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Alkylation of Nitroaromatics with Trialkyborane

N. Palani, Karamil Jayaprakash, and Shmaryahu Hoz*

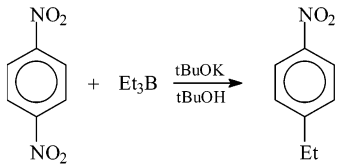
Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel 52900

shoz@mail.biu.ac.il

Received February 19, 2003

When *p*-dinitrobenzene is reacted with Et_3B in *t*-BuOH or THF in the presence of *t*-BuOK, it yields *p*-nitroethylbenzene. In this report we examine the scope of this transformation by monitoring the effect of various parameters on the reaction. It has been found that the reaction is extremely sensitive to temperature and rather insensitive to the base−solvent combination used. It is also insensitive to the steric hindrance of the base: good yields were obtained using sodium 2,6-diisopropylphenoxide or when using NaH. Alkylation was obtained with a large variety of alkylboranes ranging from linear to polycyclic. Yields drop significantly if one of the nitro groups is replaced by another electron-withdrawing group. In all cases studied (CHO, PHCO, SO_2Ph, and CN), it is the latter group which was preferentially displaced by the alkyl group. According to the suggested mechanism, the radical anion of the substrate combines with the alkyl radical released from the boranyl radical to form a Meisenheimer complex. The reaction takes place at the ring carbon bearing the highest spin density in accordance with ab initio calculations at the B3LYP/6-31+G* level.

We have recently reported a novel reaction of triethylboranes with *p*-dinitrobenzene (**1**) in the presence of base (eq 1).[1]

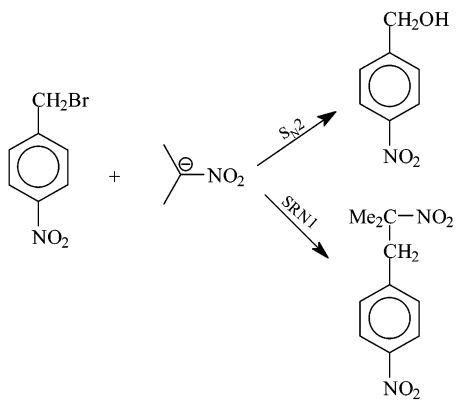


(1)

1 **2**

In this reaction a very facile replacement of one of the nitro groups occurs at room temperature within 5 min with an isolated yield of ca. 80%.

This surprising finding arose from a study aimed at examining the effect of trialkylborane on the O vs C alkylation ratio in the reaction shown in eq 2.[2]



(2)

Since C alkylation occurs via the SRN1 mechanism, **1** was added as a radical anion scavenger. This led to the discovery of the reaction shown in eq 1.

In the present paper we report the scope and limitations of this novel reaction vis-à-vis the solvent, the base, the substrate, the alkyl group, and the temperature. This work was not aimed to optimize yields but rather to explore the applicability limits of this novel reaction.

Results and Discussion

The assessment of the scope of and limitations of the alkylation reaction (except for substrate variation) was made using *p*-dinitrobenzene as the substrate. The reactions were carried out under an argon atmosphere, typically at room temperature with equivalent amounts of substrate and base and a slight excess (10%) of the borane.

Base and Solvent Effects. In Table 1 we present data for the reaction yield as a function of solvent and base variation.

The data in the table show that the reaction is practically insensitive to the nature of the base used. Phenoxides as bases were almost as good as alkoxides and even NaH and BuLi gave similar results. The reactions were not very sensitive to the steric hindrance of the base since *t*-BuOK and *i*-PrONa gave similar results and phenoxide and 2,6-diisopropylphenoxide also gave nearly the same yields. There was a small depen-

(1) Shifman, A.; Palani, N.; Hoz. S. *Angew Chem., Int. Ed.* **2000**, *39*, 944.

(2) Shifman, A.; Sprecher, M.; Hoz. S. *J. Phys. Org. Chem.* **2000**, *13*, 105−111.

