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One-pot synthesis of cyclopentane-fused 5′-aryl-4-cycloalkylamino-2,2′-bipyridines *via* the *aza*-Diels–Alder/S_N^{ipso} reactions

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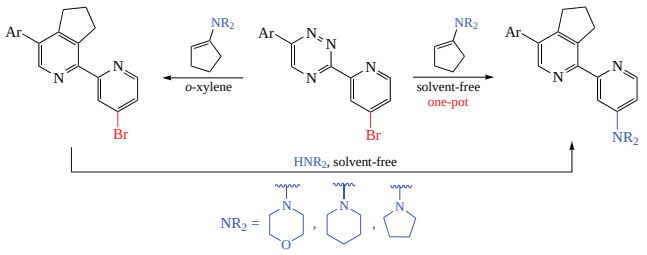
One-pot synthesis of cyclopentane-fused 5′-aryl-4-cycloalkylamino-2,2′-bipyridines based on the neat (200 °C) reaction of 3-(4-bromopyridin-2-yl)-1,2,4-triazines with enamines is reported. In the course of the transformation, consecutive *aza*-Diels–Alder reaction and nucleophilic substitution of bromine atom under the action of the liberating amine occur. The possibility of the solvent- and catalyst-free replacement of 4-positioned bromine atom in 2,2′-bipyridines by amino moieties was demonstrated.

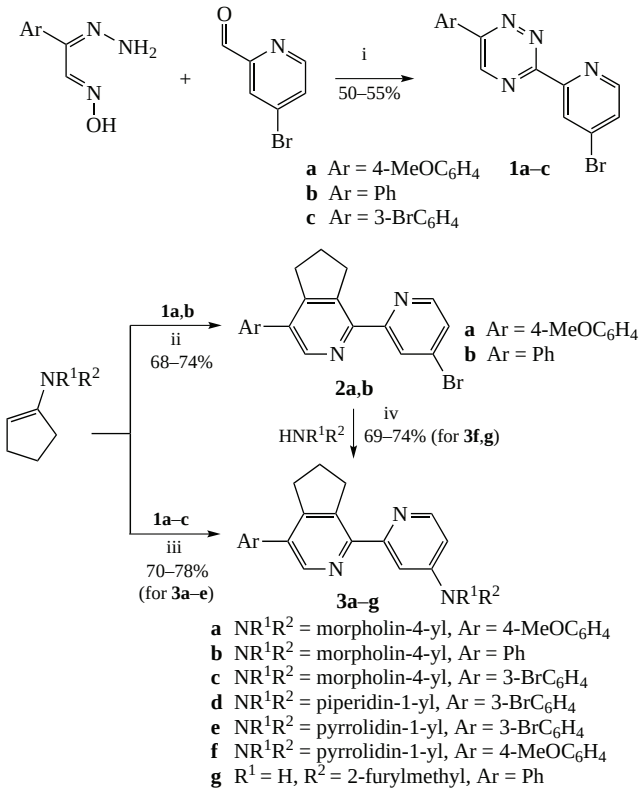


Keywords: amino-2,2′-bipyridines, 1,2,4-triazines, *aza*-Diels–Alder reaction, *ipso*-substitution, solvent-free reaction, one-pot synthesis, enamines.

One of the most promising methodology for the preparation of substituted 2,2′-bipyridines is the transformation of their 1,2,4-triazine precursors.[1] This approach attracts more attention now due to the wide possibilities for the pre-functionalization of the 1,2,4-triazine cycle, *e.g.*, by direct C–H functionalization.[2,3] In addition, by employing various dienophiles, additional functionalities can be introduced to the positions 3 and 4 of newly formed pyridine ring, in particular, fused cycloalkane fragments,[4] fused aromatic rings[5] or other aromatic substituents.[6,7] Various examples of using this methodology are recently reviewed.[8] *E.g.*, this approach was used for the obtaining potential targeting teranostics in oncology.[9] The recently published[10] reaction of 3-(2-pyridyl)-1,2,4-triazine-5-carbonitriles with 2-amino-4-aryloxazoles afforded 4-aryl-3-hydroxy-2,2′-bipyridine-6-carbonitriles.

In this article we report on the one-pot synthesis of cyclopentane-fused 5′-aryl-4-cycloalkylamino-2,2′-bipyridines by the neat reaction between 3-(4-bromopyridin-2-yl)-1,2,4-triazines **1a**–**c** and some enamines of 1-aminocyclopentene series (Scheme 1). Substrates **1** were obtained in accordance with the reported methodology[11,12] from isonitrosoacetophenone hydrazones[13] and commercially available 4-bromopyridine-2-carbaldehyde.

The further reaction of triazines **1a**–**c** with enamines was performed as previously reported[14] under solvent-free conditions at 200 °C under inert atmosphere. However, according to the analytical data no match between the obtained products and the expected compounds of type **2** was found. Based on the data of ^{1}H and ^{13}C NMR, mass-spectrometry and elemental analysis, the anticipated conversion of the 1,2,4-triazine ring to



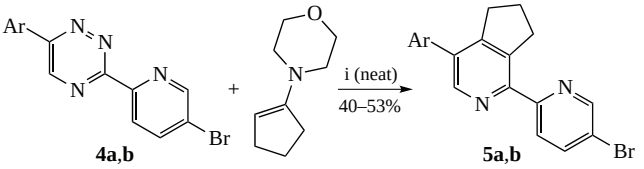
Scheme 1 *Reagents and conditions*: i, EtOH, 20 °C, 10 h, then AcOH, 118 °C, 5 min; ii, 1-morpholinocyclopentene, *o*-xylene, reflux, 3 h, then AcOH, 118 °C, 5 min; iii, 200 °C, neat, 3 h; iv, 200 °C, neat, 8 h.

