New and improved methods for the conversion of nitroalkanes into geminal chloronitroso compounds

Rafael Bou-Moreno, Sandra Luengo-Arratta, Valérie Pons, and William B. Motherwell

Abstract: The scope and limitations of a new method for the preparation of geminal chloronitroso compounds involving treatment of a nitronate anion with oxalyl chloride are described in full, and a milder, high yielding, and more chemoselective variant using the derived silyl nitronate is presented.

Key words: geminal chloronitroso, silyl nitronate.

Résumé : On présente une description complète de la portée et des limitations d'une nouvelle méthode de préparation de composés chloronitroso géminés impliquant le traitement d'un anion nitronate par du chlorure d'oxalyle et d'une légère variante, plus chimiosélective et conduisant à des rendements légèrement supérieurs, qui fait appel à l'utilisation d'un dérivé nitronate de silyle.

Mots-clés : composés chloronitroso géminés, nitronate de silyle.

[Traduit par la Rédaction]

Introduction

In recent years, the wide-ranging reactivity of the monomeric nitroso group[1,2] has served as a cornerstone for a variety of very useful reactions. As a colourful chameleon, it has been used inter alia, as a radical trap,[3] an ambident electrophile for both amination[4] and oxyamination[5] in aldol-like reactions, and perhaps most prominently, as a partner in the hetero-Diels–Alder reaction. The subset of geminally functionalized α-chloronitroso compounds, as with their α-acetoxy congeners,[6] has proven to be especially useful, since a subsequent hydrolytic cleavage leads to liberation of a free amino group. Reactions such as electrophilic amination using the Oppolzer sultam,[7] the beautiful chiral variant of the heteroene reaction by Vasella and co-workers[8] and the synthesis of *syn*-3,6-dihydro-1,2-oxazines through nitroso Diels–Alder cyclisation[5] have all benefited from this strategy.

The traditional method for the preparation or in situ generation of α-chloronitroso compounds involves the reaction of an oxime with chlorine,[9] *tert*-butyl hypochlorite,[10] or related electrophilic halogen precursors.[11] However, during the course of a synthetic program designed to explore the potential of the intramolecular variant of the nitrosoene reaction[12] using α-chloronitroso compounds,[13] competitive chloronium ion transformation of several olefinic oximes proved to be problematic. Indeed, this alternative mechanistic pathway involving the nucleophilic attack of an oxime onto a bridged cation has formed the basis of a useful alternative cyclisation method.[14]

Results and discussion

As a consequence of the this problem, it was necessary to invent a new method for the preparation of α-chloronitroso compounds that circumvented the use of an electrophilic halogen source. As outlined in Scheme 1, we reasoned that the reaction of a secondary nitronate anion (**1**) with oxalyl chloride would lead, via *O*-acylation and the subsequent capture of a chloride anion, to an intermediate (**2**) that would be predisposed to undergo a decarboxylative fragmentation reaction leading to the desired germinal chloronitroso compound (**3**). The initial *O*-acylation step finds precedent in the pioneering work of Zefirov and co-workers[15] on the [2,3] sigmatropic rearrangement of acyloxynitronic acids. Herein, we now report, in full detail,[16] on the practical implementation of this idea, together with a new and milder alternative variant.

Several important facets of this transformation were revealed in a series of preliminary experiments. Firstly, given that the isolation of a metallic nitronate salt is not an advisable practice,[17] it was important to examine a selection of bases and solvent systems for efficient generation of a reactive nitronate anion. The reaction sequence selected is shown in Scheme 2 and features hetero-Diels–Alder trapping of the product, 2-chloro-2-nitrosopropane (**4**), followed by hydrolysis to give the known isolable hydrochloride adduct (**5**).[18] Examination of the results in Table 1 reveals that the more charge separated potassium nitronates (entries 5 and 6) are superior to their lithium counterparts. The emergence of Schlosser's base as the

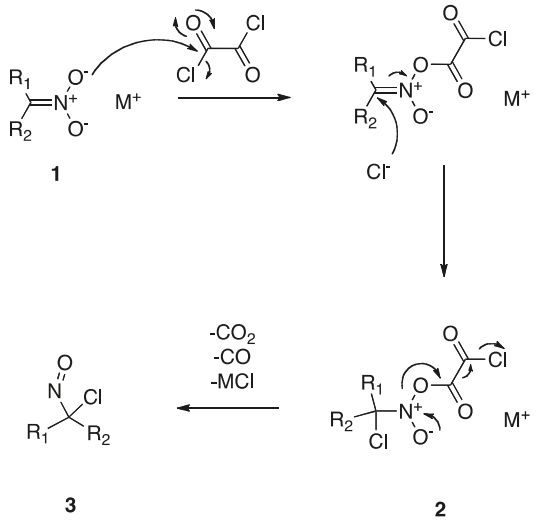
Received 29 June 2012. Accepted 6 September 2012. Published at www.nrcresearchpress.com/cjc on 17 December 2012.

R. Bou-Moreno, S. Luengo-Arratta, V. Pons, and W.B. Motherwell. Department of Chemistry, University College London, 20, Gordon Street, London, WC1H 0AJ, UK.

Corresponding author: William B. Motherwell (e-mail: w.b.motherwell@ucl.ac.uk).

This article is part of a Special Issue dedicated to Professor Derrick Clive. Dedicated with respect to Professor Derrick L. J. Clive, an Imperial scholar, a Bartonian, and a meticulous chemist.

