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Direct introduction of acetylene moieties into azines by S_N^H methodology

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ABSTRACT

The N-oxides of azines **1a–g** react with lithium and/or potassium acetylides to give the corresponding ethynylazines **2a–g**. Reaction with lithium acetylide requires subsequent acylation of the intermediate anionic adduct for rearomatization whereas in the case of potassium acetylide, *auto*-aromatization takes place.

Acetylenic derivatives of heterocycles, in particular of azines, have attracted significant attention because of their possible applications in chemistry and material science.[1] The acetylene moiety is a very desirable function from many points of view. Due to its linearity, rigidity, and extensive π-orbital network, it serves as a conjugating link between functional parts of molecular devices, and is widely used in crystal engineering.[2] Moreover, it opens routes to polymers with special properties.[3] Introduction of an ethynyl group improves photophysical[4] and magnetic properties significantly.[5] In addition, the presence of an ethynyl group offers the possibility for further functionalization of azines and construction of new heterocyclic systems.[6,7] Thus, effective and easy methods for the introduction of an acetylene moiety into azines are of great synthetic interest.

At present, the standard method for introduction of acetylenes into aromatic systems is cross-coupling reactions between suitable halogen-containing heterocycles and acetylenes in the presence of a palladium catalyst.[8] In spite of its efficacy, this method has certain limitations. There is often poor availability of the halogen-containing heterocycles, and the cost of the appropriate catalyst can be high. In addition, the application of cross-coupling reactions can be limited in pharmaceutical synthesis because of the presence of catalyst traces in the product.

Earlier, we reported on the effectiveness of aromatic nucleophilic substitution of hydrogen (S_N^H) for fuctionalization of π-deficient aromatic heterocycles.[9,10] For example, we demonstrated that 1,2,4-triazine 4-oxides react with organometallic nucleophiles such as Grignard reagents[11] and lithium carboranes[12] to give the corresponding substituted 1,2,4-triazines. Also, the similar results in the reactions of pyridine N-oxide and Grignard reagents were reported previously.[13] This method has none of the disadvantages of cross-coupling reactions because halogen-containing derivatives are not required.

Recently, we demonstrated examples of the introduction of phenyl and trimethylsilyl acetylenes into 3-(2-pyridyl)-1,2,4-triazine by reaction of the corresponding 1,2,4-triazine N-oxide with lithium acetylides.[14] This approach was adopted for the synthesis of bipyridine ligands bearing terminal acetylene and phenylacetylene moieties.[15] The success of this work led us to study the reactions with triazine oxides more comprehensively, and to see if this methodology could be applied for the synthesis of ethynyl derivatives of other azines that are less reactive than 1,2,4-triazines in the S_N^H reaction. As a result, we present herein a versatile method for the introduction of an acetylene moiety into azaheterocycles by deoxygenative nucleophilic aromatic substitution of hydrogen in azine N-oxides.

We found that the N-oxides of pyridine **1a**, quinoline **1b**, quinoxaline **1c**, and 1,2,4-triazines **1d–f** react easily with lithium phenylacetylide in THF at −50 °C to form intermediate σ^H-adducts **A**, which are aromatized by addition of an acylating agent (procedure A).[16] As a result, the appropriate phenylethynylazines **2a–f**[17] were obtained in yields of 20% for pyridine N-oxide and up to 70% for triazine oxides (Scheme 1). The relatively poor yields are due to the decomposition processes that apparently competes with the slow addition reaction.

It is noteworthy that in the case of pyridine N-oxide **1a**, increasing the reaction time or temperature resulted in ring-opening leading to the open-chain products **3** or **4**, depending on the reagent used to quench the reaction. With acetyl chloride product **3** was obtained, and in the case of acetic acid, **4** was formed. Such ring-opening was described earlier in the reaction of pyridine N-oxide with an acetylenic Grignard reagent.[18]

In contrast, reaction of 1,2,4-triazine 4-oxide **1g** with lithium trimethylsilylacetylide allowed isolation of the cyclic σ^H-adduct **5** by treating carefully the reaction mixture with acetic acid. The product proved to be relatively stable, and was aromatized by acylation with acetyl chloride (Scheme 2).[19]

In order to avoid side reactions and to optimize the yields, we attempted to modify the reaction conditions. Thus, we found that

