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A New Synthetic Route for the Preparation of 1,10-Phenanthroline Derivatives

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Dedicated to Professor Nazario Martín on the occasion of his 50th birthday

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The intermediate resulting from the addition of an organolithium reagent to 1,10-phenanthroline has been quenched with benzyl bromide. The resulting protected dihydrophenanthroline intermediate is thus stabilized and can be used for further chemical transformations. This strategy allows to modify the reactivity of the phenanthroline backbone and offers a unique opportunity to perform chemical modifications that would not be possible when starting from 1,10-phenanthroline.

Phenanthroline derivatives are important building blocks for the preparation of coordination compounds[1] and metallosupramolecular ensembles.[2] The synthesis of functionalized 1,10-phenanthroline derivatives can be achieved by constructing the polycyclic aromatic scaffold under Skraup conditions. This route, however, is tedious and the overall yields are not always very good. Direct chemical modification of 1,10-phenanthroline is also possible, but only a few reactions allow for the regioselective introduction of substituents on the 1,10-phenanthroline backbone.[3,4] Among them, the addition of organolithium derivatives followed by hydrolysis and MnO_2 oxidation has proven to be a useful tool.[4] This reaction developed in the Sauvage group is efficient for the preparation of 2-substituted- and 2,9-disubstituted-1,10-phenanthroline derivatives. To the best of our knowledge, the intermediate resulting from the addition of the organolithium reagent to 1,10-phenanthroline has only been hydrolyzed to afford an air-sensitive dihydrophenanthroline intermediate that has been always directly aromatized. In this paper, we show that the addition product can be quenched with benzyl bromide. The resulting protected dihydrophenanthroline intermediate is thus stabilized and can be used for further chemical transformations. This strategy allows for the modification of the reactivity of the phenanthroline backbone and offers a unique opportunity to perform chemical modifications that would not be possible when starting from the corresponding aromatic derivative. Finally, the benzyl group can be removed to generate a modified phenanthroline product.

The reaction conditions were first adjusted with the monoaddition product resulting from the reaction of 1,10-phenanthroline (1 equiv.) with *n*-butyllithium (1.1 equiv.) in Et_2O at 0 °C (Scheme 1). Under optimized conditions, a slight excess of benzyl bromide (1.3 equiv.) was added to the reaction mixture. After 3 h, the solvents were removed under reduced pressure. The crude product was then directly subjected to column chromatography to afford compound **1a** in 74% yield. Similarly, the treatment of 1,10-phenanthroline with *n*-hexyllithium and phenyllithium followed by the quenching with benzyl bromide gave **1b** and **1c**, respectively. The same reaction conditions were also used to prepare **3a**–**e** from compound **2**. The benzylated dihydrophenanthroline derivatives **1a**–**c** and **3a**–**e** were found reasonably stable under normal laboratory conditions and could be easily characterized. The ^{1}H NMR spectra of **1a**–**c** are characterized by two doublets with a coupling constant of ca. –15 Hz for the diastereotopic benzylic protons and three sets of signals (**1a**–**b**: δ = 3.8, 5.5, and 6.5 ppm; **1c**: δ = 5.1, 5.9, and 6.6 ppm) for the three protons of the nonaromatic six-membered ring. The same characteristic features are observed in the ^{1}H NMR spectra of **3a**–**e**.

When 1,10-phenanthroline is treated with an excess of *n*BuLi in Et_2O at room temperature for 24 h and quenched

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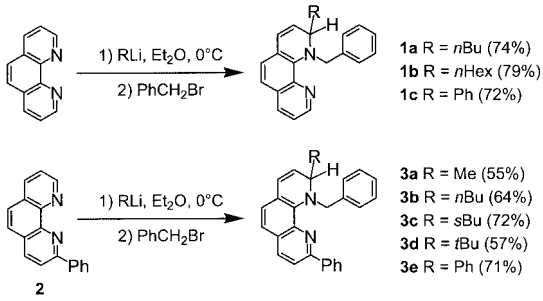
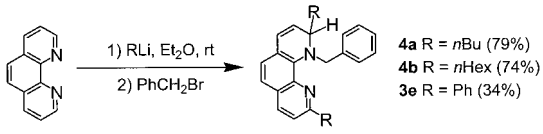


