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New chiral amino acid-derived α-acyloxynitroso reagents for asymmetric nitroso Diels–Alder reactions

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The preparation of new chiral α-acyloxynitroso derivatives **4a**–**e** as chiral dienophiles for the nitroso Diels–Alder reaction is reported. These compounds are obtained from amino acid-derived iodobenzene dicarboxylates and ketoximes, and are stable and easy-to-handle reagents. Initial studies for their nitroso Diels–Alder reactions with cyclohexadiene are also reported.

1. Introduction

Since first reported by Wichterle in 1947,[1] the nitroso Diels–Alder cycloaddition reaction has been recognized as a valuable tool in organic synthesis, and has been the subject of many mechanistical investigations as well as synthetic applications.[2] Several nitroso reagents such as arylnitroso, chloronitroso, acyl nitroso, or *N*-nitroso reagents have been designed as dienophiles for cycloaddition reactions. For some of these reagents, numerous chiral derivatives[3,4] or enantioselective catalytic systems[5] have been developed for the asymmetric nitroso Diels–Alder reaction, with very high levels of enantioselectivity being achieved. Recently, we have introduced α-acetoxynitroso derivatives as a new family of nitroso dienophiles.[6–8] These compounds, which are prepared by the treatment of ketoximes with iodobenzene diacetate,[9] are stable, easy-to-handle, and reactive surrogates for the chloronitroso derivatives. They react in cycloaddition reactions with a large panel of dienes, either in anhydrous medium in the presence of a Lewis acid or in aqueous medium (Fig. 1).[6–8]

Moreover α-acyloxynitroso derivatives that were first reported[10] in 1956 have been the subject of several pharmacological studies.[11] Most notably, in 2006, King reported these compounds as a new family of nitroxyl (HNO) donors.[12] This is of importance since the potential of nitroxyl donors in biochemistry has been well documented[13] notably for tubulin polymerization alteration[14] or the treatment of heart failure.[15]

In the search for new α-acyloxynitroso derivatives for their pharmacological potential and especially for asymmetric nitroso Diels–Alder reactions, we were interested in the preparation of chiral nitroso reagents by replacing the acetoxy group with a chiral carboxylic acid.[16] Several reports from the literature mention the preparation of chiral iodobenzene dicarboxylate by simple ligand exchange.[17] It appeared to us that α-amino acid derivatives would be good candidates as source of chirality; indeed, the preparation of amino acid-derived iodobenzene dicarboxylates has been reported in the literature.[18] Herein we report the preparation of chiral, highly enantiomerically enriched α-acyloxynitroso reagents and preliminary results concerning their asymmetric nitroso Diels–Alder reactions.

2. Results and discussion

According to the literature procedures, acetate exchange of iodobenzene diacetate with *N*-phthaloyl aminoacids **1a**–**d**[19] derived from alanine, valine, leucine, and phenylalanine was performed at 50 °C in xylene under vacuum to give the intermediate chiral iodobenzene dicarboxylate **2a**–**d**. Additionally, *N*-Boc proline **1e** was treated under the same conditions to give **2e**. The crude oily iodobenzene dicarboxylates were not isolated but treated directly with cyclohexanone oxime **3** to give the target nitroso reagents **4a**–**e** (Scheme 1, Table 1).

Compounds **4a**–**e** were obtained as blue oils after chromatographic purifications and could be stored for several months in a freezer. HPLC analysis on a chiral column confirmed that all the products were obtained in high enantiomeric excess (apart from compound **4e** for which enantiomers could not be separated), thus confirming that the synthetic sequence was performed under mild conditions and with no significant racemization.

