO*t*Bu (2.2 equiv.) or KHMDS (2.2 equiv.) in DMSO (1 mL) was added a mixture of **2** (1.2 equiv.) and nitrobenzene (50 mg) in 1 mL of DMSO at rt. Quenching with AcOH (0.5 mL), followed by usual work-up and chromatography, 95 mg of pure **4a** was obtained as white crystals in 95% yield.
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