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Highly Efficient Synthesis of *O*-(2,4-Dinitrophenyl)hydroxylamine. Application to the Synthesis of Substituted *N*-Benzoyliminopyridinium Ylides

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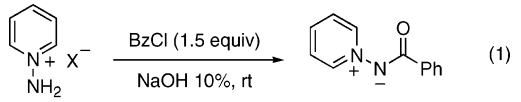
Abstract: An efficient two-step synthesis of *O*-(2,4-dinitrophenyl)hydroxylamine is described along with a comparison of its aminating efficiency with *O*-mesitylenesulfonylhydroxylamine (MSH). It was used in an expedient *N*-amination/benzoylation procedure involving various substituted pyridines, leading to polysubstituted *N*-benzoyliminopyridinium ylides, and the scope of its amination power was studied.

In our research program directed toward the development of new methods for the synthesis of substituted piperidines, we recently reported a highly regioselective addition of nucleophiles to the 2-position of *N*-benzoyliminopyridinium ylides.[1] These compounds were also shown to be useful precursors to various novel heterocyclic compounds, mainly through 1,3-dipolar cycloaddition reactions and photochemical rearrangments.[2] The common precursor for the synthesis of these compounds is the corresponding *N*-aminopyridinium salt (eq 1).



1 **2**

These salts can be prepared by direct *N*-amination of the corresponding pyridine according to the procedure of Gösl, using hydroxylamine-*O*-sulfonic acid **3**.[3] The procedure has some drawbacks, including moderate yields and the necessity to use an excess of the pyridine. Other aminating reagents can be used for this transformation, the most widely known being *O*-mesitylenesulfonylhydroxylamine (MSH) **4**.[4] An alternative method for the synthesis of *N*-benzoyliminopyridinium ylides involves the reaction of Zincke salts **6** with benzoic hydrazide;

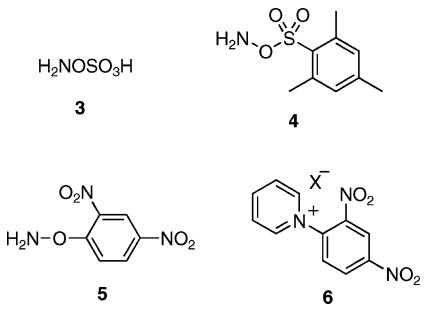
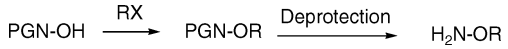


FIGURE 1. Common reagents for the synthesis of *N*-aminopyridinium ylides.

SCHEME 1



however, the scope is limited since this strategy cannot be applied to the synthesis of 2-substituted-*N*-aminopyridinium ylides.[5] A review on electrophilic aminations using MSH and related compounds has been published.[6] The main drawbacks of reagent **4** are its high cost of synthesis and instability.[7] The general method of synthesis of aminating reagents involves reaction of a *N*-protected hydroxylamine with an electrophilic reagent on the hydroxyl, followed by deprotection of the amine moiety (Scheme 1). The deprotection conditions must be compatible with the hydroxylamine functionality as well as the R group on the oxygen.

We decided to focus on *O*-(2,4-dinitrophenyl)hydroxylamine **5** because of increased *O*-aryl bond stability, permitting a broader range of *N*-protecting groups. It is reportedly more stable than *O*-sulfonyl hydroxylamine derivatives.[8] This aminating reagent and related analogues were recently used in the synthesis of novel antibacterial agents.[9] The 3-nitro analogue was also synthesized and used recently.[10] The usual method of synthesis involves the use of the expensive *N*-Boc hydroxylamine and either chloro- or fluoro-2,4-dinitrobenzene (**8a** or **8b)** as reported by Sheradsky (Scheme 2).[11]

We elected to start with *N*-hydroxyphthalimide as the *N*-protected hydroxylamine source because of its low cost. Our second goal was to use 2,4-dinitrochlorobenzene as the starting material since it is considerably cheaper than its fluoro analogue. In this paper, we wish to report the highly efficient synthesis of *O*-(2,4-dinitrophenyl)hydroxylamine **5** from inexpensive starting materials, followed by its application and scope for the amination of various aromatic heterocycles and efficient preparation of substituted *N*-benzoyliminopyridinium ylides.

