Synthesis of 3,3′-Disubstituted-2,2′-bipyridines from 1,10-Phenanthroline-5,6-quinone

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A route to 3,3′-disubstituted-2,2′-bipyridines from 1,10-phenanthroline-5,6-quinone is described. The methodology involves the 1,2-addition of an organometallic reagent to the quinone, followed by lead tetraacetate cleavage of the diol. This, in turn, is followed by Lúche or Wolf–Kishner reduction affording diols or alkanes respectively.

Bipyridines[1] have long been of interest to co-ordination chemists, and more recently, they have formed the cornerstones of work concerned with the synthesis of supramolecules.[2] Methodology for the synthesis of substituted 2,2′-bipyridines has been substantially augmented by palladium-catalyzed coupling reactions, such as the Stille[3] or Suzuki[4] reactions. Despite the success of these methodologies, alternative approaches are nevertheless useful additions to the preparative chemist's arsenal.

In this communication we report the development of a new methodology for the synthesis of symmetrical and unsymmetrically 3,3′-disubstituted 2,2′-bipyridines. This work was instigated by our need for 2,2′-bipyridines substituted in the 3- and 3′-positions. While Stille- or Suzuki-like coupling protocols would appear to be ideally suited to this end, in our work we required a method in which the 2,2′-bond was already in place.

To our surprise, the literature contains relatively few 3,3′-disubstituted 2,2′-bipyridines. Our first attempts at synthesizing these bipyridines involved utilization of a direct organometallic coupling of 3,3′-bis(bromomethyl)- and 3,3′-bis(chloromethyl)-2,2′-bipyridine with an appropriate organometallic reagent. Unfortunately both these halo compounds proved too unstable to be useful. While we were able to prepare both compounds in solution from the known 3,3′-bis(hydroxymethyl)-2,2′-bipyridine using standard protocols, attempts to isolate either of these halo compounds led to the formation of a dark gum. Electrospray mass spectrometry suggested that both bis(halomethyl)bipyridines had formed oligomeric bipyridinium salts on removal of the solvent. To our disappointment the ditosylate of 3,3′-bis(hydroxymethyl)-2,2′-bipyridine displayed similar behavior.

We then attempted addition of organolithium reagents to 3,3′-bis(carbomethoxy)-2,2′-bipyridine,[5] hoping that the organolithium reagent would add only once to each ester group, on the basis that addition in such a manner would be favored by the formation of cyclic seven-membered chelation-stabilized intermediate (Figure 1), thus avoiding formation of a tertiary carbinol. Similar rationale underpins the synthesis of ketones using α-amino esters.[6] Unfortunately, addition of 2 equivalents of the alkynyl lithium (**1**, M = Li) resulted in addition of both equivalents to the same ester carbonyl.

With the success of these direct approaches appearing unlikely, we explored addition of organometallic reagents to 1,10-phenanthroline-5,6-quinone (**2**) as a potential solution to our problem. We were encouraged to pursue this approach given the reported bis-addition of vinyl lithium to phenanthrene-9,10-quinone.[7]

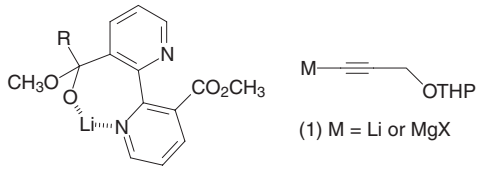


Figure 1.

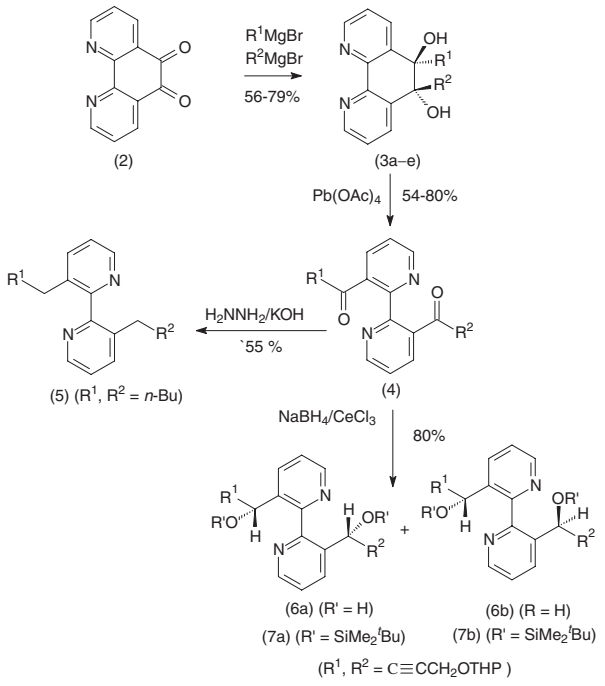
In the event, addition of 2.2 equivalents of (**1**) (M = MgBr) to 1,10-phenanthroline-5,6-quinone (**2**) proceeded smoothly in THF at −78 °C, affording the expected bis-adduct (**3**, R = C≡CCH$_2$OTHP) isolated in 79% yield. The relative stereochemistry of the product was assigned as *trans* based on analogy with published work on phenanthrene-9,10-quinone.[8,9]

A number of other Grignard reagents also added smoothly to the quinone, as shown in Table 1 (Scheme 1). However, addition of *n*-butylithium to the quinone resulted in only low yields of the expected product (Table 1, Entry 6).

