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On the Preparation of Amine *N*-Oxides by Using Dioxiranes

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Abstract: The reaction of heterocyclic aromatic amines, anilines and tertiary amines with dimethyldioxirane (DMD) was examined. Treatment of heterocyclic aromatic amines and anilines with a slight excess of DMD at 0 °C afforded the corresponding *N*-oxides in quantitative conversion yields. In addition, the oxidation was chemoselective in the presence of carbon-carbon double bonds. On the other hand, most of the tertiary amines assayed did afford also quantitative yields of the corresponding *N*-oxides, although reaction conditions, in particular regarding the amount of DMD required, depended on each substrate. Additional studies carried out on selected substrates suggested that certain *N*-oxides derived from tertiary amines deactivate DMD. © 1997 Elsevier Science Ltd.

In addition to the oxidation of unsaturated carbon-carbon moieties and the hydroxylation of C-H bonds, the reactivity with compounds containing heteroatoms (N, S, P) has constituted a major subject of interest in dioxirane chemistry.[1] Concerning the amino derivatives, the first report on the reaction of dioxiranes with amines corresponded to the conversion of pyridine into the corresponding *N*-oxide by using the dioxirane from cyclohexanone generated *in situ*.[2] The availability of isolated dimethyldioxirane (DMD) solutions facilitated the more detailed studies performed on the reactivity of primary [3-7] and secondary amines [8-10] employing this oxidation reagent. However, the cases of tertiary amines and heterocyclic aromatic amines had not received the same attention. Murray, in his classic review on the chemistry of dioxiranes, pointed out the need of critical reaction conditions for obtaining good conversion yields of amine *N*-oxides, although no specified examples were given. Furthermore, he postulated that in the presence of an excess of DMD, certain *N*-oxides formed an unstable intermediate which decomposed regenerating the starting amine with the concomitant release of oxygen. The structure of this intermediate and the nature of the oxygen evolved were not elucidated (ref. 1b). Recently, Adam et al. were able to detect the release of singlet oxygen in the oxidation of 4-*N*,*N*-dimethylaminopyridine, which gave a strong support to the hypothesis suggested by Murray.[11] In addition, the same group found evidence to postulate a S_N2 mechanism for the reaction of dioxiranes with heteroarenes.[12] In the organometallic chemistry domain, Christian et al. reported the DMD oxidation of tricarbonylchromium (0) complexes of *ortho*-substituted a-methylbenzyldimethylamines to give enantiomerically pure complexes of *ortho*-substituted styrenes via a chemoselective formation of the corresponding *N*-oxides and subsequent Cope reaction.[13,14]

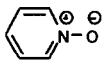
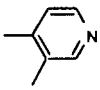
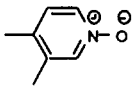
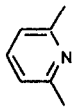
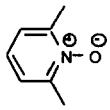
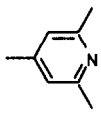
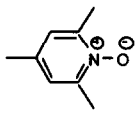
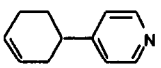
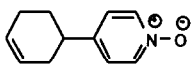
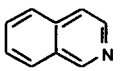
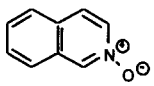
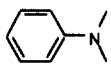
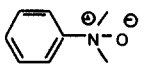
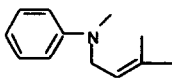
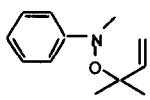
In the context of a study on the chemoselective oxidation of alkenamines carried out in our laboratory, several amine *N*-oxides were required as model compounds.[15] For this purpose, selected tertiary amines were treated with DMD, but the results obtained were erratic enough to demand further studies for establishing the scope of this reaction. The present paper reports a full account on the preparation of amine *N*-oxides by using dioxiranes. To this aim, the reactivity of a collection of substrates including aromatic heterocyclic amines, anilines and tertiary amines was examined. In some cases, the presence of a carbon-carbon double bond in the test substrates was also contemplated for obtaining additional information on the chemoselectivity features of dioxirane reactivity. Although amine *N*-oxides can be synthesized by a variety of conventional methods, the

practical advantages of DMD, *i.a.*, ease of manipulation, high reactivity under mild conditions and simple work-up procedures, would favor the use of this reagent for performing the above transformation. It is worth of noting that amine *N*-oxides are compounds of increasing interest as potential cytotoxines hypoxia-selective for the treatment of solid tumors.[16]

Results and Discussion

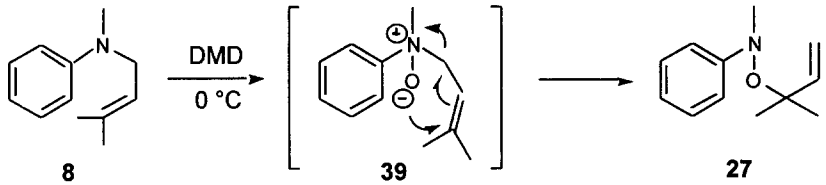
Oxidation of aromatic heterocyclic amines and anilines. The addition of a slight DMD molar excess over a solution of the amine in acetone at 0 °C led, for most of the cases assayed, to the rapid and quantitative conversion of the substrate into the corresponding *N*-oxide (Table 1).

Table 1. Oxidation of aromatic heterocyclic amines and anilines with DMD.

Substrate		Reaction product [a]	
	1		20
	2		21
	3		22
	4		23
	5[b]		24
	6		25
	7[c]		26
	8[d]		27

[a] Reactions were performed by dropwise addition of the DMD soln. in acetone (1.2 molar equiv.) over the amine maintained at 0 °C and the corresponding *N*-oxides were isolated as pure compounds in nearly quantitative yields.[b] In this case 1.0 DMD molar equiv. were used. [c] In this case 1.5 DMD molar equiv. were needed. [d] Oxidation of this aniline derivative afforded hydroxylamine ether **27**.

