A Practical Oxidative Method for the Cleavage of Hydrazide N–N Bonds

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Abstract: The selective N-oxidation of the most nucleophilic amino nitrogen atom in hydrazides is central to the development of an unprecedented methodology for the cleavage of their N–N bonds under oxidative conditions. Treatment of a series of hydrazides **1–9** with peracids such as magnesium monoperoxyphtalate hexahydrate (MMPP·6H_2O) or *meta*-chloroperbenzoic acid (*m*-CPBA) afforded the corresponding amides **10–16** in good-to-excellent yields (80–92%). The extension of the methodology to carbamate-like substrates such as **17** and **18** was also investigated, but in this case the process is synthetically useless in view of the low yields observed of carbamates **19** and **20** (≈15%). Experiments carried out with equivalent amounts of oxidant produced nitrones, such as **26**, proceeding from the dialkylamino moiety, and ^{1}H NMR experiments indicated that this product is formed by fast conversion of the parent hydrazide, without detection of the expected hydrazide *N*-oxides. In addition, the over oxidation of **26** into nitronate **25** proceeds through an unknown intermediate. This oxidative N–N bond cleavage by peracids is an alternative method for the deamination of hydrazides, and constitutes the only solution compatible with substrates carrying functionalities sensitive to reducing conditions.

Keywords: cleavage reactions · hydrazides · oxidation · pericyclic reactions · synthetic methods

Introduction

Hydrazines or their acyl-protected forms are common intermediates obtained in a growing number of synthetic routes. Remarkable recent examples of such methods are the anionic[1] or radical[2] additions to the C=N bond of hydrazones, the electroreductive coupling of ketones with hydrazones,[3] the addition of carbon nucleophiles to acylhydrazonium salts,[4] the addition of *N*-aminolactams to Michael acceptors,[5] the aza-Michael addition of hydrazines to electrophilic alkenes,[6] the radical cyclisation of *N*-allyl-α-perchlorohydrazides,[7] and the 1,3-dipolar cycloaddition of azomethine imines to dipolarophiles (see Scheme 1).[8]

In most cases, obtaining the corresponding free amines or acyl-protected derivatives is the main application for these routes and therefore, the cleavage of the N–N bond appears as a key transformation. Several reductive methods have been used for this cleavage. The most widely used are 1) Zn/H^+,[9] 2) catalytic hydrogenation by Raney-Ni,[10] PtO_2,[11] or Pd-based catalysts,[12] 3) Na(Li)/NH_3,[13] 4) SmI_2,[14] and 5) BH_3·THF.[15] Though these methods give satisfactory results in general, there are limitations and difficulties in many cases, mainly related with the harsh acidic or basic conditions required, the lack of reactivity, and/or the partial racemization of neighboring stereogenic centers. Finally, it should be noted that all available methods require strong reducing conditions that are incompatible with a number of functionalities or protecting groups.

In fact, it was during our previous work on the Staudinger-like [2+2] cycloaddition of *N*,*N*-dialkylhydrazones with functionalized ketenes (Scheme 2) that we faced serious difficulties with the reductive deamination of the resulting 1-dialkylamino azetidin-2-ones;[16] from the above-mentioned variety of methods, only large excesses of SmI_2 in the presence of hexamethylphosphoramide (HMPA) as co-solvent afforded the desired products. Moreover, these inconvenient conditions gave only low to moderate yields (42–65%). Therefore, we were forced to study alternative methodologies suitable for the cleavage of the N–N bond. In this paper, we report in full on the unprecedented oxidative cleavage of *N*,*N*-dialkylhydrazides by peracids.

