Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1856

www.rsc.org/obc

PAPER

Activation of a CH bond in polypyridine systems by acetyl hypofluorite made from F_2†

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Received 26th October 2011, Accepted 5th December 2011
DOI: 10.1039/c2ob06799d

Activation of the relatively inactive polypyridine backbone with strong electrophilic fluorine, originating from acetyl hypofluorite (AcOF) enables attack of the acetoxy moiety at the α position to the heteroatom. Derivatives of bipyridine, phenanthroline and terpyridine systems have been acetoxylated or oxygenated within a few minutes usually in very good yields.

Introduction

Bipyridine (bpy), phenanthroline (phen) and terpyridine (tpy) derivatives are important building blocks for the preparation of coordinating compounds and metallo-supramolecular ensembles. It can be asserted that, over the last five decades, one of most extensively investigated family of complexes is that of the metal-polypyridines.[1] The great interest generated by this class of complexes arises in part from their potential application in solar energy conversion,[2] photo-catalysis,[3] photo-induced charge separation and for their use as light-driven molecular machines.[4] They have also found uses in DNA and proteins studies,[5,6] as well as in small molecules recognition.[7]

Only a few synthetic routes leading to oxygen substituted polypyridines at the α position to the heteroatom were developed. A common one constitutes of a cross coupling reactions utilizing pre-functionalized pyridine rings. Such strategy requires synthesis of suitable building blocks and is frequently a multi-step procedure. Another notable pathway is hydroxylation through a rearrangement of an appropriate *N*-oxide with $SbCl_5$, a route usually suitable for simple pyridine derivatives.[8] In any event, there is no direct and efficient regiospecific substitution of the hydrogen α-to the nitrogen atom of the pyridine nucleus by an oxygenated moiety. Despite the fact that oxygenated bpy and phen ligands are important in organic heterocyclic and coordination chemistry, very few synthetic methods leading to their preparation could be found in the literature.[9] Probably the best of these routes is the dihydroxylation using certain copper salts under solvothermal conditions (180 °C, 80 h, yields below 50%).[10]

From the several reagents we have developed using elemental fluorine,[11] acetyl hypofluorite was found to be very useful.[12] Solutions of this reagent, stable for a few hours at 0 to +20 °C, are easily prepared by passing commercial nitrogen-diluted fluorine through a suspension of sodium acetate, solvated with acetic acid in $CFCl_3$ or acetonitrile. Although this hypofluorite has been utilized for various fluorination reactions,[13] surprisingly it was also employed for activation of certain simple pyridine derivatives.[14] We describe in this work a general oxygenation method for the much less reactive polypyridine systems such as bpy, phen and tpy at the α-position to the nitrogen using this reagent.

Results and discussion

Reacting 2,2′-bipyridine (**1**) with cold (0 °C) 2 mole-equivalent of AcOF for just a few minutes, resulted in 85% yield of 2-pyridyl-6-acetoxypyridine (**2**).[15] In general, achieving diacetoxylation requires larger excess of the reagent and indeed when **1** and 5,5′-dimethyl-2,2′-bipyridyl (**4**) were treated with 5 mole-equivalent of AcOF, 6,6′-diacetoxy-2,2′-bipyridine (**3**)[16] and 6,6′-diacetoxy-5,5′-dimethyl-2,2′-bipyridyl (**5**) were obtained in 90% and 95% yields respectively. The 4,4′-bipyridine (**6**) isomer was also treated with AcOF in the same manner and was acetoxylated to form 2,2′-diacetoxy-4,4′-bibyridyl (**7**) in 95% yield (Scheme 1).