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(1) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360.
(2) Reviews on *N*-iminopyridinium ylides: (a) Timpe, H.-J. *Adv. Heterocycl. Chem.* **1974**, *17*, 213. (b) Tamura, Y.; Ikeda, M. *Adv. Heterocycl. Chem.* **1981**, *29*, 71.
(3) (a) Gösl, R.; Meuwsen, A. *Chem. Ber.* **1959**, *92*, 2521. (b) Gösl, R.; Meuwsen, A. *Org. Synth.* **1963**, *43*, 1. (c) Wallace, R. G. *Aldrichimica Acta* **1980**, *13*, 3.
(4) (a) Tamura, Y.; Minamikawa, J.; Miki, Y.; Matsugashita, S.; Ikeda, M. *Tetrahedron Lett.* **1972**, *13*, 4133. (b) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239. (c) Tamura, Y.; Matsugashita, S.; Ishibashi, H.; Ikeda, M. *Tetrahedron* **1973**, *29*, 2359.
(5) (a) Tamura, Y.; Tsujimoto, N.; Mano, M. *Chem. Pharm. Bull.* **1971**, *19*, 130. (b) Tamura, Y.; Miki, Y.; Honda, T.; Ikeda, M. *J. Heterocycl. Chem.* **1972**, *9*, 865. (c) Knaus, E. E.; Redda, K. *J. Heterocycl. Chem.* **1976**, *13*, 1237.
(6) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
(7) Ning, R. Y. *Chem. Eng. News* **1973**, *51*, 37.
(8) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947.
(9) Boyles, D. C.; Curran, T. T.; Parlett, R. V. *Org. Proc. Res. Dev.* **2002**, *6*, 230.
(10) Miyazama, E.; Sakamoto, T.; Kikugawa, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 594.
(11) (a) Sheradsky, T. *J. Heterocycl. Chem.* **1967**, *4*, 413. (b) Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 3833.

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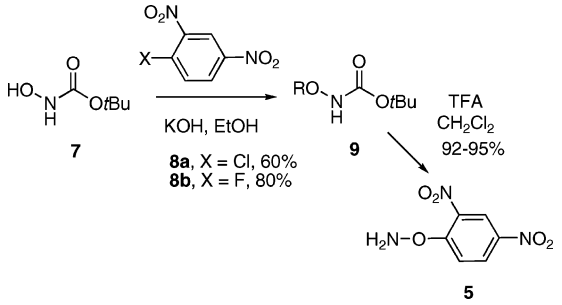
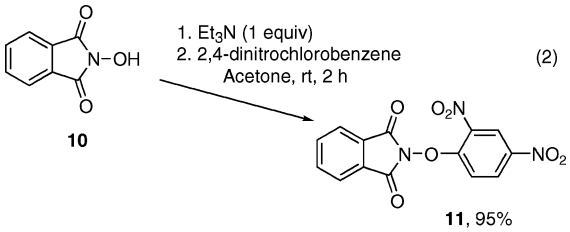
SCHEME 2



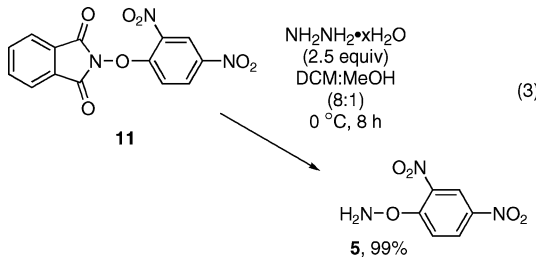
The nucleophilic aromatic substitution of chloro-2,4-dinitrobenzene (**8a**) by nucleophilic attack of *N*-hydroxyphthalimide was easily achieved in 95% yield in the presence of triethylamine in acetone (eq 2). Under these



