J. Chem. Research (S),
1999, 504–505†

Reactions of 1-(Benzotriazol-1-yl)-1-phenoxyalkane and (Benzotriazol-1-yl)ethoxyphenylmethane Anions with Nitroarenes: a New Approach to Alkyl and Aryl *p*-Nitroaryl Ketones†

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p-Nitroaryl alkyl ketones and *p*-nitroaryl aryl ketones are prepared regioselectively by reactions of non-functionalized nitroarenes and benzotriazole stabilized carbanions.

Preparations of *p*-nitroaryl aryl ketones and *p*-nitroaryl alkyl ketones have frequently been described but all published procedures access these compounds from functionalized nitroarenes. Most often, nitroaroyl chlorides are coupled with organotin reagents[1] or used as precursors of trifluoromethanesulfonic–carboxylic anhydrides which are highly reactive acylating agents.[2] Additionally, palladium-catalysed carbonylations of halogenonitroarenes with organoaluminiums[3] or boronic acids[4] have been utilized.

Oxidative nucleophilic substitution of hydrogen (ONSH) has recently been developed as a versatile method for C–C bond formation by the reactions of carbon nucleophiles with nitroarenes.[5–9] We previously demonstrated that condensations of nitroarenes with tris(benzotriazol-1-yl)methane[10] and benzotriazolyldiarylmethane carbanions[11] provide general syntheses for (*p*-formyl)nitroarenes and (*p*-nitroaryl)diarylmethanes respectively, by vicarious nucleophilic substitution (VNS) of hydrogen regiospecifically *para* to the nitro group. During our studies concerning VNS with benzotriazolyldiarylmethane carbanions, some ONSH product was observed in addition to the desired (*p*-nitroaryl)diarylmethanes.[11]

The present study describes regioselective syntheses of *p*-nitroaryl aryl ketones and *p*-nitroaryl alkyl ketones from nitroarenes utilizing 1-(benzotriazol-1-yl)-1-phenoxyalkanes **1a**–**1c** and (benzotriazol-1-yl)ethoxyphenylmethane **1d**. Compounds **1a**–**1d** were deprotonated with 1 equiv. of Bu^{n}Li and the resulting anions treated with the appropriate nitroarene to afford σ_H adducts **3a**–**3i**, which were then oxidized by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) *in situ* to afford **4a**–**4i** as solids (Scheme 1).

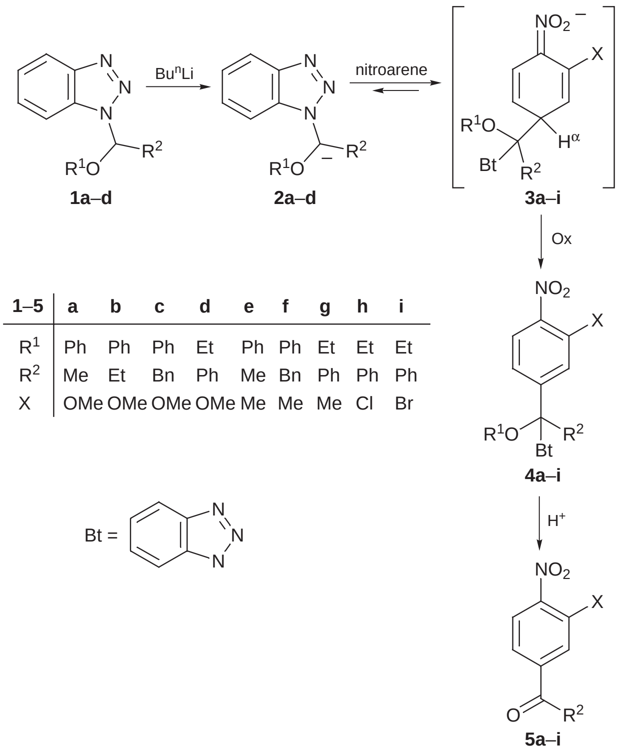
Intermediates **4a**–**4i** can be hydrolysed either as the pure compounds (Table 1, entries a to d) or, more conveniently, as crude reaction mixtures (Table 1, entries e to i), by treatment with dilute solutions of H_2SO_4 in 1,4-dioxane–water to give the desired *p*-nitroaryl alkyl ketones **5a**–**5i**.

