Metal-Free Reductive Cleavage of N–O Bonds in Weinreb Amides by an Organic Neutral Super-Electron Donor

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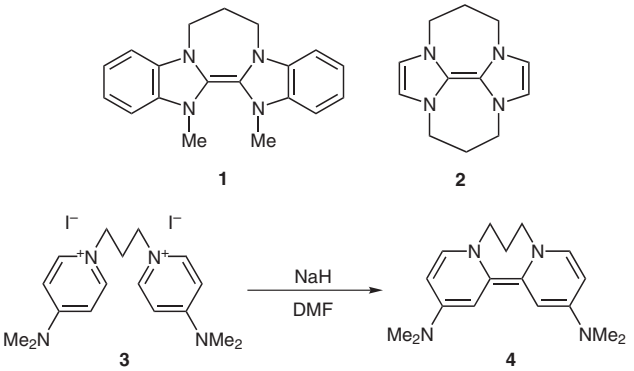
Dedicated to Sir Jack Baldwin on the occasion of his 70th birthday

Abstract: The scope of neutral organic super-electron donors as reducing agents has been extended to include the reductive cleavage of N–O bonds in Weinreb amides. This methodology proved to be applicable to a large array of substrates to afford their reduced counterparts in good to excellent yields. The variation in reactivity within the set of tested amides is rationalised.

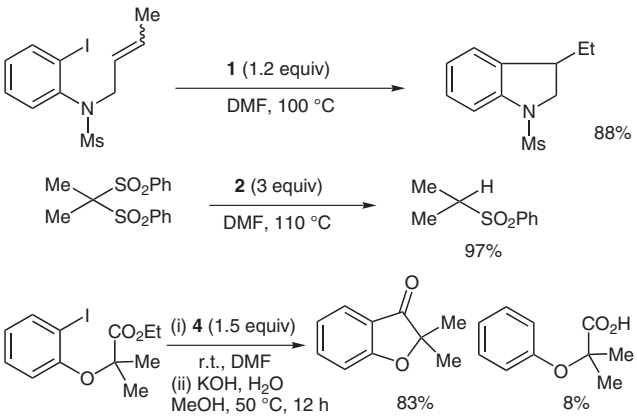
Key words: electron transfer, Weinreb amide, reduction, pyridinylidene

The N–O bond is commonly encountered in organic chemistry. It is most frequently encountered in *N*-methoxy-*N*-methylamides, (Weinreb amides), which are very well known and useful intermediates in organic synthesis.[1] Methodologies exist for the reduction of N–O bonds, and usually feature the use of metal-based reducing agents. For instance, *N*-hydroxy-2-azetidinones are reduced by $TiCl_3$, but no reaction occurs with *N*-alkoxy-2-azetidinone.[2] Oxazine cycloadducts derived from mandelic acid can also be reduced by catalytic hydrogenation, Na/Hg or $Mo(CO)_6$.[3] Samarium(II) iodide has been used to perform the reductive cleavage of N–O bonds in *N*-alkoxytrifluoroacetamides.[4] Yus et al. more recently proposed a general procedure to perform reductive N–O bond cleavage of Weinreb amides using a catalytic system featuring Li and di-*tert*-butylbiphenyl.[5a] Birch conditions have also been used by Cossy et al.[5b]

In contrast to these metal-based reducing reagents, neutral, organic, ground-state, super-electron donor reagents have recently been developed within our research group.[6–9] These are highly selective reducing agents and, being neutral, operate under mild conditions. Donor **1** (Scheme 1) effected single-electron transfer (SET) to aryl and alkyl iodides, thereby generating the corresponding radicals, which cyclised in the presence of appropriate trapping groups, such as alkenes (Scheme 2).[6] Recently, two more powerful neutral ground-state electron donors **2**[7] and **4**[8,9] have been developed within our laboratories. These reagents can transfer two electrons to substrates, including those that are more difficult to reduce. For instance, they



Scheme 1



Scheme 2

convert aryl iodides into aryl anions[7] and reductively cleave selected sulfones and sulfonamides[8,9] (Scheme 2).