(2)

reaction conditions, the *N*,*O*-disubstituted product **11** was obtained in excellent yield, without the need for further purification. These conditions played an important role for the feasibility of the substitution reaction. Earlier reports had previously shown that the potassium alkoxide derived from **10** led to a much lower yield for the substitution reaction[12] and that a fluoro substituent (**8b**) on the electrophilic component was mandatory if triethylamine was to be used as the base.[13]

The deprotection of *N*-phthalimido-*O*-aryl-substituted hydroxylamines was recently reported by Sharpless.[14] However, in our case, the high electrophilicity of the resulting hydroxylamine led to a low isolated yield of the desired compound. By using milder hydrazinolysis conditions we were able to deprotect the hydroxylamine in nearly quantitative yield (eq 3). The aminating reagent is obtained in sufficiently high purity that it can be used without any further purification.

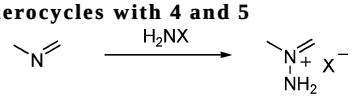


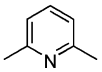
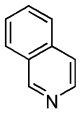
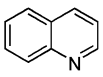
(3)

With an efficient synthesis in hand, we then developed optimal conditions for the amination reaction. A report by Tamura et al.[4b] showed **5** to have low aminating power toward pyridine, but we found that by heating at 40 °C in acetonitrile for 12 h, **5** was as efficient as MSH to

(12) Ilvespää, A. O.; Marxer, A. *Helv. Chim. Acta* **1963**, *225*, 2009.
(13) Rougny, A.; Daudon, M. *Bull. Soc. Chim. Fr.* **1976**, *5*, 833.
(14) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001**, *3*, 139.

TABLE 1. Comparison of Amination Yields of Various Aromatic Heterocycles with 4 and 5



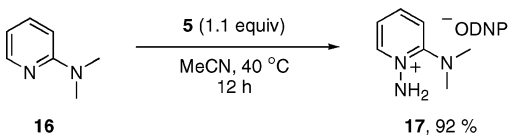
Substrate	with **5** Yield(%)[a]	with **4** Yield(%)	Ref. for **4**	Product
	98	80	4a	**13a**
	96	89	4a	**13b**
	99	70	4c	**13c**
	95	67	4c	**13d**

[a] See supporting info for experiment details.

aminate various aromatic heterocycles, as can be seen in Table 1.

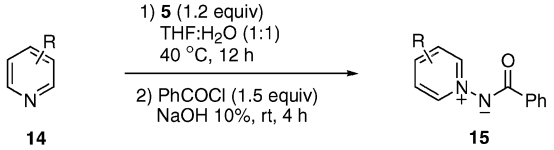
We then optimized a one-pot amination/benzoylation procedure for the synthesis of a variety of substituted *N*-benzoyliminopyridinium ylides (Table 2). The amination was done in a 1:1 mixture of THF and water at 40 °C. The use of water as a cosolvent accelerated the reaction, as shown by Yamamoto.[15] It is postulated that a stabilization of the S_N2 transition state occurs by a hydrogen bond with water. The reactions were usually allowed to react for 12 h for reproducibility sake; however, as illustrated with pyridine (entries 1−3), the reaction was nearly quantitative after 4 h. Following the amination, the reaction mixture was diluted with aqueous sodium hydroxide and treated with 50% excess of benzoyl chloride to effect the benzoylation of the pyridinium ylide. Under these conditions, the *N*-benzoyliminopyridinium ylides were obtained from the corresponding pyridines in excellent yields. The amination is high yielding with many substrates, including 2-alkyl-monosubstituted and 2,6-disubstituted pyridines (entries 5−7). The methodology is also compatible with amino-substituted pyridine (entry 9). Quinoline and isoquinoline were also transformed in high yields (entries 12 and 13); however, following amination, they were first treated with benzoyl chloride for 30 min before addition of the aqueous sodium hydroxide solution to obtain high yields. The normal procedure led to decomposition. The modest yield obtained for pyrazine (entry 11) is due to the low conversion of amination. In many cases, the *N*-benzoyliminopyridinium ylide is obtained in sufficiently high purity that it did not require any further purification.