Three cases deserve additional comments. Under the above conditions, the reaction of pyridine **5** to give the *N*-oxide **24** was chemoselective.[17] Concerning the anilines assayed, 1.5 equivalents of DMD were required for the complete conversion of compound **7** into *N*-oxide **26**. Finally, treatment of aniline **8** with DMD afforded the hydroxylamine ether **27** as unique reaction product. We anticipated that this compound could be originated from the rearrangement of the intermediate *N*-oxide **39**. When a solution of amine **8** in $CDCl_3$ maintained at -78 °C was treated with a solution of DMD in dichloromethane,[18] and the crude reaction mixture was allowed to reach -30 °C, the formation of a new compound was observed. This intermediate was identified by NMR as the *N*-oxide **39**. Thus, in comparison with the starting amine, the shift of the absorption due to the *N*-methyl group in the ^1H NMR spectrum from 2.86 up to 3.86 ppm, and the 20 ppm shift observed in the ^{13}C NMR spectrum for both the methyl and the methylene moieties linked to the quaternary nitrogen atom, were in agreement with the structure of **39**. When the crude reaction mixture was allowed to reach room temperature, only those peaks corresponding to the rearranged compound **27** could be observed in the NMR spectra. Actually, since no other intermediate could be detected, it was assumed that the rearrangement could take place in a concerted manner as described recently by Majumdar at al.[19]



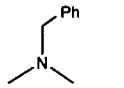
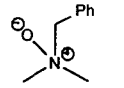
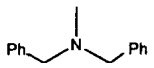
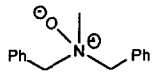
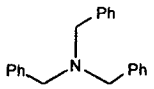
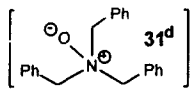
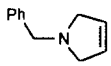
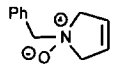
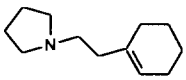
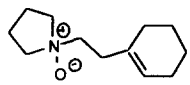
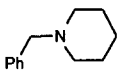
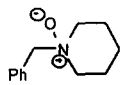
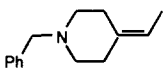
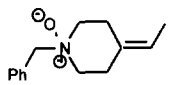
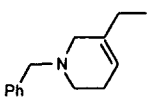
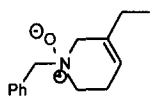
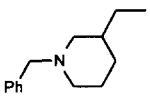
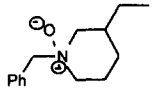
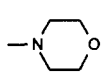
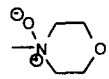
8 **39** **27**

Oxidation of tertiary amines. At this point, our next objective was the study of the oxidation of tertiary amines. Treatment of these substrates with an excess of DMD (usually within 1-2 molar equivalents) at 0 °C, led in most cases to the formation of the corresponding *N*-oxide in quantitative conversion yields (Table 2). As observed for pyridine **5**, this oxidation was chemoselective for those substrates bearing carbon-carbon double bonds.

While tributylamine underwent a facile reaction to give *N*-oxide **28**, benzylamines **10-12** showed distinctive features. The monobenzyl derivative **10** required 2 DMD equivalents to afford its corresponding *N*-oxide in quantitative yields. However, the dibenzyl derivative **11** could not be oxidized completely in spite of the DMD excesses employed (up to 5 molar equivalents), and a 1:17 amine:*N*-oxide molecular ratio was the composition of the crude reaction mixtures obtained.

The case of tribenzylamine (**12**) was noticeable: oxidation of this amine with up to 5 molar DMD equivalents led to the rapid consumption of the oxidation reagent; however, amine **12** was the major component of the crude reaction mixture and no traces of the expected *N*-oxide **31** could be detected. Actually, only minor amounts of benzaldehyde and dibenzyl nitrone were isolated as reaction products. Conversely, treatment of amine **12** with 1.5 equivalents of mCPBA led to the formation of the *N*-oxide **31** in near quantitative yield. Up to our present knowledge, this result constitutes one of the few examples of oxidation reactions where a peroxyacid shows such a higher efficiency compared to DMD. On the other hand, when the *N*-oxide **31** and DMD were allowed to react under the usual reaction conditions, a similar mixture to that obtained above was formed. All efforts carried out to detect, either chemically or spectroscopically, the possible intermediates responsible for the generation of benzaldehyde and dibenzyl nitrone were unsuccessful. In any case, the fact of obtaining the same crude reaction mixture when either the amine or the *N*-oxide was treated with DMD suggested that an interconversion between these species was taking place.

Table 2. Oxidation of tertiary amines with DMD.

Substrate		DMD (eq)	Reaction product [a]	
Bu_3N	**9**	1.2	$Bu_3\overset{\oplus}{N}-\overset{\ominus}{O}$	**28**
	**10**	2		**29**
	**11**	b		**30**
	**12**	c		**31**[d]
	**13**	2		**32**
	**14**	2		**33**
	**15**	1.2		**34**
	**16**	1.2		**35**
	**17**	2		**36**
	**18**	1.2		**37**
	**19**	1.2		**38**

[a] Reactions were carried out by dropwise addition of the indicated excess of DMD solution in acetone over the amine maintained at 0 °C and the corresponding *N*-oxides were isolated as pure compounds in nearly quantitative yields, with the exception of substrates **11** and **12**. For further details see Experimental Section. [b] In this case, treatment of **11** with 2 to 5 equivalents of DMD afforded a mixture of **11**:**30** in a 1:17 molar ratio, respectively. [c] In this case, treatment of **12** with 1 to 5 equivalents of DMD afforded a complex mixture of products from which the initial substrate was the major component. [d] *N*-Oxide **31** could be prepared by using mCPBA as oxidation reagent.

