An Efficient and Direct Synthesis of New 2,2′-Bipyridine Derivatives via Microwave-assisted Three-component Reaction

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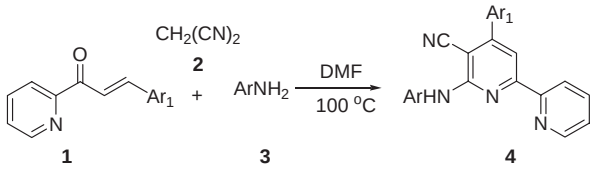
A series of new 2,2′-bipyridine derivatives were synthesized via three-component reactions of 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones, malononitrile, and aromatic amines in DMF under microwave irradiation. It is an efficient and promising synthetic strategy to construct 2,2′-bipyridine skeleton.

The pyridine ring is one of the most well-known systems among the naturally occurring heterocycles.[1] Pyridine and fused pyridine moieties are present in numerous natural products such as quinoline and isoquinoline alkaloids,[2] and nicotine and its analogues.[3] They have a vast range of potential biological activities as herbicides[4] and have been used for enrichment of cereals,[5] and for regulation of arterial pressure[6] and cholesterol levels in blood.[7] Thus, pyridine derivatives have become increasingly important and hence numerous synthetic methods of pyridine rings have been reviewed.[8] On the other hand, poly-substituted pyridines including the related bipyridines[9] are prominent building blocks in supramolecular chemistry with their π-stacking ability, direction H-bonding, and substituted-2,2′-bipyridines (BPys) ligands have attracted widespread attention[10] due to their ability to form complexes with transition metals. The applications of BPys have been found in various fields such as supramolecular chemistry,[11] asymmetric catalysis,[12] polymer and dendrimer science.[13] In addition to these fascinating potential applications, research still demanded to develop directed synthetic routes to suitable bipyridine units, as well as effective functionalization strategies.

There is a great variety of methods described in the literature to synthesize substituted 2,2′-bipyridines.[14] Many precedent methods, however, have inevitable drawbacks: in well-known Kröhnke protocol,[15] positions of functional groups were restricted, and in the Rode et al. protocol,[16] the isomeric mixtures gave rise when using Raney nickel catalysts. Other ways to build bipyridines were the extrusion of organophosphorus compounds[17] or ligand coupling with organosulfur compounds.[18] In addition, there are some modern strategies to synthesize monoalkyl-2,2′-bipyridines, e.g., the Suzuki coupling[19] or especially the Negishi-type cross-coupling reaction between pyridyl triflates and pyridyl zinc reagents,[20] which result in excellent yields of the desired products. However, even with these classical methods, it is still not fully satisfactory with regard to toxic catalyst, narrow application scope of substrates, harsh reaction conditions, generality and operational complexity due to the occurrence of several side reactions. Therefore, a simple, rapid, and efficient procedure is still strongly desired for the synthesis of these important heterocyclic compounds.

As part of an ongoing development of efficient protocols for the preparation of poly-substituted heterocycles from common intermediates, we recently discovered technically simple microwave (MW) conditions for the synthesis of new 2,2′-bipyridine derivatives using 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones as starting materials (Scheme 1).



Scheme 1. Synthetic route of 2,2′-bipyridine derivatives.

Choosing an appropriate solvent is of importance for successful MW-promoted synthesis in view of a rapid rise of temperature in the reaction mixture. In order to search for the optimum solvent, the MW-assisted reaction of 3-(4-chlorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**1c**), malononitrile (**2**), and *p*-toluidine (**3a**) was examined using HOAc, glycol, THF, DMF, and EtOH as solvent at 100 °C, respectively. The results were summarized in Table 1.

As shown in Table 1, the reaction using DMF as solvent resulted in the most excellent yield. Therefore, DMF was chosen as the solvent of this reaction.

Under these optimized reaction conditions, a series of new 2,2′-bipyridine derivatives were synthesized via three-component reactions of 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones **1** malononitrile (**2**), and aromatic amines **3** in DMF under microwave irradiation. As shown in Table 2, the scope of the reaction in regard to the aromatic amines was quite large. Not only aromatic amines containing either electron-donating groups or electron-withdrawing groups can be used, aniline also gave excellent yield. Moreover, a study of the electronic effect with various substituents on the phenyl rings of 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones was conducted. Under our reaction conditions, electron-donating substituents readily provided 2,2′-bipyridine derivatives in high yields (Table 2, Entries 4, 9, and 14). To our delight, electron-withdrawing 2,2′-bipyridine derivatives were obtained in high yields as well, as highlighted by nitro-containing compounds, which were obtained in 87 and 88% yields, respectively (Table 2, Entries 1 and 6). It is worth noting that this result is significant since there is no literature precedent for the synthesis of this type of bipyridines.