These reactions are clean and regiospecific, but typically about 50% of the starting material **1** remains unchanged: the yields calculated on reacted **1** average 50%. The conversion and yields are based either on the amount of unchanged **1** recovered (entries a to d) or according to the amount of **1** reacted from integration of the signals of the starting material **1** and the desired intermediate **4** in ^{1}H NMR spectra of crude reaction mixtures (entries e to i).

Table 1 Condensations of anions **2a**–**2d** with functionalized nitroarenes and hydrolyses of the resulting adducts **4a**–**4i** into the corresponding ketones **5a**–**5i**

Entry	R^1	R^2	X	Unchanged starting material (%)	Yield[a] **5a**–**5i** (%)
a	Ph	Me	MeO	69	99
b	Ph	Et	MeO	50	55
c	Ph	Bn	MeO	55	50
d	Et	Ph	MeO	50	70
e	Ph	Me	Me	51[b]	25
f	Ph	Bn	Me	40[b]	35
g	Et	Ph	Me	50[b]	20
h	Et	Ph	Cl	55[b]	46
i	Et	Ph	Br	30[b]	70

[a] Calculated on unrecovered starting material for entries a–d; on starting material converted for entries e–i. [b] Unchanged starting material was not recovered. Hydrolysis was performed on crude mixture.



1–5	a	b	c	d	e	f	g	h	i
R^1	Ph	Ph	Ph	Et	Ph	Ph	Et	Et	Et
R^2	Me	Et	Bn	Ph	Me	Bn	Ph	Ph	Ph
X	OMe	OMe	OMe	OMe	Me	Me	Me	Cl	Br

Scheme 1

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 2 Oxidation of intermediate **3b** with various oxidizing agents

Entry	Solvent	Oxidizing system[a]	Ratio **4b**:**1**[b]
1	THF	$KMnO_4$	1:8
2	THF	$KMnO_4$ + 18-crown-6	1:3
3	THF	DDQ	1:3
4	THF	DDQ[c]	0
5	THF	$NaMnO_4 \cdot H_2O$	1:4
6	THF/TMEDA	$NaMnO_4 \cdot H_2O$	1:3
7	Toluene	$KMnO_4$ + 18-crown-6	0

[a] 0.6 equiv. of oxidizer was employed. [b] Determined by ^1H NMR. [c] 1 equiv. of oxidizer was reacted.

While adducts **1a**–**1d** are stable, the derived anions **2a**–**2d** undergo partial degradation upon standing at −78 °C however they are apparently stabilized by nitroarenes towards decomposition and/or oxidation for up to 5 h at −78 °C. Presumably, the equilibrium of compounds **2** and **3** provides sufficient concentration of the σ_H adduct **3**. The intermediate σ_H adducts **3** are oxidized by the air dissolved in the quenching solution. When anion **2a** was treated with DDQ in the presence of *o*-nitroanisole, **1a** was recovered quantitatively. Thus, the two conditions required for the ONSH to proceed satisfactorily are fulfilled.[8]

In an attempt to improve the yields, a range of alternative oxidizing reagents were used with adduct **3b**. Compound **1b** was lithiated with Bu^nLi and the resulting anion then treated with *o*-nitroanisole. The subsequent addition of the oxidizer and warming the mixture to room temperature afforded mixtures of product **4b** and compound **1b** in the ratios reported in Table 2. However, none of the reaction conditions tested compared favorably to the use of DDQ.