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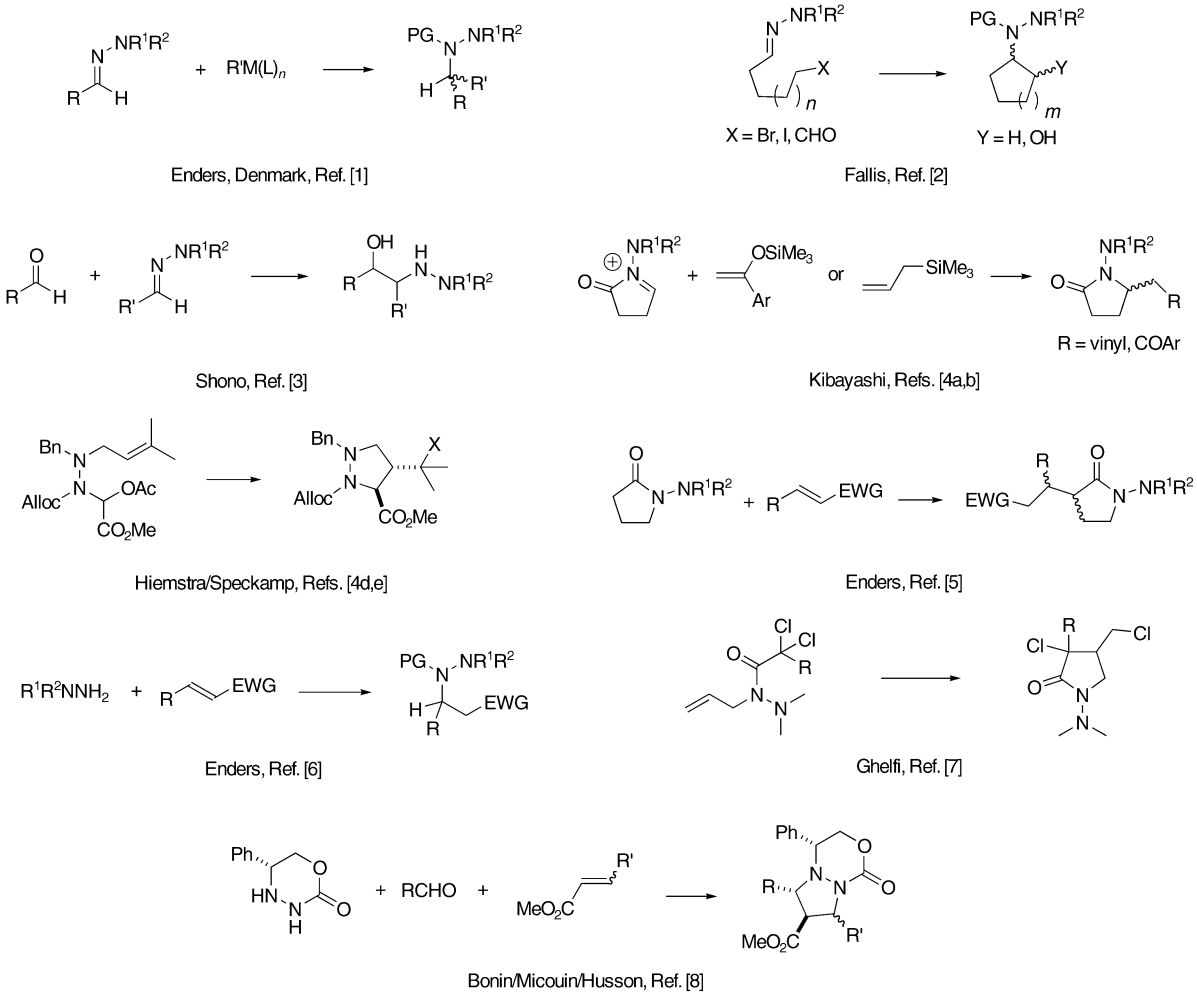
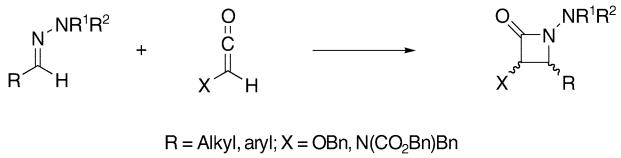


Scheme 1. Hydrazide intermediates in organic synthesis: selected examples.

Abstract in Spanish: *La N-oxidación selectiva del nitrógeno amínico de hidrazidas constituye la estrategia clave para el desarrollo de una nueva metodología para la rotura del enlace N–N en estos compuestos en condiciones oxidantes. El tratamiento de una serie de hidrazidas* ***1–9*** *con perácidos como MMPP·6 H_2O ó m-CPBA conduce a las correspondientes amidas* ***10–16*** *con rendimientos de buenos a excelentes (80–92 %). Se investigó además la extensión de la metodología a sustratos de tipo carbamato como* ***17*** *ó* ***18****, pero los rendimientos, muy inferiores (≈15 %) en este caso, hacen el procedimiento inadecuado en síntesis. En experimentos llevados a cabo sin exceso de oxidante se obtuvieron nitronas como* ***26*** *como el producto procedente del fragmento dialquilamino, y en experimentos de ^1H RMN se pudo comprobar que este producto se forma rápidamente a partir de la hidrazida de partida, sin que se detecten N-óxidos de hidrazida como intermedios. Se pudo establecer además que la oxidación de* ***26*** *a* ***25*** *transcurre a través de una especie intermedia no identificada. Este procedimiento de rotura oxidativa de enlaces N–N por perácidos representa una metodología alternativa para la desaminación de hidrazidas, y constituye la única solución disponible para sustratos sensibles a condiciones reductoras.*



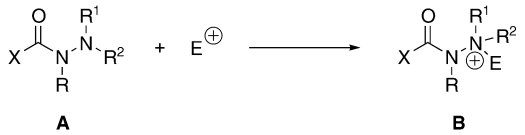
Scheme 2. [2+2] cycloaddition of *N,N*-dialkylhydrazones with ketenes.

The quaternization of a nitrogen atom is a central strategy used to weaken a C–N bond. Classic applications of this are the Cope elimination of tertiary amine oxides,[17] the Hofmann degradation of quaternary ammonium salts,[18] the Stevens rearrangement,[19] the Sommelet–Hauser rearrangement,[20] the [2,3]-sigmatropic rearrangement of allylic nitrogen ylides,[21] and the Meisenheimer rearrangement of tertiary amine oxides.[22] There are also known reactions in which the quaternization of one of the nitrogen atoms of an N–N bond results in its cleavage. The Benzidine rearrangement,[23] the Fischer indole synthesis,[24] the aza-Cope elimination from hydrazones to nitriles,[25] the acid-promoted rearrangement of aryl triazenes,[26] and the rearrangement of *N*-nitroso aryl amines (Fisher–Hepp)[27] belong to this group. Surprisingly, and in spite of the many known precedents,

there are no reports on the application of a related strategy for the deamination of hydrazides.

Results and Discussion

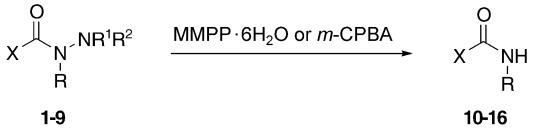
The selective quaternization of the most nucleophilic amino nitrogen of hydrazide **A** can be achieved by reaction with several types of electrophilic reagents to afford compounds of general structure **B**, according to the reaction depicted in Scheme 3.