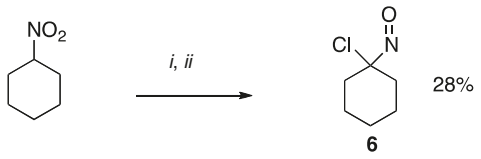
Scheme 1.



most successful is readily understood, since nitronate anion formation is a slow process subject to general base catalysis (2-nitropropane pK_a = 7.74, ratio at room temperature (rt) [$Me_2C{=}NO_2H$]/[Me_2CHNO_2] is 3×10^{-3}).[19] A second practical consideration was that a rapid single addition of oxalyl chloride to the preformed nitronate salt was necessary, since the product α-chloronitroso compound could undergo a subsequent reaction with the nitronate salt to form an oxime, probably by a single electron transfer process.[16]

Even though volatile 2-chloro-2-nitrosopropane was not isolated in these reactions, the results indicate that it can be formed in at least a 85% yield. Adduct **5** could also be isolated in a 55% yield when 1-nitrocyclohexane was used as substrate, and it was also possible to prepare and isolate pure 1-chloro-1-nitrosocyclohexane (**6**) using this method, albeit in a low yield (eq. [1]).

[1]



Reagents: (*i*) *n*-BuLi, KO-*t*-Bu, Et_2O, 0 °C; (*ii*) oxalyl chloride (2.5 equiv), 15 min.

The use of the previous protocol was also tested using three further cyclic dienes and a further comparison was made between 2-nitropropane and 1-nitrocyclohexane as geminal chloronitroso precursors. The results are shown in Table 2 and reveal that selection of the smaller reagent may be beneficial in the more hindered situations (Table 2, entry 2). The observed diastereoselectivity and higher yield with cyclohepta-3,5-diene-1-ol (Table 2, entry 3) may be a consequence of assisted hydrogen bonding from the hydroxyl group to the nitrosodienophile. Such bicyclic adducts have proven to be of value in the synthesis of complex cyclopentanoids,[6b] inositols,[20] and tropane[21] alkaloids.

While the above study had established the viability of this novel functional group transformation, it was nevertheless

Scheme 2. Reagents: (*i*) base (1.0 equiv), solvent, 0 °C; (*ii*) oxalyl chloride (5.0 equiv); (*iii*) filtration; (*iv*) MeOH, 2 mol/L HCl.

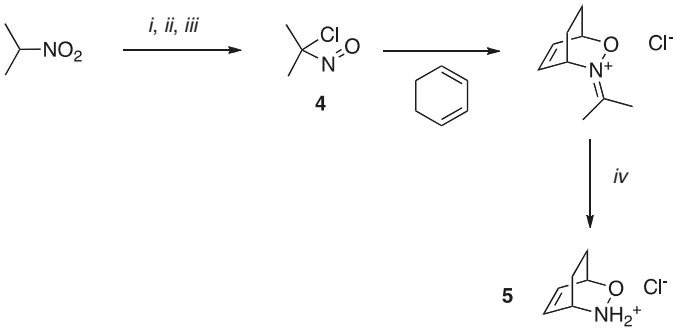


Table 1. Optimization of Scheme 2.

		Solvent (yield of **5**, %)		
Entry	Base	Et_2O	THF	Toluene
1	LDA	23	4	21
2	LiHMDS	35	37	3
3	*n*-BuLi	41	23	16
4	NaH	—	—	—
5	KO-*t*-Bu	60	51	66
6	KO-*t*-Bu/*n*-BuLi	82	56	85

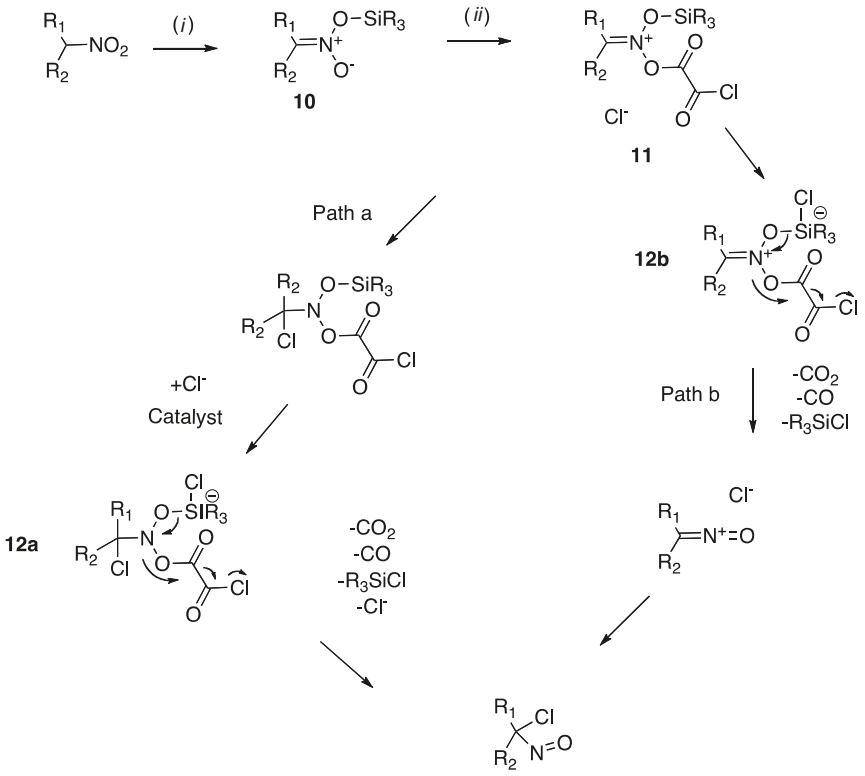
Note: THF, tetrahydrofuran; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide.