We next investigated the possibility of performing diastereoselective synthesis of chiral α-acyloxynitroso derivatives by reaction of chiral idodobenzene dicarboxylates with prochiral ketoximes such as **5**. This type of reagent would possess a stereogenic center closer to the nitroso function. Thus, the oxime was treated under the same conditions with alanine or valine-derived iodobenzene dicarboxylates **2a** and **2b**. Disappointingly, compounds **6a** and **6b** were obtained as unseparable 1.2/1 mixtures of diastereomers (Scheme 2). Moreover, the nitroso derivatives were obtained in

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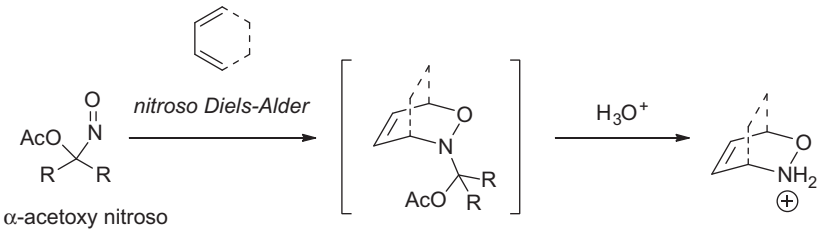
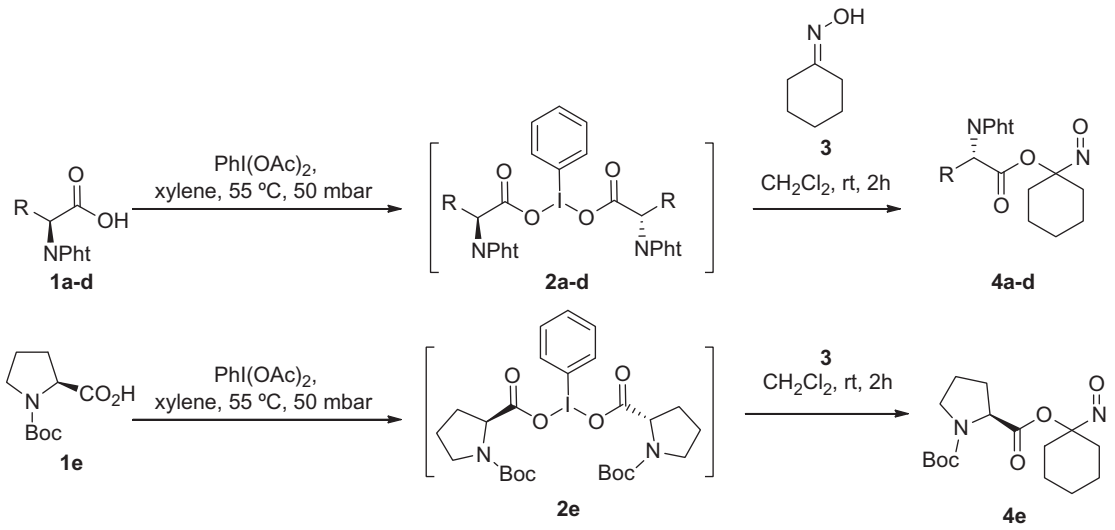


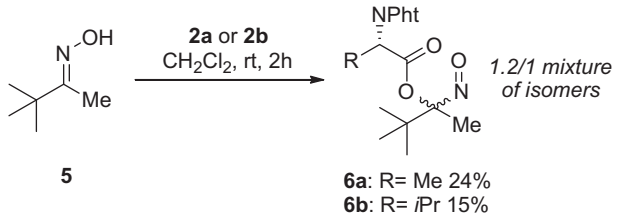
Figure 1. Nitroso Diels–Alder reactions of α-acetoxynitroso derivatives.



Scheme 1. Synthesis of chiral α-acyloxynitroso derivatives **4a–e**.

