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An expedient synthesis of 5-alkynyl-6-aryl-2,2′-bipyridines

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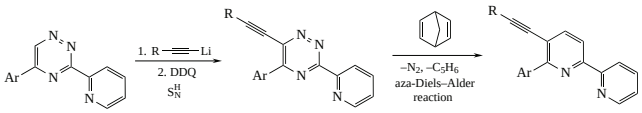
5-Alkynyl-6-aryl-2,2′-bipyridines were conveniently prepared in two steps comprising oxidative S_N^H ethynylation of 5-aryl-3-(2-pyridyl)-1,2,4-triazines at position 6. At the second step, the 1,2,4-triazine moiety was transformed into the pyridine one employing aza-Diels–Alder reaction with 2,5-norbornadiene.

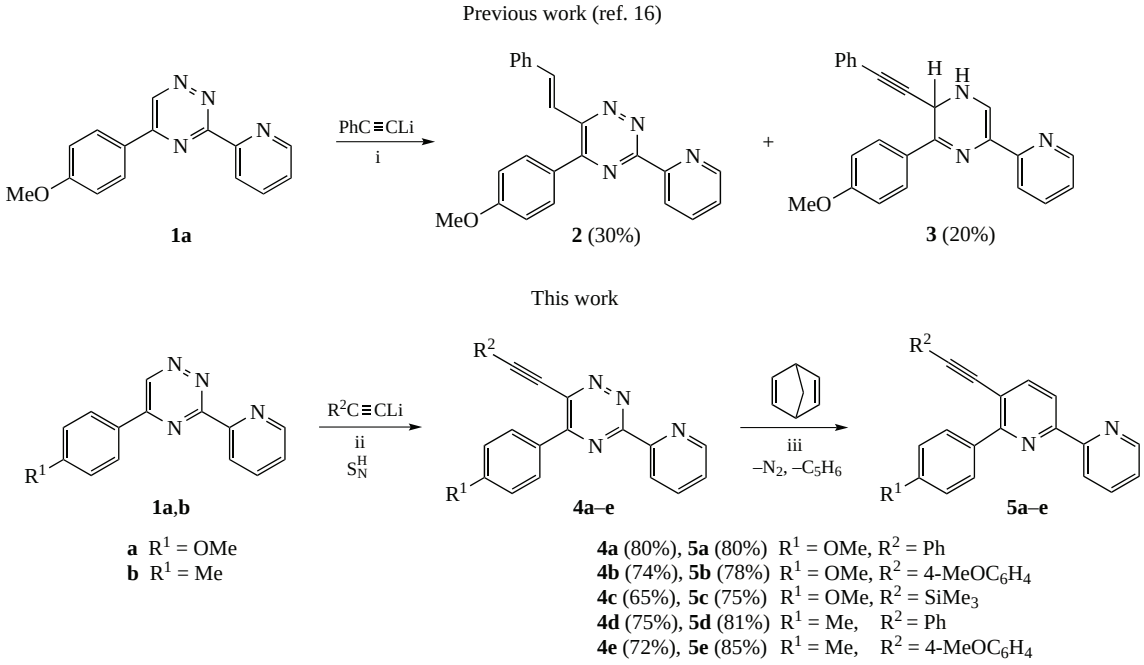


Keywords: nucleophilic substitution of hydrogen, 1,2,4-triazines, acetylenes, 2,2′-bipyridines, aza-Diels–Alder reaction.

5-Arylethynyl-2,2′-bipyridines and their fused analogues are of interest for their photophysical properties,[1] including those of their metal complexes,[2] biological activities [*e.g.*, methyl 4-(2,2′-bipyridin-5-ylethynyl)benzoate demonstrates binding affinity against human Melanocortin 4 receptor expressed in COS-7 cells[3]], and liquid crystal properties.[4] It should also be noted that the acetylene moiety is of interest from the viewpoint of further functionalization, in particular, by 'click' reactions.[5]

The main synthetic approach to such compounds is the Sonogashira cross-coupling reaction in a series of 5-bromo-bipyridines (see, *e.g.*, refs. 6,7). However, there is a few known examples of the introduction of acetylene fragments into different (hetero)aromatic systems through catalytic or non-catalytic C–H functionalization.[8] In particular, such syntheses in a 1,2,4-triazine 4-oxide series[9,10] *via* nucleophilic substitution of hydrogen[11] have been described. Unactivated forms of 1,2,4-triazines can also react with acetylides, however in this case, styryl-substituted triazines are formed as main products.[12]

On the other hand, 3-(2-pyridyl)-1,2,4-triazines are good synthetic precursors for the preparation of 2,2′-bipyridines.[13] Since the employment of S_N^H reactions in high electron-deficient 1,2,4-triazines provides the possibility of their various modification, the consequent synthesis of bipyridines with the same, sometimes unique, set of substituents becomes possible.[14]



Scheme 1 *Reagents and conditions*: i, THF/toluene (1 : 9), –78 ºC to room temperature, 18 h, then MeOH, room temperature; ii, THF/toluene (1 : 5), –78 ºC, 10 min, then DDQ, room temperature, 18 h; iii, *o*-xylene, 150 ºC (autoclave), 20 h.

