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Transition Metal Free Nucleophilic Benzylation of Nitroarenes. Umpolung of the Friedel Crafts Reaction

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Abstract. Benzyl chloride and its derivatives are efficiently deprotonated with strong bases to form *α*-chlorocarbanions. These anions are long-lived enough to enter VNS reactions with nitroarenes or nitroheteroarenes to give a variety of unsymmetrical *o*- and *p*-nitrodiarylmethanes. Selectivity of the reaction can be controlled to some extent by changing metal counterions of the base.

Keywords: Aromatic substitution; Benzylation; Nucleophilic substitution; Umpolung; VNS

Introduction

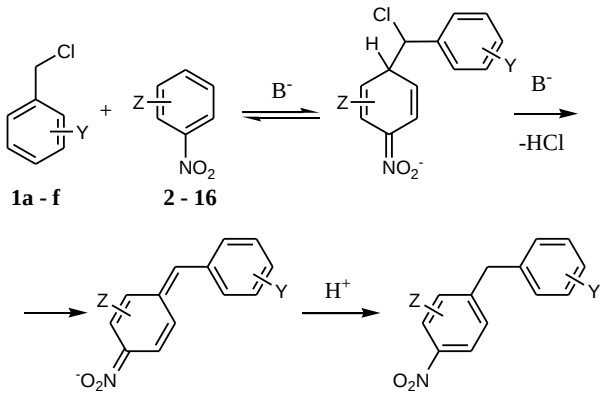
Diarylmethanes are rather simple molecules, but of substantial interest as versatile intermediates in the synthesis of pharmaceuticals, chemicals for electronics and dyes, and compounds of peculiar structure.[1] Synthesis of diarylmethanes, particularly containing a variety of substituents on both aromatic rings, is therefore of great interest. For instance, in 2018 more than 20 papers reporting various syntheses of substituted diarylmethanes were published. In spite of simplicity of their structure, practical synthesis of substituted diarylmethanes is not a simple task. The most obvious synthesis of diarylmethanes is the Friedel-Crafts type reaction of benzyl halides or other precursors of benzylic carbocations with arenes. Although apparently simple, it is severely limited in respect to substituents on both aromatic rings.[2] Similarly, reactions of benzyl halides or sulfonates with lithiated, magnesiated, etc. arenes cannot be considered as a general method.[3] Presently, the most often used way of synthesis of diarylmethanes is the transition metal catalyzed coupling of benzylic electrophiles: benzyl chlorides, benzyl trimethylammonium chlorides, benzylic esters, etc., with aryl boronic acids or aryl zinc chlorides.[4] Some less general methods, such as replacement of halogens in arenes by benzylic carbanions[5a-e] or cycloaddition of difluoroalkenes to azine *N*-oxides[5f] were also reported.

Nearly all of the mentioned reactions can in general be considered as interaction of benzylic electrophiles with aromatic nucleophiles. For many years we have developed an alternative approach to introduction of carbon substituents into aromatic rings – nucleophilic substitution of hydrogen in electron-deficient arenes.[6] Particularly valuable in this respect is vicarious nucleophilic substitution of hydrogen (VNS), that involves addition of *α*-chlorocarbanions at positions *ortho* or *para* of nitroarenes occupied by hydrogen to form anionic σ^H adducts. Subsequent base-induced *β*-elimination of HCl from these adducts produces nitrobenzylic carbanions that upon protonation give the substitution products.[7]

The VNS reaction is of general character in respect to both reaction partners. Carbanions of *α*-chloronitriles, *α*-chloroesters, *α*-chloroalkyl sulfones, haloforms, etc. react with nitroarenes and nitroheteroarenes and also with electron-deficient arenes that do not contain a nitro group, e.g. azines. It should be stressed that VNS of hydrogen proceeds faster than conventional S_NAr of halogens, so VNS proceeds efficiently in *ortho*- and *para*-halonitrobenzenes.[7,8] The key features of VNS – replacement of hydrogen in aromatic rings with carbon substituents and the reaction stoichiometry – are similar to the Friedel-Crafts reaction that proceeds with opposite polarity. We can therefore consider VNS to be in an umpolung relation to the Friedel-Crafts reaction.[9] The VNS process has found many practical applications and was used inter alia for direct introduction of alkyl and diarylmethyl substituents into nitroarenes. Recently, we reported efficient *α*-chlorobenzylation of nitroarenes via VNS reaction with carbanions of benzylidene dichlorides.[10]

Taking into account great interest in the synthesis of substituted diarylmethanes and simplicity and wide scope of VNS reactions, we decided to elaborate a general method of synthesis of diarylmethanes via VNS in nitroarenes by carbanions of substituted benzyl chlorides. It has been already shown that *p*-nitrobenzyl chloride enters VNS, but only with highly electron-deficient *m*-dinitrobenzenes.[11] Also some

chloromethyl azines: pyridines and quinolines, react with nitroarenes in the presence of strong bases according to the VNS pathway to form nitroaryl heteroarylmethanes.[12a] A multi-step procedure for VNS-like methylation of nitroarenes has also been reported.[12b] In our approach, we decided to use benzyl chloride and its derivatives that form carbanions much less stabilized than in the literature cases mentioned above.



