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Direct synthesis of nitroaryl acetylenes from acetylenes and nitroarenes *via* oxidative nucleophilic substitution of hydrogen†

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Acetylenic carbanions add to nitroarenes (dinitrobenzenes, nitro-pyridines, *etc.*) to form σ^H-adducts that are subsequently oxidized by DDQ according to the oxidative nucleophilic substitution of hydrogen (ONSH) pathway to give nitroaryl acetylenes.

Introduction of acetylenic substituents into aromatic rings is of great interest in modern organic synthesis, because the presence of such fragments adds interesting physicochemical properties[1] and particularly because they can be converted into a variety of functionalities. Of particular value for organic synthesis are interactions of the acetylenic moieties in aromatic rings with vicinal substituents to form heterocyclic or carbocyclic rings.[2] For instance, transition metal catalyzed cyclization reactions of *ortho*-amino-arylacetylenes are widely used for synthesis of indoles.[3] The most general method of introduction of acetylenic substituents into aromatic rings is the Sonogashira reaction – transition metal catalyzed substitution of halogens in aromatic rings by terminal alkynes and arylacetylenes. The reaction is of general character and, as a rule, proceeds with high yield; however, the products are contaminated with traces of transition metals that are often undesirable.[4]

There are several examples published on replacement of halogens in aromatic rings by acetylenic carbanions without using transition metal catalysts; however, the starting arenes should still contain halogens.[5] Recently, a very interesting way of introduction of acetylenic substituents into nitroarenes was reported *via* S_NAr of fluorine in *ortho*- and *para*-fluoronitroarenes by enolates α-(2-benzothiazyl)ketones followed by Julia type olefination that proceeds *via* Smiles rearrangement.[6]

It should be mentioned that lithium and potassium acetyl-enides add to electron deficient azines such as 1,2,4-triazines and triazine oxides, *etc.* Further conversion of the σ^H-adducts proceeds *via* oxidation or rearrangement to form acetylenyl or styrylazines.[7]

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All reported methods of introduction of acetylenic substituents into aromatic rings consist of replacement of halogens: transition metal catalyzed replacement of I, Br, and Cl by terminal acetylenes – Sonogashira reaction and S_NAr of fluorine in fluoronitrobenzenes by acetylenic carbanions. These are not atom economic methods, because the halogen atom introduced into the aromatic ring in the first step of the synthesis of nitroaryl acetylenes is substituted by the acetylenic moiety subsequently.

Herein, we report an atom economical method for synthesis of nitroaryl acetylenes from acetylenes and nitroarenes *via* oxidative nucleophilic substitution of hydrogen, ONSH, with acetylenic carbanions.

ONSH consists of addition of nucleophiles such as OH⁻, NH₃, ArNH₂ and particularly carbanions to nitroarenes at positions occupied by hydrogen to form σ^H adducts that are subsequently oxidized by external oxidants to form products of oxidative nucleophilic substitution of hydrogen. It should be stressed that addition of nucleophiles to halonitroarenes proceeds faster at positions occupied by hydrogen than at those occupied by halogens; hence ONSH proceeds also in halonitrobenzenes.[8] Carbanions are sensitive to oxidation; thus ONSH proceeds efficiently, provided the addition equilibrium is shifted towards the adducts. The equilibrium depends on the electrophilicity of nitroarenes, nucleophilicity of carbanions and the conditions. Carbanions should be in the form of loose ion-pairs and the reaction should be carried out at low temperature. Taking into account the versatility of ONSH in nitroarenes with a variety of nucleophiles, we expect that such reaction should be applic-able for acetylenide anions. For generation of acetylenide carbanions the most convenient base–solvent system is *n*-BuLi in THF. Since for the addition to nitroarenes carbanions should be in the form of loose ion-pairs, HMPA was added to the reaction mixture.

The first attempts at reacting nitrobenzene and *p*-chloro-nitrobenzene with lithium phenylacetylenide in THF in the presence of 1 equivalent of HMPA (calculated on used BuLi) at −70 °C with DDQ as an oxidant gave negative results.