Table 1. Solvent optimization for the synthesis of **4c**

Entry	Solvent	Time/min	Yield/%
1	HOAc	6	62
2	glycol	6	48
3	THF	6	25
4	DMF	6	85
5	EtOH	6	74

Table 2. Synthesis of 2,2′-bipyridine derivatives **4**

Entry	4	Ar_1	Aromatic amines	Yield/%
1	**4a**	3-$NO_2C_6H_4$	4-$CH_3C_6H_4NH_2$	87
2	**4b**	4-BrC_6H_4	4-$CH_3C_6H_4NH_2$	84
3	**4c**	4-ClC_6H_4	4-$CH_3C_6H_4NH_2$	85
4	**4d**	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4NH_2$	79
5	**4e**	2-thienyl	4-$CH_3C_6H_4NH_2$	76
6	**4f**	3-$NO_2C_6H_4$	$C_6H_5NH_2$	88
7	**4g**	4-BrC_6H_4	$C_6H_5NH_2$	86
8	**4h**	4-ClC_6H_4	$C_6H_5NH_2$	83
9	**4i**	4-$CH_3OC_6H_4$	$C_6H_5NH_2$	81
10	**4j**	2-thienyl	$C_6H_5NH_2$	82
11	**4k**	4-BrC_6H_4	4-$ClC_6H_4NH_2$	84
12	**4l**	4-ClC_6H_4	4-$ClC_6H_4NH_2$	87
13	**4m**	4-$CH_3OC_6H_4$	4-$ClC_6H_4NH_2$	82
14	**4n**	3,4-$OCH_2OC_6H_3$	4-$ClC_6H_4NH_2$	81

The structures of all the synthesized compounds were established on the basis of their spectroscopic data. The IR spectra of compound **4d** showed strong absorptions at 3327 and 2217 cm^{-1}, which were due to the NH group and CN triple bond, respectively. The ^1H NMR spectrum of **4d** showed a singlet at δ 2.32 due to $-CH_3$, a singlet at δ 3.87 due to $-OCH_3$, a singlet at δ 9.12 due to NH proton (exchanged with D_2O), and a singlet at δ 7.90 due to CH proton in the formed pyridine ring.

In summary, we demonstrated a rapid and direct method that offered a simple and efficient route for the one-pot, three-component synthesis of highly functionalized 2,2′-bipyridine derivatives in good to excellent yields. Particularly valuable features of this method included operational simplicity, increased safety for small-scale high-speed synthesis, and broader substrate scope.

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21 **Typical procedure for three-component reaction: preparation of compounds 4:** The reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10-mL Emrys™; reaction vial, an 3-aryl-1-(pyridin-2-yl)prop-2-en-1-one **1** (1 mmol), malononitrile (**2**) (1 mmol), aromatic amine **3** (1 mmol), DMF (1.0 mL) were mixed and then capped. The mixture was irradiated for 4–9 min at 200-W power and 100 °C. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was filtered, washed with water and EtOH (95%). The solid was purified by recrystallization from EtOH (95%). Spectra data and elemental analyses of typical compounds were summarized as follows: Compound **4d**. mp 244–245 °C; IR (KBr, ν, cm^{-1}): 3327, 2915, 2217, 1608, 1578, 1510, 1247, 1031, 836; ^1H NMR (DMSO-d_6) (δ, ppm): 9.12 (s, 1H, NH), 8.71 (d, $J = 4.0$ Hz, 1H, Py–H), 8.19 (d, $J = 8.0$ Hz, 1H, Py–H), 8.01–7.97 (m, 1H, Py–H), 7.90 (s, 1H, Py–H), 7.69 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.57 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.52–7.49 (m, 1H, Py–H), 7.20 (d, $J = 8.4$ Hz, 2H, Ar–H), 7.16 (d, $J = 8.4$ Hz, 2H, Ar–H), 3.87 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). Anal. Calcd for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28%. Found: C, 76.69; H, 5.03; N, 14.35%.

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