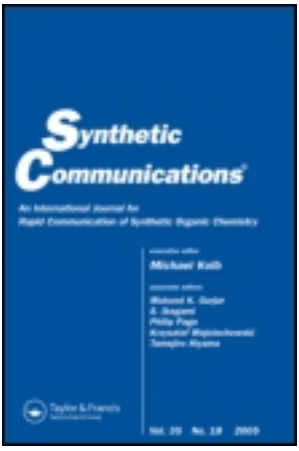


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

MILD AND CONVENIENT ONE POT SYNTHESIS OF N-HYDROXYIMIDES FROM N-UNSUBSTITUTED IMIDES

Cathy Einhorn [a], Jacques Einhorn [a] & Céline Marcadal-Abbadi [a]
[a] Université Joseph Fourier, Laboratoire de Chimie Biomimétique, LEDSS/UMR CNRS 5616, Grenoble, BP 53 - 38041, France
Published online: 16 Aug 2006.

To cite this article: Cathy Einhorn , Jacques Einhorn & Cline Marcadal-Abbadi (2001) MILD AND CONVENIENT ONE POT SYNTHESIS OF N-HYDROXYIMIDES FROM N-UNSUBSTITUTED IMIDES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:5, 741-748, DOI: 10.1081/SCC-100103264

To link to this article: http://dx.doi.org/10.1081/SCC-100103264

SYNTHETIC COMMUNICATIONS, 31(5), 741–748 (2001)

MILD AND CONVENIENT ONE POT SYNTHESIS OF *N*-HYDROXYIMIDES FROM *N*-UNSUBSTITUTED IMIDES

Cathy Einhorn,* Jacques Einhorn, and Céline Marcadal-Abbadi

Laboratoire de Chimie Biomimétique, LEDSS/UMR CNRS 5616, Université Joseph Fourier, BP 53 – 38041 Grenoble, France

ABSTRACT

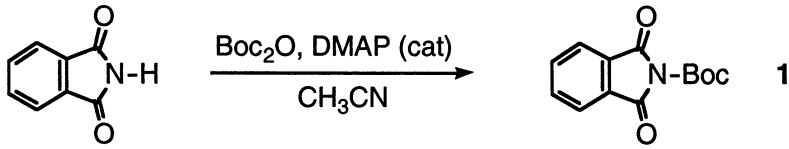
A new, one pot synthesis of various *N*-hydroxyimides from *N*-unsubstituted imides is described. Imides are first transformed into their *N*-Boc derivatives, which are next reacted with aqueous hydroxylamine, providing crystalline hydroxylammonium salts of the corresponding *N*-hydroxyimides. Filtration and acidic workup affords pure *N*-hydroxyimides.

N-Hydroxyimides are very useful and versatile intermediates in organic synthesis. For example, *N*-hydroxysuccinimide has been used in racemisation-free peptide coupling procedures.[1] *N*-Hydroxyphthalimide is useful as an *N*,*N* diprotected form of hydroxylamine, allowing the synthesis of *O*-substituted hydroxylamines.[2] *N*-hydroxyphthalimide has been recognized as a valuable catalyst for the oxidation of various organic compounds under mild conditions.[3] We have also reported recently the

* Corresponding author. Fax: 33 4 76 51 48 36; E-mail: Cathy.Einhorn@ujf-grenoble.fr

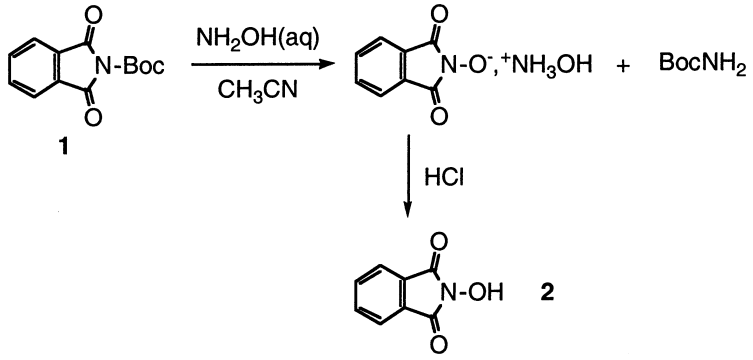
electrocatalytic properties of variously substituted *N*-hydroxyphthalimides,[4a] as well as the synthesis of the first axially chiral *N*-hydroxyimides, promising asymmetric catalysts.[4b] *N*-Hydroxyphthalimide mediated oxidations involve the corresponding phthalimide *N*-oxyl, a fairly stable but highly reactive, nitroxide-type, free radical.