Table 2. Substrates synthesized by the method in eq. [1].

				Yield (%)	
Entry	Diene	Compound	Isolated cycloadduct	**4**	**6**
1		**7**		38	34
2		**8**		40	16
3		**9**		52	50

clear that, in terms of chemoselectivity for more sensitive and highly functionalized substrates, the use of such strong bases for nitronate anion formation was not desirable. In particular, substrates prone to base induced dehydrohalogenation or enolate anion formation were problematic. We therefore reasoned, as shown in Scheme 3, that prior formation of a silyl nitronate[22] could be advantageous. Thus, reaction of **10** with

Scheme 3. Reagents: (*i*) R_3SiCl, base; (*ii*) oxalyl chloride.



oxalyl chloride could then generate an intermediate (**11**) and chloride anion capture could then occur, either on carbon (Scheme 3, path a) or via formation of an initial silicon–ate complex (Scheme 3, path b) to form analogous intermediates for decarboxylative fragmentation.

The results for a series of optimization experiments using nitrocyclododecane (**13**) are presented in Table 3 and involve a sequential sequence of in situ silyl nitronate (**14**) generation at room temperature for 30 min followed by cooling to 0 °C, the addition of of oxalyl chloride (2.5 equiv), and stirring for 2 min (Scheme 4).

Substrate **13** was chosen because the product, α-chloronitroso cyclododecane (**15**), proved to be a nonvolatile, deep blue, and highly crystalline product whose monomeric nature was confirmed by a single crystal X-ray diffraction study.[23] The reaction conditions used for generation of the various silyl nitronates (**14**) are essentially based on those developed by Palomo and co-workers.[24] As highlighted earlier, deprotonation of a nitro compound may be slow and is not trivial, with bases such as triethylamine (Table 3, entry 6) and DABCO (Table 3, entry 7) unreactive, with only 1,8-diazabicycloundec-7-ene (DBU) proving to be essential and 1.5 molar equiv proving to be optimum (Table 3, entries 12–14). The most crucial variable proved to be the nature of the organosilicon group (Table 3, entries 1–4), which has to provide a compromise between the ease of the formation and stability of the silyl nitronate against its subsequent reactivity in forming an ate complex with chloride anion to facilitate fragmentation. A comparison of entries 1–5 (Table 3) clearly reveals that the TBDMS group emerges as the most successful. To some extent, a parallel can be drawn with the relative rates of acid hydrolysis of silyl ethers[25] (Me_3Si (1) < TBDMS (10 000) < TIPS (700 000) < TBDPS (5 000 000)) inasmuch as the TMS group is much too labile and the TIPS and TBDPS groups are much too hindered in terms of nucleophilic attack at silicon. It

Table 3. Optimization of Scheme 4.

Entry	Base (equiv)	Silyl chloride (equiv)	Solvent	Yield of **15** (%)
1	DBU (1.2)	TMS (2)	CH_2Cl_2	9
2	DBU (1.2)	TBDPS (2)	CH_2Cl_2	40
3	DBU (1.2)	TIPS (2)	CH_2Cl_2	50
4[a]	DBU (1.2)	TBDMS (2)	CH_2Cl_2	65
5	DBU (1.2)	TBDMS (2)	CH_2Cl_2	72
6	Et_3N (1.2)	TBDMS (2)	CH_2Cl_2	0[b]
7	DABCO (1.2)	TBDMS (2)	CH_2Cl_2	0[b]
8	DBU (1.2)	TBDMS (2)	Hexane	66
9	DBU (1.2)	TBDMS (2)	THF	48
10	DBU (1.2)	TBDMS (2)	Et_2O	65
11	DBU (1.2)	TBDMS (2)	CH_2Cl_2[c]	70
12	DBU (1.5)	TBDMS (2)	CH_2Cl_2	80
13	DBU (2.0)	TBDMS (2)	CH_2Cl_2	76
14	DBU (1.0)	TBDMS (2)	CH_2Cl_2	65

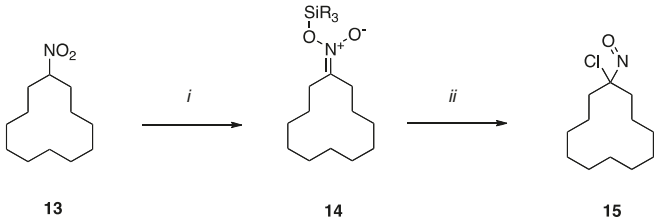
Note: DBU, 1,8-diazabicycloundec-7-ene; TMS, tetramethylsilane; TBDPS, *tert*-butyldiphenylsilyl; TIPS, triisopropylsilyl; TBDMS, *tert*-butyldimethylsilyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; THF, tetrahydrofuran.

[a]Deprotonation at 0 °C.

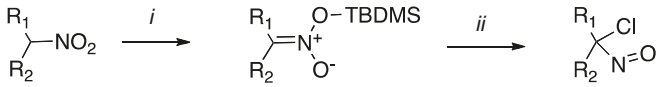
[b]No reaction.

[c]Catalytic dimethylformamide (DMF).

Scheme 4. Reagents: (*i*) base, R_3SiCl, solvent, 30 min, room temperature (rt); (*ii*) oxalyl chloride (2.5 equiv), 0 °C, 2 min.