Scheme 3. Quaternization of hydrazide amino nitrogens.

Among other possibilities (N-alkylation, N-acylation, N-nitrosation, etc.) the N-oxidation of the amino nitrogen was considered the most promising approach for our purposes on the basis of the following considerations: 1) Mild conditions and available reagents such as peracids are used. 2) Neutral, easy to handle and easily characterized intermediates are expected. 3) The cleavage of the expected hydrazide *N*-oxides could proceed by thermal activation like the closely related Meisenheimer rearrangement.

Considering the experimental simplicity and based on our previous experience[25a],[28] with these types of reagents, we decided to start the experiments using magnesium monoperoxyphtalate hexahydrate (MMPP·6H_2O) or *meta*-chloroperbenzoic acid (*m*-CPBA) as the N-oxidation agents. It was a pleasant surprise to observe that the reaction of several substrates **1–9**[7],[16] with these reagents proceeded smoothly at room temperature to afford the desired deamination products **10–16** directly, without detection of any intermediates (Scheme 4). Comparison of this behavior with that of amine oxides suggests a lower thermal stability for hydrazide amine oxides, which are assumed to be the primary intermediates formed.



Scheme 4. Deamination of hydrazides by peracids.

The results in Table 1 show the efficiency of this spontaneous process. The procedure is effectively applied to the deamination of a variety of hydrazides **1–9** carrying diverse *N*-dialkylamino moieties including dimethylamino (entries 6–8), pyrrolidin-1-yl (entry 5), pyperidin-1-yl (entry 9), and more complex structures like the chiral derivatives of prolinol (entry 1), mannitol (entry 2), or 2,5-dimethylpyrrolidine (entries 3 and 4).

The extension of the method to the deamination of carbamate-like derivatives **17** and **18**[29] was also studied. Unfortunately, the N-oxidation of this kind of substrate afforded the desired products **19–20** in low yields, along with ketones **21–22** as the major products of the reactions. The formation of the latter can be explained by aza-Cope elimination reactions from *N*-oxide intermediates to imine derivatives, such as **23**, which easily hydrolyze to the corresponding ketone under the reaction conditions. Supporting this hypothesis, imine **23** ($n=1$) was detected as an intermediate in the oxidation of **17** when *m*-CPBA was used in the presence of $NaHCO_3$ (Scheme 5).

The presence of sensitive functionalities in the chlorinated substrates **6–9** made cleavage under reductive conditions unsuccessful. In addition, these oxidative conditions, reported in our earlier work,[16] have been applied by Enders and coworkers[30] as the only suitable procedure for the deamination of optically pure 1-dialkylaminoisoindolones.

Due to the novelty of the reaction, we were also interested in its mechanism, therefore experiments were carried out to gain useful information about the reaction course. Firstly, the isolation and characterization of the product(s) derived from the amine fragment were required. In the initial experiments using excess oxidant and proline-derived hydrazides like **1** (entry 1, Scheme 6), nitrone **24** was obtained as a byproduct, but the isolated yields of this compound were repeatedly lower than 50%. Therefore, the question above was not fully answered.

Attempts to isolate or detect any other reaction products were unsuccessful. In addition, the over oxidation of **24** to afford highly polar, low-molecular-weight byproducts was considered, but this was ruled out after proving the stability of **24** against excess of MMPP under the reaction conditions. In the case of the mannitol-derived hydrazide **2**, any fragment proceeding from the dialkylamino moiety was lost during workup. Finally, the cleavage of hydrazides **3** and **4** afforded cyclic nitronate **25** in low yields (13–26%) as the only isolable byproduct. Though an excess of reagent was necessary for the deamination of hindered substrates such as **1** or **2** (entries 1 and 2), in the case of 2,5-dimethylpyrrolidine derivatives, such as **3** or **4**, the use of stoichiometric amounts of MMPP or *m*-CPBA sufficed to achieve clean and high-yielding transformations. In this case however, a different byproduct, nitrone **26**, was isolated from the amino moiety in a yield of 75–80%, which was for the first time high enough to understand the mass balance in the reaction (Scheme 7).

Taken together, the above results and considerations suggest that the reaction proceeds through the spontaneous cleavage of intermediate hydrazide *N*-oxides into the deaminated amide fragment (**10–16**) and a nitrone formed from the dialkylamino moiety, which is then further oxidized by an excess of oxidant. This last hypothesis was independently confirmed by the controlled transformation of **26** into **25** by addition of equivalent amounts of MMPP·6H_2O or *m*-CPBA under the reaction conditions. Additionally, ^1H NMR monitoring was conducted for the oxidation reactions of **4** by using 1 or 2 equivalents of dried *m*-CPBA in $CDCl_3$ (Figure 1). Due to the simplicity of spectra of the chosen