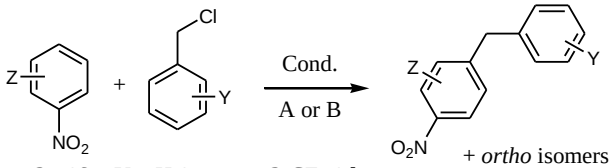
Scheme 1. The concept of VNS benzylation of nitroarenes

Results and Discussion

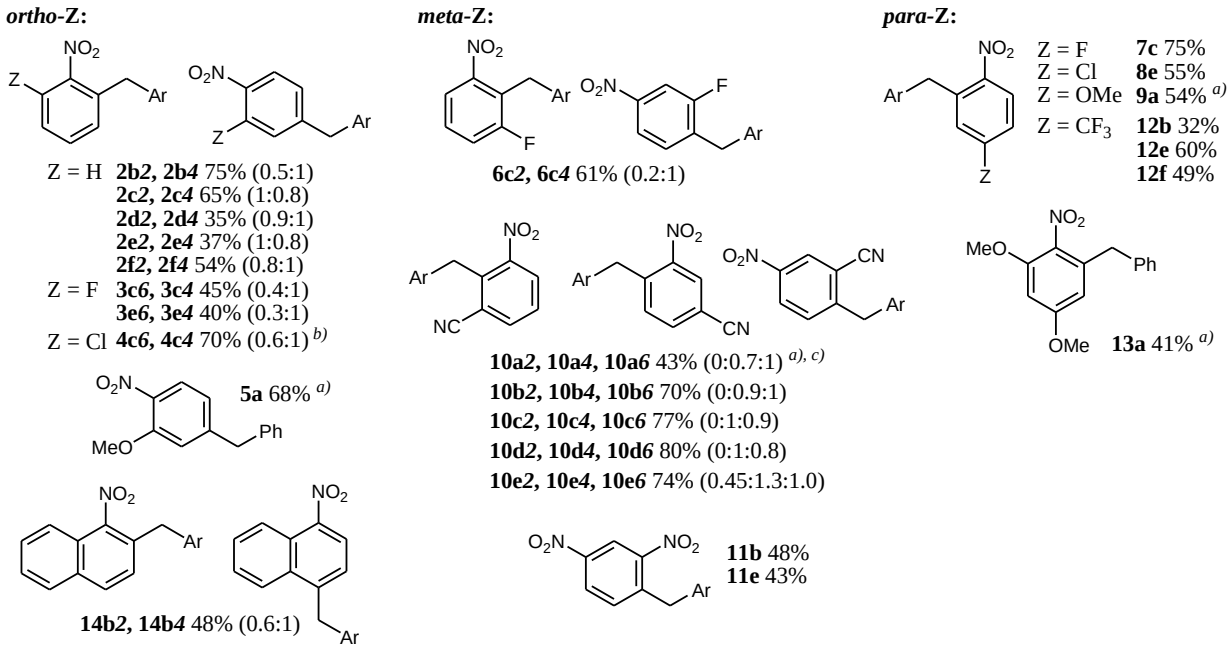
First attempts of the VNS reaction between benzyl chloride **1a** and a few nitroarenes: nitrobenzene **2**, 2-nitroanisole **5** and 4-nitroanisole **9**, carried out under conditions commonly used for such reactions (*t*-BuOK or KHMDS in THF/DMF at low temperature), were not promising. The expected products of substitution were formed in negligible yields (<10%) and most of the starting materials were recovered unchanged or decomposed. It appears that due to low C–H acidity of the methylenic group of **1a** its deprotonation by the applied base-solvents system was insufficient. After some experimentation we found that the system LDA/HMPA exhibited sufficiently strong basicity to assure deprotonation of **1a**. Under these conditions carbanions of **1a** are generated and they add to nitroarenes to form σ^H adducts that are sufficiently long-lived to undergo base induced β-elimination of HCl. Subsequent protonation of the nitrobenzylic carbanions gave nitrodiarylmethanes – products of VNS reaction (products **5a**, **9a**, **10a*4***, **10a*6***, **13a**, Scheme 3). The presence of HMPA in the system is necessary for solvation of the Li^+ cations so that aggregates of lithium salts of carbanions are destroyed and carbanions are in the form of loose ion pairs. It was shown that only in such form carbanions add efficiently to nitroaromatic rings.[13]