Scheme 5. Reagents: (*i*) DBU (1.5 equiv), TBDMSCl (2.0 equiv), CH_2Cl_2, 30 min, room temperature (rt); (*ii*) oxalyl chloride (2.5 equiv), 0 °C, 2 min.

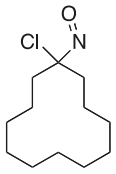
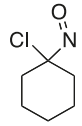
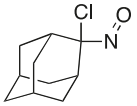
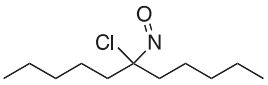
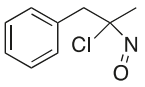
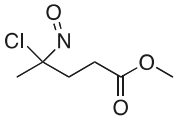
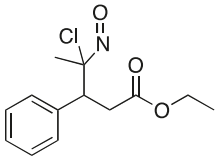
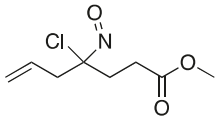
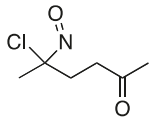
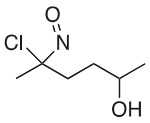


is important to note that, in the absence of a silicon electrophile, α-chloronitroso compounds were not formed, and that, in terms of solvent, dichloromethane, hexane, and diethyl ether (Table 3, entries 5, 8, and 10) can all be used. A simple NMR experiment in CD_2Cl_2 confirmed the optimum conditions noted in entry 12 (Table 3) inasmuch as complete consumption of both nitrocyclododecane and its TBDMS-protected nitronate was observed. We also note parenthetically that oxalyl chloride may be replaced by ethyl chlorooxoacetate, which afforded **15** in a slightly lower yield (52%). Initial experiments using ethyl chloroformate or the Vilsmeier reagent were, however, unsuccessful. A series of secondary nitro compounds was then subjected to the experimental conditions delineated in Scheme 5. Examination of the results (Table 4) reveals that, with simple acyclic substrates (Table 4, entries 4 and 5) and also with the macrocyclic ring (Table 4, entry 1), excellent yields can be isolated, whereas reactions containing six-membered ring systems (Table 4, entries 2 and 3) proceed with a more moderate yield. Remote ester functionality (Table 4, entries 6–8) and simple alkenes (Table 4, entry 8) are tolerated, although conversion of a secondary nitro ketone (Table 4, entry 9) proceeded with a much lower yield. Not unexpectedly, the selection of a TBDMS-protected alcohol (Table 4, entry 10) led to concomitant deprotection, but once again, conversion of the nitro group to the geminal chloronitroso moiety proceeded with an excellent yield. The superiority of the silyl nitronate variant over the initial method involving potassium *tert*-butoxide in the formation of a metallic nitronate salt is readily appreciated by comparison of the isolated yields for the two methods, especially for those more sensitive substrates prone to dehydrohalogenation (Table 4, entry 5) or competing enolate anion formation (Table 4, entries 6 and 9).

Conclusion

In summary, the foregoing study has provided proof of a concept for this novel functional group interconversion via nitronate anion chemistry. The mild reaction conditions employed using in situ generation of a silyl nitronate are especially useful in terms of functional group compatibility and will hopefully encourage the exploration of the richly adorned

Table 4. Substrates synthesized by the method in Scheme 5.

Entry	Product		Yield (%)
1	**15**		80
2	**6**		47 (28)[a]
3	**16**		58
4	**17**		78
5	**18**		80 (26)[a]
6	**19**		72 (28)[a]
7	**23**		69
8	**20**		73
9	**21**		23 (0)[a]
10	**22**		85[b]

[a]Yield using potassium nitronate and oxalyl chloride, deprotonated by KO-*t*-Bu.

[b]Substrate, *tert*-butyldimethylsilyl (TBDMS) protected nitroalcohol.

geminal chloronitroso unit in more complex molecular environments.

Experimental

General experimental

All chemicals used were purchased commercially and purified by literature methods.[26] Experiments involving moisture- and (or) air-sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen. Diethyl ether, CH_2Cl_2, hexane, tetrahydrofuran, and toluene were purified by alumina/copper catalyst columns. Flash chromatography was performed on silica gel (230–400 mesh). Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using ultraviolet (UV) radiation at 254 nm. Further visualization was possible by staining with a basic solution of potassium permanganate or a phosphomolybdic acid solution. Infrared (IR) spectra were recorded on a PerkinElmer 1605 Fourier transform (FT)-IR spectrometer. Mass spectra were recorded on Micromass 70-ES Magnetic Sector spectrometer (VG ZAB) by electron impact (EI), chemical ionization (CI), or atmospheric pressure chemical ionization (ECPI (positive model)). The ^{1}H NMR spectra were measured at 600 MHz on a Bruker A600, at 500 MHz on a Bruker Avance 500, and at 400 MHz on a Bruker 400. The ^{13}C NMR spectra were measured at 150 MHz on a Bruker A600, at 125 MHz on a Bruker Avance 500, and at 100 MHz on a Bruker 400. The spectra were obtained from solution in deuterated water, methanol, water, or chloroform, with TMS as internal standard. The residual protic solvents were 4.79 ppm for D_2O, 3.31 and 49.0 ppm for MeOD, and 7.27 and 77.2 ppm for $CDCl_3$. Compounds **6**, **7**, **8**, and **9**,[16]nitrocyclododecane,[27] 2-nitroadamantane, 6-nitroundecane,[28] 2-nitropropylbenzene,[29] methyl 4-nitropentanoate, methyl 4-nitrohept-6-enoate, 5-nitrohexane-2-one, 5-nitrosohexan-2-ol, and *tert*-butyldimethyl-(1-methyl-4-nitro-pentyloxy)silane[30] were synthesized according to and in agreement with the literature procedures.

