Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2015, **25**, 332–333

Mendeleev
Communications

Reaction of lithium 2-arylethynides with 6-aryl-3-(2-pyridyl)-1,2,4-triazines as an access to 6-aryl-5-arylvinyl-3-(2-pyridyl)-1,2,4-triazines

Albert F. Khasanov,[a] Dmitry S. Kopchuk,*[a,b] Igor S. Kovalev,[a] Olga S. Taniya,[a] Grigory V. Zyryanov,[a,b] Vladimir L. Rusinov[a,b] and Oleg N. Chupakhin[a,b]

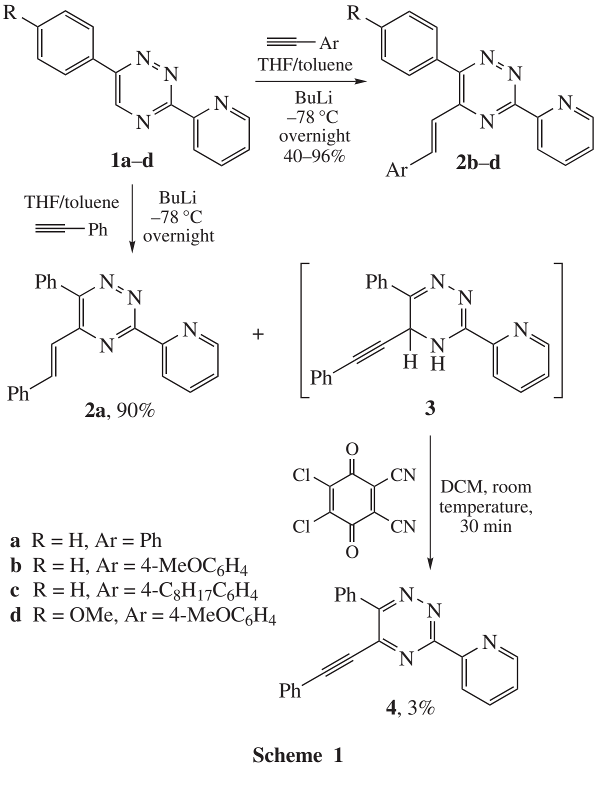
[a] *Ural Federal University, 620002 Ekaterinburg, Russian Federation*
[b] *I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, Russian Federation. E-mail: dkopchuk@mail.ru*

DOI: 10.1016/j.mencom.2015.09.003

Reaction of 6-aryl-3-(2-pyridyl)-1,2,4-triazines with lithium 2-arylethynides affords (*E*)-6-aryl-5-arylvinyl-3-(2-pyridyl)-1,2,4-triazines.

Heterocycle-equipped acetylenes are of considerable practical interest in synthetic organic chemistry.[1–5] To date, an important classical approach to such compounds is the Sonogashira cross-coupling of halogenated heterocycles.[6] So far, only a few alternative syntheses of such compounds have been developed,[7–9] in particular, an atom economic nucleophilic substitution of hydrogen.[10] For this purpose, lithium or potassium acetylides were used as nucleophiles. In addition, some aromatic systems are suitable for catalytic direct C–H functionalization with acetylene moieties.[11]

In our studies, we were aiming at non-catalyzed direct S_NH functionalization of a library of π-deficient 3-(2-pyridyl)-1,2,4-triazines since such a methodology should be truly appropriate for these heterocycles (*cf.* ref. 12). We anticipated that the compounds thus obtained on subjection to aza-Diels–Alder reaction[13] can be transformed into complex and useful as new perspective ligands 2,2′-bipyridines (*cf.* ref. 14). Only a few syntheses of ethynyl-substituted 2,2′-bipyridines from 1,2,4-triazine 4-oxides are known so far,[8] whereas reactions between 1,2,4-triazines and acetylenes are studied scarcely.[15] Here, we report the results of interaction between lithiated arylacetylenes and 5-aryl-3-(2-pyridyl)-1,2,4-triazines (Scheme 1).