C–H acidity of the methylenic groups of benzyl chlorides substituted in the ring with electron-withdrawing groups: 2,4-dichlorobenzyl chloride **1b**, 4-cyanobenzyl chloride **1c**, 3-trifluoromethyl benzyl chloride **1d**, 3-nitrobenzyl chloride **1e** and 4-(*N*,*N*-diethylaminocarbonyl)benzyl chloride **1f** is higher than that of **1a**, so they could be efficiently deprotonated under the action of KHMDS. The VNS reaction of these benzyl chlorides with a variety of nitroarenes were therefore carried out under the commonly used conditions: KHMDS, THF/DMF at low temperature, for a relatively short time (15 min). Such conditions were determined to be necessary, because the starting α-chlorobenzylic carbanions and the nitrobenzylic carbanions of the products are rather unstable species. The expected products of the substitution - nitrodiarylmethanes - were obtained in good to acceptable yields. The general scheme of the reaction is shown in Scheme 2 and the results are collected in Schemes 3 and 4. For appropriate identification, the products are numbered by a combination of the number of the nitroarene (**2**–**16**), the letter corresponding to the benzyl chloride (**a**, **b**, **c**, **d**, **e**, **f**) and, where necessary, a digit *2*, *4* or *6* indicating the site of substitution in the nitroarene ring.

As expected, substitution of hydrogen by methylenic α-chlorocarbanions of benzyl chlorides proceeded at positions *ortho* and *para* to the nitro group. Indeed, as it is shown in Scheme 3, in most cases two isomeric VNS products – 2-(6-) or 4-nitrodiarylmethanes were formed which usually could be separated by chromatography or crystallization. Only in the reactions with *para*-substituted nitrobenzenes: **7**, **8**, **9**, **12**, **14** (entries 11, 12, 13, 21-23, 25) the substitution occurred selectively at position *ortho* to NO_2. It should be stressed that even the reactions of *o*- and *p*-halonitrobenzenes (**3**, **4**, **7** and **8**, Scheme 3) proceed exclusively as substitution of hydrogen, with no traces of products of halogens substitution (classical S_NAr) detected. With *meta*-substituted nitrobenzenes, products of benzylation at the *para* and the less hindered *ortho* position were formed in nearly equal amounts. Similarly, 3-nitropyridine reacted mainly at its C-4 and C-6 positions. Only traces of benzylation between the NO_2 group and the other substituent or the ring nitrogen atom were observed, with the exception of **10e** and **6c**. In the latter example, nucleophilic attack occurred only at the positions *ortho* to the fluorine atom, which are activated by its inductive effect.

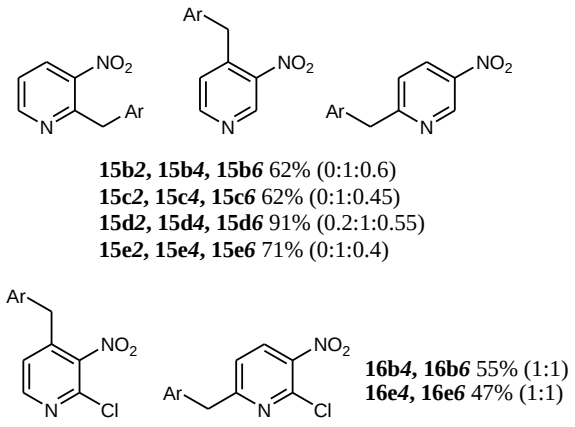


Scheme 2. VNS Benzylation of nitroarenes. Conditions A: **1** (1.2 equiv.), LDA (4 equiv.), HMPA (8 equiv.), THF/DMF, –78 °C, 15 min. Conditions B: **1** (1.2 equiv.), KHMDS (2.5 equiv.), THF/DMF, –78 °C, 15 min



Scheme 3. Results of benzylation of *o*-, *m*- and *p*-substituted nitroarenes and 1-nitronaphthalene. [a)] All reactions of **1a** performed using Conditions A (see Scheme 2). All other reactions performed using Conditions B. [b)] Reaction time 30 min. [c)] Conditions A with LDA (2.4 equiv.), HMPA (4.8 equiv.)