Table 1. Addition of organometallic reagents to 1,10-phenanthroline-5,6-quinone

Entry	Organometallic reagent	Product	Yield/ %
1	BrMgC≡CCH$_2$OTHP	3a	79
2	BrMgC≡CCH(OCH$_3$)$_2$	3b	72
3	BrMgCH=CH$_2$	3c	56
4	BrMgC≡CCH$_2$OTHP (1.1 equiv.), then BrMgC≡CCH(OCH$_3$)$_2$ (1.1 equiv.)	3d	64
5	BrMg(*n*-Bu)	3e	57
6	Li(*n*-Bu)	3e	15
7	BF$_3$·Et$_2$O/(*n*-Bu)$_3$SiCHCH=CH$_2$	8	49
8	AlCl$_3$/(*n*-Bu)$_3$SiCHCH=CH$_2$	9	51
9	TiCl$_4$/(*n*-Bu)$_3$SiCHCH=CH$_2$	9	68
10	SnCl$_4$/(*n*-Bu)$_3$SiCHCH=CH$_2$	9	81

We also investigated whether 1,4- or 1,6-addition, leading to 2,9- or 4,7-disubstitiuted phenanthrolines could be achieved. Towards this end, addition of tributylallylsilane in the presence of boron trifluoride-etherate led to the formation of a single product, isolated in 49% yield (Table 1, Entry 7). To our surprise, the product was identified as the known ring contraction product, 1,9-diazafluoren-5-one (**8**) (Figure 2).[10] Analogous ring contractions has previously been observed on treatment of the phenanthrolinequinone (**2**) with alkaline tetraoxomanganate(VII)[10] and on treatment of 1,10-phenanthroline with tetraoxomanganate-(VI).[11] An analogous two-step ring contraction has been reported for phenanthrene-9,10-quinone.[12] To our knowledge, this BF$_3$–



Scheme 1.

Et_2O-catalyzed ring contraction is unprecedented. As expected the reaction also took place in the absence of the silane. We then explored the effect of other Lewis acids in an effort to achieve addition in the desired manner.

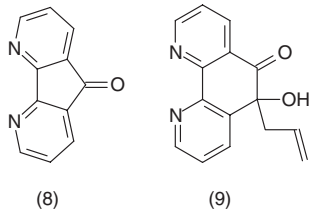


Figure 2.

All three Lewis acids used (Table 1, Entries 8–10) afforded only the monoallylated product (**9**), in moderate to good yield. The use of excess reagent and/or higher temperature failed to entice addition of a second allyl group. This demonstrates that a variety of Grignard reagents readily add to the quinone carbonyls in a controlled manner. Entry 4 also demonstrates the versatility of this methodology in preparing unsymmetrically disubstituted 3,3′-disubstituted bipyridines. It is notable that this transformation was carried out in one-pot by sequential treatment of **2** with the two Grignard reagents shown.

Further elaboration of the diols towards the desired 3,3′-disubstituted bipyridines was demonstrated for diols (**3a**), (**3d**), and (**3e**). Thus treatment of **3a**, **3d**, and **3e** with lead tetraacetate, afforded the unstable diketones (**4**, R_1, R_2 = C≡CCH_2OTHP), (**4**, R_1 = C≡$CCH(OCH_3)_2$, R_2 = C≡CCH_2OTHP), and (**4**, R_1, R_2 = *n*-Bu), in 80, 80, and 54% yields respectively. Attempted oxy-anionic Cope rearrangement on the divinyl diol (**3c**) using KH/18-Crown-6 in refluxing THF, however this only led to intractable tars.[8] Wolf–Kishner reduction of (**4**, R_1, R_2 = *n*-Bu) afforded 3,3′-di(*n*-pentyl)-2,2′-bipyridine (**5**) in 55% yield. These conditions would not be suitable for the unsaturated ketones and thus an alternative approach was explored.

Given that the instability of the diketones might pose a problem if further elaboration was required, it was decided to reduce the carbonyl groups. However, reduction of the diketone (**4**, R_1, R_2 = C≡CCH_2OTHP) proved problematic at first, with a variety of conditions failing to afford the expected diol. Eventually it was found that reduction with sodium borohydride under Lúche conditions[13] provided the diol as a chromatographically inseparable 2:1 mixture of *dl*- and *meso*-diols in 80% yield. Silylation of the diol mixture with *tert*-butyldimethylsilylchloride/4-DMAP in dichloromethane afforded the bis-silylethers (**7a**) and (**7b**) in 95% yield.

In conclusion, a methodology has been developed for the synthesis of both symmetrically and unsymmetrically 3,3′-disubstituted bipyridines commencing with phenanthroline-5,6-quinone. Unoptimized yields of around 30–60% for the three steps involved were achieved.

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