These data suggest that during the oxidation process the hydrogen atom H^α in compounds **3** (Scheme 1) is converted into an acidic proton which is transferred to the anion **2** at a rate comparable with the oxidation. Furthermore, a highly ionizing solvent favors the oxidation probably because of an increased concentration of the σ_H adduct **3**. Tetrahydrofuran promotes the transformation **3** → **4** as opposed to toluene (entries 2 and 7), while the addition of a complexing agent reinforces this effect (entries 1 and 2, 6). Since increasing the reaction time did not improve the conversion of the starting material, we assume that the oxidation of intermediate **3** is a fast process. Attempts to oxidize σ_H adduct **3** to **4** by adding the intermediate **3** to the oxidizer did not improve the conversion of **3**, while treating a two fold excess of the oxidizer with **3** resulted in the quantitative isolation of the starting material (entry 4).

In conclusion, we have developed novel regiospecific syntheses of (*p*-nitroaryl) alkyl ketones and (*p*-nitroaryl) aryl ketones starting from non-functionalized nitroarenes. Although the intermediate adducts can be isolated, the acid hydrolysis can be achieved more conveniently on the crude reaction mixtures to afford the desired ketones **5**, through a simple two step sequence.

Experimental

Compounds **1** were prepared by the procedure reported in reference 12.

General Procedure for the Preparation of Adducts **4** *and Ketones* **5**. Compound **1** (2 mmol) was dissolved in dry THF (50 mL) and cooled at −78 °C. Bu^nLi solution in hexanes (1.6 M, 1.25 ml, 2 mmol) was added, followed by the addition of the desired nitroarene (2 mmol). After 15 min a solution of DDQ (1.2 mmol) in THF (20 mL) was added and the reaction mixture was allowed to warm to room temperature overnight. Treatment with brine (50 mL) followed by extraction with Et_2O (2 × 30 mL) and concentration of the combined organic layers under reduced pressure gave a mixture of the expected adduct **4** along with unchanged **1** and nitroarene as a yellowish oil. The remaining oil was either subjected to flash column chromatography on silica gel (hexanes–ethyl acetate as eluent) to give pure products (compounds **4a**–**4d**) or used as a crude mixture for the hydrolysis (compounds **4e**–**4i**). Compound **4** was dissolved in a 15% solution of H_2SO_4 in 1,4-dioxane–water (4:1, 30 mL). The resulting solution was allowed to react at room temperature (R^1 = Et) or under reflux (R^1 = Ph) until the starting material was completely converted. After removal of the solvent under vacuum, the residue was dissolved in CH_2Cl_2 (30 mL), washed with aqueous 5% Na_2CO_3 (2 × 30 mL), dried ($MgSO_4$) and the organic layer was concentrated under reduced pressure. Purification of the crude reaction mixture by flash column chromatography on silica gel (hexanes–ethyl acetate as eluent) afforded pure ketone **5**.

We are grateful to 3M for financial support.

Received, 2nd February 1999; Accepted, 14th April 1999
Paper E/9/00891H

References

1 J. W. Labadie, D. Tueting and K. J. Stille, *J. Org. Chem.*, 1983, **48**, 4634.
2 F. Effenberger and G. Epple, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 9.
3 N. A. Bumagin, A. B. Ponomaryov and I. P. Beletskaya, *Tetrahedron Lett.*, 1985, **26**, 4819.
4 T. Ishiyama, H. Kizaki, N. Miyaura and A. Suzuki, *Tetrahedron Lett.*, 1993, **34**, 595.
5 M. Makosza and K. Stalinski *Tetrahedron*, 1998, **54**, 8797.
6 M. Makosza and K. Stalinski, *Synthesis*, 1998, 1631.
7 M. Makosza and M. Sypniewski, *Tetrahedron*, 1994, **50**, 4913.
8 M. Makosza, K. Stalinski and C. Klepka, *Chem. Commun.*, 1996, 837.
9 M. K. Bernard, *Tetrahedron Lett.*, 1995, **36**, 2169.
10 A. R. Katritzky and L. Xie, *Tetrahedron Lett.*, 1996, **51**, 347.
11 A. R. Katritzky and D. Toader, *J. Org. Chem.*, 1997, **62**, 4137.
12 A. R. Katritzky, X. Lan, J. Z. Yang and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409.