Synthesis of *N*-benzoyliminopyridinium ylide from 2-amino-substituted pyridine proved to be problematic. However, as seen in eq 4, the amination step proceeds with excellent yield.

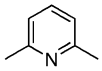
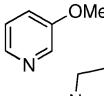
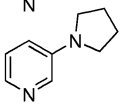
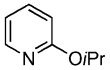
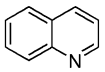
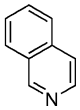


(4)

TABLE 2. Synthesis of *N*-Benzoyliminopyridinium Ylide Derivatives



14 **15**

Entry	Pyridine	Yield (%)[a]	Product
1[b]		61	
2[c]		96	**15a**
3		96	
4		99	**15b**
5		98	**15c**
6		93	**15d**
7		95	**15e**
8		94	**15f**
9		91	**15g**
10		54	**15h**
11		43	**15i**
12		93	**15j**
13		94	**15k**

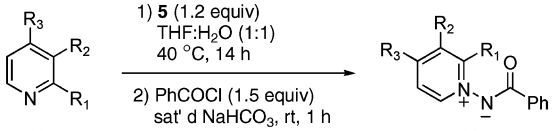
[a] Isolated yield after work-up, recrystallization or flash chromatography. [b] Reaction time is 1 h. [c] Reaction time is 4 h.

To test the scope and limitations of **5**, we examined the amination of pyridines bearing electron-withdrawing groups at various positions; the results are summarized in Table 3. 2-Substituted pyridines failed to react with **5** under various conditions (entries 1−3). 3-Substituted pyridines (entries 4−7) were more difficult to aminate, the worst case being 3-cyanopyridine (entry 5), where only traces of amination were observed. Although the amination of 4-substituted pyridines proceeded more easily, we observed the same trend, that the cyano-substituted pyridine was the most difficult to aminate. In all cases, the yields of the pyridinium ylides were directly related to the conversion of amination observed.

In conclusion, we have developed a highly efficient and inexpensive synthesis of *O*-(2,4-dinitrophenyl)hydroxylamine. It is a good alternative to MSH for the amination of various hetereoaromatics, being noticeably more stable and cheaper. This aminating reagent was applied to a one-pot amination/benzoylation procedure leading to substituted *N*-benzoyliminopyridium ylides in excellent yields. We also showed the scope of its amination efficiency. These compounds are useful starting materials for the synthesis of polysubstituted piperidines.

(15) Yamamoto, F.; Oae, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 77.

TABLE 3. Synthesis of *N*-Benzoyliminopyridinium Ylides from Electron-Poor Pyridines



18 **19**

Entry	R_1	R_2	R_3	Yield(%)[a]	Product
1	F	H	H	0	**19a**
2	Cl	H	H	0	**19b**
3	CN	H	H	0	**19c**
4	H	Cl	H	94	**19d**
5	H	CN	H	<5	**19e**
6	H	COPh	H	49	**19f**
7	H	CO_2Me	H	67	**19g**
8	H	H	CN	42	**19h**
9	H	H	COPh	75	**19i**
10	H	H	CO_2Me	85	**19j**

[a] See Supporting Information for experiment details.

