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Two convenient and high-yielding preparations of 6,6′-dimethyl-2,2′-bipyridine by homocoupling of 6-bromopicoline

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Abstract

6-Bromopicoline can be reductively homocoupled to provide 6,6′-dimethyl-2,2′-bipyridine in high yield either by an Ni·bpy catalysed electrosynthesis or by a catalytic modification of the Ullmann synthesis employing $Pd(OAc)_2$. Either procedure is operationally simple and represents a considerable improvement over most known syntheses of this important disubstituted bipyridine.

Keywords: 6-bromopicoline; 6,6′-dimethyl-2,2′-bipyridine; electrosynthesis; reductive homocoupling; Ullmann coupling.

Heteroaromatic chelates based on 2,2′-bipyridine (bpy, **1**) are amongst the most important ligands for inorganic cations.[1] Homologation at the 6/6′ positions leads to more exotic ligands of the podand, coronand and cryptate type bearing additional ligating groups.[2] Among the most common starting materials for achieving this is 6,6′-dimethyl-2,2′-bipyridine (dmbp, **2**), which is usually transformed by NBS[3] or NCS[4] halogenation to the bis-halomethyl derivatives (**3**) as a first step in elaborating the side chains.

Despite the importance of **2**, its' synthesis remains less than satisfactory, a fact to which the numerous preparations that have been reported attest. These involve organometallic[5a,e,f,h] and/or toxic or unpleasant reagents,[5a,f,g] low yields,[4,5b,c,e–j] high temperatures,[4,5b,c,i,j] as well as laborious and/or long reaction/purification procedures,[5b,c,k] often requiring chromatography[5d] or vacuum distillation.[5b,c] The best method in terms of yield and execution appears to be the reductive homocoupling[5d] of 6-bromopicoline[5b] (Br-pic) using a nickel complex reducing agent. The main drawback in this method is the use of 4 equivalents of PPh_3 which necessitates chromatography for the purification of the product.

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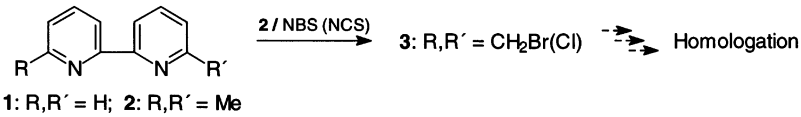
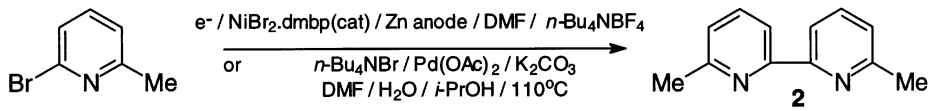


Of the general approaches known for the synthesis of symmetrical bipyridines, the homocoupling of halopyridines, such as that promoted by low-valent nickel[6] or $Pd(OAc)_2$,[7] (and thereby avoiding the need to handle organometallic reagents and intermediates!) is the most promising, both from a standpoint of yield and operation. Nonetheless, the former of these methods,[6a] apart from requiring stoichiometric PPh_3, proved capricious in our hands for the preparation of **2** from Br-pic. In that procedure, low valent nickel catalysis employs zinc powder as a reductant in order to prepare the Ni(0) species in situ from $NiCl_2$. According to a different protocol recently disclosed by Nédélec, Périchon and co-workers, aryl halides can be reductively cross-coupled in a simple electrosynthesis, catalytic in nickel *and devoid of* PPh_3, wherein the Ni(0) moiety is generated at constant current density. Thus clean reactions are achieved with activated alkyl halides,[8] 3-thienylzinc bromide,[9] 2-chloropyrimidine and 2-chloropyrazine[10] as well as 2-halopyridines[11] to yield the corresponding coupling products.

We would like to report two simple and mild methods for the multigram preparation and ready isolation and purification of **2** in good yields. Firstly, adapting Nédélec and Périchon's procedure and homocoupling two moles of Br-pic[12] instead of one mole each of aryl halide and 2-halopyridine we were able to reproducibly prepare **2** in good yield. Secondly, the recently published[7] variant of the Ullmann reaction using catalytic $Pd(OAc)_2$ can also be applied to Br-pic:



Although the electroreductive coupling proceeds cleanly at room temperature it does so somewhat more slowly than in the case of heterocouplings using aryl-[11] or activated alkyl-halides.[8] This observation manifests itself in our inability to run the reaction at a current density of 200 mA typically employed in the examples cited above.[8–11] Attempts to do so invariably resulted in potential overload of up to 3 V (versus Ag/AgCl) and large-scale substrate reduction. Consequently it is advisable to apply a current density of about 120 mA. The reduction in rate in this coupling involving Br-pic can be explained in terms of the inherently lower reactivity of halopyridines as compared to aryl halides in the rate determining oxidative addition of a reductively generated Ni(0)·bipy species to the organic halide.[6]

Notwithstanding these conjectures, we consider the preparation of **2** at hand to be a considerable improvement over existing ones. It is operationally simple in that it can be carried out at room temperature in a wide-mouthed Erlenmeyer flask fitted with an appropriately pierced rubber stopper carrying gas inlet and outlet tubes, a zinc-rod anode and a copper wire for nickel foam cathode connection via a simple clip. We have used DMF both freshly distilled and after prolonged storage over molecular sieves with no apparent reduction in yield. The nickel cathode can be used repeatedly.[13] The production of Zn^{2+} salts from the sacrificial anode does not affect the reaction, and work-up and purification are not only easy, but gratifyingly avoid chromatography, the only side products being water soluble salts.