Table 1. Oxidative deamination of hydrazides

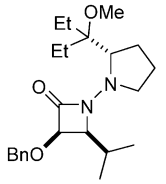
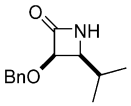
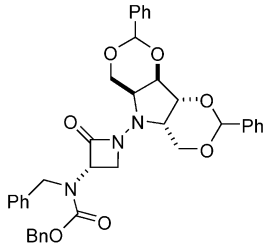
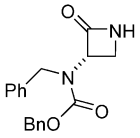
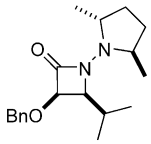
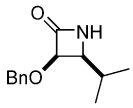
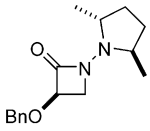
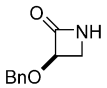
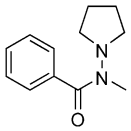
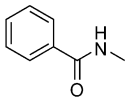
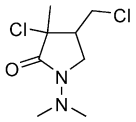
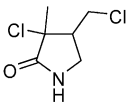
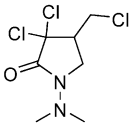
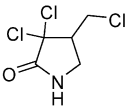
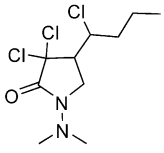
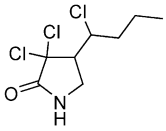
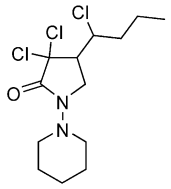
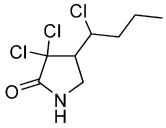
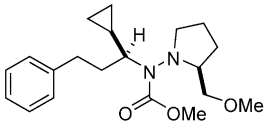
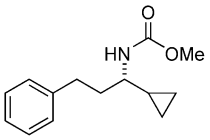
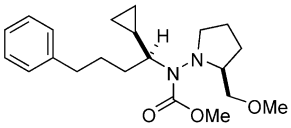
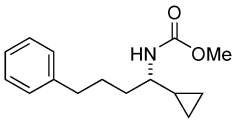
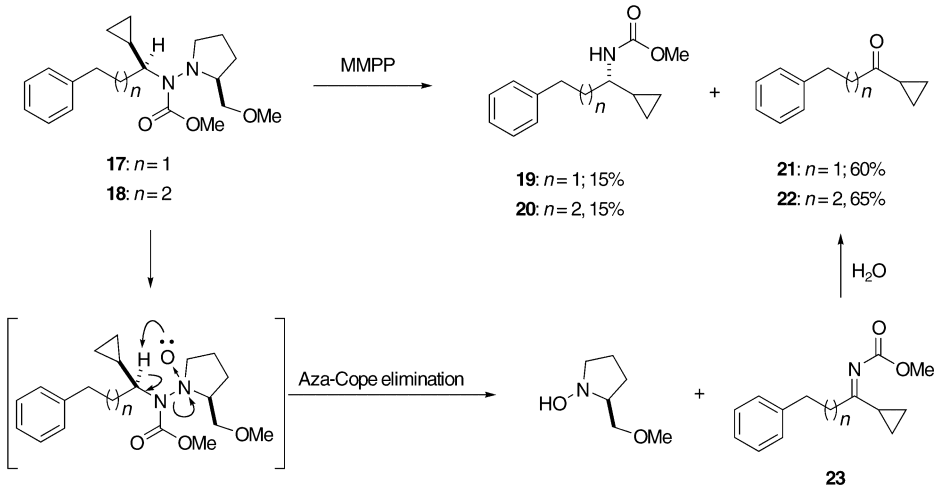
Entry	Hydrazide	MMPP [equiv]	*t* [h]	Product	Yield[a] [%]
1	 **1**	6	4	 **10**	88
2	 **2**	12	6	 **11**	82
3	 **3**	1.1	2	 **10**	91
4	 **4**	1.1	0.5	 **12**	82
5	 **5**	3	0.5	 **13**	82
6	 **6**	3	0.5	 **14**	80
7	 **7**	3	2	 **15**	82
8	 **8**	3	0.5	 **16**	92

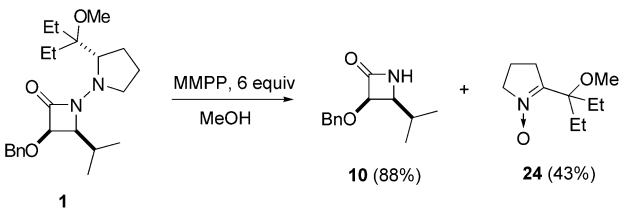
Table 1. (Continued)

Entry	Hydrazide	MMPP [equiv]	*t* [h]	Product	Yield[a] [%]
9	 **9**	3	0.5	 **16**	89
10	 **17**	6	24	 **19**	15[b]
11	 **18**	6	24	 **20**	15[c]

[a] Isolated yield. [b] Ketone **21** was isolated as major product in 60% yield. See text and Scheme 5. [c] Ketone **22** was isolated as major product in 65% yield. See text and Scheme 5.



Scheme 5. Oxidation of methoxycarbonyl derivatives **17** and **18**.

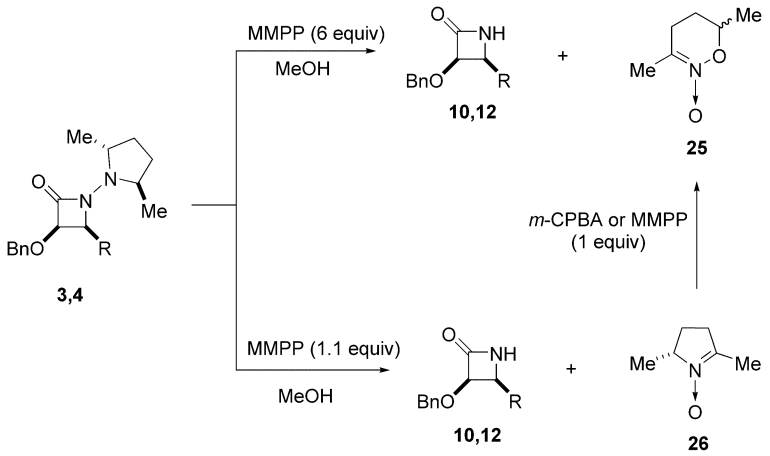


Scheme 6. Cleavage of proline derivative **1** by excess of MMPP.