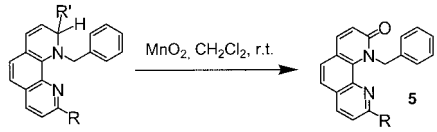
Scheme 1.

with water, a tetrahydrophenanthroline derivative is obtained. MnO_2 oxidation of this oxygen-sensitive intermediate yields 2,9-dibutyl-1,10-phenanthroline.[4] When the treatment with *n*BuLi is followed by reaction with an excess of benzyl bromide, compound **4a** can be isolated in 79% yield. Benzylation at the two N atoms was never observed even in the presence of a large excess of benzyl bromide, most probably for steric reasons. Interestingly, the monobenzylated tetrahydrophenanthroline intermediate was readily oxidized under air to afford **4a** and the use of MnO_2 or other oxidant was not required.[5] The reaction of 1,10-phenanthroline with an excess of *n*-hexyllithium and phenyllithium followed by the quenching with benzyl bromide afforded **4b** and **3e**, respectively. Whereas **4a** and **4b** were thus obtained in good yields, compound **3e** was only isolated in 34% yield. This is mainly associated with the poor solubility in Et_2O of the intermediate resulting from the addition of 2 equiv. of PhLi to 1,10-phenanthroline (Scheme 2).

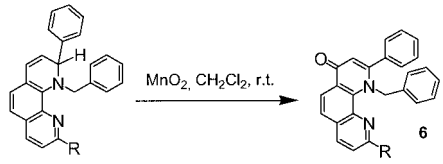


Scheme 2.

Derivative **1a** was first treated with MnO_2 in order to see if this reagent could achieve the debenzylation/aromatization to afford the corresponding phenanthroline. To our surprise, an oxidative carbon–carbon bond cleavage occurred thus leading to compound **5a** (Scheme 3). This behavior was indeed general and treatment of the benzylated dihydrophenanthroline derivative bearing a methyl, *n*-butyl or *n*-hexyl substituent with MnO_2 gave the corresponding benzylated phenanthrolin-2-one derivative in excellent yields. Compound **5d** was also obtained by reaction of **3c** (*s*Bu) or **3d** (*t*Bu) with MnO_2. The yields were however low. Indeed, the oxidation of **3c** and **3d** was very slow. After 24 h, the starting material was not completely consumed and decomposition occurred. However, except for **5d** and unreacted starting material, no other product could be isolated. In contrast, no oxidative cleavage of the phenyl–C bond occurred upon treatment of **1c** and **3e** with MnO_2. In both cases, oxidation took place at the 4-position of the phenanthroline core thus leading to phenanthrolin-4-one derivatives **6a** and **6b**.[6] Structural assignment of the phenanthrolinone **5a**–**d** and **6a**–**b** was based on ^{1}H- and ^{13}C-, 2D-COSY- and NOESY NMR spectroscopic data. It is worth noting that the signal corresponding to the benzylic protons appeared as a broad singlet in the ^{1}H NMR spectra recorded at room temperature for all of these compounds. Variable-temperature NMR studies revealed a perfectly reversible narrowing of this signal and a sharp singlet was observed at ca. 80 °C. In contrast, an AB quartet was observed at low temperature (–40 °C). The later observations indicate restricted rotation of the benzyl substituent. Crystals suitable for X-ray crystal structure analysis were obtained for **5a** and **5d** (Figure 1).[7] In both cases, analysis



Starting material	Product (yield)
1a R = H, R' = *n*Bu	**5a** R = H (81%)
1b R = H, R' = *n*Hex	**5a** R = H (82%)
4a R = R' = *n*Bu	**5b** R = *n*Bu (73%)
4b R = R' = *n*Hex	**5c** R = *n*Hex (66%)
3a R = Ph, R' = Me	**5d** R = Ph (99%)
3b R = Ph, R' = *n*Bu	**5d** R = Ph (89%)
3c R = Ph, R' = *s*Bu	**5d** R = Ph (13%)
3d R = Ph, R' = *t*Bu	**5d** R = Ph (28%)



Starting material	Product (yield)
1c R = H	**6a** R = H (78%)
3e R = Ph	**6b** R = Ph (96%)

Scheme 3.