The reaction commence with the attack of the electrophilic fluorine of the acetyl hypofluorite on the basic electrons of the nitrogen atom of the pyridine system thus activating the α position to the nitrogen atom toward nucleophilic attack. Since the acetoxy residue is in the vicinity, the ion pair collapses rapidly followed by HF elimination and aromatic restoration, both very strong driving forces. In the case of bpy from the two possible resonance structures, **A** is clearly the dominant one because of the extended conjugation (Scheme 2). A somewhat similar mechanism could be found in Shreeve's work dealing with *N*,*N*-difluoro-bipyridinium salts treated with base.[17]

There is a substantial difference, however, between compounds containing one pyridine nucleus and derivatives

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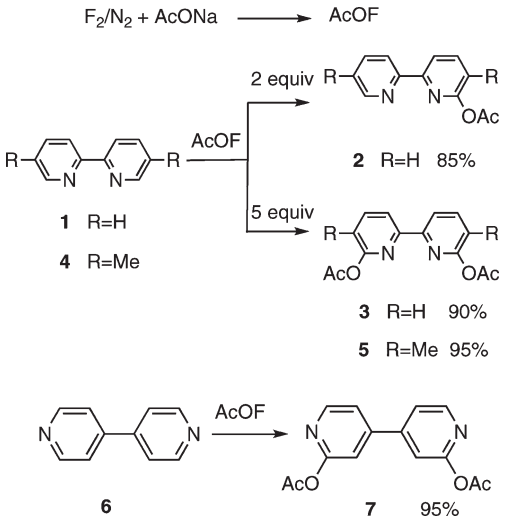
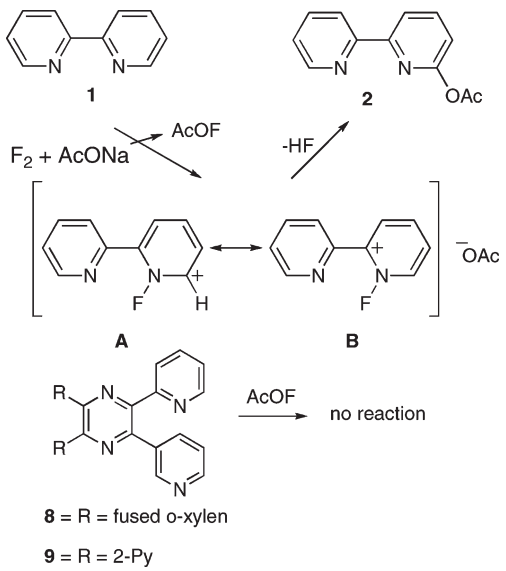
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob06799d

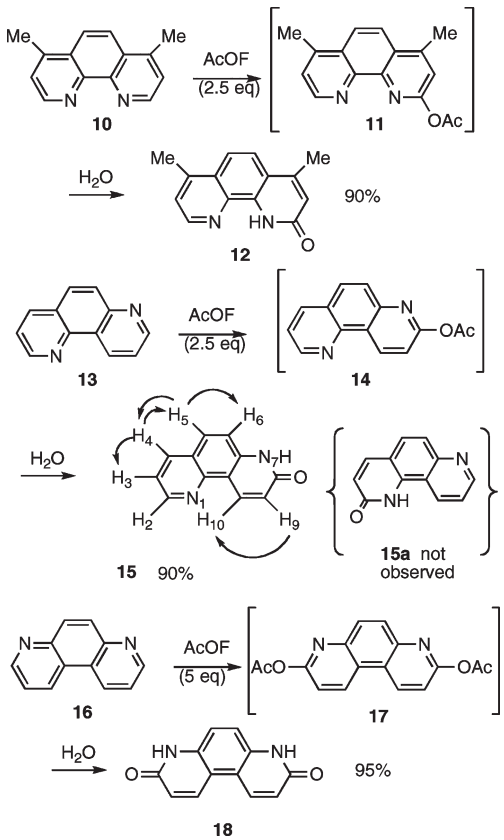


Scheme 1 Oxygenation of bipyridines with AcOF.