Table 1
Synthesis of chiral α-acyloxynitroso derivatives **4a–e**

Entry	Substrate	R	Product	Yield	ee
1	**1a**	Me	**4a**	53%	>93%
2	**1b**	*i*Pr	**4b**	61%	>96%
3	**1c**	*i*Bu	**4c**	74%	>96%
4	**1d**	$PhCH_2$	**4d**	71%	>94%
5	**1e**		**4e**	56%	nd



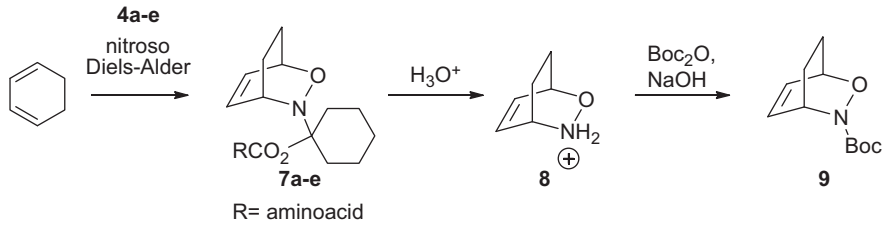
Scheme 2. Synthesis of α-acyloxynitroso reagents from a prochiral ketoxime.

low yields. Nevertheless, HPLC analysis of **6a** and **6b** proved that all the stereoisomers were enantiomerically pure.

With a set of chiral α-acyloxynitroso reagents **4a–e** in hand, their Diels–Alder reactions with 1,3-cyclohexadiene were examined. The cycloaddition reaction leads to an aminoacetal **7** which is not isolated, but hydrolyzed to give the bicyclic dihydrooxazine **8** together with the recovered aminoacid **1**. Protection of **8** as its Boc carbamate gave the final compound **9**, which was analyzed for its enantiomeric purity by HPLC (Scheme 3).

Optimizations were carried out using proline-derived nitroso dienophile **4e** (Table 2). As expected, reactions were faster in protic solvents especially in water (entry 3), giving better yields of cycloadducts. The same conditions were applied to the other dienophiles **4a–e**. The results are reported in Table 2.

Although the Boc-protected dihydrooxazine **9** was obtained in moderate yields, enantiomeric excesses were rather low, indicating a low diastereoselectivity in the cycloaddition step. Interestingly, cycloadditions with the proline-derived nitroso dienophile **4e** gave the opposite enantiomer to those obtained with the other non-cyclic amino acid-derived compounds. Comparison of specific



Scheme 3. Nitroso Diels–Alder reactions of compounds **4a–e** with 1,3-cyclohexadiene.

Table 2
Diastereoselective nitroso Diels–Alder reactions of chiral α-acyloxynitroso derivatives **4a**–**e** with 1,1-cyclohexadiene

Entry	Nitroso	Conditions	Time	Yield	ee[a]
1	**4e**	EtOH, rt	6 h	36%	−10%
2	**4e**	Toluene, rt	6 h	26%	−10%
3	**4e**	H_2O, 0 °C–rt	3 h	32%	−17%
4	**4a**	H_2O, 0 °C–rt	3 h	58%	13%
5	**4b**	H_2O, 0 °C–rt	3 h	43%	10%
6	**4c**	H_2O, 0 °C–rt	3 h	46%	10%
7	**4d**	H_2O, 0 °C–rt	3 h	49%	11%

[a] The sign−means that the opposite enantiomer of **9** was obtained.

rotations with literature data[2f] indicated that cycloadducts obtained from nitroso derivatives **4a**–**d** have the (1*R*,4*S*)-configuration for (+)-**9** whereas the proline-derived nitroso compound **4e** led to the (1*S*,4*R*)-cycloadduct (−)-**9** (Scheme 4).

We are currently investigating the influence of the amino acid (structure, protecting group) in order to optimize the stereoselectivity and to rationalize the sense of asymmetric induction.

3. Conclusion

In conclusion, we have prepared a set of new, chiral, amino acid-derived nitroso reagents. These compounds were found to be chemically and configurationally stable, and reactive toward dienes such as 1,3-cyclohexadiene. The scope and applications of this procedure, as well as mechanistic insights are currently in progress in our laboratory.