10.1021/jo034218q CCC: $25.00
Published on Web 05/02/2003

TABLE 1. Variation of Base/Solvent for the Reaction of 1 and Triethylborane[a]

no.	base	solvent	% yield (**2a**)[b]
1	*t*-BuOK	*t*-BuOH	85
2	*t*-BuOK	THF	75[c]
3	*t*-BuOK/18-crown-6	THF	25[d]
4	*t*-BuOLi	THF	66
5	*i*-PrONa	*i*-PrOH	75
6	PhOK	*t*-BuOH	74
7	PhOK/18-crown-6	*t*-BuOH	26[e]
8	ArOK[f]	THF	84
9	NaH	THF	70
10	*n*-BuLi	THF	79

[a] Reactions were conducted for 5 min at room temperature. [b] Yields are calculated from the ^{1}H NMR spectrum of the crude reaction mixture. [c] The formation of aproximately 15% of *p*-*t*-butoxynitrobenzene was found. [d] *p*-*t*-Butoxynitrobenzene was the major product in this reaction (75%). [e] Majority of **1** (66%) remained unreacted and 18% of *p*-phenozynitrobenzene was formed. [f] Ar = 2,6-diisopropylbenzene.

dence on the cation as yields were somewhat smaller with Li than with K (see entries 2 and 4 in Table 1).

On the assumption that tight coordination, somehow hampers the reaction, we examined the effect of crown ether and expected improved yields. The striking result was that the yield dropped significantly (compare entries 2 and 3 and entries 6 and 7 in Table 1). The addition of crown ether seems to enhance the formation of the *p*-alkyl/aryloxynitrobenzenes. This may imply that the ion-pair dissociation caused by the crown ether by affecting the equilibrium established between the base and the borane increases the amount of free base which can then react with the aromatic substrate via the traditional SNAr mechanism. Alternatively, the small amount of free base which exists in the reaction mixture becomes nucleophilicaly more reactive when not complexed to its counterion.

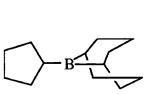
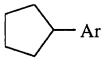
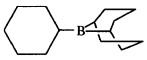
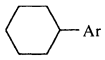
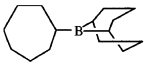
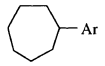
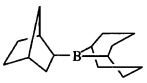
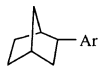
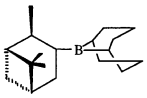
The reaction is not very solvent sensitive. Only relatively small differences were observed between the three solvents used, *t*-BuOH, THF, and *i*-PrOH. It should be pointed out, however, that the yields in THF were slightly lower than those in *t*-BuOH as some direct attack by *t*-BuO$^-$ occurred giving rise to the formation of *p*-*t*-butoxynitrobenzene. However, excess (2 equiv) of triethylborane circumvents this difficulty, increasing the yield to 85%.

Borane Effect. Standard conditions were employed with the exception that the reaction time was 30 min. The data are presented in Table 2.

Unlike solvent and base variations which seem to have only a miniscule effect on the yield, changing the alkyl groups on the borane made a big difference. A change from Et to Bu caused a 20% decrease in the yield (entries 1 and 2 in Table 2). When a mixture of Et_3B and Bu_3B where allowed to react with **1** in *t*-BuOH for 10 min, the relative yields of the *p*-ethyl and *p*-butyl derivatives were 1.7 and 1.0, respectively.

We are not sure whether the data with the mixed boranes (entries 3−6 in Table 2), can be used to demonstrate the effect of the size of the alkyl group on the yields since these reagents were prepared in situ by reacting the corresponding olefin with 9BBN. The low yield could be attributed to a low yield in the reagent preparation step rather than to the alkylation reaction itself. Indeed,

TABLE 2. Effect of Alkyl Group on the Yield in the Reaction with 1[c]

No	Borane	Base/Solvent	Producta[a]	Yield(%)[b]
1.	Et_3B	*t*-BuOK/*t*-BuOH	Et-Ar **2a**	85
2.	Bu_3B	*t*-BuOK/*t*-BuOH	Bu-Ar **2b**	65
3.		PhOK / THF	 **2c**	30
4.		PhOK / THF	 **2d**	30
5.		PhOK / THF	 **2e**	22
6.		PhOK / THF	 **2f**	18
7.		*t*-BuOK/*t*-BuOH	 **2g**	54