Scheme 2 Reaction mechanism of the acetoxylation of polypyridines.

containing polypyridine rings. In the case of the former group the carbocation developed α to the heteroatom is less destabilized by the electronegative fluorine atom compared to polypyridine systems. This fact enabled a relatively long life-time of the carbocation in simple pyridines to the extent that nucleophilic elements from the solvents could compete with the acetate anion resulting eventually in α-chloro, bromo or alkoxy derivatives.[14] In the case of polypyridines the second electron withdrawing ring further deactivates the first one that bears the positive charge, resulting in much shorter lifetimes of the respective carbocation, counting for the fact that there is a total absence of any elements originating from the solvent when one is used. This could be further demonstrated by compounds such as 6,7-dimethyl-2,3-di(2-pyridyl)quinoxaline (**8**) and tetra-2-pyridinylpyrazine (**9**) where the relevant pyridine rings were so electron depleted that no reaction between them and AcOF could take place.



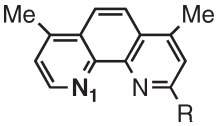
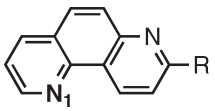
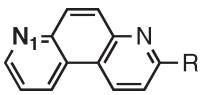
Scheme 3 Oxygenation of phenanthrolines with AcOF.

The described oxygenating reaction is also operable with phenanthrolines. Treating 5,6-dimethyl-1,10-phenanthroline (**10**) and 1,7-phenanthroline (**13**) with acetyl hypofluorite produced the 2-acetoxy derivatives **11** and **14** (not purified) in 90% yield. 4,7-Phenanthroline (**16**) could, however, form the diacetoxy derivative **17**. These compounds as well as other acetoxy pyridine derivatives could be quantitatively hydrolyzed to the corresponding 4,7-dimethyl-1,10-phenanthrolin-2-one (**12**), 1,7-phenanthrolin-8-one (**15**)[18] and 4,7-phenanthroline-3,8-dione (**18**), either spontaneously or in the aqueous acidic reaction mixture at 50 °C in nearly quantitative yield (Scheme 3).

Although mono oxygenation of 1,7-phenanthroline (**13**) resulted after hydrolysis in a single compound, two potential products **15** and **15a** could, at least in theory, be formed (Scheme 3). In order to determine which nitrogen (*N*-1 or N-7) is attacked by AcOF, we preformed some NOE experiments. Strong NOE was observed between H-4 to H-3 and H-5 as well as between H-5 to H-4 and H-6. The vinyl proton H-9, however, displayed an NOE only to H-10 thereby establishing that electrophilic fluorine in AcOF attacks at N-7 generating **15** only as shown in Scheme 3.

An interesting issue is the fact that **16** could be doubly oxygenated in the vicinity of both nitrogen atoms forming eventually the diamide **18**. This is in contrast to compounds **10** and **13** which could be oxygenated only once producing, after hydrolysis, the amides **12** and **15**, no matter how large excess of the reagent was used. This could be explained by examining the products after the first oxygenation. While in the cases of **10** and **13** we could expect a full conjugation between the oxygen function

Table 1 Mulliken charge on the nitrogen atom

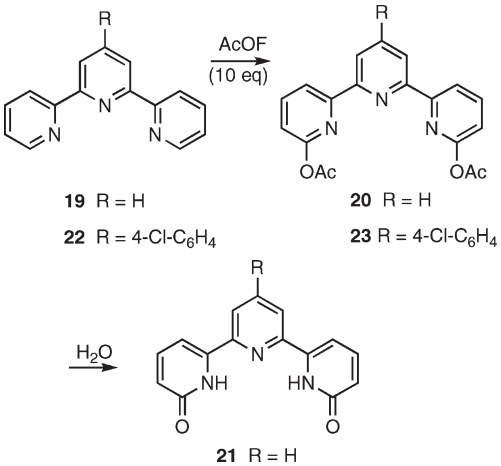
Compound	N_1[a]
	**10** R = H, −0.1319 **11** R = OAc, −0.1241
	**13** R = H, −0.1690 **14** R = OAc, −0.1675
	**16** R = H, −0.2002 R = OAc, −0.2038

[a] Atomic units.

and the remote nitrogen atom which considerably reduces its basicity, in the case of **16** there is a cross conjugation diminishing the electron withdrawing effect of the oxygen on the far away nitrogen atom which still remains quite basic and thus allows an additional molecule of AcOF to attack it.

