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Aza-Favorsky reaction with regioisomeric C- and N-linked 1,4-bis(imino)benzenes: synthetic and reactivity dissimilarities

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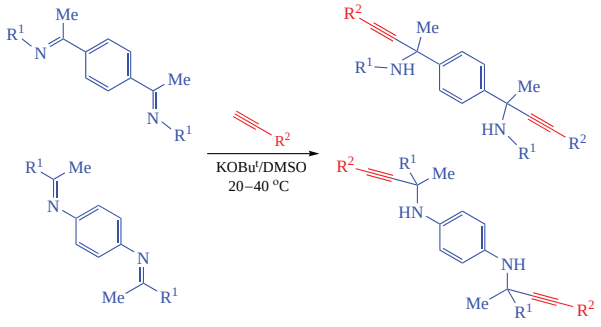
Structurally analogous C- and N-linked 1,4-bis(imino)-functionalized benzenes react with acetylenes in the KOBu^t/DMSO superbase system to give the corresponding bis-(propargylamino)-containing derivatives in 62–82% yields (C-linking) or 38–42% yields (N-linking). In the latter case, with phenylacetylene, the yields of mono- and bisadducts were 32 and 38%, respectively. The observed dissimilarities between both bisimine chemotypes in the reactivity and synthetic outcomes imply the long-range adverse repulsive interaction between nitrogen anionic center and the second nitrogen atom in the N-linked 1,4-bis(imino) benzenes.



Keywords: acetylenes, imines, diamines, propargylic amines, superbases, ethynylation.

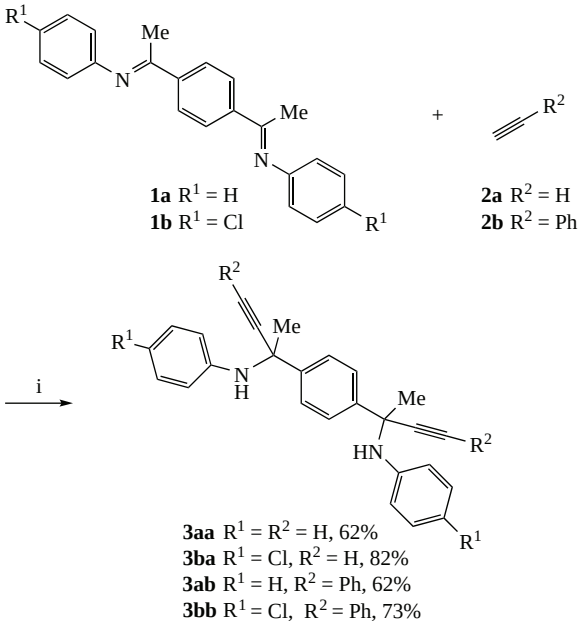
The recently discovered superbase-promoted C=N bond ethynylation (formally the aza-Favorsky reaction)[1] is now receiving a fruitful development owing to its obvious synthetic advantages such as the straightforward access to a variety of substituted propargylic amines, mild conditions, available starting materials, inexpensive easy-to-handle catalytic systems, one-pot high-yield implementation and atom economy. Today, this reaction is becoming a springboard to create not only internal[1] and terminal[2] propargylic amines, but also 1-azadienes,[3] benzyl imidazo[1,2-*a*]pyridines and imidazolyl stilbenes.[4]

In the light of these findings, we have assumed that the nucleophilic addition of acetylenes to the C=N bonds of C- and N-linked 1,4-bis(imino)-functionalized benzenes **1a**–**c** (Schemes 1, 2) would offer a new simple route to novel aromatic bis-propargylamines. Here it is worthwhile to note that diamines containing one or more triple bonds were reported to exhibit diverse biological effects,[5] useful technical properties,[6] and can be unique precursors for the assembling of novel functional molecules.[7]