Pyrroline 13 required 2 molar equivalents of DMD to give *N*-oxide 32. When higher excesses were employed or the reaction was carried out at higher temperatures, the formation of a pyrrole derivative was also observed.

The case of amines **16** and **17** was also interesting. Both of them afforded quantitative conversion yields of their corresponding *N*-oxides upon treatment with DMD (a slight excess for **16** and 2 molar equivalents for **17**). However, all attempts for obtaining the epoxy derivatives by treatment with additional DMD excesses were unsuccessful; in fact, after 30 minutes the *N*-oxides remained unaltered but DMD had been consumed (cf. ref. 15).

In conclusion, preparation of amine *N*-oxides by using DMD is a simple and valuable procedure which takes place, in general, in quantitative conversion yields, although reaction conditions depend upon the amine used. This oxidation is chemoselective in front of carbon-carbon double bonds and it complements the methodology developed in our laboratory for the chemoselective epoxidation of alkenamines.[15] However, the scope of the reaction is restricted to those *N*-oxides that do not induce the deactivation of the oxidation reagent. In any case, the practical advantages of oxidation reactions with DMD would justify the use of this reagent as the procedure of choice for the preparation of amine *N*-oxides. Finally, the stability of DMD in the presence of the herein reported set of amine *N*-oxides has been also subject of further research and results obtained will be reported elsewhere.

Experimental Section

The IR spectra were recorded in film layer or CCl_4 solution by using a Bomen model MB120 apparatus and absorptions are given in cm^{-1}. The NMR spectra (^1H, 300 MHz; ^{13}C NMR, 75 MHz) were recorded with a Varian Unity 300 spectrometer; they were performed in neutralized $CDCl_3$ solutions and chemical shifts are given in ppm downfield from tetramethylsilane for ^1H and deuteriochloroform for ^{13}C. The GC-MS-EI spectra (70 eV) were obtained using a Fisons model MD 800 mass spectrometer coupled to a Fisons GC 8000 apparatus, which was equipped with a 25 m HP-5 capillary column. High-resolution mass spectra (HRMS) were performed on a VG Autospec-Q apparatus (Mass Spectrometry Service, CID. Elemental analyses were carried out with a Carlo Erba 1108 instrument (Microanalysis Service, CID).

DMD solutions in acetone (80 mM) were prepared as described elsewhere.[20] The concentrated, "acetone free" DMD solutions, were obtained according to the procedure developed in our laboratory.[18] Unless stated otherwise, organic extracts coming from the working up of crude reaction mixtures were dried under $MgSO_4$, filtered and evaporated to render the corresponding residues, which were purified as specified.

Amines.

Amino derivatives **1-7**, **9-13** and **19** were commercially available and used as received.

***N*-methyl-*N*-(3-methylbut-2-en-1-yl)aniline (8).** A solution of *N*-methylaniline (5 g, 47 mmol), 3,3-dimethylacrylic acid (5 g, 50 mmol), DCC (13.3 g, 65 mmol) and DMAP (0.6 g, 5 mmol) in CH_2Cl_2 (100 mL), was stirred for 48 h at 25 °C. The crude reaction mixture was filtered and the residue was purified by flash chromatography eluting with 3:1 hexane:EtOAc to render 5.5 g of the *N*-phenyl-*N*-methyl-3-methyl-2-butenamide intermediate (61% yield), as an oil [21]: ^1H-NMR: 7.42-7.22 (3 H, H_{Ar}), 7.16-7.11 (2 H, H_{Ar}), 5.46

(br, 1 H, H-2), 3.29 (s, 3 H, N-CH_3), 2.09 (d, 3 H, J = 1 Hz, CH_3), 1.65 (d, 3 H, J = 1 Hz, CH_3); ^{13}C-NMR: 167.2 (CO), 150.1 (C-4), 144.2 (C_{Ar}, C-1), 129.3 (CH), 127.0 (CH), 126.9 (CH), 117.6 (CH_{Ar}, C-4), 36.9 (N-CH_3), 27.0 (CH_3, C-5), 20.1 (CH_3, C-5'); MS: 191 (M^+, 6), 149 (8), 107 (100), 77 (15).

Following the procedure reported by Borch,[22] the above intermediate (3 g, 16 mmol) and triethyloxonium tetrafluoroborate (3.3 g, 17.5 mmol) were allowed to react in CH_2Cl_2 (6 mL) for 20 h at 20 °C. The solvent was evaporated and the salt was redissolved in anhydrous EtOH (13 mL). Then, $NaBH_4$ (0.66 g, 17.5 mmol) was added portionwise over the above solution, maintaining the temperature within -10 and 0 °C, and the mixture was stirred for 20 h at 20 °C. The crude reaction mixture was poured into H_2O, extracted with methyl *tert*-butyl ether and dried. The residue obtained after elimination of solvent was purified by flash chromatography eluting with 9:1 hexane: methyl *tert*-butyl ether to give pure compound **8** (1.8 g, 65% yield) as a colorless oil. **8** [23,24]: IR (film): 2968, 2912, 1598, 1504, 1323, 748, 690; ^{1}H-NMR: 7.20 (t, 2 H, J = 7.5 Hz, H_{Ar}-3, H_{Ar}-5), 6.74-6.64 (3 H, H_{Ar}-2, H_{Ar}-3, H_{Ar}-4), 5.19 (t, J = 6 Hz, H-2), 3.87 (d, 2 H, J = 6 Hz, H-1), 2.86 (s, 3 H, N-CH_3), 1.70 (s, 6 H, CH_3); ^{13}C-NMR: 149.7 (C_{Ar}, C-1), 134.4 (C-3), 129.0 (CH_{Ar}, C-3, C-5), 120.8 (CH_{Ar}, C-4), 116.3 (C-2), 112.9 (CH_{Ar}, C-2, C-6), 50.4 (C-1), 37.8 (N-CH_3), 25.6 (CH_3), 17.8 (CH_3); MS: 175 (M^+, 28), 160 (19), 120 (14), 107 (100), 77 (30), 69 (38).