substrate and the clean reaction achieved under these conditions, the spectra recorded at different reaction times could be easily analyzed. The reaction performed with equivalent amounts of oxidant indicated a fast and clean transformation of the starting material into the products **12** and **26**; no signals assignable to the proposed hydrazide *N*-oxide intermediate could be identified (Figure 1, spectrum 1). When the reactions were performed with a twofold excess of oxidant, a complex mixture was observed after a short reaction time (spectrum 2). In this spectrum, it was also possible to identify peaks corresponding to the deaminated product **12** and the nitrone **26**, but other signals corresponding to the nitronate **25** and an unknown intermediate were also identified. The spectra recorded at longer reaction times (spectrum 3) indicated a smooth evolution of **26** into **25** through the mentioned intermediate, which was completed after 1.5 h at room temperature (spectrum 4). In the case of substrate **1**, it seems reasonable to assume that the corresponding over oxidation of **24** is strongly hindered for steric reasons.

Assuming that the N-oxidation of the amine is the first step of the reaction, it follows that the resulting hydrazide *N*-oxides are unstable compounds that spontaneously react to afford the final products. According to this hypothesis, a search in literature databases reveals that these products are not known.

The collected information made us consider two possible reaction mechanisms:



Scheme 7. Cleavage of *trans* (*R*,*R*)-2,5-dimethylpyrrolidin-1-yl derivatives.

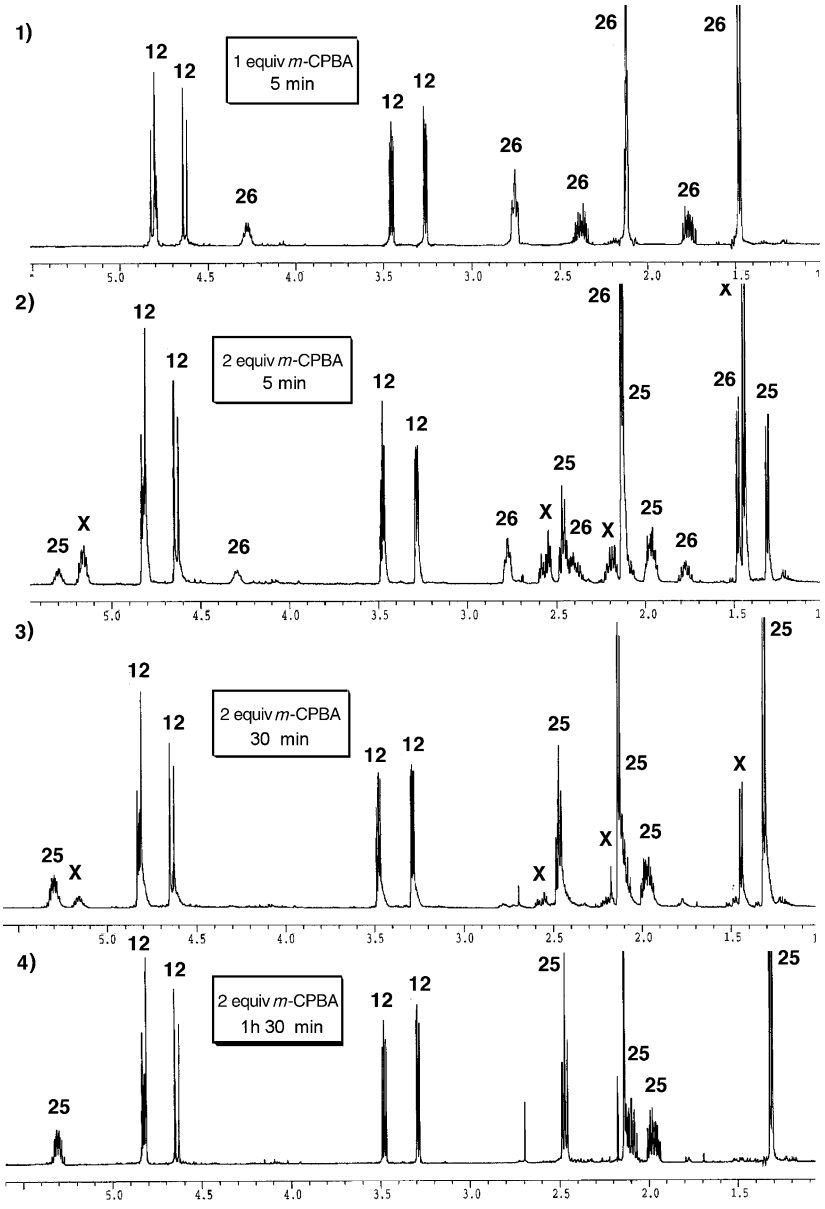


Figure 1. ^{1}H NMR experiments for the oxidation of **4** by *m*-CPBA.