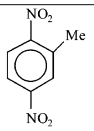
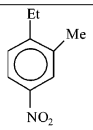
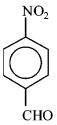
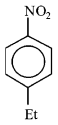
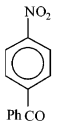
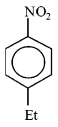
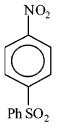
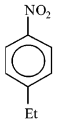
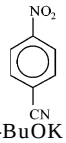
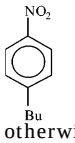
[a] Ar = $C_6H_4NO_2$. [b] Yields calculated from the ^{1}H NMR spectrum of the crude reaction mixture. [c] Reactions were carried out for 30 min at room temperature.

the yield of the reaction with the pinene derivative (entry 7 in Table 2) which was not prepared in situ was remarkably higher. However, since the purpose of this work was not to develop new synthetic methods for alkylation of aromatic nuclei but rather to explore the limits of a new reaction, we did not attempt to optimize the yields. We should also add that this procedure is not suitable for phenylation since no phenylation was observed after reacting **1** overnight with Ph_3B and *t*-BuOK in THF.

Substrate Effect. The best yields were obtained with *p*-dinitrobenzene as a substrate. We have tried other substrates, which we divide into two groups: substrates which showed measurable reactivity under the reaction conditions (yielding even few percents of **2**, Table 3) and substrates that gave no product under the reaction conditions (Chart 1).

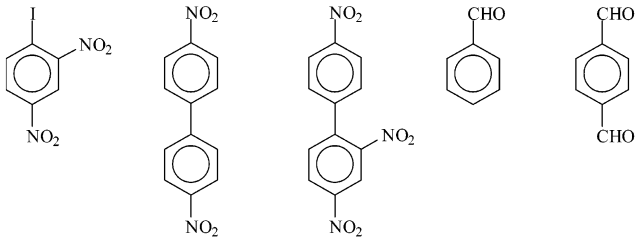
The introduction of a Me group at an ortho position of **1** rendered the two nitro groups inequivalent (entry 1, Table 3). Two products were obtained. The replacement of the group α to the methyl was five times more facile than the replacement of the other nitro group. An interesting result was obtained with *p*-nitrobenzaldehyde (entry 2, Table 3). In this case although only few percent of the product were obtained, it was remarkable that the CHO group and not the nitro group was replaced. Since the CHO group in benzaldehyde can be easily removed by hydrogen abstraction followed by decarbonylation, we have examined also the corresponding benzophenone (entry 3, Table 3). This gave 7% isolated yield of **2** thus demonstrating the direct displacement of the PhCO/HCO function. We found that second to **1** in its ability to react

TABLE 3. *p*-Alkylation of Substrates Other Then PDNB[a]

	Substrate	Reaction time (Temperature)[b]	Product	Yield (%)[c]
1		10 min. (RT)		76[d] (I)
2		ON (RT)		7(N) 6(I)
3		ON (RT)		7(I)
4		ON (RT)		10 (I)
5		1 hr. (reflux)		22[e] (I)

[a] Using *t*-BuOK in THF and Et_3B unless otherwise noted. [b] ON = overnight; RT = room temperature. [c] I = isolated yield; N = NMR yield. [d] Replacement of the nitro ortho to the Me group was five times more than replacement of the nitro group meta to the Me. [e] With Bu_3B.