DFT calculations (B3LYP/6-31+G(d)) support the above reasoning. We focused on the Mulliken charge distribution each nitrogen atom bears before and after oxygenation of the mentioned above phenanthroline skeletons. Although the differences are not striking, the trend is clear. From Table 1 we could see that only the mono oxidized **16** retain enough negative charge on the second nitrogen atom allowing an additional amide formation. The reduced basicity of the second nitrogen in **10** and **13**, however, causes the reaction to be terminated after mono oxygenation. These conclusions are in line with the experimental outcome mentioned above.

Terpyridines produced similar results. Due to the extended aromaticity, these molecules display enhanced chemical stability and as a result any modification reaction on the polypyridine skeleton is somewhat more difficult. Indeed, these derivatives required much larger excess of acetyl hypofluorite to achieve the desired oxygenation, but the electronic structures enabled both nitrogen atoms to be attacked by the electrophilic fluorine. Around 10 mole-equivalent of AcOF were used in order to transfer 2,2′:6′,2″-terpyridine (**19**) to pyridine-2,6-dipyridone **21**, *via* its respective diacetate **20**, in 85% overall yield. It should be noted that **21** is a known compound prepared in the past by a total synthesis in less than 25% yield.[19] Similarly 4′-(4-chlorophenyl)-2,2′:6′,2″-terpyridine (**22**) was acetoxylated to **23** in 80% yield (Scheme 4).



Scheme 4 Oxygenation of terpyridines with AcOF.

Conclusion

It has been demonstrated that acetyl hypofluorite can serve as a powerful regioselective oxygenating agent for various polypyridine derivatives, a task very difficult to achieve by any other means. The fact that it is made from diluted fluorine should not deter chemists from working with it. Thus, for example, fluorine is less toxic than chlorine,[20] and in concentrations of 10–20% in N_2 is also much less corrosive than both chlorine and bromine. Working with it is not as complicated as one may think. Technical commercial fluorine can be diluted on the spot[21] or premixed fluorine/nitrogen mixtures could be purchased.

Experimental section

^{1}H NMR spectra were recorded using a 400 MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The proton broadband decoupled ^{13}C NMR spectra were recorded at either 50.2 MHz or at 100.5 MHz. Here too, $CDCl_3$ served as a solvent and Me_4Si as an internal standard. MS was measured under CI, ESI or APPI conditions.

General fluorination procedure

Fluorine is a strong oxidant and corrosive material. In organic chemistry, it is mostly used after dilution with nitrogen or helium. Such dilution can be achieved by using either an appropriate copper or monel vacuum line constructed in a well-ventilated area or simply purchasing prediluted fluorine. A detailed description for simple setup had appeared in the past.[21] The reactions themselves are carried out in regular glassware. If elementary precautions are taken, work with F_2 is simple and we have had no bad experience working with it.

Preparation of AcOF and its reaction with polypyridines

A mixture of 10–15% F_2 in N_2 was bubbled into a cold (−45 °C) suspension of 2 g of AcONa·AcOH dispersed in 100 mL of CH_3CN and 10 mL of AcOH all placed in a standard glass vessel. The solvated salt could be made by leaving anhydrous AcONa over AcOH in a closed desiccator for at least 24 h. The amount of the AcOF thus obtained could be easily determined by reacting aliquots of the reaction mixture with aqueous KI solution and titrating the liberated iodine. After the desired concentration of AcOF is achieved (usually 0.1–0.15 M), the oxidizing solution was added in portions of 10–20 ml each to the desired solid polypyridine derivative. The reactions were carried out on scales of 1–5 mmol using 2.5–10 fold excess of AcOF, with conversions higher than 95%. They were usually

monitored by TLC or NMR and in most cases were completed within a few minutes. The reaction was terminated by pouring it into $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$ and evaporation of the solvent. The crude product was usually purified by vacuum flash chromatography (Merck silica gel 60H) with petroleum ether/ethyl acetate serving as eluent or by recrystallization. Several of the products are known and referenced, but frequently not adequately described. In such cases their properties are given below.