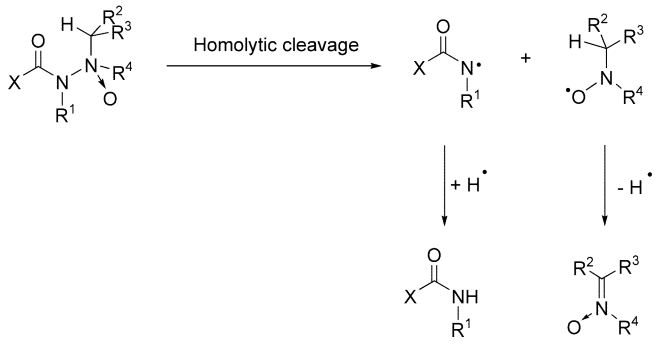
1) Homolytic N–N bond cleavage in the intermediate hydrazide *N*-oxides to afford relatively stable amidyl and nitroxide free radicals, which give final products after an intermolecular radical quench (Scheme 8).
2) A pericyclic process that can be viewed as the concerted retro-1,2-addition of the enolic form of the amide to the nitrone (Scheme 9).

We tentatively propose this second mechanism on the basis of three considerations.

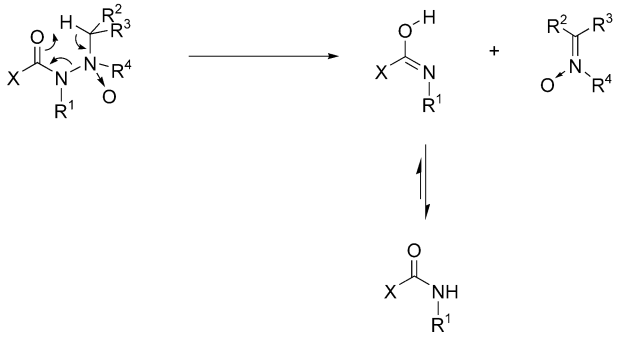
The first consideration is that bicyclic substrates **27** and **28**[8] were transformed into the corresponding *N*-oxides **29** and **30** (Scheme 10), which were isolated as crystalline, stable compounds. Attempts to promote the thermal rearrangement of **29** or **30** into compounds **31** or **32** were unsuccessful. The unusual stability of these compounds can be explained if, according to the proposed pericyclic mechanism, they are unable to reach the conformation required for the N–N bond cleavage, while their relative stability would be difficult to explain if the homolytic N–N bond cleavage mechanism is assumed.

The second consideration is that if a radical mechanism operates, it would constitute a kind of aza-Meisenheimer[22] reaction and, accordingly, similar radical recombinations and side reactions would be expected. Moreover, a partial disproportion of nitroxide radicals into nitrone and hydroxylamine is well established.[31] However, no traces of hydroxylamines were detected in the reaction mixtures.

Finally the different behavior of amide-like (**1**–**9**) and carbamate-like substrates (**17**, **18**) suggests that the nature of the carbonyl strongly influences the course of the reaction, a fact



Scheme 8. Homolytic cleavage of the N–N bond.



Scheme 9. N–N bond cleavage through a pericyclic mechanism.

which is easier to understand assuming the proposed mechanism.

Conclusion

In summary, the unprecedented strategy outlined for the oxidative N–N bond cleavage of hydrazides by peracids could be successfully applied for the deamination of a variety of substrates under mild conditions. In practice, this methodology provides not only an efficient solution for particular systems where other methods fail[16] or produce undesired racemizations,[30] but appears as the only solution compatible for substrates carrying functionalities sensitive to reducing conditions.

Experimental Section

General methods: Melting points were determined by means of a metal block and are uncorrected. Optical rotations were measured at room temperature. FT-IR spectra were recorded for KBr pellets or films. EI-mass spectra were recorded at 70 eV, by using an ionizing current of 100 mA, an accelerating voltage of 4 kV, and a resolution of 1000 or 10000 (10% valley definition). The reactions were monitored by TLC. Purification of the products was carried out by chromatography (silica gel). The boiling range of the light petroleum ether was 40–65 °C.

General procedure for N–N bond cleavage of hydrazides: MMPP·6 H_2O (0.55–6 mmol) was added to a solution of hydrazide **1**–**9**, **17**, or **18** (1 mmol) in methanol (5 mL); this mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The mixture was then diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated, and the residue purified by flash chromatography. Eluants, yields, and spectral and analytical data for compounds **10**–**16**, **19**, and **20** are as follows.

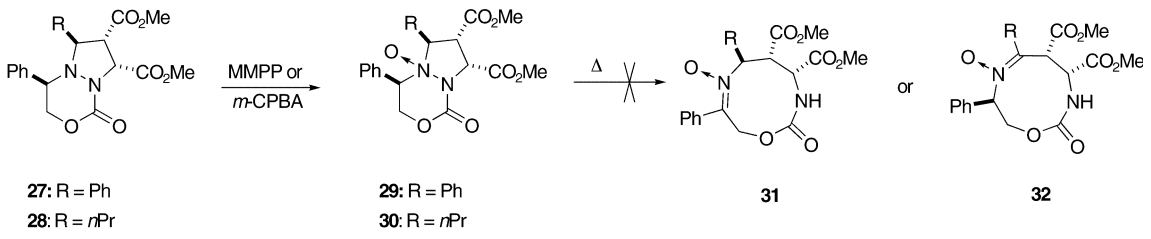
(3*R*,4*S*)-3-Benzyloxy-4-isopropylazetidin-2-one (10) and 5-(1-ethyl-1-methoxypropyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (24): From **1**, flash chromatography (3:1 toluene/AcOEt) gave 193 mg (88%) of crystalline **10**. M.p. 85–86 °C; $[\alpha]_D^{26} = +120.4$ ($c = 1.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 1.9–2.1 (m, 1H), 3.35 (dd, $J = 4.9$, 9.2 Hz, 1H), 4.67 (dd, $J = 2.9$, 4.9 Hz, 1H), 4.72 (d, $J = 11.9$ Hz, 1H), 4.94 (d, $J = 11.9$ Hz, 1H), 6.41 (br s, 1H), 7.2–7.4 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.8$, 18.9, 28.0, 60.8, 72.5, 81.9, 127.5, 127.6, 128.3, 137.3, 169.3 ppm; IR (film): $\tilde{\nu} = 3262$, 1760 cm^{-1}; MS (CI): m/z (%): 220 (60) [M^++1], 192 (21), 91 (100); elemental analysis calcd (%) for $C_{13}H_{17}NO_2$: C 71.20, H 7.81, N 6.39; found: C 71.16, H 8.00, N 6.46.