Donor **4** is easily prepared by deprotonation of disalt **3**. Its scope as a powerful, neutral, ground-state electron donor **4** has so far been limited to the successful reductive cleavage of sulfones, aryl iodides, and alkyl halides. We were keen to expand the scope of reductive cleavages that could be performed. This paper presents the results of our study on the reductive cleavage of N–O bonds of Weinreb amides.

Weinreb amide substrates were easily synthesised, either from the commercially available acid chloride counterpart or from the commercially available carboxylic acid counterpart that was firstly activated in situ with oxalyl chlo-

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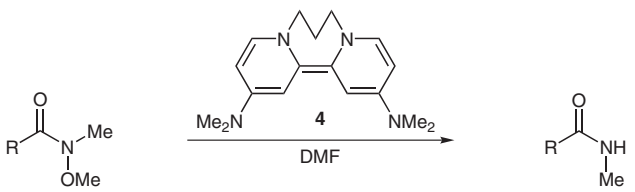


Scheme 3

ride and DMF, and *N*,*O*-dimethylhydroxylamine hydrochloride. Results of successful reductive N–O bond cleavage of Weinreb amides (Scheme 3) are presented in Table 1.

Table 1 Cleavage of Weinreb Amides by Donor **4** in DMF Solution

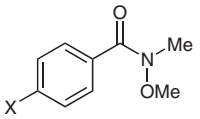
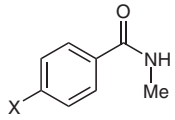
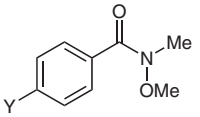
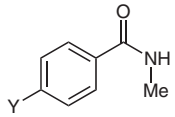
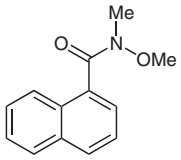
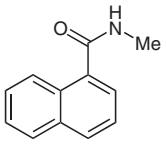
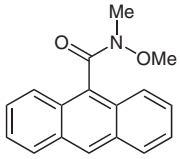
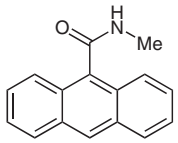
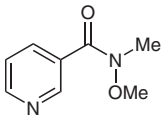
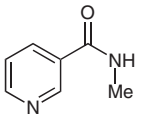
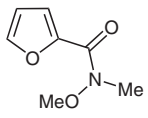
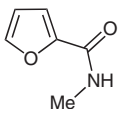
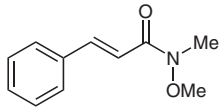
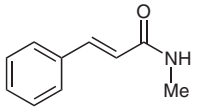
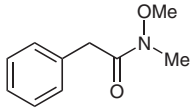
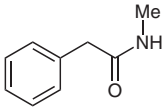
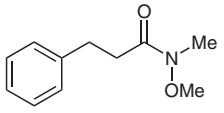
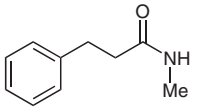
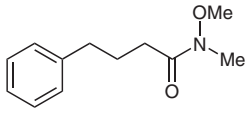
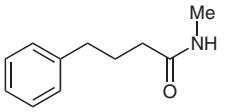
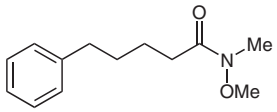
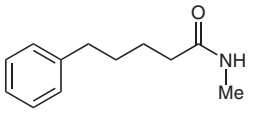
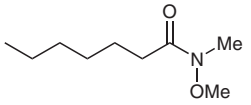
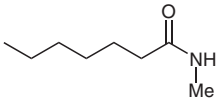
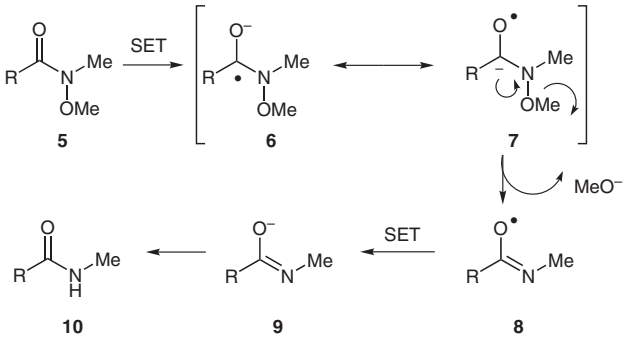
Entry	Reagent	Reaction conditions	Product	Yield (%)
		**4** (1.5 equiv) r.t.		
1a	X = H (LUMO 2.93 eV)		X = H	80
1b	X = F		X = F	88
1c	X = Cl		X = Cl	83
1d	X = CN		X = CN	87
		**4** (1.5 equiv) 100 °C		
2a	Y = OMe		Y = OMe	81
2b	Y = NMe_2		Y = NMe_2	86
3		**4** (1.5 equiv) r.t.		92
4		**4** (1.5 equiv) r.t.		91
5		**4** (1.5 equiv) r.t.		81
6		**4** (1.5 equiv) 100 °C		83
7		**4** (1.5 equiv) r.t.		94
8	 LUMO (3.89 eV)	**4** (1.5 equiv) r.t.		76
9	 LUMO (4.09 eV)	**4** (1.5 equiv) 100 °C		77

