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Towards benign syntheses of bipyridines: versatile approach to supramolecular building blocks

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Abstract—Chiral and achiral bipyridines are readily accessible via a solvent-free Michael addition involving solid NaOH, followed by treatment with ammonium acetate in acetic acid, as a 'one pot' more benign protocol, affording pure products in high yield, typically >80%.

1. Introduction

Bipyridine chiragens have been complexed to an extensive number of metals over the latter two decades.[1–6] Such complexes, especially those derived from pinene and camphor, have been shown to form supramolecular helicates,[4,5] with a growing number demonstrating catalytic properties.[6] Conventional synthesis of such bipyridines from chiral exocyclic enone precursors use volatile organic solvents, harsh conditions, have low atom efficiency and display only moderate to low yields.[2,7–9] In embracing the principals of green chemistry,[10] we have developed a facile synthesis to such compounds involving a solvent-free Michael addition reaction, which results in a dramatic improvement in yield relative to traditional methods. Bergman and coworkers[11] reported a three step synthesis of mono-substituted 2,2′-bipyridines via a dihydropyran from an aldol condensation product and sequential nitrogen insertion to form the substituted pyridine. Although this method displays moderate yields (21–57%) it is limited to aryl substitution at the 4-position of one of the pyridine units.

Bipyridines are typically synthesized via a Friedländer reaction, whereby an aminoaldehyde and an enolizable ketone undergo a double condensation;[6] or from the reaction between an exocyclic enone and an acetylpyridinepyridinium halide in the presence of ammonium acetate; a variation on the Kröhnke condensation reaction.[2,12] These reactions seldom afford an overall yield greater than 50% and are generated by multi-step processes which inevitably lead to an expensive, time consuming protocol with considerable waste and are energy intensive.

In an age where there is a growing concern surrounding the long-term effects arising from the unsustainable use and subsequent disposal of organic solvents, a new more benign field of research has inevitably awoken. The internationally recognized 12 principles of green chemistry, as defined by Anastas and Warner,[10] has led to significant advances in energy conservation and waste minimization, as defined by the *E* factor (=waste (kg)/1 kg product).[13] Synthetically this has led to the evolution and development of viable alternative reaction media to traditional volatile organic solvents; a field of research dominated by ionic liquids.[14] We too have investigated and continue to probe for more benign bio-sustainable reaction media.[15] However, we have pursued a paradoxical shift away from conventional synthetic methodologies, by engaging the use of solvent-free reactions.[16] By eliminating the need for solvent and thereby minimizing waste and cost, we have found that many conventional reactions readily proceed in near quantitative yield with minimal or no workup.[15–17] Continuing on from our advances in the 'green' synthesis of triarylpyridine molecules we sought to extend our studies to bipyridines, adopting the principals of green chemistry.

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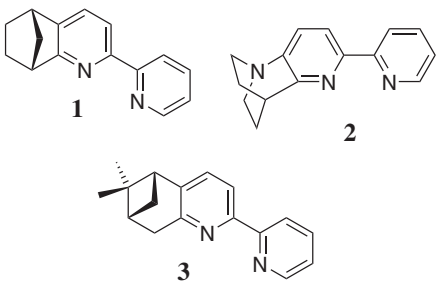
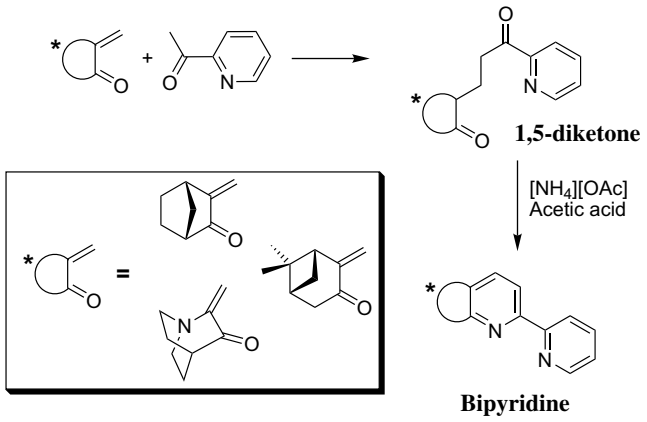
Herein, a more benign, simple and versatile route to both chiral and achiral bipyridines in good yield has been demonstrated by the synthesis and characterization of two new bipyridines, **1** and **2**, chiral and achiral, respectively. We also report the synthesis of the much publicized chiral 5,6-pinene-bipyridine, **3** via this new synthetic approach, as a direct comparison to existing protocols and methodologies.