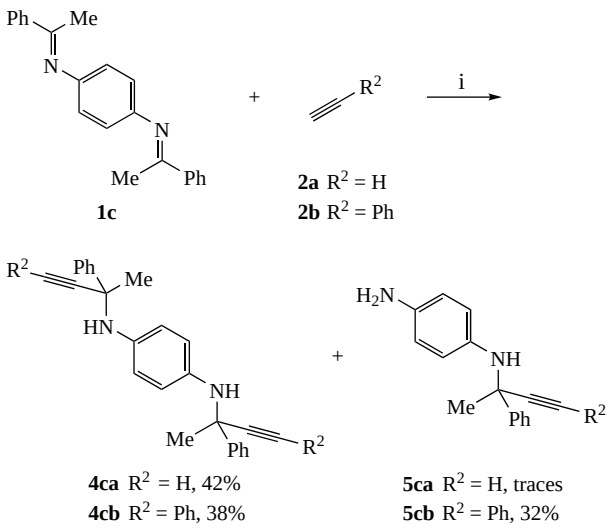
Along with the synthetic expectations, there are arisen some interesting reactivity issues concerning the long-range transmittance of the C=N bond separated by the benzene ring and attached to it either with C or N atoms. In this communication, we report preliminary results on the aza-Favorsky reaction between C- and N-linked 1,4-bis(imino)-functionalized benzenes **1a**–**c** and acetylenes. It turned out that bisimine **1a** (synthesized *via* the condensation of 1,4-diacetylbenzene with aniline) reacted with excess acetylene gas **2a** in the KOBu^t/DMSO system (**1a**/KOBu^t molar ratio of 1:2) at room temperature for 1 h to selectively give C-linked 1,4-bis(α-amino-propargyl)benzene **3aa** as two diastereomers (in *ca*. equimolar ratio) in 62% yield, no monoadduct being detected (see Scheme 1).† The ^{1}H NMR spectrum of the reaction mixture contained only signals of bisadduct **3aa** and a broadened signals for polymer products (probably polyacetylene). Moderate yield of bisamine **3aa** is probably due to the losses during unoptimized isolation by column chromatography. Bisadduct **3ba** as two diastereomers (~ 1:1) in 82% yield was obtained from bisimine **1b** and acetylene **2a** under the same conditions. The chlorine containing bisimine **1b** was chosen as having additional possibilities for further modification of the products and to better distinguish their NMR patterns.

† *The reaction of bisimines* **1** *with acetylene gas (typical procedure).* A mixture of bisimine **1** (0.5 mmol) and KOBu^t (1 mmol, 0.11 g) in DMSO with 0.5% of water content (45 ml) was placed into a 0.25 dm^3 steel Parr reactor equipped with mechanical stirrer and manometer. The reactor was fed with acetylene under pressure from commercially available acetylene cylinder (initial pressure at ambient temperature was ~ 16 atm) and then decompressed to atmospheric pressure to remove air. The reactor was fed with acetylene again and kept at 20–22 °C (for bisimines **1a**,**b**) or at 40 °C (for bisimine **1c**) for 1 h. The mixture was diluted with water (50 ml) and extracted with Et_2O (4 × 20 ml). The combined organic extracts were washed with H_2O (3 × 20 ml) and dried over K_2CO_3. Ether was evaporated under reduced pressure, and the bisadduct (**3aa**, **3ba**, **4ca**) was purified by column chromatography (SiO_2, hexane–diethyl ether with gradient from 1:0 to 0:1).

The reaction of bisimines **1** *with phenylacetylene (typical procedure).* A mixture of bisimine **1** (1 mmol), phenylacetylene (3 mmol, 0.31 g) and KOBu^t (2 mmol, 0.22 g) in DMSO (6 ml) was stirred at 40 °C (oil bath) for 2 h (for bisimines **1a**,**b**) or 1 h (for bisimine **1c**). The reaction mixture was diluted with H_2O (20 ml) and extracted with Et_2O (7 × 5 ml). The combined organic extract was washed with H_2O (3 × 5 ml) and dried over K_2CO_3. Ether was evaporated under reduced pressure. The residue was washed with cold Et_2O (3 × 1 ml) to leave pure bisadduct **3ab**, **3bb** or **4cb**. In the case of bisimine **1c**, monoadduct **5cb** was isolated from the Et_2O extract by column chromatography (SiO_2, hexane–ethyl acetate, 10:1).



Scheme 1 *Reagents and conditions*: i, KOBu^t, DMSO, 20–22 °C, 1 h (for acetylene gas); 40 °C, 2 h (for phenylacetylene).