CHART 1

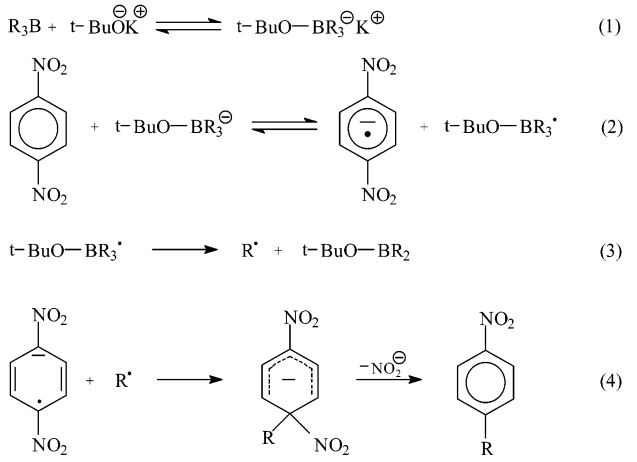


under the reaction conditions was *p*-nitrobenzonitrile (entry 5, Table 3). This substrate gave a relatively high yield of the product **1**. Again, it is not the nitro group which is displaced but rather the cyano group. It should be pointed out that in this case the reaction mixture was refluxed for 1 h. At room temperature and under normal conditions the yield was poor.

Temperature Effect. The reaction rate is highly temperature dependent. Applying the standard conditions, namely, equivalent amounts of substrate and base and a slight excess of the borane, the amount of unreacted starting material left after a reaction time of 2 h was 100% at −15 °C, 30% at 0 °C, and 7% at 10 °C, whereas at room temperature (ca. 25 °C) 0−5% of the starting material was left after 5−10 min. This large temperature dependence is indicative of a relatively high activation energy.

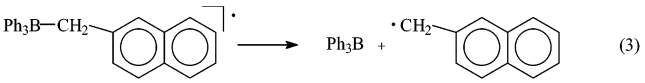
Reaction Mechanism. A possible mechanism for the alkylation reaction is shown in Scheme 1. Upon mixing, the borane forms a complex with the *t*-BuO^- (step 1). This complex can transfer an electron only to a very good

SCHEME 1



electron acceptor. This probably explains why best results are obtained with the highly electrophilic **1** (step 2).[3]

Step 3 in Scheme 1 involves the cleavage of the boranyl radical to dialkylalkoxy borane and alkyl radical. This process is characteristic not only of $R_3BOR'\cdot$, which is believed to have "only a fleeting existence",[4] but also of $R_4B\cdot$. In fact, Schuster et al. determined the rate constant for the cleavage of Ph_3BCH_2Naphthyl radical[5] (as in eq 3) to be 1×10^{11} s^{-1}.



Indeed, in our studies, NaH and BuLi were also very effective in inducing the alkylation reaction. The high rate by which the boranyl radical splits off an alkyl radical is probably the major reason for the successful alkylation. A slow release of alkyl radical would enable an efficient out of cage escape of the boranyl radical leading ultimately to reduced yields and probably also to many side products.

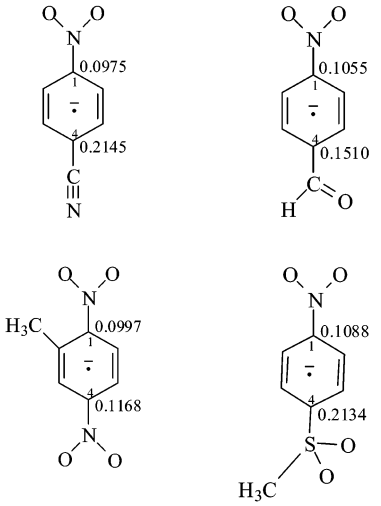
That free radicals do not participate significantly in the reaction can be inferred also from the reaction in *i*-PrOH. The latter is known to be a good hydrogen radical donor and yet yields are not reduced significantly in that solvent indicating that free alkyl radicals do not play a key role in this reaction.

When the two para substituents on the substrate aromatic ring are not identical, a choice must be made regarding the site of alkylation. Namely, which of the two groups, i.e., NO_2 vs COR, NO_2 vs CN, NO_2 vs SO_2Ph, and NO_2 vs NO_2 (with an ortho Me group), will be displaced. We assumed that the released alkyl radical will react with the ring carbon bearing the largest spin density (step 4). We have calculated, using Gaussian 98[6] at the B3LYP/6-31+G* level,[7] the spin densities for the substrates given in Chart 2. As can be seen, in all cases, the largest spin density was indeed on the carbon atom where the alkylation took place. In the case of the ortho Me

(3) It should be pointed out that we have carried out the simple ethylation reaction also in the dark with no observable changes in the rate or yield. Thus, the reaction is not catalyzed by laboratory lights.