A considerable number and diversity of the examples collected in Scheme 3 and 4 demonstrates that the reaction is of general character and of wide scope with respect to substituents on both aromatic rings and therefore it may serve as a versatile tool in organic synthesis. It is thus of great interest to learn what factors govern the orientation and control the ratio of the isomers. In our early studies, it was shown that orientation is governed by a complicated interplay of steric and electronic effects.[6,7] Sterically demanding methinic carbanions react preferentially at positions *para*, although when these positions are occupied, substitution can occur at positions *ortho*.

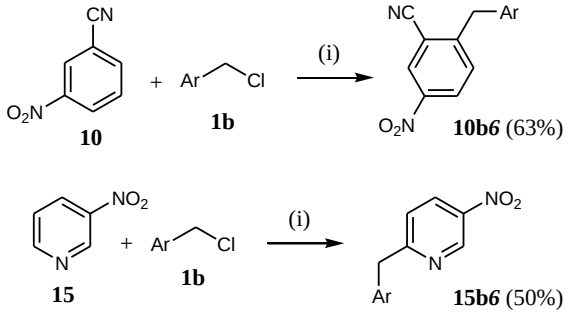


Scheme 4. Benzylation of nitropyridines

Orientation of VNS of methylenic carbanions is controlled by the conditions, structure of the nucleophile and the nature of the substituents in the nitroaromatic ring. The VNS reaction proceeds via two independent steps: reversible addition of α-chlorocarbanions to nitroarenes to form σ^H adducts, followed by base induced β-elimination of HCl, thus overall orientation of substitution is an interplay of these processes. Orientation of the initial addition is governed by the relation of electrophilicities of various positions in the nitroaromatic rings. Under conditions that disfavour dissociation, hence equilibration of the addition (low temperature and high concentration of strong base that ensures high rate of β-elimination), the substitution proceeds at the most electron-deficient positions. We can consider such orientation as kinetically controlled. Effect of substituents on the electrophilicity of various positions in nitroarenes was determined using VNS with carbanion of chloromethyl phenyl sulfone as a model nucleophile.[14] On the other hand, under conditions that favour equilibration: higher temperature and lower base activity, the orientation is controlled by the relative rates of β-elimination of isomeric σ^H adducts according to the Curtin-Hammett principle. It is then thermodynamically controlled. For instance, in the reaction of model carbanion of chloromethyl phenyl sulfone the ratio of *o*-/*p*-isomers under kinetic control is 3:1, whereas under thermodynamic control only *para* isomer is formed.[14]

The reactions of unstable carbanions of benzyl chlorides **1a-f** with nitroarenes have to be carried out at low temperatures in the presence of excess of strong base, so they probably proceed under kinetic control. We could therefore expect that the substitution in nitrobenzene should occur preferentially at positions *ortho*, whereas orientation in substituted nitrobenzenes should correlate with electrophilicity of various positions of the ring determined earlier.[14] As it is evident from the results presented in Scheme 3, this is not the case. Moreover, we cannot learn the orientation of the substitution under thermodynamic control simply due to instability of carbanions of **1a-e**.

An interesting question is whether and how substituents Y in the benzyl chloride ring affect the orientation. Inspection of the ratio of isomeric products of the reaction of nitrobenzene **2** with a series of substituted benzyl chlorides **1b**, **1c**, **1d**, **1e** and **1f** carried out under the standard conditions (Scheme 3) indicates that chlorobenzyl carbanions with more electron-withdrawing groups in the ring (4-CN, 3-CF_3, 3-NO_2, 4-$CONEt_2$) give nearly equal amounts of *ortho* and *para* substitution products, whereas dichloro derivative **1b** shows preference for *para* substitution. This may be due to its sterical demands (a chlorine atom *ortho* to the chloromethyl group). A similar, but a less pronounced trend can be observed with 3-cyanonitrobenzene **10**. Some irregularities are perhaps associated with moderate yields of the products. In our opinion, orientation is not substantially affected by the nature of substituents Y.



Scheme 5. Selective benzylation in the presence of lithium base. (i): LiHMDS, HMPA, THF/Toluene, –78 °C, 15 min. Ar = 2,4-dichlorophenyl

One might expect that the ratio of regioisomers could be influenced by the reaction conditions, that is solvent and the nature of base which affect the state of the ion pairs of the carbanions. Earlier, we observed a strong preference for substitution *ortho* to the nitro group in reactions of carbanions of $PhSO_2CH_2Cl$ in *t*-BuOK/THF system.[15] Indeed, in the reaction of **10** with **1c** carried out in the presence of KHMDS in DMF/THF, KHMDS in THF and LiHMDS in THF/HMPA/toluene, the ratios of attack *ortho* and *para* to the NO_2 group were 1.1, 0.44 and 0.18, respectively, with the respective total yields of 77%, 70% and 50%. Reactions of **10** and **15** with chloride **1b** gave exclusively products of substitution *para* to NO_2 (Scheme 5), similarly to benzylation of 2-methoxynitrobenzene with **1a** in the presence of LDA and HMPA (product **5a** in Scheme 3). These results demonstrate that some control of regioselectivity of benzylation is indeed possible.