Experimental Section

2-(2,4-Dinitrophenoxy)-1*H*-isoindole-1,3(2*H*)-dione (11). Triethylamine (21.5 mL, 0.154 mol) was added in one portion to a suspension of *N*-hydroxyphthalimide (25.0 g, 0.153 mol) in 500 mL of acetone, and the mixture was stirred at room temperature. The reaction mixture turned dark red, and the *N*-hydroxyphthalimide slowly dissolved. The reaction was stirred until it became a homogeneous solution (ca. 10 min). 2,4-Dinitrochlorobenzene (31.0 g, 0.153 mol) was then added in one portion, and the reaction was stirred at room temperature for 2 h. After this time, a bright yellow suspension was formed, and the reaction mixture was poured into 500 mL of ice water. The precipitate was filtered and washed three times with 100 mL of cold MeOH. The solid was compressed and washed with three 100-mL portions of hexanes and dried under vacuum to afford **11** as an off white solid (48.0 g, 95% yield): R_f 0.92 (50% EtOAc/Hexanes); mp 186 °C, lit. mp 186 °C;[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 2.6 Hz, 1H), 8.44 (dd, J = 9.3, 2.7 Hz, 1H), 8.03−7.97 (m, 2H), 7.95−7.90 (m, 2H), 7.46 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 156.7, 143.4, 137.5, 136.0, 129.7, 128.9, 124.9, 122.8, 116.0; IR (neat) 3094, 1732, 1600, 1523, 1347, 870 cm^{-1}; LRMS (APCI, Neg) *m*/*z* calcd for $C_{14}H_7N_3O_7$ $[M - H]^-$ 328.0, observed 328.0.

***O*-(2,4-Dinitrophenyl)hydroxylamine (5).** A solution of hydrazine hydrate (10.0 mL, 0.177 mol) in 60 mL of MeOH was added in one portion to a solution of **11** (20.0 g, 60.7 mmol) in 400 mL of CH_2Cl_2 at 0 °C. The reaction mixture rapidly became bright yellow, and a precipitate was formed. The suspension was allowed to stand at 0 °C for 8 h, cold aqueous HCl (1 N, 400 mL) was added, and the reaction was shaken rapidly at 0 °C. The mixture was rapidly filtered through a loose cotton plug on a Büchner funnel, and the precipitate was washed three times with 50 mL of MeCN. The filtrate was poured into a separatory funnel, and the organic phase was separated. The aqueous phase was extracted twice with 100 mL of CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, affording **5** (12.1 g, 99% yield, 95% pure as determined by ^{1}H NMR using an internal standard) as an orange solid. An analytically pure sample can be obtained by

recrystallization from EtOH: R_f 0.39 (50% EtOAc/Hexanes); mp 112 °C, lit. mp 112 °C;[4b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, J = 2.7 Hz, 1H), 8.44 (dd, J = 9.4, 2.7 Hz, 1H), 8.07 (d, J = 9.4 Hz, 1H), 6.42 (s(br), 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 140.8, 136.5, 129.6, 122.2, 116.6; IR (neat) 3323, 3259, 3118, 1603, 1516, 1339, 834, 742 cm^{-1}; LRMS (APCI, Neg) m/z calcd for $C_6H_5N_3O_5$ $[M - H]^-$ 198.0, observed 198.0.

General Amination/Benzoylation Procedure. *N*-Benzoyliminopyridinium Ylide (15a). Pyridine (0.100 mL, 1.24 mmol) and **5** (272 mg, 1.36 mmol) were added to 0.5 mL of a (1:1) mixture of H_2O and THF. The reaction flask was sealed, and the resulting suspension was stirred at 40 °C for 12 h. During this period, the reaction mixture turned dark red. The reaction was poured into aqueous NaOH (2.5 N, 6 mL) at room temperature, and benzoyl chloride (0.215 mL, 1.84 mmol) was slowly added. After 4 h, the reaction was diluted with 5 mL of H_2O and extracted three times with 10 mL of $CHCl_3$. The combined organic phases were washed once with 5 mL of 2.5 N NaOH. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording **15a** as a beige solid (236 mg, 96% yield): mp 174 °C, lit. mp 179 °C;[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 5.9 Hz, 2H), 8.16 (d, J = 5.7 Hz, 2H), 7.87 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.0 Hz, 2H), 7.48−7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 143.5, 137.4, 130.3, 128.1, 128.0, 126.1; IR (neat) 1548, 1465, 1332, 762, 710 cm^{-1}; HRMS (MAB) m/z calcd for $C_{12}H_{10}N_2O$ [M] 198.0793, observed 198.0798.

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Supporting Information Available: General experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Epsztajn, J.; Lunt, E.; Katritzky, A. R. *Tetrahedron* **1970**, *26*, 1665.