***N*-[2-(1-Cyclohexen-1-yl)ethyl]pyrrolidine (14)**. A solution of 1,4-dibromobutane (21.6 g, 0.1 mol) in toluene (100 mL) was added dropwise to a suspension of 2-cyclohexenylethylamine (12.5 g, 0.1 mol) and $NaHCO_3$ (84 g, 1 mol) in the same solvent (250 mL), and the mixture was stirred for 7 days at 100 °C. The crude reaction mixture was poured into water and the organic fraction was washed with $NaHCO_3$ and dried. The residue obtained after elimination of solvent was purified by distillation to render amine **14** as a colorless oil (102 °C/0.3 Torr; 10.7 g, 60 % yield). **14**: IR (film): 2958, 2927, 2781, 1438, 1350, 1120; ^{1}H NMR: 5.41 (s, 1 H, H-4'), 2.52-2.46 (6 H, H-2, H-5, H-1'), 2.17-2.11 (2 H, H-2'), 1.98-1.90 (4 H, H-3, H-4), 1.78-1.73 (4 H, H-5', H-8'), 1.63-1.51 (4 H, H-6', H-7'); ^{13}C NMR: 135.1 (C-3'), 121.1 (C-4'), 54.6 (C-1'), 53.4 (C-2, C-5), 36.8 (C-8'), 27.9 (C-2'), 24.9 (C-5'), 22.7 (C-3, C-4), 22.3 (CH_2), 21.7 (CH_2); MS: 179 (M^+, 9), 84 (100). Elemental analysis for $C_{12}H_{21}N$. Calculated: C, 80.37; H 11.81; N, 7.82. Found: C, 80.34; H, 11.83; N, 7.82.

***N*-Benzylpiperidine (15)**. Benzyl bromide (0.15 mL, 2.3 mmol) was added over a suspension of piperidine (0.10 g, 1.2 mmol) and K_2CO_3 (0.32 g, 2.3 mmol) in THF (3 mL) and the mixture was stirred for 20 h at 40 °C (TLC monitoring). The crude reaction mixture was poured into $NaHCO_3$ solution, extracted with CH_2Cl_2 and dried. The residue obtained after elimination of solvent was purified by preparative TLC eluting with 7:3 hexane: methyl *tert*-butyl ether to give piperidine **15** as a colorless oil (0.13 g, 62 % yield) **15**. [25]: ^{1}H NMR: 7.38-7.19 (5 H_{Ar}), 3.48 (s, 2 H), 3.39 (t, 4 H, J = 5 Hz, H-2, H-6), 1.64-1.53 (4 H, H-3, H-5), 1.48-1.36 (2 H, H-4); ^{13}C NMR: 138.7 (C_{Ar}), 129.3 (CH_{Ar}), 128.1 (CH_{Ar}), 126.9 (CH_{Ar}, C-4), 63.8 (CH_2), 54.4 (C-2, C-6), 25.9 (C-3, C-5), 24.3 (C-4); MS: 175 (M^+, 35), 98 (57), 91 (100), 84 (45), 65 (16).

***N*-Benzyl-4-ethylidenpiperidine (16)**. A solution of BuLi (1.1 equiv.) in THF was added over a solution of ethyltriphenylphosphonium bromide (3.7 g, 10 mmol) in THF (50 mL) at -78 °C, and the mixture was stirred for 40 min at -20 °C. Then, a solution of *N*-benzyl-4-piperidone (1.89 g, 10 mmol) in THF (10 mL) was added dropwise to the red ylide solution. The mixture was stirred for 30 more minutes at -20 °C, and then until it reached room temperature and all piperidone had reacted (GC monitoring). The final crude reaction mixture

was poured into H_2O and extracted with hexane. The organic fractions were washed with $NaHCO_3$ and dried. The residue obtained after solvent elimination was purified by flash chromatography, eluting with 6:1 hexane:EtOAc to give pure amine **16** as a colorless oil (1.63 g, 81% yield). **16**: IR (film): 2947, 2935, 2898, 2794, 1454, 1132, 1028, 736, 698; ^{1}H NMR: 7.39-7.18 (5 H, H_{Ar}), 5.17 (q, 1 H, J = 6.5 Hz, CH=), 3.49 (s, 2 H, benzylic), 2.40 (t, 4 H, J = 8.5 Hz, H-2, H-6), 2.51 (t, 2 H, J = 5.5, H-3a, H-5a), 2.18 (t, 2 H, J = 5.5 Hz, H-3b, H-5b), 1.56 (d, 3 H, J = 6.5 Hz, CH_3); ^{13}C NMR: 138.8, 136.4, 129.1 (C-3, C-5), 128.1 (C-2, C-6), 126.8 (C-4), 116.2 (CH=), 63.1 (benzylic), 55.2 (CH_2), 54.4 (CH_2), 35.9 (CH_2), 27.7 (CH_2), 12.6 (CH_3); MS: 201 (M^+, 30), 124 (31), 110 (34), 91 (100). Elemental analysis for $C_{14}H_{19}N$. Calculated: C, 83.53; H 9.51; N, 6.96. Found: C, 83.55; H, 9.54; N, 6.97.