2-Pyridyl-6-acetoxypyridine (**2**)[15] was prepared from 2,2′-bipyridine (**1**) (0.4 g, 2.6 mmol) as described above, using 2.5 equiv of the oxidizing solution. A white solid (0.46 g, 85% yield) was obtained: mp 73–74 °C; ^{1}H NMR ($CDCl_3$) 8.68–8.66 (1 H, m), 8.35–8.32 (2 H, m), 7.92 (1 H, t, J = 7.9 Hz), 7.80 (1 H, td, J_1 = 7.7, J_2 = 1.8 Hz), 7.31 (1 H, ddd, J_1 = 7.5, J_2 = 4.8, J_3 = 1.1 Hz), 7.10 (1 H, dd, J_1 = 8.0, J_2 = 0.7 Hz), 2.39 ppm (3 H, s); ^{13}C NMR ($CDCl_3$) 169.26, 157.44, 155.82, 155.13, 149.38, 140.44, 137.09, 124.19, 121.58, 119.36, 116.45, 21.51 ppm; MS (CI) m/z 215.1 $(M + H)^+$.

6,6′-Diacetoxy-2,2′-bipyridine (**3**)[16] was prepared from 2,2′-bipyridine (**1**) (0.4 g, 2.6 mmol) as described above, using 5 equiv of the oxidizing solution. A white solid (0.62 g, 90% yield) was obtained with physical constants in accordance to the ones in the literature.

6,6′-Diacetoxy-5,5′-dimethyl-2,2′-bipyridine (**5**) was prepared from 5,5′-dimethyl-2,2′-bipyridyl (**4**) (0.7 g, 3.8 mmol) as described above, using 5 equiv of the oxidizing solution. A pale yellow product (1.08 g, 95% yield) was obtained, mp starting to decompose at 210 °C; ^{1}H NMR ($CDCl_3$) 8.17 (2 H, d, J_1 = 7.8 Hz), 7.68 (2 H, d, J_1 = 7.8 Hz), 2.39 (3 H, s), 2.24 ppm (3 H, s); ^{13}C NMR ($CDCl_3$) 168.95, 156.19, 152.43, 141.50, 125.68, 119.93, 21.13, 16.04 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2O_4$ 323.1008 (M + Na), found 323.1010. Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.69; H, 5.16; N, 9.22.

2,2′-Diacetoxy-4,4′-bipyridyline(**7**) was prepared from 4,4′-bipyridine (**6**) (0.5 g, 3.2 mmol) as described above, using 5 equiv of the oxidizing solution. A pale beige product (0.82 g, 95% yield) was obtained: mp 178–181 °C; ^{1}H NMR ($CDCl_3$) 8.28 (2 H, d, J_1 = 7.7 Hz), 7.90 (2 H, t, J_1 = 7.8 Hz), 7.11 (2 H, d, J_1 = 8.0 Hz), 2.40 ppm (3 H, s); ^{13}C NMR ($CDCl_3$) 169.20, 157.39, 154.53, 140.47, 119.68, 116.85, 21.48 ppm; HRMS (APPI) m/z calcd for $C_{14}H_{12}N_2O_4$ 295.0695 (M + Na), found 295.0696. Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.46; H, 4.30; N, 10.36.

4,7-Dimethyl-1,10-phenanthrolin-2(1*H*)-one (**12**) was prepared from 5,6-dimethyl-1,10-phenanthroline (**10**) (0.4 g, 1.9 mmol) as described above, using 2 equiv of the oxidizing solution. After hydrolysis, a pale beige product (0.38 g, 90% yield) was obtained: mp 202–203 °C; ^{1}H NMR ($CDCl_3$) 10.73 (1 H, br), 8.75 (1 H, d, J_1 = 4.3 Hz), 7.73 (2 H, q, J_1 = 9.3 Hz), 7.38 (1 H, d, J_1 = 4.3 Hz), 6.70 (1 H, s), 2.74 (3 H, s), 2.58 ppm (3 H, s); ^{13}C NMR ($CDCl_3$) 161.91, 149.00, 148.74, 144.79, 136.55, 135.44, 128.05, 123.97, 122.47, 121.84, 117.80, 116.93, 19.40, 18.91 ppm; HRMS (APPI) m/z calcd for $C_{14}H_{12}N_2O$ 225.1028 $(M + H)^+$, found 225.1031. Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.68; H, 5.34; N, 12.28.