It should be stressed that the process is of practical value as it can be executed on gram scale. From 5 mmol of 3-fluoronitrobenzene we obtained 4-cyanobenzylation products **6c*2*** and **6c*4*** in 74% total yield and 0.2:1 ratio, which is even better than the result at the standard 0.5 mmol scale (see Scheme 3). The yields reported in Scheme 3 and 4 were obtained in experiments according to one standard procedure, without attempts of optimization of individual examples, thus in many cases they can be probably substantially improved. For example, performing the reaction of **4** with **1c** for 30 min instead of the standard 15 min time period improved the yield from 42% to 70%. The scope of our benzylation protocol can be probably extended on benzyl bromides, as a single experiment with 2,4-dichlorobenzyl bromide and nitroarene **10** gave the benzylation product in similar yield and selectivity (75%, **10b*4***:**10b*6*** 0.8:1) as with **1b**.

We also attempted reactions with secondary benzyl chlorides. Unfortunately, the reaction between 2-chloronitrobenzene and 1-chloro-1-(4'-chlorophenyl)ethane was dominated by elimination of HCl from the latter substrate.

Conclusion

α-Chlorocarbanions generated via deprotonation of benzyl chloride and a variety of its derivatives add to nitroarenes at positions *ortho* and/or *para* to form anionic σ^H adducts that undergo base-induced β-elimination of HCl and subsequent protonation to give substituted *o*- and *p*-nitrodiarylmethanes. The reported method of nucleophilic benzylation is of general character with respect to substituents in both aromatic rings and the nature (homo- or heterocyclic) of the ring of the electrophilic partner. It can be viewed as a nucleophilic alternative to the classical Friedel-Crafts benzylation applicable to electron-deficient aromatic systems.

Experimental Section

General synthetic procedure for benzylation of nitroarenes in the presence of LDA. 2M LDA solution in THF (2 mmol, 1 mL) and anhydrous THF (1 mL) were placed in a flame-dried Schlenk flask under Ar and cooled to –78 °C. Then HMPA (4 mmol, 0.73 mL) was added and a solution of nitroarene (0.5 mmol) and **1a**, **1b** or **1d** (0.6 mmol) in THF (1 mL) was added dropwise with vigorous magnetic stirring. After 15 min 2M $HCl_{(aq)}$ (2 mL) was added, followed by AcOEt (5 mL) and brine (5 mL). The phases were separated, the organic phase was washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 and evaporated. The products were purified by column chromatography on silica gel using hexanes–AcOEt 10:1

or hexanes–AcOEt 5:1, unless specified otherwise in the descriptions of particular compounds.

General synthetic procedure for benzylation of nitroarenes the presence KHMDS. 1M KHMDS solution in THF (1.25 mmol, 1.25 mL) was placed in a flame-dried Schlenk flask under Ar and cooled to −78 °C. A solution of nitroarene (0.5 mmol) and **1b-f** (0.6 mmol) in DMF (1 mL) was added dropwise with vigorous magnetic stirring. After 15 min (or 30 min; see notes to Scheme 3) 2M $HCl_{(aq)}$ (2 mL) was added, followed by AcOEt (5 mL) and brine (5 mL). The work-up and purification of products as in the above procedure with LDA.

Large scale preparation of **6c*2***/**6c*4*** was performed identically, multiplying all quantities by a factor of 10.

General synthetic procedure for benzylation of nitroarenes in the presence of LiHMDS. 1M LiHMDS solution in toluene (1.25 mmol, 1.25 mL) was placed in a flame-dried Schlenk flask under Ar and cooled to −78 °C. Then HMPA (2.5 mmol, 0.44 ml) was added and a solution of nitroarene (0.5 mmol) and **1b** or **1c** (0.6 mmol) in THF (1 mL) was added dropwise with vigorous magnetic stirring. After 15 min 2M $HCl_{(aq)}$ (2 mL) was added, followed by AcOEt (5 mL) and brine (5 mL). The work-up and purification of products as in the above procedure with LDA.

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