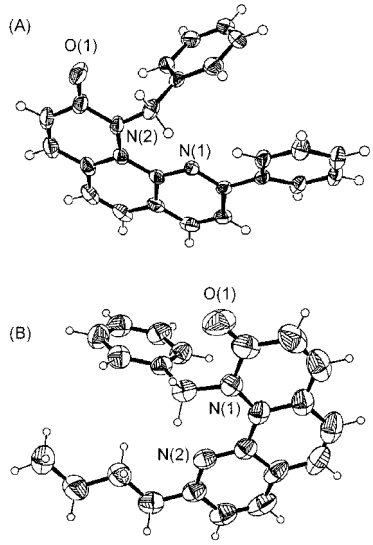
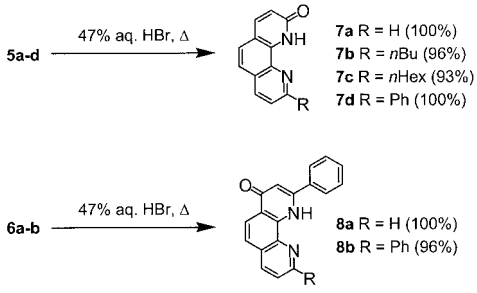


Figure 1. (A) ORTEP view with partial numbering of compound **5b**, thermal ellipsoids include 50% of the electron density. (B) ORTEP view with partial numbering of compound **5d**, thermal ellipsoids include 30% of the electron density.

of the crystal lattice revealed stacked pairs of enantiomeric conformers having their benzylic groups in opposite orientations (Figure S1, Supporting Information). This is in perfect agreement with the ^{1}H NMR observations.

Debenzylation of **5a**–**d** and **6a**–**b** was easily achieved by treatment with a 47% aqueous HBr solution (Scheme 4).[8] Phenanthrolinone derivatives **7a**–**d** and **8a**–**b** were thus obtained in excellent yields (90–98%). The ^{1}H- and ^{13}C NMR spectroscopic data and elemental analyses were in full agreement with the proposed structures. Furthermore, the structure of compound **7d** was confirmed by X-ray crystal diffraction (Figure 2).[7]



Scheme 4.

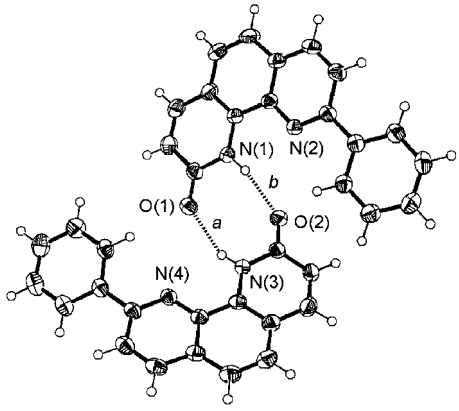


Figure 2. ORTEP view with partial numbering of the H-bonded dimer of compound **7d**, thermal ellipsoids include 50% of the electron density (*a*: 2.108 Å; *b*: 2.168 Å).

In conclusion, we have developed a new synthetic method for the preparation of phenanthrolinone derivatives based on the peculiar chemical reactivity of benzylated dihydrophenanthroline derivatives. Further work is under way in our laboratories to extend this new concept for the preparation of other families of phenanthroline derivatives.

Supporting Information (see also the footnote on the first page of this article): Experimental details for the preparation of compounds **1**–**8** and spectroscopic data for all new compounds.

Acknowledgments

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[5] The oxidation of di- or tetrahydrophenanthroline intermediates resulting from the reaction of 1,10-phenanthroline with an organolithium reagent followed by quenching with water occurs under air but is not very efficient and in addition undefined degradation products are obtained. In this case, the use of an oxidant (MnO_2) is necessary to perform clean aromatization, see ref.[4]

[6] The oxidation at the 4-position of the phenanthroline core leading to phenanthrolin-4-one derivatives is in line with previous experimental observations. Indeed, treatment of *N*-alkylphenanthrolinium salts with MnO_2 led to 1-alkyl-1,10-phenanthrolin-2-one; see: M. R. Johnson, D. Bell, L. Shanaman, *Heterocycles* **1997**, *45*, 1059–1069.

[7] Full data collection parameters and structural data are available as CIF files. CCDC-615458 (for **5b**), -615459 (for **5d**), and 615460 (for **7d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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