4. Experimental

General procedure for the preparation of α-acycloxynitroso reagents **4a**–**e**: to a solution of the protected amino-acid **1a**–**e** (2.6 equiv) in xylene (10 mL/mmol) was added iodobenzene diacetate (1.2 equiv) and the suspension was concentrated at 50–60 °C under 50 mbar with a rotovapor. The crude chiral iodobenzene dicarboxylate **2a**–**e** was redissolved in dichloromethane (10 mL/mmol) and the solution was cooled to 0 °C. Cyclohexanone oxime **3** (1 equiv) was added portionwise over 5 min and the mixture was stirred 30 min at 0 °C and 2 h at rt. The reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The blue residue was purified by flash chromatography on silica gel (EtOAc/cyclohexane = 5/95–10/90) to give the desired α-[α-aminoacyloxy]nitroso compound **4a**–**e** as a blue oil.

4.1. (2*S*)-(1′-Nitroso-1′-cyclohexyl)-2-phthalimido propionate 4a

Yield: 53%. ^{1}H NMR ($CDCl_3$): 7.86 (dd, *J* = 5.6; 3.0 Hz, 2H), 7.73 (dd, *J* = 5.6; 3.0 Hz, 2H), 5.19 (q, *J* = 7.2 Hz, 1H), 2.01–1.29 (m, 10H), 1.78 (d, *J* = 7.2 H, 3H); ^{13}C NMR ($CDCl_3$): 167.5, 167.4, 134.3, 131.8, 125.1, 123.6, 47.8, 29.2, 29.0, 24.5, 21.4, 21.3, 15.3; IR (neat): 2942, 2865, 1755, 1722, 1561, 1468, 1451, 1391, 1220, 1147, 1076, 883; 721; HRMS (ESI): calcd: 353.1108 ($C_{17}H_{18}N_2O_5$Na; M+Na); found: 353.1115; $[\alpha]_D$ = +27.9 (*c* 0.66, CH_2Cl_2). HPLC: ee = 93% (ADH; hexane/EtOH 90/10; 25 °C) rt major: 11.2 min; minor: 45.2 min.

4.2. (2*S*)-(1′-Nitroso-1′-cyclohexyl)-3-methyl-2-phthalimido butyrate 4b

Yield: 61%. ^{1}H NMR ($CDCl_3$): 7.89 (dd, *J* = 5.7; 3.2 Hz, 2H), 7.75 (dd, *J* = 5.7; 3.2 Hz, 2H), 4.78 (d, *J* = 8.8 Hz, 1H), 2.93–2.79 (m, 1H), 2.09–1.28 (m, 10H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): 167.8, 166.6, 134.4, 131.7, 125.1, 123.6, 58.2, 29.4, 28.9, 28.4, 24.5, 21.4, 21.3, 21.1, 19.6; IR (neat): 2943, 2872, 1761, 1717, 1563, 1467, 1450, 1388, 1192, 1142, 721; HRMS (ESI): calcd: 381.1421 ($C_{19}H_{22}N_2O_5$Na; M+Na); found: 381.1428; $[\alpha]_D$ = +86.1 (*c* 0.55, CH_2Cl_2). HPLC: ee = 96% (ADH; hexane/EtOH 95/5; 25 °C) rt major: 6.62 min; minor: 11.44 min.

