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para-Formylation of Nitroarenes *via* Vicarious Nucleophilic Substitution of Hydrogen with Tris(benzotriazol-1-yl)methane

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Abstract: Reaction of nitroarenes **1** with tris(benzotriazol-1-yl)methyl **2** anion afforded *para*-bis(benzotriazol-1-yl)methylated products **3** which, upon treatment with zinc bromide and hydrochloric acid, yielded the corresponding *p*-nitroarylaldehydes **4** in good yields.

Direct substitution of a formyl group or its equivalent at a carbon atom is a valuable synthetic transformation which has attracted extensive studies.[1] Although numerous methods for the direct formylation of arenes *via* electrophilic attack are known,[1,2] they are not applicable to nitroarenes due to the electron deficient nature of the latter. Recently, vicarious nucleophilic substitution of hydrogen (VNS) has emerged as a versatile technique for the introduction of a variety of substituents into electrophilic arenes.[3,4] Several methods for formylating nitroarenes *via* VNS have been developed by Makosza *et al* : (i) Tris(phenylthio)methane reacts with nitroarenes under basic conditions to give *para*-bis(phenylthio)methyl-substituted nitroarenes[5] capable of further hydrolysis to *p*-formyl nitroarenes;[6] however, the VNS step suffers from low yields and the hydrolysis requires the use of a toxic heavy metal salt. (ii) Trichloro- and tribromo-methyl carbanions generated by the deprotonation of haloforms with nitroarenes introduce dihalomethyl substituents *ortho* and *para* to the nitro group, which in turn could be hydrolized to nitroarylaldehydes;[7,8] however, this approach is not suitable for *para*-formylation, since the dihalomethylation usually occured at both *ortho* and *para* positions with an *ortho* preference. (iii) Nitrobenzyl aryl sulfones, prepared from nitroarenes and chloromethyl aryl sulfones by VNS, react with the aminating reagent 3,3-pentamethyleneoxaziridine followed by cleavage to give nitrobenzaldehydes;[9] however, these sulfonylmethylations give mixtures of *para*- and *ortho*-isomers,[10] which limits the applicability of this approach.

Work from our laboratory has demonstrated that benzotriazole is a good leaving group which can be used in place of a halogen in many reactions.[11-14] This property, coupled with the ready accessibility and the unique reactivities of its derivatives, suggested its potential to provide efficient methods for functionalizing nitroarenes *via* VNS. Recently, Bernard reported that reactions of 1-(phenylsulfonylmethyl)benzotriazole with nitroarenes produced benzotriazolylmethyl substituted nitroarenes as the result of the elimination of the

sulfonyl group instead of the benzotriazolyl group.[15] We have now found the first examples in which the benzotriazolyl group functions as a leaving group in the course of VNS. Thus, tris(benzotriazol-1-yl)methane is an efficient reagent for the introduction of the bis(benzotriazol-1-yl)methyl group into the *para* position of nitroarenes. Subsequent hydrolysis of the resulting bis(benzotriazol-1-yl)methyl nitroarenes provides easy access to various *p*-nitroarylaldehydes.

Scheme 1

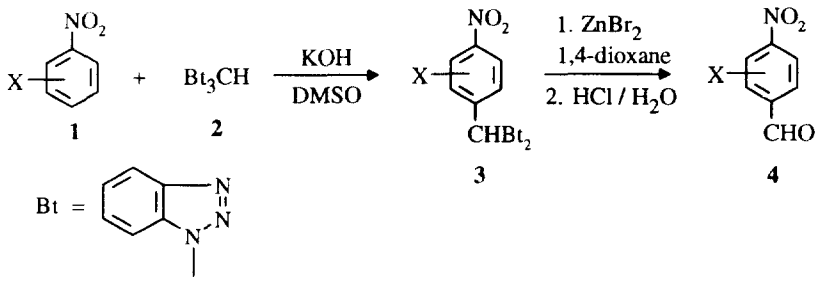

Table 1. Preparations of Intermediates **3a-e** and of *p*-Nitroarylaldehydes **4a-g**

X (in 1)	3	yield [a] (%)	m.p. (°C)	Calcd (Found) C	H	N	4	yield [b] (%)	m.p. (°C)	Calcd (Found) C	H	N
H	a	85	89-90	61.45 (61.24	3.53 3.55	26.40 26.29)	a	86 (90)[c]	104-106 (105-107[22])	55.62 (55.78	3.34 3.12	9.27 9.18)
2-Ph	b	68	100-101	67.11 (67.26	3.83 3.82	21.91 22.05)	b	75 (92)[c]	oil	68.70 (68.66	3.99 3.97	6.17 6.16)
2-NO_2	c	61	154-155	54.81 (54.71	2.91 2.75	26.91 26.63)	c	69	60-62 (62.5[25])	-	-	-
2-Br	d	64	175-176	50.68 (50.75	2.69 2.46	21.78 21.61)	d	71	101-102 (97-99[26])	36.55 (36.79	1.75 1.50	6.09 5.97)
C_4H_4[d]	e	50	217-218	65.55 (65.70	3.59 3.43	23.27 23.40)	e	74	107-108 (106-107[27])	65.67 (65.87	3.51 3.37	6.96 7.04)
3-F							f	41	108-109	49.72 (49.72	2.38 2.13	8.28 8.17)
2-Cl							g	84	60-61 (58-59[28])	45.41 (45.69	2.18 1.96	7.57 7.48)

[a] Yield of isolated 3. [b] Overall yield from starting nitroarene 1. [c] Yield of the hydrolysis step from pure 3. [d] 1-Nitronaphthalene.