Further elution with 20:1 CH_2Cl_2/MeOH afforded 24 mg (43%) of nitrone **24**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.75$ (t, $J = 7.4$ Hz, 6H), 1.68 (dq, $J = 7.4$, 14.8 Hz, 2H), 1.97–2.08 (m, 2H), 2.49 (dq, $J = 7.4$, 14.8 Hz, 2H), 2.79–2.84 (m, 2H), 3.11 (s, 3H), 4.01–4.08 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 7.9$, 16.7, 22.8, 32.9, 47.4, 64.4, 81.9, 150.9 ppm; IR (KBr): $\tilde{\nu} = 2966$, 1739, 1647 cm^{-1}; MS (EI): m/z (%): 185 (5) [M^+], 168 (32), 156 (100); HRMS calcd for $C_{10}H_{19}NO_2$: 185.1416; found: 185.1413.

Benzyl ester of (*S*)-benzyl-(2-oxoazetidin-3-yl)carbamic acid (11): From **2** (0.3 mmol), flash chromatography (7:1 toluene/acetone) gave 76 mg (82%) of **12**. $[\alpha]_D^{22} = -8.8$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_6$]DMSO, 90 °C): $\delta = 3.14$ (dd, $J = 2.9$, 5.5 Hz, 1H), 3.31 (t, $J = 5.5$ Hz, 1H), 4.49 (d, $J = 15.9$ Hz, 1H), 4.61 (d, $J = 15.9$ Hz, 1H), 4.90 (dd, $J = 2.9$, 3.5 Hz, 1H), 5.12 (d, $J = 12.6$ Hz, 1H), 5.16 (d, $J = 12.6$ Hz, 1H), 7.40 (br s, 1H), 7.22–7.34 ppm (m, 10H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 90 °C): $\delta = 47.0$, 55.6, 70.2, 72.2, 132.2, 132.3, 132.7, 132.9, 133.4, 141.0, 143.5, 160.5, 172.0 ppm; IR (KBr): $\tilde{\nu} = 3299$, 1771, 1708 cm^{-1}; MS (CI): m/z (%): 311 (68) [M^++1], 283 (6), 239 (7), 221 (5), 91 (100); elemental analysis calcd (%) for $C_{18}H_{18}N_2O_3$: C 69.66, H 5.85, N 9.03; found: C 69.59, H 6.19, N 9.11.

3,6-Dimethyl-5,6-dihydro-4*H*-[1,2]oxazine 2-oxide (25): From **3** and MMPP (3 mmol), flash chromatography (3:1 toluene/AcOEt) gave 193 mg (88%) of crystalline **10** and 17 mg (13%) of nitronate **25**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (d, $J = 6.6$ Hz, 3H), 1.94–2.01 (m, 1H), 2.08–2.14 (m, 1H), 2.14 (s, 3H), 2.46–2.48 (m, 2H), 5.28–5.31 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.7$, 26.7, 29.7, 39.4, 62.3, 206.7 ppm; IR (KBr): $\tilde{\nu} = 2928$, 2856, 1641 cm^{-1}; MS (CI): m/z (%): 130 (100) [M^++1], 114 (72), 112 (98); HRMS calcd for $C_6H_{12}NO_2$: 130.0868; found: 130.0867.

(*R*)-3-Benzyloxyazetidin-2-one (12) and (*R*)-2,5-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (26): From **4** (0.3 mmol), flash chromatography (3:2 toluene/AcOEt) gave 146 mg (82%) of crystalline **12**. M.p. 80–82 °C; $[\alpha]_D^{22} = +54.9$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.28$ (dd, $J = 2.2$, 4.9 Hz, 1H), 3.47 (t, $J = 4.9$ Hz, 1H), 4.67 (d, $J = 11.6$ Hz, 1H),



27: R = Ph
28: R = *n*Pr
29: R = Ph
30: R = *n*Pr
31
32

Scheme 10. Oxidation of bicyclic substrates **27** and **28**.

4.81–4.84 (m, 1H), 4.86 (d, $J=11.6$ Hz, 1H), 5.93 (brs, 1H), 7.3–7.4 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=44.1$, 72.2, 82.5, 128.1, 128.5, 136.9, 168.3 ppm; IR (KBr): $\tilde{\nu}=3311$, 1731, 1461 cm^{-1}; MS (CI): *m/z* (%): 178 (100) [M^++1], 150 (31), 91 (84); elemental analysis calcd (%) for $C_{10}H_{11}O_2N$: C 67.78, H 6.23, N 7.90; found: C 67.45, H 6.25, N 7.90.