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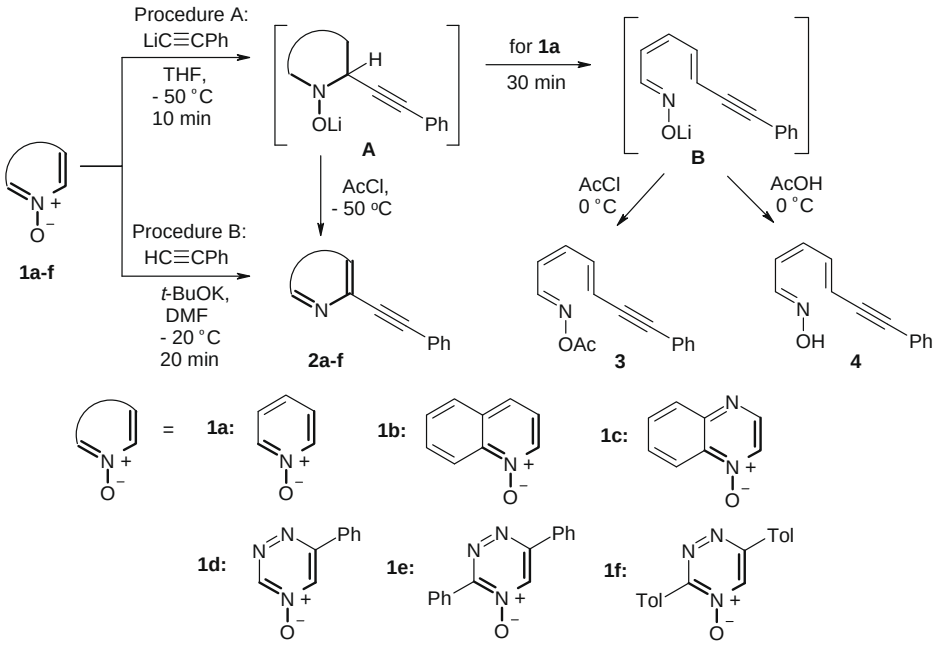
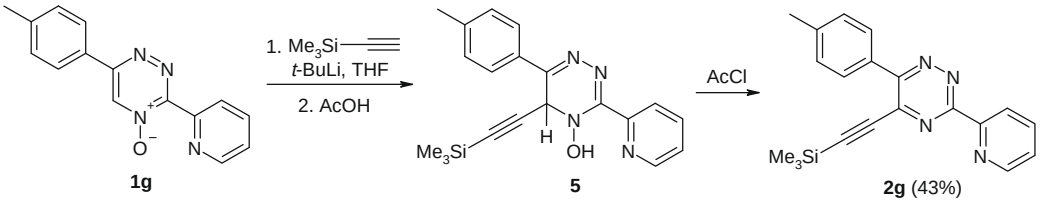


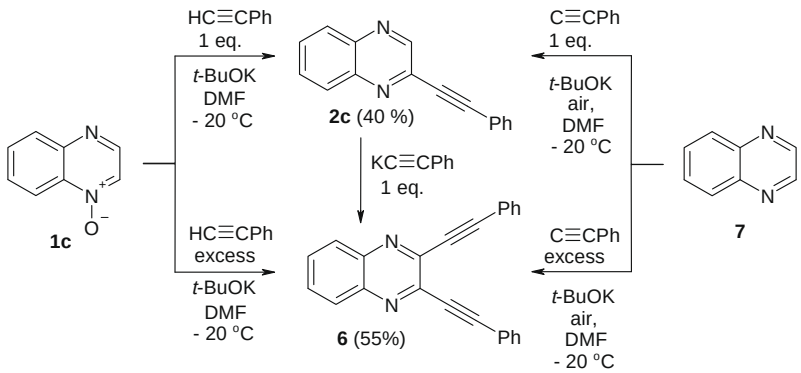
Scheme 1.



Scheme 2.

the azine N-oxides **1a**–**f** readily reacted with potassium phenylacetylide generated from phenylacetylene in the presence of a three-fold excess of potassium *tert*-butoxide in dry DMF (procedure B).[16] These conditions induced the *auto*-aromatization of the intermediate σ^H-adducts with loss of oxygen. Hence, there was no need for further acylation or protonation to obtain aromatic products **2a**–**f**. This difference in behavior between lithium and potassium phenylacetylide can be explained by the much higher polarity of the solvent as well as the difference between the O-metal bond characters in the σ^H-adducts: the O–Li bond is rather covalent, whereas the O–K bond is ionic. The ionic character of the latter promotes elimination of hydroxide and *auto*-aromatization. The yields of the acetylenic derivatives were 35%, 50%, and 40% for products **2a**,**b**,**c**, respectively.

The reaction of quinoxaline N-oxide **1c** with phenylacetylene gave an unexpected result. When a twofold excess of potassium phenylacetylide was used, 2,3-bis(phenylethynyl)quinoxaline **6** was obtained (Scheme 3). Further studies revealed that treatment of monosubstituted quinoxaline **2c** with 1 equiv of potassium phenylacetylide under the same conditions also gave **6** in moderate yield. It was found that quinoxaline **7** also reacts with 1 equiv of phenylacetylene yielding the monosubstituted product **2c**, while



Scheme 3.

with 2 equiv of phenylacetylene gives the disubstituted product **6**. In the case of quinoxaline **7**, the presence of an N-oxide function was not necessary. When the reactions were carried out under conditions that exclude air, the yields of products **2c** and **6** were much lower. We can therefore assume that the σ^H-adducts are oxidized by atmospheric oxygen. At present, we cannot explain why such easy oxidative *auto*-aromatization takes place only in the case of quinoxaline.

In conclusion, the reported method for the direct introduction of acetylenes into heterocyclic systems using $S_N{}^H$ methodology is a versatile tool for the synthesis of a series of ethynyl azines. The method requires no expensive reagents, and can be used as a complementary method to Sonogashira cross-coupling reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.070.