Whereas sterically crowded amines can easily be oxidized to hydroxylamines or even directly to nitroxides,[5] *N*-unsubstituted imides cannot be oxidized to *N*-hydroxyimides nor to *N*-oxyl radicals. Therefore, the imide functional group has generally not been considered as a convenient precursor of the corresponding *N*-hydroxyimide. We report herein a non-oxidative synthesis of *N*-hydroxyimides from *N*-unsubstituted imides. Our approach is related to a procedure known for a long time and described by Nefkens who prepared *N*-hydroxyphthalimide by reaction of *N*-(ethoxycarbonyl)-phthalimide with hydroxylamine and triethylamine in refluxing ethanol.[6] *N*-(Ethoxycarbonyl)-phthalimide (Nefkens Reagent) was prepared in a first step by reacting ethyl chloroformate in DMF with potassium phthalimide or with phthalimide and triethylamine.[7] As our aim was to develop a one pot procedure, operating under mild conditions, we first investigated the transformation of phthalimide into various *N*-carbamoyl- or *N*-sulfonylimides. The preparation of *N*-(*tert*-butoxycarbonyl)-phthalimide was particularly simple and efficient using di-*tert*-butyldicarbonate and a small amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) in acetonitrile at room temperature. A 97% of *N*-Boc derivative **1** was isolated alter a very simple workup (Scheme l).[8]



Scheme 1.

Gratifyingly, **1** was an excellent precursor of *N*-hydroxyphthalimide **2**: when an acetonitrile solution of **1** was treated with a commercial aqueous solution of hydroxylamine at room temperature, the solution rapidly turned orange. After stirring overnight an orange precipitate formed which was probably the hydroxylammonium salt of *N*-hydroxyphthalimide.[9] Filtration and acidic workup of the precipitate furnished pure **2**. Soluble *tert*-butylcarbamate **3** byproduct was eliminated in the filtrate (Scheme 2).



Scheme 2.

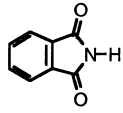
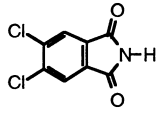
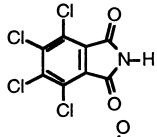
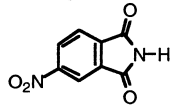
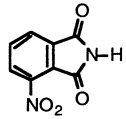
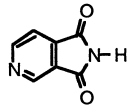
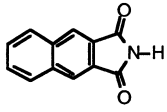
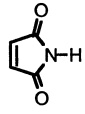
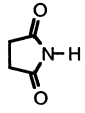
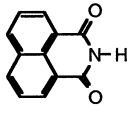
The whole synthesis was easily amenable to a straightforward one pot procedure: after completion of the first step, hydroxylamine was directly added to the reaction medium and the final product isolated as its hydroxylammonium salt without the need of any purification step. It proved to be fairly general, provided that the amounts of di-*tert*-butyldicarbonate and of DMAP were adapted to each case (TLC control for the completion of the first step): variously substituted *N*-hydroxyphthalimides have been obtained in very good yields (Table, entries 1–5). *N*-hydroxyimides with heterocyclic or naphtalenic fused rings have also been synthetised with nearly quantitative yields (entries 6,7). Although the procedure failed in the case of maleimide (entry 8), it seems efficient for the synthesis of aliphatic or six membered ring *N*-hydroxyimides (entries 9 and 10).

In summary, this procedure offers a new and straightforward access to *N*-hydroxyimides from *N*-unsubstituted imides. Its mildness and efficiency should render it of great value in the case of stereochemically labile compounds[4b] or of compounds with sensitive functionalities that do not allow the use of more classical methods.