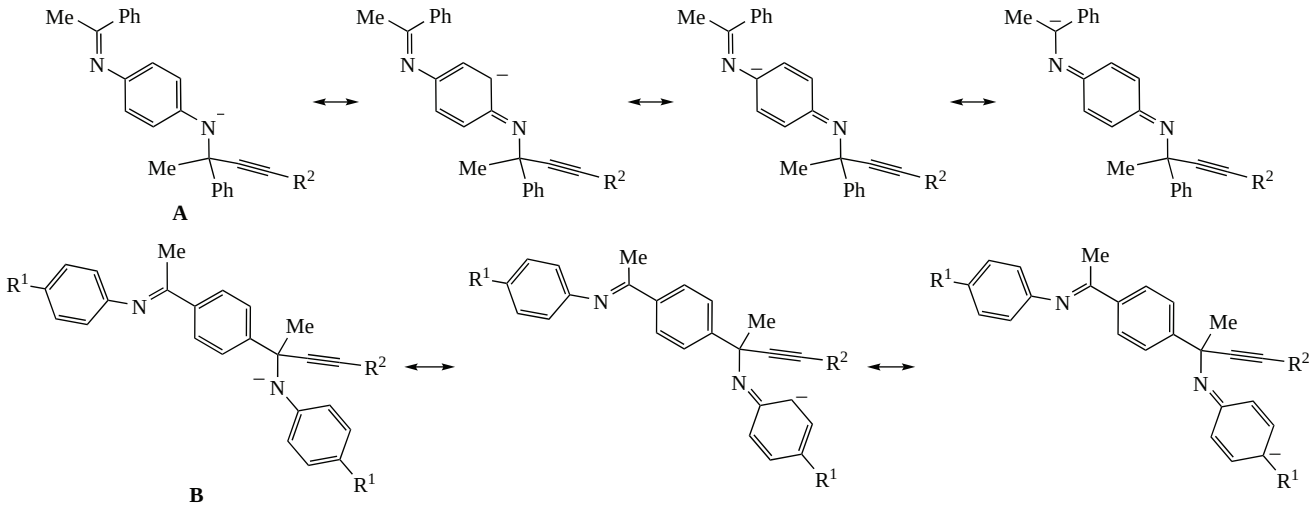


Scheme 2 *Reagents and conditions*: i, KOBu^t, DMSO, 40 °C, 1 h.

After short optimization, it was found that the reaction of bisimines **1a**,**b** with phenylacetylene **2b** (3 equiv.) proceeded smoothly upon a slight heating (40 °C) in the same superbase system. Under these conditions, the yields of bis(propargylamino)benzenes **3ab** and **3bb** were 62 and 73%, respectively, with full conversion of the starting diimines **1** (see Scheme 1). Bisadducts **3ab** and **3bb** were also obtained as two diastereomers (~ 1 : 1).

At the same time, N-linked 1,4-bis(imino)-containing benzene **1c** (obtained by condensation of 1,4-diaminobenzene and acetophenone) reacted with excess acetylene gas **2a** at 40 °C to furnish a mixture of mono- and diethynylation products in ~ 1 : 9 ratio (NMR). After aqueous work-up and chromatographic purification, monoethynylation product underwent hydrolysis of the unreacted imino group. Eventually, only 1,4-bis(propargylamino)benzene **4ca** was isolated in 42% yield (see Scheme 2). Given the modest yield of bisadduct **4ca**, we have checked, whether this reaction was reversible. The isolated product **4ca** was kept under the same reaction conditions (KOBu^t/DMSO, 40 °C, 1 h). After standard work-up and purification, bisadduct **4ca** was recovered almost quantitatively (96% yield), which indicated the irreversibility of this reaction. The reaction between bisimine **1c** and phenylacetylene **2b** (3 equiv.) proceeded under the same conditions: 1 : 2 (**4cb**) and 1 : 1 (**5cb**) adducts were obtained in 38 and 32% yield, respectively (see Scheme 2). Apparently, products **4ca** and **4cb** are also mixtures of diastereomers, albeit in their spectra only one set of signals is present that may be caused by remote location of chiral centers.

A greater excess phenylacetylene (4 equiv.) did not lead to the increase in the yield of either the double ethynylation product **4cb** or monoadduct **5cb**. This result can be explained by the addition of acetylenic carbanion to the one of C=N bonds and the formation of N-centered anionic intermediate **A** (Scheme 3), in which resonance-like partial anion transfer to the second C=N bond occurs due to the through conjugation over the benzene ring that hinders the addition of the next acetylenic carbanion to this bond. In other words, there takes place the long-range p-π-p adverse repulsive interaction between nitrogen anionic center and the second nitrogen atom or the second C=N bond. As a result, in the ultimate state of this interaction, the carbon atom of the second imine group becomes less electrophilic. On the contrary, in the case of C-linked 1,4-bis(imino)-funtionalized benzenes **1a**,**b** the above repulsive p–π–p



Scheme 3

electronic communication in the corresponding intermediate **B** between N-centered anion and the second imino group is disconnected by quaternary carbon atom (see Scheme 3). Consequently, the negative charge on nitrogen atom is delocalized over neighboring phenyl substituent that facilitates the ethynylation.

In summary, a convenient access to unique propargylic bisamines *via* KOBu^t/DMSO-promoted double aza-Favorsky reaction of C- and N-linked 1,4-bis(imino)-finctionalized benzenes has been sketched.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.017.

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