Scheme 1

The starting 1,2,4-triazines were prepared as previously reported.[16] Lithiation of arylacetylenes was performed *in situ* in THF on treatment with BuLi at –78 °C. After addition of 1,2,4-triazine derivatives **1** and usual workup we discovered surprisingly that the major products were neither expected σ^H-adducts nor the aromatic arylethynyl-substituted 1,2,4-triazines, but 1,2,4-triazine styrene derivatives **2** (see Scheme 1),[†] with styrenes **2b–d** having been the only products isolated in almost quantitative yields in most cases.

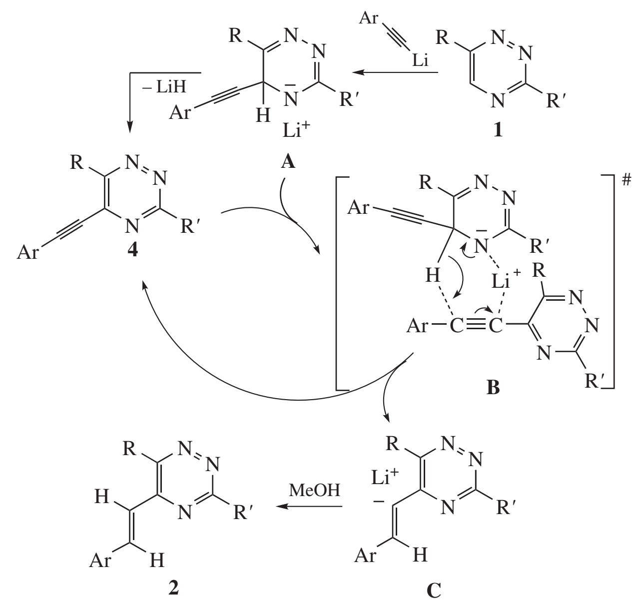
In the case of 1,2,4-triazine **1a** and lithiated phenylacetylene, σ^H-adduct **3** was also detected in 3–4% yield along with the major product **2a** (^{1}H NMR data). For more reliability, the crude mixture **2a** and **3** was treated with oxidant 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in DCM at room temperature for 30 min, which gave compounds **2a** and **4** separated by column chromatography.

In 2007, the Carroll's group obtained 3-methyl-5-phenylethynyl-1,2,4-triazine in 17% yield[15] along with relative styrene derivative in 33% yield. However, they did not bring discussion on this event.

The structure of products **2** and **4** was determined by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.[†] Compounds **2** are characterized by two doublets of (*E*)-ethene-1,2-diyl moiety in the ^{1}H NMR spectra with *J* of 15.5–16 Hz. Their ^{13}C NMR spectra do not contain signals of *sp*-hybridized carbon atoms in the region of 90–100 ppm. As conversely, ^{13}C NMR of compound **4** contains such signals at 86.5 and 100.8 ppm. σ-Adduct **3** was detected in the mixture by characteristic signals of the hydrogen atom at the sp^3-hybrid carbon in the ^{1}H NMR spectrum at 5.89 ppm and NH proton signal at 10.45 ppm, which correlates with the previously published spectral data for similar adducts.[17]

We would propose a plausible mechanism of the process studies (Scheme 2). Since the reaction is carried out under strictly anhydrous conditions, we assume that partial aromatization of the adduct **A** giving acetylene **4** occurs from elimination of lithium hydride molecule. Next, hydrogen transfer from adduct **A** onto acetylene **4** proceeds in the active complex **B**. This results in lithiated styrene **C** and the reformation of acetylene **4** which can participate in subsequent cycle of transformations. Ultimate quenching with methanol finalizes **C** → **2** conversion.

[†] For synthetic procedure and characteristics of compounds **2a–d** and **4**, see Online Supplementary Materials.



Scheme 2

According to literature, some other styryl-substituted heterocycles were prepared by the direct C–H functionalization of terminal acetylenes. These procedures are mostly catalytic, for example, CuI-catalyzed reaction of substituted pyridines with arylacetylenes in the presence of substituted chloroformate and the excess of base,[18] $SnCl_4$–Bu_3N-catalyzed reaction of hydroxyquinolines, hydroxypyridines and *N*-Tf-hydroxyindoles with unsubstituted acetylene in the presence of acetic anhydride,[19] zirconia-catalyzed reaction of dimethylpyrazines with alkynes,[20] and the reaction of substituted pyridines with acetylenes in the presence of ruthenium derivatives.[21] Very few examples are available for the non-catalytic synthesis of heterocyclic analogues of stilbene, namely, reaction of methyl propiolate with 3-amino-4*H*-thieno[3,4-*c*](2*H*)chromen-4-one[22,23] or 2-phenyl-4-(pyrrolidin-1-yl)thiophene,[24] and reaction of 2-phenyl-1,3-benzodiazine with arylalkynes in the presence of bases[25] (in this case the authors propose an experimentally-confirmed radical reaction mechanism).