6,7-dihydro-5*H*-cylcopenta[*c*]pyridine one really took place. However, the further unexpected substitution of the bromine atom in 2-pyridyl moiety by the amine residue occurred to finally afford 4-amino-2,2′-bipyridines **3a**–**e** in yields up to 78% (see Scheme 1). The ^{1}H NMR spectra showed a noticeable upfield shift of the signals for the 2-pyridyl residue and contained the signals for the corresponding NCH_2 protons at 3.4–3.9 ppm.

In addition, the structure of product **3c** was ultimately confirmed by XRD analysis (Figure 1).† The compound is crystallized in the centrosymmetric space group. The bipyridine moiety of the compound is, in general, planar, and has an s-*trans* configuration of the N atoms. The bromophenyl substituent is turned toward plane of the bipyridine moiety, the morpholine cycle adopts a *chair* conformation with planar configuration of the N-atom. In addition, π–π-stacking between molecules of **3c** was observed (see Online Supplementary Materials, Figure S1).

Further experiments demonstrated that the same reaction carried out in refluxing *o*-xylene at 143 °C afforded only the typical bromine-containing products **2a**,**b** in yields up to 74% when no *ipso*-substitution of the bromine atom took place. Interestingly, the reaction of bromopyridines **2a**,**b** with some aliphatic amines under solvent-free conditions at 200 °C resulted in the *ipso*-substitution products **3f**,**g** (see Scheme 1).

It should be noted that in the case of 3-(5-bromopyridin-2-yl)-1,2,4-triazines **4** containing bromine atom in different position of 2-pyridyl moiety, as previously reported,[15] the neat reaction afforded only bromopyridines **5** (Scheme 2). Analysis of the literature has shown that *ipso*-substitution of a bromine atom with aliphatic amine residues is more typical for the C^4 position of the pyridine ring than for C^3 one. However, in most cases the reactions are realized in the presence of a catalyst.[16] Only few examples of displacement of the bromine atom at C^4 position of the pyridine cycle in the absence of a catalyst were reported,[17] for example, under high pressure[18] or on heating.[19,20] In the pyridine moiety the presence of acceptor groups (ester[21] or nitro[22]) next to bromine atom at position of C^4 or C^3 increases its susceptibility to the nucleophilic attack. In contrast to 4-bromopyridines, 3-bromopyridines possess lower reactivity, therefore, the *ipso*-substitution of bromine atom in compounds of type **4** did not proceed even at elevated temperatures (see Scheme 2).



a Ar = Ph
b Ar = 4-$MeOC_6H_4$

Scheme 2 *Reagents and conditions*: i, 200 °C, neat, 3 h (ref. 15).

It should be noted that 2,2′-bipyridines with amine moiety at C^4 position are of interest due to their biological activity, in particular, fungicidal,[23] antiviral[24] activity, enzymes inhibition,[25] as well as anticancer activity of their ruthenium(II) complexes.[26] Photophysical properties of iridium[27] and ruthenium[28] complexes of similar 2,2′-bipyridine ligands were also reported.

In summary, we have developed a convenient one-pot synthesis of cyclopentane-fused 5′-aryl-4-cycloalkylamino-2,2′-bipyridines by means of the reaction between 3-(4-bromopyridin-2-yl)-1,2,4-triazines and a number of enamines in neat at 200 °C. The transformation proceeds in two steps, such as *aza*-Diels–Alder reaction and *ipso*-substitution of bromine atom by the amine residue. For compounds **3f**,**g** these two steps can be carried out separately. Prospects of further work in this direction are associated with exploring the possibilities of obtaining 2,2′-bipyridines with various amines residues, as well as the study of their applied properties, first of all photophysical ones.

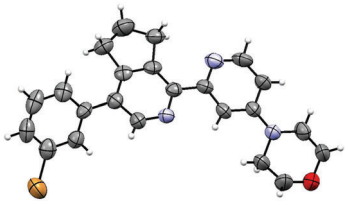


Figure 1 X-ray structure of bipyridine **3c**. Thermal ellipsoids are drawn at 50% probability.

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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.2022.07.007.

† *Crystal data for* **3c**. $C_{23}H_{22}BrN_3O$ (M = 436.34), monoclinic, space group $P1_{21}/c_1$ at 295(2) K, a = 11.5920(15), b = 5.7099(8) and c = 29.910(5) Å, α = 90°, β = 94.832(13), γ = 90°, V = 1972.7(5) Å^3, Z = 4, d_{calc} = 1.462 g cm^{-3}, μ(MoKα) = 2.102 mm^{-1}, F(000) = 888. Total of 11946 reflections were collected (3966 independent reflections, R_{int} = 0.0886) and used in the refinement, which converged to wR_2 = 0.1522, GOOF 0.931 for all independent reflections [R_1 = 0.1837 was calculated for 3966 reflections with $I > 2\sigma(I)$].

The XRD experiment was accomplished on equipment of the ‘SAOC’ centre for collective use IOS UB RAS using the automated ‘Xcalibur 3’ diffractometer on standard procedure (MoKα-irradiation, graphite monochromator, ω-scans with 1° step). Empirical absorption correction was applied. The collection, data reductions and refinement of the unit cell parameters were carried out using the CrysAlisPro program.[29] The structures were solved with the ShelXS structure solution program using direct method and refined with the ShelXL[30] refinement program using Least Squares minimization in anisotropic approximation for non-hydrogen atoms. The H-atoms at the CH-bonds were added in the calculated positions and refined isotropically in the riding model; an H-atom of the OH-group was refined independently.

CCDC 2117784 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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