Experimental procedures

Ethyl 4-nitro-3-phenylpentanoate

To a solution of 2-nitroethane (1.80 g, 24 mmol) and ethyl cinnamate (3.52 g, 20 mmol) in acetonitrile (10 mL), DBU (3.05 g, 20 mmol) was added at room temperature at once. After stirring the solution for 24 h, water (50 mL) was added dropwise over 5 min. The mixture was acidified with 2 mol/L HCl (20 mL) and extracted with Et_2O (3 × 50 mL).The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (petroleum spirit/Et_2O 9:1) afforded the desired product (2.88 g, 48%). IR (neat, cm^{-1}): 3066, 2986, 1734, 1549, 1455, 1389, 1177, 702. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.10 (3H, t, J = 7.2 Hz, CH_3), 1.35 (3H, d, J = 6.7 Hz, CH_3), 2.66 (1H, dd, J = 15.6, 4.9 Hz, CH_2), 2.78 (1H, dd, J = 15.6, 10.0 Hz, CH_2), 3.62–3.69 (1H, m, CH), 3.94–4.05 (2H, m, CH_2), 4.69–4.75 (1H, m, CH), 7.17–7.20 (2H, m, CH_{Ar}), 7.26–7.35 (3H, m, CH_{Ar}). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1 (CH_3), 17.9 (CH_3), 35.9 (CH_2), 46.5 (CH_3), 60.8 (CH_2), 87.2 (CH), 128.1 (CH), 128.3 (2CH), 129.2 (2CH), 137.6 (C), 170.6 (CO). MS *m/z*: 252 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{13}H_{18}NO_4$: 252.1236; found: 252.1230.

General experimental procedure for *gem*-chloronitroso preparation

To a cooled (0 °C) solution of nitro compound (1.00 mmol) in anhydrous CH_2Cl_2 (3 mL) under a N_2 atmosphere, DBU (0.22 mL, 1.5 mmol) and chloro-*tert*-butyldimethylsilane (TBDMSCl) (0.30 g, 2.0 mmol) were added successively. After stirring for 30 min at rt, the mixture was cooled at 0 °C and oxalyl chloride (0.21 mL, 2.5 mmol) was added at once. The evolution of gas occurred and a deep blue reaction mixture was formed. (Caution: The evolution of gas could be very vigorous!) After stirring the solution for a further 2 min, petroleum spirit (20 mL) and water (5 mL) were then added consecutively dropwise over 1 min. The aqueous layer was extracted with petroleum spirit (2 × 10 mL), the combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure using a cold bath, and protected from direct light. The isolated material was purified by flash chromatography on silica gel, affording the desired product.

1-Chloro-1-nitrosocyclododecane (15)[31]

Prepared from nitrocyclododecane (213 mg, 1.00 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (185 mg, 80%) as a deep blue solid; mp (petroleum spirit) 55–56 °C (lit.[31] mp 55–57 °C). IR (neat, cm^{-1}): 2928, 2861, 1577, 1560, 1469, 1445, 726. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (14H, s, CH_2), 1.62–1.50 (2H, m, CH_2), 1.85–1.69 (4H, m, CH_2), 2.49–2.39 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3 (CH_2), 22.2 (CH_2), 22.7 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 32.7 (CH_2), 119.0 (C). MS *m/z*: 232 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{12}H_{23}NO^{35}Cl$: 232.1468; found: 232.1474. Anal. calcd for $C_{12}H_{22}ClNO$ (%): C 62.19, H 9.57, N 6.04; found: C 62.32, H 9.77, N 5.99.

2-Chloro-2-nitrosoadamantane (16)[32]

Prepared from 2-nitroadamantane (423 mg, 2.50 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (320 mg, 58%) as a deep blue oil. IR (neat, cm^{-1}): 2914, 2865, 1561, 1454. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97–1.83 (6H, m, CH_2, CH), 2.12–1.98 (4H, m, CH_2, CH), 2.37–2.29 (2H, m, CH_2, CH), 2.47 (2H, s, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.0, 27.1, 34.5, 34.7, 37.1, 37.7 (CH_2, CH), 114.4 (C). MS *m/z*: 166 ([M – Cl]$^+$), 167 ([M – Cl]$^+$), 168 ([M – Cl]$^+$), 200 ([M + H]$^+$), 201 ([M + H]$^+$), 202 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{10}H_{15}NO^{35}Cl$: 200.0848; found: 200.0842.

6-Chloro-6-nitrosoundecane (17)[32]

Prepared from 6-nitroundecane (503 mg, 2.50 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (430 mg, 78%) as a deep blue oil. IR (neat, cm^{-1}): 2955, 2931, 2868, 1579, 1464, 1380, 721. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83–0.91 (6H, m, CH_3), 0.91–1.00 (2H, m, CH_2), 1.21–1.39 (10H, m, CH_2), 2.23–2.34 (2H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9 (CH_2), 22.3 (CH_2), 22.8 (CH_2), 31.6 (CH_2), 37.6 (CH_2), 122.7 (C). MS *m/z*: 220 ([M + H]$^+$), 221 ([M + H]$^+$), 222 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_{11}H_{23}NO^{35}Cl$: 220.1468; found: 220.1471.