In conclusion, we have found an efficient access to aza-analogues of 2,2′-bipyridines, namely 6-aryl-3-(2-pyridyl)-5-styryl-1,2,4-triazines, which seem promising as new ligands. A significant difference in reactivity between 1,2,4-triazines and 1,2,4-triazine 4-oxides in reactions of nucleophilic substitution of hydrogen with lithiated arylacetylenes was disclosed since 4-oxides are converted to arylethynylated 1,2,4-triazines as products of deoxygenation aromatization.[8,9] A plausible reaction mechanism of this transformation is proposed, and the scope limitations of this reaction are under study now.

This work was supported by the Russian Science Foundation (grant no. 15-13-10033).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.09.003.

References

1 (*a*) M. M. Heravi and S. Sadjadi, *Tetrahedron*, 2009, **65**, 7761; (*b*) A. K. Verma, R. R. Jha, R. Chaudhary, R. K. Tiwari, K. S. K. Reddy and A. Danodia, *J. Org. Chem.*, 2012, **77**, 8191.

2 (*a*) E. C. Taylor, J. E. Macor and J. Pont, *Tetrahedron Lett.*, 1987, **43**, 5145; (*b*) Z. Ma, F. Ni, G. H. C. Woo, S.-M. Lo, P. M. Roveto, S. E. Schaus and J. K. Snyder, *Beilstein J. Org. Chem.*, 2012, **8**, 829; (*c*) S. Fadel, Y. Hajbi, M. Khouili, S. Lazar, F. Suzenet and G. Guillaumet, *Beilstein J. Org. Chem.*, 2014, **10**, 282.

3 (*a*) D. Pasini, *Molecules*, 2013, **18**, 9512; (*b*) H. Hiroki, K. Ogata and S.-I. Fukuzawa, *Synlett*, 2013, **24**, 843; (*c*) S. Kovács, K. Zih-Peréni, Á. Révész and Z. Novák, *Synthesis*, 2012, **44**, 3722.

4 (*a*) A. C. Benniston, A. Harriman, D. J. Lawrie, A. Mayeux, K. Rafferty and O. D. Russell, *Dalton Trans.*, 2003, 4762; (*b*) H. S. Joshi, R. Jamshidi and Y. Tor, *Angew. Chem. Int. Ed.*, 1999, **38**, 2722.

5 (*a*) S. Yamaguchi and T. M. Swager, *J. Am. Chem. Soc.*, 2001, **123**, 12087; (*b*) J.-S. Yang and T. M. Swager, *J. Am. Chem. Soc.*, 1998, **120**, 11864; (*c*) T. L. Andrew and T. M. Swager, *J. Polym. Sci., Part B: Polym. Phys.*, 2011, **49**, 476.

6 (*a*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874; (*b*) M. Karak, L. C. A. Barbosa and G. C. Hargaden, *RSC Adv.*, 2014, **4**, 53442; (*c*) M. Bakherad, *Appl. Organomet. Chem.*, 2013, **27**, 125; (*d*) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084.

7 S. Anabuki, S. Tokuji, N. Aratani and A. Osuka, *Org. Lett.*, 2012, **14**, 2778.

8 (*a*) D. N. Kozhevnikov, V. N. Kozhevnikov, A. M. Prokhorov, M. M. Ustinova, V. L. Rusinov, O. N. Chupakhin, G. G. Aleksandrov and B. Köenig, *Tetrahedron Lett.*, 2006, **47**, 869; (*b*) A. M. Prokhorov, P. A. Slepukhin and D. N. Kozhevnikov, *J. Organomet. Chem.*, 2008, **693**, 1886.