No expected products were produced. This was, apparently, because acetylenide carbanions, although the acetylenes are weak CH acids (pK_a of phenylacetylene 28.8),[9] are surprisingly weak nucleophiles and with relatively weak electrophiles such as these nitroarenes do not form σ^H adducts in a degree sufficient to afford ONSH. On the other hand, with a much stronger electrophile, *m*-dinitrobenzene, the reaction proceeded satisfactorily, giving a mixture of two isomeric 2,4- and 2,6-dinitrotolanes **1a** and **1a'** (isolated yields 55% and 15% respectively). A linear acetylenic carbanion can also add at highly sterically hindered position 2 of *m*-dinitrobenzene. It should be noted that the methylenic carbanion of chloromethyl phenyl sulfone adds to **1** exclusively at position 4.[10]

The preliminary results indicated that for ONSH with carbanions of phenylacetylene and other acetylenes, nitroarenes of high electrophilic activities should be used. For selection of the appropriate, sufficiently active nitroarenes, we have used reported values of the electrophilic activities of nitroarenes and nitroheteroarenes determined by measurements of relative rates of the addition of carbanions of chloromethyl phenyl sulfone to a variety of nitroarenes and nitroheteroarenes as a rate limiting step of the vicarious nucleophilic substitution of hydrogen, VNS.[11] The electrophilic activities are quantitatively expressed as the relation of rates of the addition of this carbanion to various nitroarenes to the rate of the addition at the *ortho* positions of nitrobenzene.[11]

On the basis of this criterion we have selected a series of highly active nitroarenes. However, under the conditions used for *m*-dinitrobenzene **1**, 1-nitronaphtalene **5** (*e* = 4600) and *m*-trifluoromethylnitrobenzene **4** (*e* = 5000) did not react with lithium phenylacetylenide. Probably an acetylenide carbanion was too much associated with a lithium cation to react with less active nitroarenes than *m*-dinitrobenzene. To increase the activity of the carbanion, HMPA was used not as a reagent, but as a co-solvent. Indeed, under these conditions,[12] the desired reactions proceed satisfactorily. The expected products were obtained in moderate yields (42% in the case of 1-nitronaphtalene **5** and 51% for *m*-trifluoromethyl-nitrobenzene **4**; a mixture of isomers **4a** and **4a'** was formed in the last case). These are the first examples of ONSH reactions in nitrobenzenes with carbanions formed from acetylenes. Unfortunately, even when HMPA was used as a co-solvent, *p*-chloronitrobenzene (*e* = 130) was still inactive under the reaction conditions and the corresponding product was not formed. The results of the ONSH reaction of acetylenes with nitroarenes are shown in Tables 1 and 2.

The reaction of lithium phenylacetylenide with 2,4-dinitroanisole **2** (*e* = 9000) gave three products of substitution of hydrogen at position 5-, **2a** (10%); 3-, **2a'** (45%) and the methoxy group **1a** (17%). Nucleophilic substitution of the methoxy group in **2** is a common process that often proceeds faster than S_NAr of chlorine.[13] Preferred addition at position 3- is due to the conjugation of the electron-donating methoxy group with the nitro groups. A similar effect of the conjugation on the orientation of the nucleophile addition to 2,4-dinitroanisole **2**, 2,4-dinitrophenolate and 2,4-dinitro-*N*-methylaniline was observed in the vicarious