2-Chloro-2-nitrosopropylbenzene (18)[33]

Prepared from 2-nitropropylbenzene (165 mg, 1.00 mmol), purification (petroleum spirit 100%) produced the corresponding chloronitroso product (147 mg, 80%) as a deep blue oil. IR (neat, cm^{-1}): 3033, 2928, 1713, 1583, 1563, 1496, 1455, 1447, 1373, 1087, 736, 700. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.77 (3H, m, CH_3), 3.64–3.74 (2H, m, CH_2), 7.15–7.22 (2H, m, CH), 7.28–7.35 (3H, m, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.7 (CH_3), 44.4 (CH_2), 115.5 (C), 127.6 (CH), 128.3 (CH), 128.7 (CH), 130.9 (CH), 133.6 (C). MS *m/z*: 153 ([M – NO]$^+$), 154 ([M – NO]$^+$), 155 ([M – NO]$^+$). HR-MS *m/z* ([M – NO]$^+$) calcd for $C_9H_{10}{}^{35}Cl$: 153.0471; found: 153.0469.

Methyl 4-chloro-4-nitrosopentanoate (19)

Prepared from 4-methyl-4-nitropentanoate (161 mg, 1.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (127 mg, 72%) as a deep blue oil. IR (neat, cm^{-1}): 2955, 1737, 1585, 1563, 1438, 1197, 1174. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.80 (3H, s, CH_3), 2.14–2.24 (1H, m, CH_2), 2.36–2.46 (1H, m, CH_2), 2.57–2.67 (1H, m, CH_2), 2.88–2.98 (1H, m, CH_2), 3.67 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.2 (CH_3), 28.5 (CH_2), 33.4 (CH_2), 51.9 (CH_3), 115.5 (C), 172.3 (CO). MS *m/z*: 149 ([M – NO]$^+$) 150 ([M – NO]$^+$), 151 ([M – NO]$^+$). HR-MS *m/z* ([M – NO]$^+$) calcd for $C_6H_{10}{}^{35}ClO_2$: 149.0364; found: 149.0368.

Methyl 4-chloro-4-nitrosohept-6-enoate (20)

Prepared from methyl 4-nitrohept-6-enoate (187 mg, 1.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (150 mg, 73%) as a deep blue oil. IR (neat, cm^{-1}): 2954, 1737, 1582, 1563, 1437, 1199, 1174. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.96–2.06 (1H, m, CH_2), 2.30–2.40 (1H, m, CH_2), 2.63–2.73 (1H, m, CH_2), 3.26–3.04 (3H, m, CH_2), 3.68 (3H, s, CH_3), 5.16–5.25 (2H, m, CH_{allyl}), 5.54–5.66 (1H, m, CH_{allyl}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0 (CH_2), 32.0 (CH_2), 41.7 (CH_2), 51.9 (CH_3), 119.1 (C), 121.2 (CH_2), 129.4 (CH), 172.3 (CO). MS *m/z*: 206 ([M + H]$^+$), 207 ([M + H]$^+$), 208 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_8H_{13}NO_3{}^{35}Cl$: 206.0584; found: 206.0589.

5-Chloro-5-nitrosohexan-2-one (21)

Prepared from 5-chloro-5-nitrohexan-2-one (290 mg, 2.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (75 mg, 23%) as a deep blue oil. IR (neat, cm^{-1}): 2933, 1718, 1584, 1564, 1424, 1365, 1167. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.84 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.24–2.34 (1H, m, CH_2), 2.46–2.63 (2H, m, CH_2), 2.89–2.99 (1H, m, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.6 (CH_3), 30.0 (CH_2), 32.0 (CH_2), 38.4 (CH_3), 116.2 (C), 206.2 (CO).

Ethyl 4-chloro-4-nitroso-3-phenylpentanoate (23)

Prepared from ethyl 4-nitro-3-phenylpentanoate (251 mg, 1.00 mmol), purification (petroleum spirit/Et_2O 98:2) produced the corresponding chloronitroso product (185 mg, 69%) as a deep blue oil. IR (neat, cm^{-1}): 2982, 1733, 1582, 1455, 1374, 1160. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.04 (3H, t, J = 7.2 Hz, CH_3), 1.47 (3H, s, CH_3), 2.18 (1H, dd, J = 16.1, 4 Hz, CH_2), 2.79 (1H, dd, J = 16.1, 10.8 Hz, CH_2), 3.92 (2H, m, CH_2), 5.00 (1H, dd, J = 10.8, 4.0 Hz, CH), 7.31–7.38 (3H, m, CH_{Ar}), 7.43–7.47 (2H, m, CH_{Ar}). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1 (CH_3), 23.7 (CH_3), 35.5 (CH_2), 47.4 (CH_3), 60.8 (CH_2), 119.5 (C), 128.3 (CH), 128.6 (2CH), 129.9 (2CH), 136.5 (C), 170.7 (CO). MS *m/z*: 239 ([M – NO]$^+$), 240 ([M – NO]$^+$), 241 ([M – NO]$^+$). HR-MS *m/z* ([M – NO]$^+$) calcd for $C_{13}H_{16}{}^{35}ClO_2$: 239.0839; found: 239.0845.