***N*-Benzyl-3-ethyl-1,2,5,6-tetrahydropyridine (17).** Following a procedure described elsewhere,[26] benzyl bromide (16.6 mL, 140 mmol) was added dropwise to a solution of 3-ethylpyridine (10 g, 93 mmol) in anh. THF (100 mL), and the mixture was maintained under reflux for 6 h. The residue obtained after elimination of solvent was recrystallized from a CH_2Cl_2:Et_2O mixture to give *N*-benzyl-3-ethylpyridinium bromide. Then, a solution of this salt (23 g) in anh. MeOH (180 mL) was treated with $NaBH_4$ (6.4 g, 0.17 mol, added portionwise), and the mixture was stirred for 2 h at 0 °C. The crude reaction mixture was poured into a NaCl solution, MeOH was evaporated under vacuum and the residue was extracted with CH_2Cl_2 and dried. Purification by flash chromatography eluting with 85:15 hexane: methyl *tert*-butyl ether afforded pure compound **17** as a colorless oil (12.3 g, 73% yield). **17** [26]: ^{1}H NMR: 7.39-7.21 (5 H, H_{Ar}), 5.44 (m, 1 H, H-4), 3.58 (s, 2 H, benzylic), 2.88 (s, 2 H, H-2), 2.50 (t, 2 H, J = 5.5 Hz, H-6), 2.13 (m, 2 H, H-5), 1.92 (qd, 2 H, J_1 = 7.5 Hz, J_2 = 1.5 Hz, $\underline{CH_2}CH_3$), 0.99 (t, 3 H, J = 7.5 Hz, $CH_2\underline{CH_3}$); ^{13}C NMR: 138.2 (C_{Ar}, C-1), 137.7 (C-3), 129.2 (C_{Ar}, C-3, C-5), 128.1 (C_{Ar}, C-2, C-6), 126.9 (C_{Ar}, C-4), 117.5 (C-4), 62.9 (benzylic), 55.9 (CH_2, C-2), 49.7 (CH_2, C-6), 27.8 (CH_2, C-5), 25.8 ($\underline{CH_2}CH_3$), 11.9 ($CH_2\underline{CH_3}$); MS: 201 (M^+, 13), 186 (13), 172 (39), 91 (100).

***N*-Benzyl-3-ethylpiperidine (18).** Following the procedure reported by Sajiki,[27] a solution of amine **17** (0.10 g, 0.5 mmol) and NH_4OAc (0.02 g, 0.25 mmol) in abs. EtOH (30 mL) was subjected to hydrogenation in the presence of 5% Pd/C (1 atm, 20 °C). When the reaction was completed (13 h, GC monitoring), the crude reaction mixture was filtered through Celite®. The residue obtained after solvent elimination was purified by flash chromatography eluting with 4:1 hexane methyl *tert*-butyl ether, to give piperidine **18** as a colorless oil (0.054 g, 53% yield). **18** [28]: ^{1}H NMR: 7.35-7.20 (5 H, H_{Ar}), 3.67 (d, 1 H, J = 13 Hz, benzylic), 3.59 (d, 1 H, J = 13 Hz, benzylic), 2.95 (d, 2 H, J = 11 Hz, H-2, H-6), 2.04-1.48 (7 H, H-2, H-6, H-3, H-4, H-5), 1.20 (m, 2 H, $\underline{CH_2}CH_3$), 1.05 (t, 3 H, J = 7.5 Hz, $CH_2\underline{CH_3}$).; ^{13}C NMR: 136.3 (C_{Ar}, C-1), 129.8 (CH_{Ar}, C-3, C-5), 128.3 (CH_{Ar}, C-2, C-6), 127.5 (CH_{Ar}, C-4), 62.6 (benzylic), 59.2 (CH_2, C-2), 53.4 (CH_2, C-6), 36.9 (CH, C-3), 30.0 (CH_2), 27.1 (CH_2), 24.5 ($\underline{CH_2}CH_3$), 11.1 ($CH_2\underline{CH_3}$).; MS: 203 (M^+, 32), 126 (28), 112 (41), 91 (100).

Oxidation of aromatic heterocyclic amines and anilines: general procedure. A solution of DMD in acetone was added dropwise to a solution of the corresponding amine (0.10 g) in CH_2Cl_2, maintained at 0 °C, and the mixture was stirred at this temperature until reaction was completed (in all cases less than an hour). The elimination of excess of reagent and solvents under vacuum afforded the *N*-oxide in nearly quantitative yields (see Table 1).

3,4-Dimethylpyridine *N*-oxide (21). In this case 1.2 DMD equivalents were needed and the *N*-oxide was isolated as a white solid. **21** [29]: ^{1}H NMR: 7.98 (s, 1 H, H_{Ar}-2), 8.90 (d, 1 H, J = 7.5, H_{Ar}-6), 6.96 (d, 1 H, J = 7 Hz, H_{Ar}-5), 2.19 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3).

2,6-Dimethylpyridine *N*-oxide (22). In this case 1.2 DMD equivalents were needed and the *N*-oxide was isolated as a white solid. **21** [29]: ^{1}H NMR: 7.30-6.95 (3 H, H_{Ar}), 2.47 (s, 6 H, CH_3).

2,4,6-Trimethylpyridine *N*-oxide (23). In this case 1.2 DMD equivalents were needed and the *N*-oxide was isolated as a white solid. **23** [30]: ^{1}H NMR: 6.88 (s, 2 H, H_{Ar}), 2.41 (s, H, *o*-CH_3), 2.19 (s, *p*-CH_3); ^{13}C NMR: 147.6 (C_{Ar}, C-2, C-6), 135.5 (C_{Ar}, C-4), 124.3 (CH_{Ar}, C-3, C-5), 19.7 (*p*-CH_3), 17.7 (*m*-CH_3).