4.3. (2*S*)-(1′-Nitroso-1′-cyclohexyl)-4-methyl-2-phthalimido pentanoate 4c

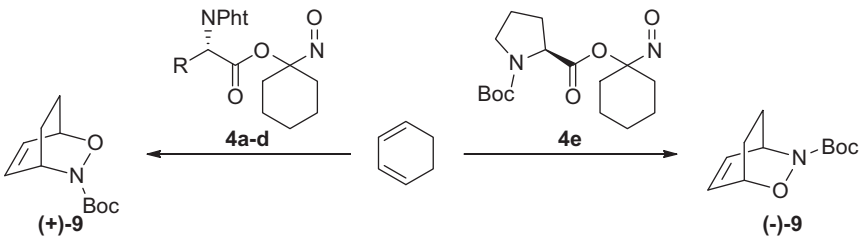
Yield: 74%. ^{1}H NMR ($CDCl_3$): 7.87 (dd, *J* = 5.7; 3.2 Hz, 2H), 7.74 (dd, *J* = 5.7; 3.2 Hz, 2H), 5.16 (dd, *J* = 11.4; 4.4 Hz, 1H), 2.52–2.39 (m, 1H), 2.06–1.27 (m, 12H), 0.99 (d, *J* = 7.0 H, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): 167.7, 167.6, 134.3, 131.9, 125.0, 51.1, 37.4, 29.3, 29.1, 25.3, 24.6, 23.2, 21.5, 21.4, 21.2; IR (neat): 2939, 2869, 1754, 1716, 1563, 1470, 1452, 1386, 1244, 1207, 1148, 720; HRMS (ESI): calcd: 395.1577 ($C_{20}H_{24}N_2O_5$Na; M+Na); found: 395.1589; $[\alpha]_D$ = +32.4 (*c* 0.44, CH_2Cl_2). HPLC: ee = 96% (ADH; hexane/EtOH 90/10; 25 °C) rt major: 5.02 min; minor: 6.09 min.

4.4. (2*S*)-(1′-Nitroso-1′-cyclohexyl)-3-phenyl-2-phthalimido propionate 4d

Yield: 71%. ^{1}H NMR ($CDCl_3$): 7.78 (dd, *J* = 5.7; 3.2 Hz, 2H), 7.67 (dd, *J* = 5.7; 3.2 Hz, 2H), 7.24–7.13 (m, 5H), 5.40 (t, *J* = 8.3 Hz, 1H), 3.67 (d, *J* = 8.3 Hz, 2H), 2.08–1.30 (m, 10H); ^{13}C NMR ($CDCl_3$): 167.4, 166.6, 136.6, 134.4, 134.2, 131.5, 128.9, 128.8, 128.6, 127.0, 125.4, 123.6, 123.5, 53.5, 34.6, 29.2, 29.0, 24.5, 21.4, 21.3; IR (neat): 2940, 2864, 1755, 1717, 1562, 1454, 1387, 1232, 1149, 720; HRMS (ESI): calcd: 429.1421 ($C_{23}H_{22}N_2O_5$Na; M+Na); found: 429.1421; $[\alpha]_D$ = −76.5 (*c* 0.44, CH_2Cl_2). HPLC: ee = 94% (ADH; hexane/EtOH 90/10; 25 °C) rt major: 8.67 min; minor: 17.74 min.

4.5. (2*S*)-(1′-Nitroso-1′-cyclohexyl)-1-tertbutyloxycarbonyl-1-pyrrolidine-2-carboxylate 4e

Yield: 56%. ^{1}H NMR ($CDCl_3$, 2 Boc rotamers): 4.42–4.35 (m, 1H, Boc rotamers), 3.61–3.35 (m, 2H, Boc rotamers), 2.42–1.45 (m, 14H, Boc rotamers), 1.47 (s, 4.5H, 1 rotamer), 1.45 (s, 4.5H, 1



Scheme 4. Stereodivergent cycloadditions of nitroso dienophiles **4a**–**e**.

rotamer); ^{13}C NMR ($CDCl_3$, 2 Boc rotamers): 170.8 (Boc rotamers), 154.4 (1 rotamer), 154.0 (1 rotamer), 124.2 (1 rotamer), 124.0 (1 rotamer), 80.3 (1 rotamer), 79.7 (1 rotamer), 59.3 (1 rotamer), 59.2 (1 rotamer), 46.7 (1 rotamer), 46.4 (1 rotamer), 31.3, 30.3, 29.5, 29.4, 29.3, 29.1, 28.5 (1 rotamer), 28.4 (1 rotamer), 24.7, 24.5, 23.5, 21.7, 21.5, 21.2; IR (neat): 2934, 2861, 1757, 1703, 1450, 1393, 1253, 1164, 1119, 935; HRMS (ESI): calcd: 349.1734 ($C_{16}H_{26}N_2O_5Na$; M+Na); found: 349.1746; $[\alpha]_D = -84.0$ (*c* 0.608, CH_2Cl_2).

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