Herein, we report a PASE (pot atom and step economy) approach to 5-alkynyl-6-aryl-2,2′-bipyridines by nucleophilic substitution of hydrogen with the subsequent aza-Diels–Alder reaction.

Available[15] 5-aryl-3-(2-pyridyl)-1,2,4-triazines **1** were used as starting compounds (Scheme 1). Previously,[16] we described the reaction of 6-unsubstituted 1,2,4-triazines with lithium phenylacetylide when the main product was 6-styryl-substituted 1,2,4-triazine **2** and the expected σ^H-adduct **3** was the minor one. Obviously, this method is not very suitable for the preparation of the desired compounds in our case. However, we have herein found that the process can be directed solely to 6-alkynyl-1,2,4-triazines **4** by application of oxidant (DDQ) after 10 min of the reaction start thus providing formation of the desired compounds **4** in up to 80% yields. At the next step, the triazine cycle was transformed into pyridine one by the autoclave reaction with 2,5-norbornadiene, which afforded desired 5-alkynylbipyridines **5** in up to 85% yields (see Scheme 1). It should be emphasized that our protocol is catalyst-free, which seems to be a good alternative to the Sonogashira cross-coupling.

The structure of new compounds was confirmed by ^{1}H, ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis (see Online Supplementary Materials for details). In particular, ^{1}H NMR spectra of alkynyltriazines **4** are characterized by the disappearance of the 6-positioned singlet for the proton present in the preceding reactants **1**, and by the appearance of signals for substituents at ethynyl moieties. As a result of the conversion of triazines **4** to pyridines **5**, the presence of two doublets of the new pyridine ring can be observed. As for compounds **5**, the sp-hybridized carbon signals are detected in ^{13}C NMR spectra. The spectral data of compound **4a** correspond to the previously described ones.[16]

In summary, we have developed a PASE approach to 5-alkynyl-6-aryl-2,2′-bipyridines based on readily available 5-aryl-3-(2-pyridyl)-1,2,4-triazines through the consequent S_N^H and aza-Diels–Alder reactions. In other words, we have developed the new version of the nucleophilic substitution of hydrogen by avoiding the formation of 6-styryl-substituted triazines. It should also be noted that the S_N^H reaction is realized in the series of unactivated 1,2,4-triazines rather than their oxides as previously described. The present synthetic protocol is an interesting alternative to the Sonogashira cross-coupling in aspect of obtaining β-ethynylpyridines.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.019.

References

1 (*a*) E. Birckner, U.-W. Grummt, A. H. Göller, T. Pautzsch, D. A. M. Egbe, M. Al-Higari and E. Klemm, *J. Phys. Chem. A*, 2001, **105**, 10307; (*b*) A. Harriman, M. Hissler and R. Ziessel, *Phys. Chem. Chem. Phys.*, 1999, **1**, 4203.

2 (*a*) M. Karnahl, S. Krieck, H. Görls, S. Tschierlei, M. Schmitt, J. Popp, D. Chartrand, G. S. Hanan, R. Groarke, J. G. Vos and S. Rau, *Eur. J. Inorg. Chem.*, 2009, 4962; (*b*) J. Vicente, J. Gil-Rubio, N. Barquero, P. G. Jones and D. Bautista, *Organometallics*, 2008, **27**, 646; (*c*) C. Goze, D. V. Kozlov, D. S. Tyson, R. Ziessel and F. N. Castellano, *New J. Chem.*, 2003, **27**, 1679; (*d*) M. Shiotsuka, Y. Inui, Y. Sekioka, Y. Yamamoto and S. Onaka, *J. Organomet. Chem*., 2007, **692**, 2441.

3 B. H. Lange and T. W. Schwartz, *Patent WO 2003055477 A1*, 2003.

4 F. Camerel, G. Ulrich and R. Ziessel, *Org. Lett*., 2004, **6**, 4171.

5 (*a*) C. Wang, D. Ikhlef, S. Kahlal, J.-Y. Saillard and D. Astruc, *Coord. Chem. Rev*., 2016, **316**, 1; (*b*) I. R. Knyazeva, V. I. Matveeva, V. V. Khrizanforova, V. V. Syakaev, Yu. H. Budnikova, W. D. Habicher and A. R. Burilov, *Mendeleev Commun*., 2019, **29**, 388; (*c*) C. H. C. Zacchi, S. S. M. Federighi, F. R. Gadelha, F. T. Martins, R. B. Alves and Â. de Fátima, *Mendeleev Commun*., 2018, **28**, 195; (*d*) A. A. Druzina, A. V. Shmalko, E. P. Andreichuk, O. B. Zhidkova, I. D. Kosenko, A. Semioshkin, I. B. Sivaev, S. Mandal, Z. Shen and V. I. Bregadze, *Mendeleev Commun*., 2019, **29**, 628.