5-Chloro-5-nitrosohexan-2-ol (22)

Prepared from 5-chloro-5-nitrohexan-2-one (290 mg, 2.00 mmol), purification (petroleum spirit/Et_2O 90:10) produced the corresponding chloronitroso product (140 mg, 85%) as a deep blue oil. IR (neat, cm^{-1}): 3308, 2969, 2932, 1582, 1445, 1375, 1134, 1032, 931. ^1H NMR (600 MHz, C_6D_6) δ: 0.82–0.88 (3H, m, CH_3), 0.97–1.10 (1H, m, CH_2), 1.41 (3H, s, CH_3), 1.91–2.01 (1H, m, CH_2), 2.57–2.67 (1H, m, CH_2), 3.30–3.40 (1H, m, CH_2). ^{13}C NMR (150 MHz, C_6D_6) δ: 23.5 (CH_3), 24.1 (CH_3), 33.0 (CH_2), 35.2 (CH_2), 67.0 (CH), 117.4 (C). MS *m/z*: 166 ([M + H]$^+$). HR-MS *m/z* ([M + H]$^+$) calcd for $C_6H_{13}NO_2{}^{35}Cl$: 166.0635; found: 166.0625.

Acknowledgements

The authors would like to thank Dr. A.E. Aliev for his collaboration on the NMR study and Dr. S. Coles for his collaboration on the X-ray diffraction. The authors would also like to thank Dr.Dr. R. Hay-Motherwell for her generous permission to finance this study.

References

(1) (a) Pulacchini, S.; Sibbons, K. F.; Shastri, K.; Motevalli, M.; Watkinson, M.; Wan, H.; Whiting, A.; Lightfoot, A. P. *Dalton Trans.* **2003**, (10): 2043. doi:10.1039/b210285d; (b) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, (18): 2058. doi:10.1039/b206430h; (c) Iwasa, S.; Fakhruddin, A.; Tsukamoto, Y.; Kameyama, M.; Nishiyama, H. *Tetrahedron Lett.* **2002**, *43* (35), 6159. doi:10.1016/S0040-4039(02)01277-7; (d) Iwasa, S.; Tajima, K.; Tsushima, S.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42* (34), 5897. doi:10.1016/S0040-4039(01)01119-4; (e) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *Chem. Commun. (Camb.)* **2001**, (18): 1812. doi:10.1039/b106338n; (f) Jenkins, N. E.; Ware, R. W., Jr.; Atkinson, R. N.; King, S. B. *Synth. Commun.* **2000**, *30* (5), 947. doi:10.1080/00397910008087108; (g) Martin, S. F.; Hartmann, M.; Josey, J. A. *Tetrahedron Lett.* **1992**, *33* (25), 3583. doi:10.1016/S0040-4039(00)92508-5; (h) Kirby, G. W.; Sweeny, J. G. *J. Chem. Soc. Chem. Commun.* **1973**, (19): 704. doi:10.1039/c39730000704.

(2) (a) Streith, J.; Defoin, A. *Synlett* **1996**, *1996* (03), 189. doi:10.1055/s-1996-5366; (b) Feuer, P. *The Chemistry of the Nitro and Nitroso Groups;* John Wiley: New York, 1969.

(3) For a review of spin traps see Janzen, E. G. *Acc. Chem. Res.* **1971**, *4,* 31. doi:10.1021/ar50037a005.

(4) (a) Yamamoto, Y.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80* (4), 595. doi:10.1246/bcsj.80.595; (b) Filip, S. V.; Sewald, N. *Synthesis* **2005**, *20,* 3565; (c) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126* (13), 4128. doi:10.1021/ja049849w; (d) Gouverneur, V.; Ghosez, L. *Tetrahedron* **1996**, *52* (21), 7585. doi:10.1016/0040-4020(96)00268-2.

(5) (a) Guo, H.-M.; Cheng, L.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun. (Camb.)* **2006**, (4), 429. doi:10.1039/b514194j; (b) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44* (45), 8293. doi:10.1016/j.tetlet.2003.09.057.

(6) (a) Calvet, G.; Guillot, R.; Blanchard, N.; Kouklovsky, C. *Org. Biomol. Chem.* **2005**, *3* (24), 4395. doi:10.1039/b513397a. (b) Calvet, G.; Dussaussois, M.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2004**, *6* (14), 2449. doi:10.1021/ol0491336.

(7) (a) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31* (7), 991. doi:10.1016/S0040-4039(00)94411-3; (b) Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114* (14), 5900. doi:10.1021/ja00040a086.

(8) Krebe, G.; Vasella, A.; Felber, H.; Ritter, A.; Ascherl, B. *Recl. Trav. Chim. Pays Bas* **1986**, *105,* 295. doi:10.1002/recl.19861050911.

(9) (a) Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Fluor. Chem.* **1995**, *70* (2), 207. doi:10.1016/0022-1139(94)03119-K; (b) Oxenrider, B. C.; Rogic, M. M. *J. Org. Chem.* **1982**, *47* (13), 2629. doi:10.1021/jo00134a023; (c) Sakai, I.; Kawabe, N.; Ohno, M. *Bull. Chem. Soc. Jpn.* **1979**, *52* (11), 3381. doi:10.1246/bcsj.52.3381; (d) Schenk, C.; De Boer, T. J. *Recl. Trav. Chim. Pays Bas* **1979**, *98* (1), 18. doi:10.1002/recl.19790980108; (e) Müller, E.; Fries, D.; Metzger, H. *Chem. Ber.* **1954**, *88,* 1449. doi:10.1002/ber.19540871012.