(4) Kochi, J. K.; Krusic, P. J. *J. Am. Chem. Soc.* **1969**, *91*, 3942.
(5) Chatterjee, S.; Davis, P. D.; Gottschalk, P.; Kurz, M. E.; Sauerwein, B.; Yang, X.; Schuster, G. B. *J. Am. Chem. Soc.* **1990**, *112*, 6329.

CHART 2. Spin Densities



group, the differences in spin densities between the two positions are the smallest, and indeed, in this case the two products were obtained in a ratio of 5:1 in correspondence with the respective spin densities.

Experimental Section

The ^{1}H NMR spectra were recorded on a 300 MHz spectrometer with $CDCl_3$ as solvent and TMS as reference. Chemical ionization mode was used for the high-resolution mass spectra.

Materials. Analytical grade *t*-BuOH and tetrahydrofuran (THF) were purified prior to use by the usual procedures.[8] 2,4,4′-Trinitrobiphenyl (Chart 1) was prepared by the reported procedure (mp 176 °C, lit. 176 0 °C).[9] All other chemicals were of analytical grade, were obtained from various commercial sources, and were used as such. Coloumn chromatography was performed using 230−400 mesh silica gel.

Typical Procedure for the Alkylation of 1 (Synthesis of 2a, b, and g). A 56 mg (0.5 mmol) portion of K-*t*-OBu dissolved in 5 mL of dry *t*-BuOH or THF was placed in a flame-dried flask closed with rubber septum and purged with argon. A 0.6 mL (0.6 mmol) portion of a 1 M solution of the borane in THF was injected through the septum. The mixture was stirred for 2 min, and 84 mg (0.5 mmol) of **1**, dissolved in 1 mL of dry *t*-BuOH or THF was injected into the above solution. The mixture was stirred for 5−10 min at room temperature. The reaction was quenched with 5 mL of 3% hydrochloric acid and was extracted using 20% methylene chloride in hexane (5 mL, three times). The combined organic layers were washed with water and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure. The crude compound was purified by flash column chromatography over silica gel. The compounds were characterized by their ^{1}H NMR as well as mass specta.

Procedure for the Synthesis of Compounds 2c−f. The corresponding boranes for these compounds were prepared in situ in the following way: The respective cyclo-olefin (0.7 mmol) was dissolved in 2 mL of THF. One milliliter of a 0.5 M solution of 9-borabicyclononane (9-BBN) was injected into the olefin/THF mixture which was heated at 50−60 °C for 6 h, under an atmosphere of argon. The mixture was then cooled to room temperature and used for alkylation as in the above procedure.

All compounds except **2g** are reported in the literature, and their physical data have been reported.[10] Compound **2g** (oil) was characterized on the basis of its ^{1}H NMR and HRMS data. ^{1}H NMR data for **2g** (300 MHz, $CDCl_3$, TMS, δ ppm): 0.877 (d, 3H, 7.5 Hz), 1.17 (s, 3H), 1.12−1.15 (m, 1H), 1.30 (s, 3H), 1.84−1.95 (m, 2H), 2.04−2.09 (m, 2H), 2.40−2.57 (2H), 3.09−3.15 (m, 1H), 7.46 (d, 2H, 9 Hz), 8.18 (d, 2H, 9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$, TMS, δ ppm): 20.9, 23.0, 28.4, 35.0, 37.2, 39.2, 41.7, 45.0, 45.8, 47.9, 123.7, 129.1, 146.2, 157.3. HRMS: calculated for (M + 1) ion 260.163216; observed 260.165054.

Supporting Information Available: Archive files containing energies and structures of the DFT computed radical anions of Chart2 (S1) and ^{1}H and ^{13}C NMR for compound **2g** (S2). This material is available free of charge via the Internet at http://pubs.acs.org.

JO034218Q

(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.4; Gaussian, Inc.: Pittsburgh, PA, 1998.

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