Table 1 Synthesis of nitroaryl acetylenes from dinitrobenzenes (isolated yields are given)
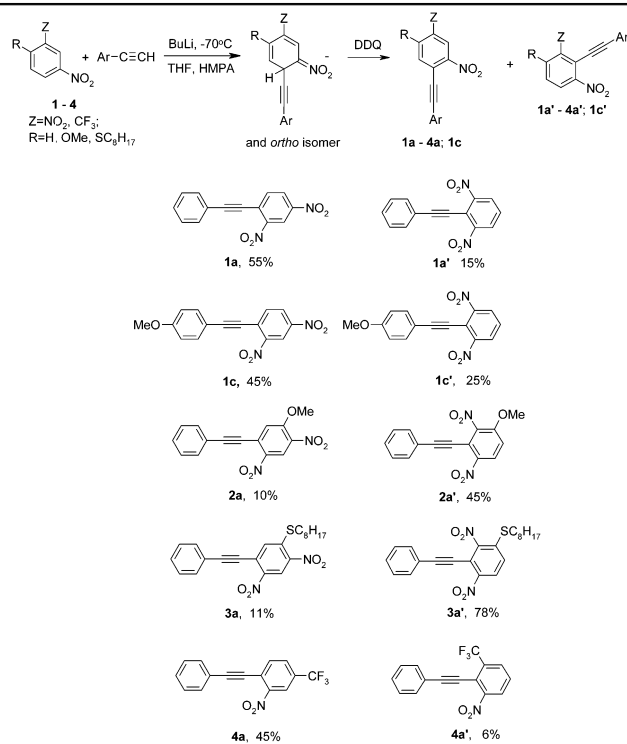
Table 2 Synthesis of nitroaryl acetylenes from 1-nitronaphtalene and nitropyridines (isolated yields are given)
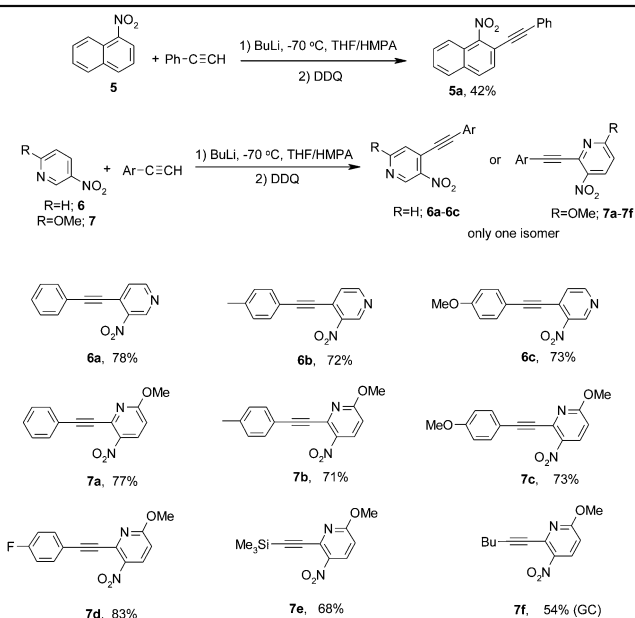

nucleophilic substitution (VNS) reaction with the methylenic carbanion of chloromethyl phenyl sulfone.

Due to strong conjugation in the phenolate and aniline, the VNS reaction in these nitroarenes proceeds exclusively at position 3-, whereas conjugation in the anisole is much weaker, so VNS proceeds at position 5-.[14]

A very good yield was achieved in the reaction of phenyl-acetylene with sulfide **3** (78% of isomer **3a′** and 11% of isomer **3a**). It is an important result, because it is known that sulfides inhibit transition metal catalyzed reactions.

The ONSH with acetylenide carbanions proceeds particularly efficiently in 3-nitropyridine **6** (e = 72 000) and 2-nitro-5-methoxy-pyridine **7** (e = 17 000), which are much more active than nitroarenes **4** and **5**. In both the nitropyridines the substitution proceeds selectively in one position. In the case of 3-nitropyridine **6** the reaction proceeds at position 4-, whereas substitution in **7** occurs selectively at position 2-. As in the case of **2**, the orientation in **7** is governed by the conjugation of the methoxy and the nitro group (Scheme 1). Such an effect on orientation was observed also in the VNS in methoxynitro-pyridines with methylenic α-chloro carbanions.[15]
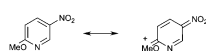
Scheme 1

A series of arylacetylenes and TMS-acetylene in the reaction with **7** gave expected products **7a–7e** in good yields (72–83%). Regarding the acetylene moiety, this method is of general character. Good results were obtained for phenylacetylenes with a strong electron donor (–OMe), a weak electron donor (–Me) and a weak electron acceptor group (–F). The TMS group in trimethylsilylacetylene is resistant under conditions of the reaction and the expected product **7e** was obtained in good yield (68%). On the other hand, the yield of the reaction with *n*-butyl acetylene under the standard conditions was only moderate (40%). It appears that it was because alkyl acetylenes under basic conditions can rearrange into allenes. Indeed, when the generated lithium acetylenide was immediately mixed with **7**, the yield of **7e** was somewhat higher (54%; GC yield).

In conclusion, we have developed a transition metal free, atom economical method for synthesis of nitroaryl acetylenes from acetylenes and nitroarenes, *via* direct replacement of hydrogen. The method consists of addition of lithium acetylenides to electron-deficient nitroarenes carbo- and heterocyclic to form σ^H^-adducts, which are subsequently oxidized by DDQ, giving nitroaryl-acetylenes. Regarding the acetylene moiety, this method is of general character. On the other hand, the reaction is limited to highly electrophilic nitroarenes; nevertheless, it is the simplest way of introduction of an acetylenic moiety into nitroaromatic rings.

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