4-(Cyclohex-3-en-yl-)pyridine *N*-oxide (24). In this case 1.0 DMD equivalents were used for minimizing double bond epoxidation and the *N*-oxide was isolated (preparative TLC, 95:5 CH_2Cl_2:MeOH) as a pale yellow oil. **24**: IR (CCl_4): 3029, 2920, 2839, 1483, 1253, 1172, 1033, 837, 655; ^{1}H NMR: 8.16 (d, 2 H, J = 7 Hz, H_{Ar}-2, H_{Ar}-6), 7.15 (d, 2 H, J = 7 Hz, H_{Ar}-3, H_{Ar}-5), 5.77 (a, 2 H, H-3', H-4'), 2.84 (m, 1 H, H-1'), 2.40-1.50 (6 H, CH_2, H-2', H-5', H-6'); ^{13}C NMR: 146.8 (C_{Ar}, C-4), 138.8 (CH_{Ar}, C-2, C-6), 127.2 (C-3'), 125.4 (C-4'), 124.4 (CH_{Ar}, C-3, C-5), 38.5 (C-1'), 32.0 (C-2'), 28.7 (C-5'), 24.9 (C-6'); MS: 175 (M^+, 3), 159 (65), 130 (30), 105 (100), 78 (25), 51(28). HRMS for $C_{11}H_{13}NO$. Calculated: 175.099714. Found: 175.099960.

***N*,*N*-Dimethylaniline oxide (26).** In this case 1.5 DMD equivalents were needed to achieve the complete conversion of amine **7**. **26** [31]: ^{1}H NMR: 7.94 (d, 2 H, J = 7.5 Hz, H_{Ar}-2, H_{Ar}-6), 7.47-7.28 (3 H, H_{Ar}-3, H_{Ar}-4, H_{Ar}-5), 3.57 (s, 3 H, CH_3).

***N*-Phenyl-*N*-methyl-*O*-(1,1-dimethyl-2-propenyl)hydroxylamine (27).** A solution of DMD in CH_2Cl_2 [18] (1 equiv.) was added to a solution of amine **8** in $CDCl_3$ at -78 °C and the reaction was monitored by NMR at -30 °C to detect the formation of the corresponding amine oxide **39** (^{1}H NMR: 7.70-7.53 (5 H_{Ar}), 5.14 (t, 1 H, J = 8 Hz, H-2), 4.57 (dd, 1 H, J_1 = 8.5 Hz, J_2 = 13 Hz, H_a-1), 4.49 (dd, 1 H, J_1 = 8 Hz, J_2 = 13 Hz, H_b-1), 3.86 (s, 3 H, NCH_3), 1.71 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3); ^{13}C NMR: 150.6, 146.3, 131.7 (CH_{Ar}, C-4), 130.6 (CH_{Ar}, C-3, C-5), 120.7 (CH_{Ar}, C-2, C-6), 110.5 (C-2), 72.4 (C-1), 56.3 (CH_3N), 26.2 (CH_3), 18.4 (CH_3)). When the crude reaction mixture reached room temperature, the formation of hydroxylamine ether **27** was observed. This compound was purified by preparative TLC eluting with 1:1 hexane: methyl *tert*-butyl ether, and isolated in near quantitative conversion yield. **27**: IR (CCl_4): 2979, 2923, 2877, 1598, 1490, 1151, 1114, 919, 763, 696; ^{1}H NMR: 7.30-7.18 (t, 2 H, J = 7.5 Hz, H_{Ar}-3, H_{Ar}-5), 7.12-7.07 (d, 2 H, J = 7.5 Hz, H_{Ar}-2, H_{Ar}-6), 6.93 (t, 1 H, J = 7 Hz, H_{Ar}-4), 6.05 (dd, 1 H, J_1 = 10.5 Hz, J_2 = 17.5 Hz, H-2), 5.16 (dd, 1 H, J_1 = 1 Hz, J_2 = 17.5 Hz, H_a-3), 5.05 (dd, 1 H, J_1 = 1 Hz, J_2 = 10.5 Hz, H_b-3), 3.03 (s, 3 H, N-CH_3), 1.35 (s, 6 H, CH_3); ^{13}C NMR: 155.2 (C_{Ar}, C-1), 143.4 (C-2), 128.4 (CH_{Ar}, C-3, C-5), 121.6 (CH_{Ar}, C-4), 116.9 (CH_{Ar}, C-2, C-6), 113.2 (C-3), 80.6 (C-1), 48.9 (CH_3N), 24.8 (CH_3); MS: 191 (M^+, 6), 123 (100), 106 (38), 77 (25), 69 (17). Elemental analysis for $C_{12}H_{17}NO$. Calculated: C, 75.34; H 8.96; N, 7.33. Found: C, 75.30; H, 8.94; N, 7.28.

Oxidation of tertiary aliphatic amines: general procedure. A solution of DMD in acetone (within 1-2 equivalents depending upon the case) was added dropwise to a solution of the corresponding amine (0.10 g) in CH_2Cl_2, maintained at 0 °C, and the mixture was stirred at this temperature until reaction was completed (in all cases less than an hour). Unless stated otherwise, treatment of the crude reaction mixture as indicated above afforded the *N*-oxide in nearly quantitative yields (see Table 2).

Tributylamine *N*-oxide (28). In this case 1.2 equivalents of DMD were needed to obtain the expected oxide as a white solid. **28** [32]: ^{1}H NMR: 3.09-3.00 (6 H, H-2), 1.80-1.65 (6 H, H-3), 1.42-1.19 (6 H, H-4), 0.906 (t, 9 H, J = 7 Hz, H-5); ^{13}C NMR: 65.8 (C-2), 25.0 (C-3), 20.0 (C-4), 13.7 (C-5).