EXPERIMENTAL

Imides, di-*tert*-butyldicarbonate, 4-*N*,*N*-dimethylaminopyridine and hydroxylamine (50 wt % in water) were commercial grade and were used without purification. Acetonitrile was dried over 4 Å molecular sieve prior to use. Analytical thin layer chromatography (TLC) was performed using Merck 60F 254 plates. Visualisation of the developed chromatogram was performed by UV absorbance or ethanolic phosphomolybdic acid. Infrared spectra were recorded on a Perkin Elmer IR 397 or a Nicolet Impact 400

Table.

Entry	Imide	Boc_2O (eq)	DMAP (mol %)	Yield[a]	mp	(mp litt)
1		1.1	1	92	232–233	(233)[b]
2		1.5	1	100	198–200	(195–197)[10]
3		2.2	10	97	252–254	(254)[11]
4		1.1	5	99	167–169.5	(168–170)[12]
5		1.1	5	94	159–162	
6		1.5	2	100	233	(232–233)[13]
7		1.1	1	94	248–249	
8		1.1	1	–	–	
9		1.1	1	83	95–96	(95–98)[b]
10		1.5	10	80	281–283	(284)[b]

[a]Yield of isolated N-hydroxyimide.
[b]Melting point of a commercial sample.

spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC200 or a Bruker WM250 spectrometer (200 and 250 MHz respectively). Chemical shifts are reported in ppm on the δ scale relative to tetramethylsilane (TMS) as an internal standard.^{13}C NMR spectra were also recorded on a Bruker AC200 or a Bruker WM250 (50 and 62.5 MHz respectively) with complete proton decoupling. Chemical shifts are reported in ppm relative to tetramethylsilane on the δ scale. Mass spectra were obtained on a Nermag mass spectrometer. Melting points have been determined on a Büchi 530 apparatus and are uncorrected. Elemental analyses were performed at the Service Central d'Analyses of the C.N.R.S. in Vernaison.

N-(*tert*-Butoxycarbonyl)-phthalimide 1

To a suspension of phthalimide (1.47 g, 10 mmol) in 5 ml of anhydrous acetonitrile, at room temperature, were added di-*tert*-butyldicarbonate (2.29 g, 10.5 mmol), followed by DMAP (12 mg, 1 mol%). Fast CO_2 evolution was accompanied by progressive dissolution of the phthalimide. After 30 min at room temperature an homogeneous solution was obtained. TLC (dichloromethane-ethyl acetate 9:1) indicated no remaining starting material. Solvent was removed under reduced presure. The remaining solid was recrystallized from hexane-ethyl acetate (9:1). Compound **1** (2.4 g, 97%, in two crops) was obtained as slightly beige plates; mp 97–98°C (litt[8] 97.4°C). ^{1}H NMR ($CDCI_3$) δ 7.95–7.80 (m, 4H) 1.63 (s, 9H).

N-Hydroxyphthalimide 2

To a solution of **1** (1.235 g, 5 mmol) in 5 ml of acetonitrile at room temperature was added an aqueous solution of hydroxylamine (0.61 ml of a 50 wt % aqueous solution, 10 mmol). An orange colour developed rapidly. After stirring the mixture overnight at room temperature, an orange precipitate had formed. Addition of 10 ml of ether allowed the precipitation of all the orange material, which was filtered, washed with ether and dried. A yellowish-orange powder (843 mg) was obtained, which corresponds to a 95% yield of hydroxylammonium salt of **2**.[9] This salt was dispersed in 15 ml of water and diluted HCl was added until pH 1. The aqueous medium was extracted with ethyl acetate (3×20 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure, leaving an almost colourless solid (712 mg, 100% from the hydroxylammonium salt), mp 232–233°C. Usual spectroscopic data were identical to those of a commercial sample.