6 Y.-B. Zhou, Y.-Q. Wang, L.-C. Ning, Z.-C. Ding, W.-L. Wang, C.-K. Ding, R.-H. Li, J.-J. Chen, X. Lu, Y.-J. Ding and Z.-P. Zhan, *J. Am. Chem. Soc*., 2017, **139**, 3966.

7 J. Chen and C. Lu, *Patent CN 109678896 A*, 2019.

8 D. S. Kopchuk, O. S. Taniya, A. F. Khasanov, A. P. Krinochkin, I. S. Kovalev, T. A. Pospelova, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 2019, **55**, 490 (*Khim. Geterotsikl. Soedin*., 2019, **55**, 490).

9 A. M. Prokhorov, P. A. Slepukhin and D. N. Kozhevnikov, *J. Organomet. Chem.*, 2008, **693**, 1886.

10 A. M. Prokhorov, M. Makosza and O. N. Chupakhin, *Tetrahedron Lett*., 2009, **50**, 1444.

11 (*a*) V. N. Charushin and O. N. Chupakhin, *Russ. Chem. Bull., Int. Ed*., 2019, **68**, 453 (*Izv. Akad. Nauk, Ser. Khim*., 2019, 453); (*b*) O. N. Chupakhin and V. N. Charushin, *Tetrahedron Lett*., 2016, **57**, 2665; (*c*) V. N. Charushin and O. N. Chupakhin, *Top. Heterocycl. Chem*., 2014, **37**, 1.

12 (*a*) F. I. Carroll, S. V. Kotturi, H. A. Navarro, S. W. Mascarella, B. P. Gilmour, F. L. Smith, B. H. Gabra and W. L. Dewey, *J. Med. Chem*., 2007, **50**, 3388; (*b*) A. F. Khasanov, D. S. Kopchuk, I. S. Kovalev, O. S. Taniya, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *Mendeleev Commun.*, 2015, **25**, 332.

13 (*a*) O. C. Pfueller and J. Sauer, *Tetrahedron Lett*., 1998, **39**, 8821; (*b*) S. P. Stanforth, B. Tarbit and M. D. Watson, *Tetrahedron Lett*., 2003, **44**, 693; (*c*) V. N. Kozhevnikov, D. N. Kozhevnikov, T. V. Nikitina, V. L. Rusinov, O. N. Chupakhin, M. Zabel and B. Koenig, *J. Org. Chem*., 2003, **68**, 2882; (*d*) V. N. Kozhevnikov, O. V. Shabunina, D. S. Kopchuk, M. M. Ustinova, B. König and D. N. Kozhevnikov, *Tetrahedron*, 2008, **64**, 8963.

14 (*a*) D. N. Kozhevnikov, V. N. Kozhevnikov, A. M. Prokhorov, M. M. Ustinova, V. L. Rusinov, O. N. Chupakhin, G. G. Aleksandrov and B. König, *Tetrahedron Lett*., 2006, **47**, 869; (*b*) M. I. Savchuk, A. F. Khasanov, D. S. Kopchuk, A. P. Krinochkin, I. L. Nikonov, E. S. Starnovskaya, Ya. K. Shtaitz, I. S. Kovalev, G. V. Zyryanov and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 2019, **55**, 554 (*Khim. Geterotsikl. Soedin*., 2019, **55**, 554); (*c*) A. P. Krinochkin, D. S. Kopchuk, I. S. Kovalev, S. Santra, G. V. Zyryanov, A. Majee, V. L. Rusinov and O. N. Chupakhin, *ChemistrySelect*, 2020, **5**, 2753.

15 D. S. Kopchuk, I. L. Nikonov, A. F. Khasanov, K. Giri, S. Santra, I. S. Kovalev, E. V. Nosova, S. Gundala, P. Venkatapuram, G. V. Zyryanov, A. Majee and O. N. Chupakhin, *Org. Biomol. Chem*., 2018, **16**, 5119.

16 A. F. Khasanov, D. S. Kopchuk, I. S. Kovalev, A. P. Krinochkin, G. V. Zyryanov, V. L. Rusinov and O. N. Chupakhin, *AIP Conf. Proc*., 2019, **2063**, 040024.

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