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16. *Procedure A for the synthesis of the ethynyl azines* ***2a–g***: A solution of lithium phenylacetylide in THF, prepared by addition of butyllithium (1.05 mmol) to a solution of phenylacetylene (1 mmol) in 10 ml of THF, was added with stirring to a solution of N-oxide **1** (1 mmol) in 10 ml of THF at −50 °C under an argon atmosphere. After 10 min, acetyl chloride (1.05 mmol) was added to the reaction mixture at the same temperature. The solvent was removed, the residue was dissolved in chloroform, and the corresponding ethynylazine was isolated by column chromatography. *Procedure B.* A solution of N-oxide **1** (1 mmol) in 10 ml of dry DMF was added with stirring to a suspension of potassium phenylacetylide at −20 °C under an argon atmosphere, which was prepared by addition of phenylacetylene (1 mmol) to a suspension of potassium *tert*-butoxide (2 mmol) in 10 ml of dry DMF. After 30 min, acetic acid (2 mmol) was added to the reaction mixture at the same temperature. Then, water (100 ml) was added, and the resulting suspension was treated with chloroform. The organic phase was dried over sodium sulfate, and the corresponding phenylethynylazine was isolated by column chromatography.
17. *Compound* **2a**: Yield 35% (obtained by procedure B). Mp: 32 °C (from hexane). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.23 (m, 1H, H-5), 7.25–7.40 (m, 3H, Ph), 7.52 (m, 1H, H-3), 7.59–7.63 (m, 2H, Ph), 7.67 (m, 1H, H-4), 8.61 (m, 1H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 88.55, 89.16, 122.20, 122.69, 127.09, 128.33, 128.92, 131.99, 136.10, 143.41, 150.01. HRMS (EI): $C_{13}H_9N$ requires M^+, 179.0735, found 179.0737. Compound **2b**: Yield 50% (obtained by procedure B). Mp: 58 °C (from hexane). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.40 (m, 3H, Ph), 7.55 (m, 1H, H-6), 7.61 (m, 2H, Ph), 7.61 (d, J = 8.0 Hz, 1H, H-3), 7.73 (m, 1H, H-7), 7.81 (dd, J = 8.0, 1.0 Hz, 1H, H-8), 8.14 (dd, J = 8.0, 1.0 Hz, 1H, H-5), 8.15 (d, J = 8.0 Hz, 1H, H-4). HRMS (EI): $C_{17}H_{11}N$ requires M^+, 229.0891, found 229.0882. Compound **2c**: Yield 40% (obtained by procedure B). Mp 61 °C (from hexane). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.43 (m, 3H, Ph), 7.69 (m, 2H), 7.79 (m, 2H, Ph), 8.11 (m, 2H), 8.99 (s, 1H, H-3). Found: C, 83.30; H, 4.49; N, 7.15. Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Compound **2d**: Yield 65% (obtained by procedure A). Mp 113 °C (from acetonitrile). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.37–7.61 (m, 8H), 8.12 (m, 2H), 9.61 (s, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 85.54, 100.80, 120.46, 128.44, 128.69, 129.36, 130.69, 130.79, 132.57, 133.88, 142.16, 155.08, 159.37. HRMS (EI): $C_{17}H_{11}N_3$ requires M^+, 257.0953, found 257.0963. Compound **2e**: Yield 70% (obtained by procedure A). Mp 175 °C (from acetonitrile). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.38–7.58 (m, 11H), 8.17 (m, 2H), 8.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 86.38, 99.57, 120.74, 128.37, 128.64, 128.85, 129.29, 130.38, 130.56, 131.70, 132.53, 134.09, 134.38, 141.85, 156.62, 161.39. HRMS (EI): $C_{23}H_{15}N_3$ requires M^+, 333.1266, found 333.1254. Compound **2f**: Yield 63% (obtained by procedure A). Mp 165 °C (from acetonitrile). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 2.47 (s, 6H, $2CH_3$), 7.41 (m, 5H, Ph), 7.46 (m, 2H, Ph), 7.60 (m, 2H, Ph), 8.08 (m, 2H, Ph), 8.40 (m, 2H, Ph). Found: C, 83.15; H, 5.21; N, 11.65. Calcd for $C_{25}H_{19}N_3$: C, 83.08; H, 5.30; N, 11.63.
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19. Compound **5**: Yield 56%. Mp 168 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$, ppm): 0.25 (s, 9H, $SiMe_3$), 2.41 (s, 3H, CH_3), 5.82 (s, 1H), 7.25 (m, 2H, Ph), 7.42 (ddd, J = 7.8, 4.7, 1.2 Hz, 1H, Py), 7.73 (d, 2H, Ph), 7.91 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H, Py), 8.67 (dd, J = 7.8, 1.2, 1H, Py), 9.56 (dd, J = 4.7, 1.2 Hz, 1H, Py), 10.17 (s, 1H). Found: C, 66.65; H, 5.91; N, 15.65. Calcd for $C_{20}H_{22}N_4OSi$: C, 66.27; H, 6.12; N, 15.46.