General One Pot Procedure for the Synthesis of *N*-Hydroxyimides

To a suspension of imide (10 mmol) in 5 ml of acetonitrile at room temperature were added di-*tert*-butyldicarbonate (1.1–2.2 eq, see table) followed by DMAP (1−10 mole%, see Table). Evolution of CO_2 was accompanied by the dissolution of the imide. In some cases, the *N*-Boc derivative crystallized from the reaction medium. Progress of the reaction was monitored by TLC. When no starting material remained, an aqueous solution of hydroxylamine (0.61 ml of a 50 wt % aqueous solution, 10 mmol) was added. After stirring the mixture overnight at room temperature, addition of 10 ml of ether led to the precipitation of most of the hydroxylammonium salt of the *N*-hydroxyimide. The solid was filtered, washed thoroughly with ether and dried. It was next dispersed in 15 ml of water and diluted HCl was added until pH 1. *N*-Hydroxyimides of low solubility in aqueous media were filtered, washed with water and dried. In the case of more water-soluble *N*-hydroxyimides, the aqueous phase was saturated with NaCl and extracted several times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. *N*-Hydroxyimides so obtained were generally of sufficient purity for most synthetic purposes. Analytically pure samples were obtained after recrystallisation from the suitable solvent or sublimation in vacuum.

4,5-Dichloro-*N*-hydroxyphthalimide

Pale yellow powder, 2.32 g, 100%; mp 198–200°C after sublimation (litt[10] 195-197°C). ^{1}H NMR (200 MHz) δ (DMSO *d6*) 8.10 (s, 2H), 11.03 (s, 1H); ^{13}C NMR (62.5 MHz) δ (DMSO *d6*) 125.2, 128.8, 137.2, 162.4; IR (KBr) cm^{-1} 3514, 3453, 1715, 1384.

3,4,5,6-Tetrachloro-*N*-hydroxyphthalimide

Orange powder, 2.76 g, 97%; mp 252–254°C after sublimation (litt[11] 254°C). ^{1}H NMR (200 MHz) δ (DMSO *d6*) 11.22 (s, 1H); ^{13}C NMR (62.5 MHz) δ (DMSO *d6*) 125.8, 127.9, 166.1, 171.2; IR (KBr) cm^{-1} 3586, 3494, 1734, 1370.

4-Nitro-*N*-hydroxyphthalimide

Yellow crystals, 2.06 g, 99%; mp 167-169.5°C, after recrystallisation from ethanol (litt[12] 168–170°C). ^{1}H NMR (200 MHz) δ (DMSO *d6*)

8.01–8.66 (m, 3H), 11.14 (s, 1H); ^{13}CNMR (62.5 MHz) δ (DMSO *d6*) 117.6, 124.4, 129.6, 130.3, 133.8, 151.3, 162.4, 162.5; IR (KBr) cm^{-1} 3147, 1727, 1545, 1347.

3-Nitro-*N*-hydroxyphthalimide

Yellow powder, 1.95 g, 94%; mp 159–162°C, after sublimation. ^{1}H NMR (200 MHz) δ (DMSO *d6*) 7.98–8.27 (m, 3H), 11.11 (s, 1H); ^{13}C NMR (62.5 MHz) δ (DMSO *d6*) 120.7, 126.7, 128.3, 130.7, 136.1, 143.9, 159.7, 162.1; IR (KBr) cm^{-1} 3147, 1717, 1545, 1547; MS (DCI, NH_3 + isobutane) m/z 226 ($MH^+ + NH_3$, 100%). Anal. Calcd. for $C_8H_4N_2O_5$: C, 46.16; H, 1.94; N, 13.46. Found: C, 45.94; H, 1.96; N, 13.57.

N-Hydroxy-3,4-pyridinedicarboximide

Pale yellow crystals, 1.64 g, 100%; mp 233°C, after recrystallisation from ethanol (litt[13] 232–233°C). ^{1}H NMR (200 MHz) δ (DMSO *d6*) 7.81–8.08 (m, 3H), 11.04 (s, 1H); ^{13}C NMR (50 MHz) δ (DMSO *d6*) 116.5, 123.1, 136.6, 143.2, 156.1, 162.8, 163.3; IR (KBr) cm^{-1} 3500, 1721, 1431.