1,7-Phenanthrolin-8-one (**15**)[18] was prepared from 1,7-phenanthroline (**13**) (0.6 g, 3.3 mmol) as described above, using 2 equiv of the oxidizing solution. After hydrolysis, a beige product (0.58 g, 90% yield) was obtained: mp > 300 °C (decomposition); ^{1}H NMR (DMSO-d_6) 8.98–8.96 (2 H, m), 8.39 (1 H, dd, J_1 = 8.0, J_2 = 1.6 Hz), 8.07 (1 H, d, J_1 = 8.9 Hz), 7.58–7.54 (2 H, m), 6.68 ppm (1 H, d, J_1 = 9.7 Hz); ^{13}C NMR (DMSO-d_6) 162.34, 150.81, 144.28, 140.26, 136.59, 135.84, 130.84, 123.27, 121.47, 120.72, 116.99, 113.99 ppm; HRMS (ESI) m/z calcd for $C_{12}H_8N_2O$ 197.0715 $(M + H)^+$, found 197.0719.

4,7-Phenanthroline-3,8(4*H*,7*H*)-dione (**18**) was prepared from 4,7-phenanthroline (**16**) (0.6 g, 3.3 mmol) as described above, using 5 equiv of the oxidizing solution. A beige product (0.67 g, 95% yield) was obtained: mp > 300 °C (decomposition); ^{1}H NMR (DMSO-d_6) 8.54 (2 H, d, J_1 = 9.6 Hz), 7.50 (2 H, s), 6.64 ppm (2 H, d, J_1 = 9.6 Hz); ^{13}C NMR (DMSO-d_6) 161.26, 135.05, 134.72, 122.90, 119.07, 114.08 ppm; HRMS (ESI) m/z calcd for $C_{12}H_8N_2O_2$ 213.0664 $(M + H)^+$, found 213.0667.

6,6-(Pyridine-2,6-diyl)dipyridin-2(1*H*)-one (**21**)[19] was prepared from 2,2′:6′,2″-terpyridine (**19**) (0.5 g, 2.1 mmol) as described above, using 10 equiv of the oxidizing solution. After hydrolysis, a white product (0.48 g, 85% yield) was obtained with physical properties matching those in the literature.

6,6″-Diacetoxy-4′-(4-chlorophenyl)-2,2′:6′,2″-terpyridine (**23**) was prepared from **22** (0.4 g, 1.2 mmol) as described above, using 10 equiv of the oxidizing solution. A beige product (0.42 g, 80% yield) was obtained: mp 177–179 °C; ^{1}H NMR ($CDCl_3$) 8.59–8.57 (4 H, m), 7.98 (2 H, t, J_1 = 8.0 Hz), 7.79 (2 H, d, J_1 = 8.5 Hz), 7.49 (2 H, d, J_1 = 8.5 Hz), 7.15 (2 H, d, J_1 = 8.0), 2.4 ppm (3 H, s); ^{13}C NMR ($CDCl_3$) 169.30, 157.45, 155.64, 155.14, 149.46, 140.42, 136.94, 135.43, 129.30, 128.84, 119.70, 119.45, 116.77, 29.84 ppm; HRMS (APPI) m/z calcd for $C_{25}H_{18}N_3O_4Cl$ 460.1064 $(M + H)^+$, found 460.1059.

Acknowledgements

This work was supported by the USA-Israel Binational Science Foundation (BSF), and by the Israel Science Foundation. We wish to express our gratitude to Prof. Y. Kashman from our school for his help with the NOE experiments. Y. H. thanks the Israel Ministry of Science and Technology for a scholarship.

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