9 A. M. Prokhorov, M. Mąkosza and O. N. Chupakhin, *Tetrahedron Lett.*, 2009, **50**, 1444.

10 O. N. Chupakhin, V. N. Charushin and H. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, 1994.

11 (*a*) Z.-L. Wang, L. Zhao and M.-X. Wang, *Org. Lett.*, 2012, **14**, 1472; (*b*) S. Murata, C. Seo, M. Kujime and T. Sugimoto, *Heterocycles*, 2000, **53**, 1259; (*c*) S. H. Kim, J. Yoon and S. Chang, *Org. Lett.*, 2011, **13**, 1474.

12 D. N. Kozhevnikov, V. L. Rusinov and O. N. Chupakhin, *Adv. Heterocycl. Chem.*, 2002, **82**, 261.

13 (*a*) G. R. Pabst, O. C. Pfüller and J. Sauer, *Tetrahedron*, 1999, **55**, 8045; (*b*) A. Rykowski, D. Branowska and J. Kielak, *Tetrahedron Lett.*, 2000, **41**, 3657; (*c*) D. S. Kopchuk, I. L. Nikonov, G. V. Zyryanov, I. S. Kovalev, V. L. Rusinov and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 2014, **50**, 907 (*Khim. Geterotsikl. Soedin.*, 2014, 983).

14 (*a*) V. N. Kozhevnikov, D. N. Kozhevnikov, T. V. Nikitina, V. L. Rusinov, O. N. Chupakhin, M. Zabel and B. König, *J. Org. Chem.*, 2003, **68**, 2882; (*b*) A. M. Prokhorov, D. N. Kozhevnikov, V. L. Rusinov, O. N. Chupakhin, I. V. Glukhov, M. Yu. Antipin, O. N. Kazheva, A. N. Chekhlov and O. A. Dyachenko, *Organometallics*, 2006, **25**, 2972; (*c*) I. S. Kovalev, D. S. Kopchuk, A. F. Khasanov, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Mendeleev Commun.*, 2014, **24**, 117.

15 F. Ivy Carroll, S. V. Kotturi, H. A. Navarro, S. Wayne Mascarella, B. P. Gilmour, F. L. Smith, B. H. Gabra and W. L. Dewey, *J. Med. Chem.*, 2007, **50**, 3388.

16 V. N. Kozhevnikov, O. V. Shabunina, D. S. Kopchuk, M. M. Ustinova, B. König and D. N. Kozhevnikov, *Tetrahedron*, 2008, **64**, 8963.

17 (*a*) D. N. Kozhevnikov, N. N. Kataeva, V. L. Rusinov and O. N. Chupakhin, *Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 1295 (*Izv. Akad. Nauk, Ser. Khim.*, 2004, 1243); (*b*) I. A. Utepova, A. A. Musikhina, O. N. Chupakhin and P. A. Slepukhin, *Organometallics*, 2011, **30**, 3047.

18 R. E. Beveridge and B. A. Arndtsen, *Synthesis*, 2010, 1000.

19 K. Akamatsu, R. Amemiya and M. Yamaguchi, *Heterocycles*, 2004, **63**, 1839.

20 A. S. Guram and R. F. Jordan, *J. Org. Chem.*, 1992, **57**, 5994.

21 (*a*) J. M. Lynam, L. M. Milner, N. S. Mistry, J. M. Slattery, S. R. Warrington and A. C. Whitwood, *Dalton Trans.*, 2014, **43**, 4565; (*b*) D. G. Johnson, J. M. Lynam, N. S. Mistry, J. M. Slattery, R. J. Thatcher and A. C. Whitwood, *J. Am. Chem. Soc.*, 2013, **135**, 2222.

22 E. S. Fondjo, D. Döpp and G. Henkel, *Tetrahedron*, 2006, **62**, 7121.

23 M. M. Abdelkhalik, A. M. Negm, A. I. Elkhouly and M. H. Elnagdi, *Heteroat. Chem.*, 2004, **15**, 502.

24 D. N. Reinhoudt, J. Geevers and W. P. Trompenaars, *J. Org. Chem.*, 1981, **46**, 424.

25 D. Zhao, Q. Shen, Y.-R. Zhou and J.-X. Li, *Org. Biomol. Chem.*, 2013, **11**, 5908.

Received: 1st April 2015; Com. 15/4593