Table 1 Cleavage of Weinreb Amides by Donor **4** in DMF Solution (continued)

Entry	Reagent	Reaction conditions	Product	Yield (%)
10	 LUMO (4.05 eV)	**4** (1.5 equiv) 100 °C		67
11	 LUMO (4.15 eV)	**4** (1.5 equiv) 100 °C		60
12	 LUMO (5.27 eV)	**4** (5 equiv) 100 °C		43

The reductive cleavage of the N–O bonds of Weinreb amides was successfully applied to a large range of substrates. Furthermore, according to the substitution pattern, tuning of the reaction conditions allowed complete reductive cleavage to be achieved. In the case of monoaromatic system (Table 1, entries 1a–d), with or without an electron-withdrawing group in the *para* position, smooth N–O bond cleavage was achieved at room temperature using as little as 1.5 equivalents of electron donor **4**. Reduced product was isolated from the reaction mixture in very high yields (80–88%) after aqueous workup and chromatography. Nevertheless, when the same reaction conditions were applied to electron-rich aromatic Weinreb amides (Table 1, entries 2a and 2b), little conversion was observed. Increasing the numbers of equivalents of electron donor **4** seemed to have little effect on conversion at room temperature. However, increasing the temperature from room temperature to 100 °C brought the reaction to completion allowing isolation of the reduced amides in very high yields (81–86%). Smooth reductive N–O bond cleavages were also achieved for polycyclic aromatic Weinreb amides at room temperature using 1.5 equivalents of electron donor **4**. Naphthalene- and anthracene-derived Weinreb amides were successfully reduced to their corresponding amides in excellent yields (Table 1, entries 3 and 4). The reaction was also applied to heteroaromatic substrates. Reductive N–O bond cleavage occurred at room temperature for the pyridine derivative (entry 5), whereas, heating the reaction mixture at 100 °C proved necessary to ensure complete conversion in the case of the electron-rich furan derivative (Table 1, entry 6). When the carbonyl functional group was conjugated with an alkene double bond, smooth reductive cleavage of N–O bond was also possible and allowed isolation of the corresponding reduced amide in excellent yield (Table 1, entry 7). This methodology appears to be very specific, with no reduction of the alkene double bond being observed.

The reaction was also successfully applied to a range of substrates where the Weinreb amide functional group is not conjugated to any π-system. Smooth reductive cleavage of the N–O bond was observed for the benzyl substrate (Table 1, entry 8) at room temperature using as little as 1.5 equivalents of electron donor **4** to afford its reduced counterpart in high yield (76%). However, increasing the length of the carbon chain made the reaction more difficult. For example, the reductive cleavage of N–O bonds of Weinreb amides in entries 9–11 had to be performed at high temperature to afford their reduced counterparts in good yields, ranging from 60% to 77%. The reaction was also successfully applied to an alkyl substrate (Table 1, entry 12). However, in this case, 5 equivalents of **4** at 100 °C proved necessary to achieve the reductive N–O bond cleavage to afford its reduced counterpart in modest yield (43%).