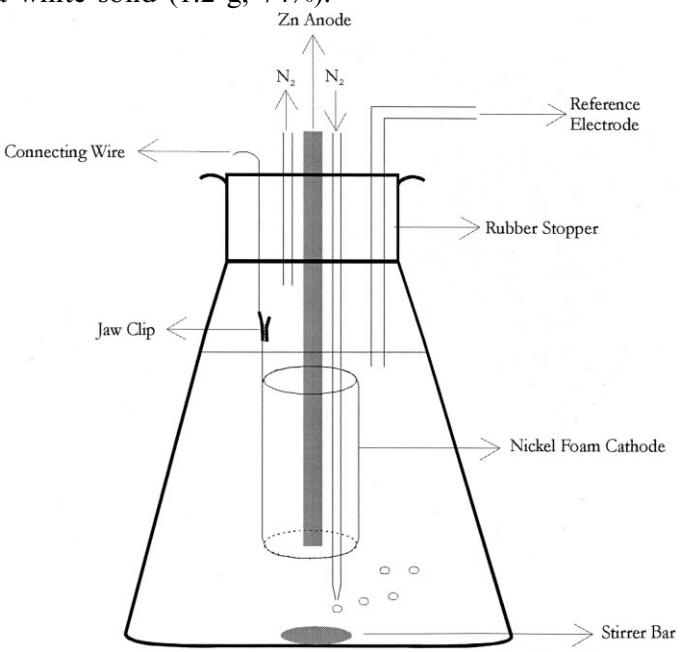
Alternatively, we have employed Lemaire's $Pd(OAc)_2$ catalysed procedure[7] for effecting exactly the same coupling. Thus **2** can be prepared in good yield and multigram quantities from readily available 6-bromopicoline.[5b,12] We recommend either method for the synthesis of 6,6′-dimethyl-

2,2′-bipyridine to be considered amongst first line choices for obtaining this important intermediate.

*Preparation of 6,6′-dimethyl-2,2′-bipyridine (**2**)*:

(a) By electroreductive homocoupling of 6-bromopicoline: A wide-mouthed Erlenmeyer flask was charged with a solution of 1,2-dibromoethane (188 mg, 1 mmol) and *n*-Bu_4NBF_4 (380 mg, 1.16 mmol) in distilled DMF (230 mL) and then equipped with a pierced rubber stopper carrying a zinc rod anode, a copper wire and a jaw-clip holding the nickel foam cathode ($\approx$25 cm^2) wrapped around the anode in a cylindrical fashion (anode–cathode distance $\approx$1 cm), as well as gas inlet and outlet tubes (see diagram). After passing N_2 for 10 min the solution was electrolysed at −2 V (versus Ag/AgCl) for 1 hour. A DMF solution of $NiBr_2$·dmbp[14] [$NiBr_2$ (425 mg, 1.94 mmol, 6.7 mol%)/dimethylbipyridine (**2**) (357 mg, 1.94 mmol, 6.7 mol%)/DMF (20 mL)/rt/overnight] was then added, followed by Br-pic (5 g, 29.07 mmol). A current of 120 mA was applied[15] and the reaction was monitored by TLC. Concurrent with the consumption of starting material, the end-point was indicated by a colour change from wine-red to dark brown. The solvent was removed in vacuo and the semi-solid residue taken up in $CHCl_3$. Washing with aq. NH_3 until the organic phase was light yellow, back extraction of the aqueous phases, drying (Na_2SO_4), filtration and concentration gave an ocre solid, which was washed with cyclohexane to provide pure 6,6′-dimethyl-2,2′-bipyridine (**2**) (1.8 g, 67%, mp = 88–89°C) (lit.[4] = 88–89°C). After removal of the solvent the filtrate crystallised. Slurrying in cyclohexane and renewed filtration provided more product (226 mg, 8%).

(b) By $Pd(OAc)_2$ catalysed homocoupling of 6-bromopicoline: A mixture of Br-pic[5b,12] (3 g, 17.44 mmol), *n*-Bu_4NBr (2.81 g, 8.7 mmol, 0.5 equiv.), $Pd(OAc)_2$ (196 mg, 0.87 mmol, 5 mol%) and K_2CO_3 (2.41 g, 17.44 mmol, 1 equiv.) in DMF:H_2O, 2.4:1 (2.4 mL) was heated to 110°C under N_2. Then isopropyl alcohol (1.34 mL) was added and the flask was tightly stoppered. Stirring was continued at 110°C for 2 days. The cooled reaction mixture was diluted with water and extracted with EtOAc. Drying (Na_2SO_4), filtration and evaporation afforded a brown oil which was chromatographed (eluent: *n*-hex:EtOAc, 4:1) to give the desired 6,6′-dimethyl-2,2′-bipyridine (**2**) as a white solid (1.2 g, 74%).



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12. The inclusion of the preparation of Br-pic from 6-aminopicoline[5b] on a 100 gram scale in an undergraduate practical course attests to its reliability — Professor H. Uzar, Universität Siegen, Germany, private communication.
13. In order to obtain best yields, it is advisable to clean the nickel foam before use by immersion in 6 M HCl for 10 min followed by sequential sonication in water and ethanol (10 min each) and drying in a desiccator.
14. Where dmbp (**2**) is not available, bpy (**1**) can be used with equal success. It is preferable to use **2** as a ligand in the catalytic species in as much as it avoids contamination of the product, which, in the former case can be used without recrystallisation.
15. It is best to monitor the current in such a way as to maintain the potential at ≥ -1.55 V in order to avoid reduction of Br-pic. In doing this, the current drops periodically to about 80 mA, slowly returning however to its original value.