(10) (a) Archibald, T. G.; Garver, L. C.; Baum, K.; Cohen, M. C. *J. Org. Chem.* **1989**, *54* (12), 2869. doi:10.1021/jo00273a019; (b) Lee, G. A. *Synthesis* **1982**, *1982* (6), 508. doi:10.1055/s-1982-29860; (c) Labaziewicz, H.; Riddel, F. G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2926. doi:10.1039/p19790002926; (d) Barnes, M. W.; Patterson, J. M. *J. Org. Chem.* **1976**, *41* (4), 733. doi:10.1021/jo00866a044; (e) Dieckmann, H.; Lüttke, W. *Angew. Chem. Int. Ed. Engl.* **1968**, *7* (5), 387. doi:10.1002/anie.196803871.

(11) (a) Kumar, V.; Kaushik, M. P. *Synlett* **2007**, *19,* 2937 doi:10.1055/s-2007-992369; (b) Gupta, A. K.; Dubey, D. K.; Kaushik, M. P. *Org. Prep. Proced. Int.* **2005**, *37* (3), 294. doi:10.1080/00304940509354964.

(12) Motherwell, W. B.; Roberts, J. S. *Chem. Commun.* **1972**, 329. doi:10.1039/C39720000329.

(13) Luengo-Arratta, S. Intramolecular Ene Reactions of Functionalised Nitroso Compounds. Ph.D. Thesis, University of London, 2010.

(14) (a) Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Kennewell, P.; Thornton-Pett, M. *Tetrahedron* **2001**, *57* (6), 1119. doi:10.1016/S0040-4020(00)01084-X; (b) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128* (12), 3908. doi:10.1021/ja0602997.

(15) Daineko, V. I.; Proskurnina, M. V.; Skornyakov, Y. V.; Trofimov, B. A.; Zefirov, N. S. *Russ. J. Org. Chem.* **2002**, *38* (10), 1431. doi:10.1023/A:1022593300268.

(16) Bou-Moreno, R.; Luengo-Arratta, S.; Motherwell, W. B. *Tetrahedron Lett.* **2011**, *52* (17), 2097. doi:10.1016/j.tetlet.2010.11.031.

(17) Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38* (7), 1418. doi:10.1021/jo00947a040.

(18) (a) Defoin, A.; Joubert, M.; Heuchel, J.-M.; Strehler, C.; Streith, J. *Synthesis* **2000**, *2000* (12), 1719. doi:10.1055/s-2000-8214; (b) Kesler, E. *J. Heterocycl. Chem.* **1980**, *17* (5), 1113. doi:10.1002/jhet.5570170555.

(19) For a detailed discussion of deprotonation and tautomerization see Nielsen, A. T. In *The Chemistry of the Nitro and Nitroso Group;* Feuer, H., Ed.; Interscience: New York, 1969; p 349.

(20) Kresze, G.; Dittel, W. *Justus Liebigs Ann. Chem.* **1981**, 610. doi:10.1002/jl;ac.198119810407.

(21) (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Org. Chem.* **1985**, *50* (11), 1818. doi:10.1021/jo00211a006; (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1984**, *25* (44), 5091. doi:10.1016/S0040-4039(01)91127-X.

(22) (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia (Aarau)* **1979**, *33,* 1; (b) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86* (5), 751. doi:10.1021/cr00075a002; (c) Weber, W. P. *Silicon Reagents for Organic Synthesis;* Springer-Verlag: Berlin, 1983.

(23) Coles, S. J.; Gale, P. A. *Chem. Sci.* **2012**, *3* (3), 683. doi:10.1039/c2sc00955b.

(24) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28* (44), 5361. doi:10.1016/S0040-4039(00)96730-3.

(25) (a) Greene, T. W.; Wuts, G. M. *Protective Groups in Organic Synthesis,* 3rd ed.; Wiley-Interscience: London, 1999; p 114; (b) Keana, F. W.; Eckler, P. E. *J. Org. Chem.* **1976**, *41* (17), 2850. doi:10.1021/jo00879a012; (c) Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63* (3), 697. doi:10.1002/hlca.19800630320; (d) Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1981**, *46* (26), 5348. doi:10.1021/jo00339a018.

(26) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals,* 2nd ed.; Pergamon Press Ltd.: New York, 1980.

(27) Kornblum, N.; Singh, H. K.; Kelly, W. J. *J. Org. Chem.* **1983**, *48* (3), 332. doi:10.1021/jo00151a011.

(28) (a) Ballini, R.; Barboni, L.; Filippone, P. *Chem. Lett.* **1997**, *5* (5), 475. doi:10.1246/cl.1997.475; (b) Olah, G. A.; Ramaiah, P.; Lee, C.-S.; Surya Prakash, G. K. *Synlett* **1992**, *1992* (4), 337. doi:10.1055/s-1992-22006.

(29) Bhattacharjya, A.; Mukhopadhyay, R.; Pakrashi, S. C. *Synthesis* **1985**, (9), 886. doi:10.1055/s-1985-31372.

(30) Gissot, A.; N'Gouela, S.; Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69* (26), 8997. doi:10.1021/jo0489824.

(31) Mackor, A.; DeBoer, T. *Recl. Trav. Chim. Pays Bas* **1970**, *89* (2), 151. doi:10.1002/recl.19700890206.

(32) Terent'ev, A. O.; Krylov, I. B.; Ogibin, Y. N.; Nikishin, G. I. *Synthesis* **2006**, *2006* (22), 3819. doi:10.1055/s-2006-950304.

(33) Diekmann, H.; Lüttke, W. *Angew. Chem. Int. Ed., Engl.* **1968**, *7,* 387. doi:10.1002/anie.196803871.