N-Hydroxy-2,3-naphtalenedicarboximide

Pale yellow crystals, 2 g, 94%; mp 248–249°C, after recrystallisation from ethanol. ^{1}H NMR (200 MHz) δ (DMSO *d6*) 7.72–8.43 (m, 6H), 10.97 (s, 1H); ^{13}C NMR (50 MHz) δ (DMSO *d6*) 124.3, 124.7, 129.3, 130.3, 134.9, 163.6; IR (KIBr) cm^{-1} 3450, 1708, 1448; MS (DCI, NH_3 + isobutane) m/z 215 (MH_2^+, 100%), 231 ($MH^+ + NH_3$, 93%). Anal. Calcd. for $C_{12}H_2NO_5$: C, 67.59; H, 3.31; N, 6.57. Found: C, 67.37; H, 3.29; N, 6.59.

N-Hydroxysuccinimide

Colourless crystals, 0.95 g, 93%; mp 95–96°C, after recrystallisation from ethyl acetate. Usual spectroscopic data identical to those of a commercial sample.

N-Hydroxy-1,8-naphtalenedicarboximide

Yellows crystals, 1.71 g, 80%; mp 282–284°C, after recrystallisation from ethanol. Usual spectroscopic data identical to those of a commercial sample.

REFERENCES AND NOTES

1. (a) Anderson, G.W.; Zimmerman, J.E.; Callahan, F.M. *J. Am. Chem. Soc.* **1964**, *86*, 1839–1842. (b) Zimmerman, J.E.; Anderson, G.W. *J. Am. Chem. Soc.* **1967**, *89*, 7151–7152.
2. See for example: (a) Rougny, A.; Daudon, M. *Bull. Soc. Chim.* **1976**, 833–838. (b) Ace, K.W.; Hussain, N.; Lathbury, D.C.; Morgan, D.O. *Tetrahedron Lett.* **1995**, *36*, 8141–8144. (c) Bonaccorsi, F.; Giorgi, R. *Synthetic Commun.* **1997**, *27*, 1143–1147.
3. (a) Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J.L. *Chem, Commun.* **1997**, 447–448 and references cited therein. (b) Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem Commun.* **1999**, 727–728. (c) Matsunaka, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1999**, *40*, 2165–2168. (d) Eikawa, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1999**, *64*, 4676–4679.
4. (a) Gorgy, K.; Lepretre, J.C.; Saint-Aman, E.; Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J.L. *Electrochemica Acta.* **1998**, *44*, 385–393. (b) Einhorn, C.; Einhorn, J.; Marcadal-Abbadi, C.; Pierre, J.L. *J. Org. Chem.* **1999**, *64*, 4542–4546.
5. Aurich, H.G. In *Nitrones, Nitronates and Nitroxides*, Patai, S.; Rappoport, Z. Eds; John Wiley & Sons : New York, 1989, p. 318.
6. Nefkens, G.H.L.; Tesser, G.I. *J. Am. Chem. Soc.* **1961**, *83*, 1263.
7. Nefkens, G.H.L. *Nature*, **1960**, *185*, 309–310.
8. *N*-Boc pthalimide has recently been described, see: Tavecchia, P.; Marazzi, A.; Dallanoce, C.; Trani, A.; Ciciliato, I.; Ferrari, P.; Selva, E.; Ciabatti, R. *J. Antibiot.* **1996**, *49*, 1249–1257. In our procedure acetonitrile was used in the place of dioxane and no triethylamine was necessary.
9. This salt has not been characterized. It may be in equilibrium with *o*-(*N*-hydroxycarbamoyl)-benzohydroxamic acid; see: Khan, M.N. *J. Chem. Sec. Perkin Trans. II* **1988**, 213–219.
10. Villiger, V. *Chem. Ber.* **1909**, 3529–3549.
11. Orndorff, W.R. *J. Am. Chem. Soc*, **1912**, *48*, 495–498.
12. Chan, C.L.; Lien, E.J.; Tokes, Z.A. *J. Med. Chem.* **1987**, *30*, 509–514.
13. Hurd, C.R.; Bethurne, V.G. *J. Org. Chem.* **1970**, *35*, 1471–1475.

Received in the U.K. March 15, 2000