***N,N*-dimethylbenzylamine *N*-oxide (29).** In this case 2 equivalents of DMD were needed to obtain the expected oxide as a pale yellow oil. **28** [33]: ^{1}H NMR: 7.52-7.44 (2 H, H_{Ar}-2, H_{Ar}-6), 7.42-7.35 (3 H, H_{Ar}-3, H_{Ar}-4, H_{Ar}-5), 4.38 (s, 2 H, CH_2), 3.10 (s, 6 H, N-$C\underline{H}_3$); ^{13}C NMR: 131.5 (C-2, C-6), 130.2 (C-1), 129.2 (C-4), 128.3 (C-3, C-5), 75.9 (CH_2), 57.5 (N-$\underline{C}H_3$).

***N,N*-Dibenzylmethylamine *N*-oxide (30).** In this case addition of 2-5 equivalents of DMD led to a mixture of **30:11** in a 17:1 molar ratio. **30** [34]: ^{1}H NMR: 7.47-7.42 (4 H, H_{Ar}-2, H_{Ar}-6), 7.30-7.21 (6 H, H_{Ar}-3, H_{Ar}-4, H_{Ar}-5), 4.29 (s, 4 H, CH_2), 2.68 (s, 3 H, N-$C\underline{H}_3$); ^{13}C NMR: 132.2 (C-2, C-6), 130.3 (C-1), 129.2 (C-4), 128.2 (C-3, C-5), 74.0 (CH_2), 53.3 (N-$\underline{C}H_3$).

Oxidation of tribenzylamine. Treatment of amine **12** with 5 equivalents of DMD led to a crude reaction mixture which was purified by preparative TLC eluting with 1:1 hexane:methyl *tert*-butyl ether to give: benzaldehyde (31% yield) and dibenzylnitrone [35] [38% yield; ^{1}H NMR: 8.24-8.16 (2 H, H_{Ar}), 7.39-7.30 (9 H, 8 H_{Ar}, H-1), 4.99 (s, 2 H, CH_2); MS: 211 (14), 181 (12), 91 (100), 65 (29)]. Preparation of tribenzylamine *N*-oxide (31): a solution of *m*-CPBA (0.45 g, 2.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of amine **12** (0.50 g, 1.7 mmol) in 10 mL of the same solvent, maintained at 0 °C, and the mixture was stirred until reaction was completed (TLC monitoring). The crude reaction mixture was poured into $NaHCO_3$ solution, extracted with CH_2Cl_2, washed thoroughly with Na_2CO_3 solution and dried. The residue obtained after solvent elimination afforded the expected oxide in 85% yield. **31** [36]: ^{1}H NMR: 7.59-7.54 (6 H, H_{Ar}-2. H_{Ar}-6), 7.35-7.19 (9 H, H_{Ar}-3, H_{Ar}-4, H_{Ar}-5), 4.28 (s, 6 H, CH_2); ^{13}C NMR: 132.3 (C-2, C-6), 130.8 (C-1), 129.2 (C-4), 128.4 (C-3, C-5), 70.3 (CH_2).

***N*-Benzyl-3-pyrroline *N*-oxide (32).** In this case 2 equivalents of DMD were needed to obtain the expected oxide. **32**: IR (CCl_4): 3400-3000, 1647, 1637, 1456, 906, 761, 705, 653; ^{1}H NMR: 7.62-7.55 (2 H, H_{Ar}-2, H_{Ar}-6), 7.41-7.34 (3 H, H_{Ar}-3, H_{Ar}-4, H_{Ar}-5), 5.84 (s, 2 H, H-3, H-4), 4.53 (s, 2 H, CH_2), 4.43 (d, 2 H, J = 14 Hz, H_a-2, H_a-5), 4.19 (d, 2 H, J = 14 Hz, H_b-2, H_b-5); ^{13}C NMR: 132.1 (CH_{Ar}, C-2, C-6), 130.5 (C_{Ar}, C-1), 129.4 (CH_{Ar}, C-4), 128.4 (CH_{Ar}, C-3, C-5), 74.6 (CH_2, C-2, C-5), 71.9 (CH_2); MS: 175 (M^+, 1), 91 (100), 83 (17). HRMS for $C_{11}H_{13}NO$. Calculated: 175.099714. Found: 175.099074.

***N*-[2-(1-Cyclohexen-1-yl)ethyl]pyrrolidine *N*-oxide (33).** In this case 2 equivalents of DMD were needed and the expected oxide was a hygroscopic solid. 33: IR (CCl_4): 3045, 2933, 2854, 2837, 1448, 1438, 929; ^{1}H

NMR: 5.51 (s, 1 H, H-4'), 3.60-3.15 (6 H, H-2, H-5, H-1'), 2.72-2.43 (4H, H-2', H_a-3, H_a-4), 2.10-1.85 (6 H, H-5', H-8', H_b-3, H_b-4), 1.70-1.45 (4 H, H-6', H-7'); ^{13}C NMR: 133.5 (C-3'), 123.1 (C-4'), 67.9 (C-2, C-5), 66.4 (C-1'), 32.0 (C-8'), 28.3 (C-2'), 24.9 (C-5'), 22.5 (CH_2), 21.9 (CH_2), 21.4 (CH_2, C-3, C-4); MS: 195 (M^+,0.5), 98 (100), 86 (34), 70 (22). HRMS for $C_{12}H_{21}NO$. Calculated: 195.162314. Found: 195.162164.