An overview of the synthetic details are summarized in Scheme 1. Typically, the Michael addition product is formed quantitatively by grinding the enone and the acetyl pyridine in the presence of solid sodium hydroxide using a pestle and mortar. Over a period of ca. 10 min associated with constant aggregating of the mixture, the solid 1,5-diketone intermediate is formed. In all three cases a eutectic melt forms during the mixing process which solidifies on standing, a common occurrence with solvent-free reactions of organic compounds.[18] At this stage the Michael addition product can be isolated by triturating the solid with hexanes and chromatographic methods. During our studies of this reaction we noted that the product decomposed and reverted to the starting materials if the mixing process exceeded beyond 10 min or if the reaction mixture was left to stand for long periods of time without removing the base. We attribute this reversible process to the deliquescent properties of sodium hydroxide; indeed the products of the three grinding reactions can be stored in a dry box indefinitely without the need for removing the catalyst.

The NMR studies show that the reaction is essentially quantitative; subsequently the isolation of the intermediate is not required prior to the final step. Consequently, the reaction mixture was immediately treated with ammonium acetate in glacial acetic acid without further purification. The removal of the acetic acid following the ring closure condensation and aerial oxidation produced the isolated bipyridine products in high yields >81% (overall isolated yield). Although this stage of the synthesis required the use of a solvent, it should be noted that the low vapour-pressure of the acetic acid allows for the use of an air condenser during the reflux, following the workup process the acetic acid can be efficiently regenerated and used as part of a batch process. The solvent chosen is also a naturally renewable source in alignment with the principals of green chemistry.[10]



Scheme 1.

The process finds limitation in the solvent step of the reaction, and the limiting problems associated with separating the products from the acetic acid solution. This represents an engineering challenge, an area we are currently pursuing, along with the physical properties and applications of the novel pyridines described herein which will be reported in due course. At this stage we have demonstrated proof of concept in being able to gain access to chiral and achiral pyridines **1**–**3** in high yield using a versatile new protocol, and the chemistry is likely to have wide-ranging implications in gaining access to bipyridines of higher complexity.

2. Representative experimental procedures

2.1. Synthesis of the 1,5-diketone of 1

2-Acetylpyridine (668 mg, 5.51 mmol) and 3-methylen-2-norbornone (674 mg, 5.51 mmol) were ground together in the presence of NaOH(s) (200 mg) using a mortar and pestle, until an orange powder was formed (ca. 5 min).

2.2. Synthesis of bipyridine 1

The 1,5-diketone was added to a solution of ammonium acetate (2 g, excess) in glacial acetic acid (100 cm^3) and heated to reflux (2 h). The crude product precipitated from the blue reaction media as a pale yellow solid and was purified by recrystallization from ethyl acetate (ca. 1 cm^3). Yield: 103 mg (84%, 4.64 mmol). Mp 77 °C. Anal. found (expected): C 81.1 (81.1), H 6.1 (6.4), N 12.9 (12.6)%. MS (ESI^+, 30 eV) for $C_{15}H_{15}N_2$ ($[M + H]^+$) calcd: 223.29; found: 223. ^1H NMR (300 MHz, $CDCl_3$, 300 K): $\delta = 8.55$ (d, $^3J = 8.0$ Hz, 1H, pyridine *ortho* to N), 8.25 (d, $^3J = 8.0$ Hz, 1H, pyridine *meta* to pyridine, *ortho* to chiral pyridine bond), 7.97 (d, $^3J = 7.7$ Hz, 1H, chiral pyridine *meta* to N), 7.68 (m, 1H, pyridine *para* to N), 7.42 (d, $^3J = 7.7$ Hz, 1H, chiral pyridine *para* to N), 7.16 (m, 1H, pyridine *meta* to pyridine, *para* to chiral pyridine bond), 4.30–1.30 (m, 8H, aliphatic).

2.3. Synthesis of bipyridines 2 and 3

Products **2** and **3** were synthesized as above, using 2-methylene-3-quinuclidinone hydrochloride hydrate and

a fresh pre-prepared sample of pinocarvone, respectively.[19] ^{1}H and ^{13}C NMR data were comparable to literature values.[2]

2.4. Bipyridine 2

Two equivalents (with respect to the enone) of the base were used. Yield 343 mg (81%). Anal. found (expected): C 75.7 (75.9), H 6.4 (6.4), N 17.3 (17.7)%. FAB MS $[M]^+$ calcd: $C_{15}H_{15}N_3$, 237.30; found: 237.

2.5. Bipyridine 3

Yield 1.57 g (91%). Anal. found (expected): C 81.5 (81.6), H 7.6 (7.3), N 11.0 (11.2)%. FAB MS for $C_{15}H_{18}N_2$ ($[M]^+$) calcd: 250.34; found: 250. Optical rotation $[\alpha]_D^{22} = -27.5^\circ$ ($c = 1$, $CHCl_3$).

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