Scheme 4

With these results in mind, the general mechanism is proposed in Scheme 3 for the reduction of Weinreb amides. In the simplest scenario, single-electron transfer (SET) from the neutral ground-state electron donor **4** to the LUMO of the Weinreb amide π-system of the molecule **5** would occur. The LUMO of the Weinreb amide group is principally π* in character, and the electron then requires to be transferred to the σ* the N–O bond giving rise to cleavage of that bond. The result is an enolyl radical **8** that can subsequently receive another electron from **4** by SET. The arising enolate **9** abstracts a proton from the reaction medium (see related paper in this issue) and subsequently

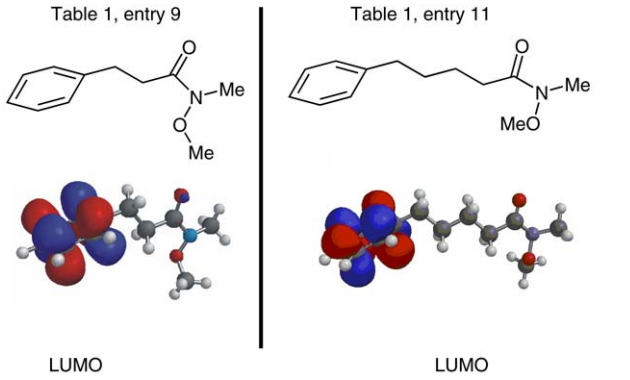


Figure 1 LUMO for Weinreb amides (Table 1, entries 9 and 11)

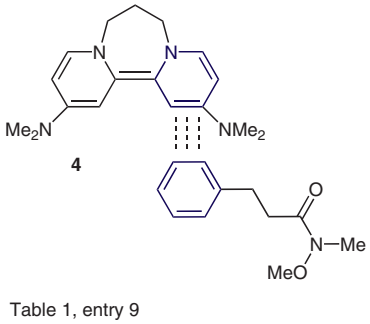


Figure 2 Proposed π-stacking interaction between donor **4** and arene ring on substrate

rearranges to give, after workup and purification, reduced compound **10** (Scheme 4).

The more electron-rich the carbonyl group, the more difficult the N–O bond reductive cleavage. Thus, the initial electron transfer is the crucial step of this reaction. If the first electron transfer from **4** to the Weinreb amide substrate **5** is quite easy, then the reaction can be performed easily using mild conditions. Otherwise, when the carbonyl group is conjugated with an electron-rich group or not conjugated, then the initial SET may be more difficult.

The most interesting facet, however, relates to the comparison between entries for the homologous amides in entries 1a and 8–12 in Table 1. Inspection of the LUMO orbitals for these cases shows that the LUMO is associated with the arene ring (Figure 1). When this is conjugated with the Weinreb amide, then the energy of the LUMO is lowest (2.93 eV, see entry 1a, Table 1) among this series, and cleavage occurs most easily. Inserting one methylene group between the arene and the carbonyl (entry 8) increases the LUMO to 3.89 eV, but the LUMO still spans the Weinreb amide group to some extent as well as the arene. Inserting two, three, and four methylenes between the arene and the carbonyl group raises the LUMO to 4.09 eV, 4.05 eV, and 4.15 eV, respectively. In all of these cases, the LUMO is associated with the arene π-system, but not with the Weinreb amide group. Moving onto entry 12, which features no arene, then the LUMO energy moves to 5.27 eV. The LUMO energy qualitatively correlates with the ease of cleavage of the N–O bond. Thus it may be that, where an aryl ring is present in a substrate, initial transient electron transfer occurs to the arene, and this is passed on intramolecularly to the Weinreb amide group. When an aryl ring is not present, the electron transfer is more difficult, and the reaction requires more forcing conditions, is less efficient, and affords a lower yield (entry 12). This is therefore an interesting example of a neighbouring-group electron-transfer effect, reminiscent of the amazing workings of ribonucleotide reductases[10] and certain peptides.[11]

An alternative rationalisation of the varying ease of reduction might arise from π-stacking of the donor **4** with the arene group of a Weinreb amide (Figure 2). If electron transfer to the arene were discounted, then the role of the arene could be to retain the electron donor close to the Weinreb amide through a π-stacking interaction, an advantage that should become less apparent as the distance between the amide and the aryl ring increased. Interestingly, subtle mechanistic points of this type would not be apparent if the reduction had been conducted by a more powerful and less selective reducing agent.