***N*-Benzylpiperidine *N*-oxide (34).** In this case 1.2 equivalents of DMD were needed to obtain the expected oxide as a solid. **34** [25]: ^{1}H NMR: 7.50-7.47 (2 H_{Ar}, H-3, H-5), 7.38-7.35 (3 H_{Ar}, H-2, H-4, H-6), 4.32 (br, 2 H, benzylic), 3.13-3.00 (4 H, H-2, H-6), 2.33 (2 H, H_a-3, H_a-5), 1.68 (d, 1 H, J = 13 Hz, H_a-4), 1.53 (2 H, H_b-3, H_b-5), 1.19 (tq, 1 H, J_1 =4 Hz, J_2 =13 Hz, H_b-4).; ^{13}C NMR: 132.4 (CH_{Ar}, C-2, C-6), 129.9 (C_{Ar}, C-1), 129.3 (CH_{Ar}, C-4), 128.3 (CH_{Ar}, C-3, C-5), 75.8 (benzylic), 64.2 (C-2, C-6), 22.0 (C-4), 20.6 (C-3, C-5).; MS: 191 (M^+, 7), 100 (69), 91 (100), 55 (41).

***N*-Benzyl-4-ethylidenpiperidine *N*-oxide (35).** In this case 1.2 equivalents of DMD were needed to obtain the expected oxide as a hygroscopic solid. **35**: IR (CCl_4): 3400-2900, 1643, 1456, 973, 767, 705, 561; ^{1}H NMR: 7.53-7-50 (2 H, H_{Ar}-3, H_{Ar}-5), 7.41-7.37 (3 H, H_{Ar}-2, H_{Ar}-4, H_{Ar}-6), 5.27 (q, 1 H, J = 7 Hz, CH=), 4.48 (s, 2 H, benzylic), 3.35-3.01 (5 H, H-2, H-6, i H_a-3 or H_a-5), 2.81 (t, 1 H, J = 15 Hz, H_a-3 or H_a-5), 2.45 (d, 1 H, J = 15 Hz, H_b-3 or H_b-5), 2.07 (d, 1 H, J = 11 Hz, H_b-3 or H_b-5), 1.55 (d, 6 H, J = 7 Hz, CH_3); ^{13}C NMR: 132.3 (CH_{Ar}, C-2, C-6), 130.7, 129.4, 129.3 (CH_{Ar}, C-4), 128.2 (CH_{Ar}, C-3, C-5), 118.9 (CH=), 75.1 (benzylic), 64.1 (C-2 or C-6), 63.3 (C-2 or C-6), 29.8 (C-3 or C-5), 22.0 (C-3 or C-5), 12.5 (CH_3).; MS: 217 (M^+, 3), 161 (19), 126 (38), 91 (100), 81 (65), 77 (46). HRMS for $C_{14}H_{19}NO$. Calculated: 217.146664. Found: 217.146564.

***N*-Benzyl-3-ethyl-1,2,5,6-tetrahydropyridine N-oxide (36).** In this case 2 equivalents of DMD were needed to obtain the expected oxide as an oil. **36** [26]: ^{1}H NMR: 7.64-7.55 (2 H, H_{Ar}-3, H_{Ar}-5), 7.45-7.12 (3 H, H_{Ar}-2, H_{Ar}-4, H_{Ar}-6), 5.59 (s, 1 H, H-4), 4.37 (s, 2 H, benzylic), 3.73 (d, 1 H, J = 15.5 Hz, H_a-2), 3.55 (d, 1 H, J = 15.5 Hz, H_b-2), 3.42-3.17 (2 H, H-6), 2.80-2.20 (2 H, H-5), 1.93 (q, 2 H, J = 7.5 Hz, $\underline{CH_2}CH_3$), 1.02 (t, 3 H, J = 7.5 Hz, $CH_2\underline{CH_3}$); ^{13}C NMR: 133.5 (C-3), 132.2 (CH_{Ar}, C-2, C-6), 129.9 (C_{Ar}, C-1), 129.2 (CH_{Ar}, C-4), 128.1 (CH_{Ar}, C-3, C-5), 116.2 (C-4), 71.2 (benzylic), 66.5 (C-2), 61.1 (C-6), 27.0 (C-5), 22.9 ($\underline{CH_2}CH_3$), 11.2 ($CH_2\underline{CH_3}$); MS: 217 (M^+, 5), 134 (16), 91 (100).

***N*-Benzyl-3-ethylpiperidine *N*-oxide (37).** In this case 1.2 equivalents of DMD were needed to obtain the expected oxide as an oil. **37**: IR (CCl_4): 3400, 2962, 2933, 2880, 1654, 1458, 732, 702; ^{1}H NMR: 7.53-7.48 (2 H_{Ar}, H-3, H-5), 7.43-7.35 (3 H_{Ar}, H-2, H-4, H-6), 4.58 (s, 2 H, benzylic), 3.37 (da, 2 H, J = 11.5, H_a-2, H_a-6), 3.01 (td, 1 H, J_1 = 3, J_2 = 12, H_b-6), 2.68 (t, 1 H, J = 11.5, H_b-2), 2.44-2.20 (2 H, H-3, H_a-5), 1.83 (d, 1 H, J = 14 Hz, H_a-4), 1.60 (d, 1 H, J = 14 Hz, H_b-4), 1.25-1.10 (2 H, $\underline{CH_2}CH_3$), 0.88 (t, 3 H, J = 7 Hz, $CH_2\underline{CH_3}$), 0.83 (m, 1 H, H_b-5); ^{13}C NMR: 132.8 (CH_{Ar}, C-2, C-6), 129.8 (CH_{Ar}, C-4), 129.4 (C_{Ar}, C-1), 128.7 (CH_{Ar}, C-3, C-5), 75.6 (CH_2, benzylic), 68.1 (C-2), 63.0 (C-6), 32.3 (C-3), 28.1 (CH_2), 26.1 (CH_2), 19.9 ($\underline{CH_2}CH_3$), 10.7 ($CH_2\underline{CH_3}$); MS: 203 (M^+, 23), 126 (29), 112 (41), 91 (100).). HRMS for $C_{14}H_{21}NO$. Calculated: 219.162314. Found: 219.162098.

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