Tris(benzotriazol-1-yl)methane (**2**) is readily prepared from benzotriazole and chloroform in the presence of sodium hydroxide and tetrabutylammonium bromide (TBAB).[16] Reactions of **2** with nitroarenes in the presence of potassium hydroxide in DMSO at room temperature afforded *p*-bis(benzotriazol-1-yl)methyl nitroarenes **3** according to the VNS mechanism (Scheme 1). Thus, compounds **3a-e** were isolated in 50-85%

yields (Table 1).[17] Of special interest is that the substitution occurred exclusively at the position *para* to the nitro group evidently due to the bulkiness of tris(benzotriazol-1-yl)methyl carbanion. Transformation of the bis(benzotriazol-1-yl)methyl groups to formyl groups was readily achieved in almost quantitative yield by treating **3** with zinc bromide and hydrochloric acid in refluxing 1,4-dioxane as exemplified by the conversions of **3a** and **3b** into the corresponding aldehydes **4a** and **4b**.[18]

Conveniently, it is not necessary to separate the intermediates **3** for the formylation of nitroarenes. Accordingly, tris(benzotriazol-1-yl)methane (**2**) was treated with nitroarenes **1a-e**, and the crude products thus obtained were subjected to hydrolysis with hydrochloric acid in the presence of zinc bromide to provide the corresponding *para*-formylated products **4a-g** in 41-86% overall yields.[19] Interestingly, as shown in Table 1, the overall yields of **4** from this one-pot procedure are higher in all cases than the yields of isolated **3**. Presumably compounds **3** were not completely stable to column chromatography.

In these reactions, steric demands of the tris(benzotriazol-1-yl)methyl anion were pronounced. The reaction proceeded satisfactorily with nitrobenzene (**1a**), *ortho*-substituted nitrobenzenes (**1b-d**) and 1-nitronaphthalene (**1e**). However, the yield for 3-fluoronitrobenzene (**1f**) was low and the method failed for 3-phenylnitrobenzene. Attempts to *ortho*-formylate *para*-substituted nitrobenzenes, such as 4-methylnitrobenzene, were unsuccessful.

In conclusion, we have shown that tris(benzotriazol-1-yl)methane (**2**) is an excellent reagent for the conversion of a nitroarene to the corresponding *p*-nitroarylaldehyde. Significant features of this methodology include high regioselectivity, good yields, and the ready availability of the starting materials. *p*-Nitroarylaldehydes have been previously prepared by the oxidation of *p*-methylnitroarenes[20] and *p*-(hydroxymethyl)nitroarenes,[21,22] by the reduction of the corresponding esters,[23] and from the palladium-catalyzed reaction of *p*-halonitroarenes with carbon monoxide and tin hydride.[24] However, the present approach directly from nitroarenes complements these methods and should be of substantial practical interest.

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17. **Preparation of *para*-[Bis(benzotriazol-1-yl)methyl]nitroarenes 3a-e. General Procedure.** To a mixture of tris(benzotriazol-1-yl)methane (**2**) (2.9 g, 8 mmol), the appropriate nitroarene (**1**) (8 mmol) and potassium hydroxide (2.8 g, 50 mmol), under argon, was added DMSO (40 mL). The highly colored solution was stirred at 20 °C overnight. The mixture was poured into aqueous hydrochloric acid (3%, 200 mL) and the aqueous layer extracted with chloroform (4 × 100 mL). The combined organic layer was washed with water (5 × 80 mL), dried over $MgSO_4$ and evaporated at reduced pressure to give the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 3/2). The products **3a-e** were fully characterized by ^1H and ^{13}C NMR spectroscopy.
18. **Hydrolysis of [Bis(benzotriazol-1-yl)methyl]nitroarenes 3. General Procedure.** To a solution of **3** (8 mmol) in 1,4-dioxane (100 mL) was added $ZnBr_2$ (3.6 g, 16 mmol). After the mixture was refluxed for 30 min, hydrochloric acid (conc. 7 mL) was added. The mixture was further refluxed for 4 h. The solvent was evaporated at reduced pressure and water (200 mL) was added to the residue. The mixture was extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with NaOH (5%, 2 × 60 mL) and water (1 × 60 mL), dried over $MgSO_4$ and evaporated to give the crude product, which was purified by short column (silica gel, hexane/ethyl acetate = 5/1).
19. **Preparation of *p*-Nitroarylaldehydes 4a-g from Nitroarenes. General Procedure.** Tris(benzotriazol-1-yl)methane (**2**) was treated with an appropriate nitroarene according to the procedure described above.[17] After work-up, the crude product **3** was subjected to hydrolysis following the procedure described above.[18] The products **4a-g** were fully characterized by ^1H and ^{13}C NMR spectroscopy.
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