In conclusion, electron donor **4** carries out the reductive cleavage of N-O bonds in Weinreb amides, and the reaction was successfully applied to a large array of substrates. The reactivity of these amides is intimately dependent on their structure.

Reduction of 4-Chloro-*N*-methoxy-*N*-methylbenzamide (Table 1, entry 1c); Typical Procedure

In a centrifuge tube under argon at room temperature, precursor salt **3** (0.810 g, 1.5 mmol, 1.5 equiv) and NaH (0.6 g, 15 mmol, 15 equiv) were washed with anhydrous hexane (3×). Excess of hexane was removed by a flow of argon. Anhydrous DMF (15 mL) was then added to the resulting fine white powder and the mixture was then stirred at r.t. under argon for 3 h. The resulting dark purple suspension was then centrifuged and the upper liquid phase was transferred to 4-chloro-*N*-methoxy-*N*-methylbenzamide (0.199 g, 1 mmol, 1 equiv) via a cannula. The mixture was then stirred at r.t. under argon overnight, after which it was then diluted with EtOAc (100 mL) and washed with water (100 mL). The aqueous phase was further extracted with EtOAc (2 × 50 mL). Combined organic phases were then further washed with water (2 × 50 mL) and brine (50 mL). The resulting organic extract was finally dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was then adsorbed onto silica and purified by flash chromatography (CH_2Cl_2–EtOAc 95:5) to afford 4-chloro-*N*-methylbenzamide as a fine white powder (0.141 g, 83%); mp 158-160 °C; IR (film): 3340, 3076, 2957, 1637, 1603, 1571, 1553, 1490, 1406, 1327, 1301, 1275, 1165, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.02 (d, *J* = 4.9 Hz, 3 H, CH_3), 6.15 (br s, 1 H, NH), 7.39–4.43 (m, 2 H, Ar-H), 7.69–7.72 (m, 2 H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.9 (CH_3), 128.3 (CH), 128.8 (CH), 133.0 (C), 137.6 (C), 167.2 (C); MS (CI^+): *m/z* (%) = 187 $[M + NH_4]^+$ (13), 172, $[M + H]^+$ (28), 170 $[M + H]^+$ (100), 136 (29), 93 (18); MS: *m/z* $[M + H]^+$ calcd for C_8H_9ClNO (^{35}Cl): 170.0368; found: 170.0368.

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References

(1) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (c) Aidhen, I. S.; Ahuja, J. *Tetrahedron Lett.* **1992**, *33*, 5431. (d) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (e) Selvamurugan, V.; Aidhen, I. S. *Tetrahedron* **2001**, *57*, 6065. (f) Mislin, G. A.; Burger, A.; Abdallah, M. A. *Tetrahedron* **2004**, *60*, 12139. (g) Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, *7*, 1427. (h) Kangani, C. O.; Kelley, D. E.; Day, B. W. *Tetrahedron Lett.* **2006**, *47*, 6289. (i) Hisler, K.; Tripoli, R.; Murphy, J. A. *Tetrahedron Lett.* **2006**, *47*, 6293.

(2) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410.

(3) Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602.

(4) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755.

(5) (a) Yus, M.; Radivoy, G.; Alonso, F. *Synthesis* **2001**, 914. (b) Taillier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2145.

(6) Murphy, J. A.; Khan, T. A.; Zhou, S.; Thomson, D. W.; Mahesh, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1356.

(7) Murphy, J. A.; Zhou, S.; Thomson, D. W.; Schoenebeck, F.; Mahesh, M.; Park, S. R.; Tuttle, T.; Berlouis, L. E. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5178.

(8) Schoenebeck, F.; Murphy, J. A.; Zhou, S.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* **2007**, *129*, 13368.

(9) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoenebeck, F.; Zhou, S.-Z.; Turner, A. T. *Org. Lett.* **2008**, *10*, 1227.

(10) Stubbe, J.; Nocera, D. G.; Yee, C. S.; Chang, M. C. Y. *Chem. Rev.* **2003**, *103*, 2167.

(11) Giese, B. *Bioorg. Med. Chem.* **2006**, *14*, 6139.