Further elution with 20:1 CH_2Cl_2/MeOH afforded 41 mg (72%) of nitrone **26.** $[\alpha]_D^{25}=+13.7$ ($c=1.1$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.46$ (d, $J=6.7$ Hz, 3H), 1.67–1.79 (m, 1H), 2.06 (dd, $J=3.1$, 1,5 Hz, 3H), 2.27–2.39 (m, 1H), 2.65–2.71 (m, 2H), 4.09–4.19 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=12.9$, 18.5, 25.0, 30.9, 67.9, 143.5 ppm; IR (KBr): $\tilde{\nu}=2983$, 1683, 1381 cm^{-1}; MS (EI): *m/z* (%): 113 (100) [M^+], 98 (62), 71 (19); HRMS calcd for $C_6H_{11}NO$: 113.0841; found: 113.0843.

3-Chloro-3-methyl-4-chloromethyl-2-pyrrolid-2-one (14): From **6** (1 mmol), flash chromatography (diethyl ether/petroleum ether 9:1) gave 146 mg (80%) of crystalline **14**. M.p. 89–90°C; ^{1}H NMR (300 MHz, $CDCl_3$): major diasteroisomer: $\delta=1.77$ (s, 3H), 2.60–2.70 (m, 1H), 3.19 (dd, $J=9$, 10 Hz, 1H), 3.55–3.61 (m, 1H), 3.71 (dd, $J=9$, 11 Hz, 1H), 3.84 (dd, $J=5$, 11 Hz, 1H), 6.91 ppm (brs, 1H); minor diasteroisomer: $\delta=1.63$ (s, 3H), 3.01–3.07 (m, 1H), 3.25–3.30 (m, 1H); 3.48 (m, 1H), 3.71 (m, 1H), 3.77 (m, 1H); 6.99 ppm (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): major diasteroisomer: $\delta=24.6$, 42.1, 43.5, 49.7, 67.8, 174.4 ppm; minor diasteroisomer: $\delta=21.1$, 41.9, 43.0, 50.5, 67.0, 174.6 ppm; IR (KBr): $\tilde{\nu}=3410$, 3327, 1710 cm^{-1}; MS (EI): *m/z* (%):185 (8) [M^+], 183 (43) [M^+], 181 (59) [M^+], 91 (55), 89 (100); HRMS calcd for $C_6H_9Cl_2NO$: 181.0061; found: 181.0067.

3,3-Dichloro-4-chloromethylpyrrolid-2-one (15): From **7** (1 mmol), flash chromatography (diethyl ether/petroleum ether 9:1) gave 164 mg (82%) of crystalline **15**. M.p. 95–96°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.13$–3.23 (m, 1H), 3.28 (dd, $J=8.3$, 10 Hz, 1H), 3.61–3.74 (m, 1H), 3.75 (dd, $J=10$, 11.4 Hz, 1H), 4.00 (dd, $J=4.2$, 11.4 Hz, 1H), 6.91 ppm (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=40.8$, 43.5, 53.5, 82.9, 169.0 ppm; IR (KBr): $\tilde{\nu}=3423$, 1729 cm^{-1}; MS (EI): *m/z* (%): 205 (9) [M^+], 203 (29) [M^+], 201 (31) [M^+], 162 (14) [M^+], 160 (42), 158 (45), 113 (10), 111 (65), 109 (100); HRMS calcd for $C_5H_3Cl_3NO$: 200.9515; found: 200.9516.

3,3-Dichloro-4-(1-chlorobutyl)pyrrolid-2-one (16): From **8** (1 mmol), flash chromatography (diethyl ether/petroleum ether 3:1) gave 223 mg (92%) of crystalline **16**. M.p. 83–84°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): $\delta=$ 0.99 (t, $J=7.3$ Hz, 3H), 1.52–1.57 (m, 1H), 1.70–1.89 (m, 2H), 2.22–2.38 (m, 1H), 3.04–3.13 (m, 1H), 3.25 (dd, $J=9.0$, 10.5 Hz, 1H), 3.68–3.75 (m, 1H), 4.25–4.33 (m, 1H), 7.58 ppm (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta=13.2$, 18.9, 37.3, 44.3, 56.4, 61.6, 82.8, 169.1 ppm; IR (KBr): $\tilde{\nu}=$ 3420, 1715 cm^{-1}; MS (70 eV, EI): *m/z* (%): 245 (8) [M^+], 243 (11) [M^+], 208 (14), 104 (75) , 55 (100); HRMS calcd for $C_8H_{12}Cl_3NO$: 242.9984; found: 242.9977. Starting from **9**, the same product was obtained in 89% yield, and had identical characterization data.

Methyl ester of (*S*)-(1-cyclopropyl-3-phenylpropyl)carbamic acid (19) and 1-cyclopropyl-3-phenylpropan-1-one (21): From **17** (0.5 mmol), flash chromatography (10:1 hexane/AcOEt) gave 52 mg (60%) of **21**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.7$–0.9 (m, 2H), 0.9–1.0 (m, 2H), 1.8–2.0 (m, 3H), 2.8–3.0 (m, 4H), 7.1–7.4 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=10.9$, 20,8, 30.9, 45.3, 126.1, 128.6, 128.8, 141.1, 210.5 ppm; HRMS calcd for $C_{12}H_{14}O$: 174.1045; found: 174.1048.

Eluted second crystalline **19** (17.5 mg, 15%). M.p. 73–75°C; $[\alpha]_D^{23}=-0.9$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.15$–0.7 (m, 4H), 0.7–0.9 (m, 1H), 1.7–2.0 (m, 2H), 2.68 (t, $J=7.0$ Hz, 2H), 3.1 (brs, 1H), 3.65 (s, 3H), 4.65 (brs, 1H), 7.1–7.4 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=2.6$, 3.8, 16.6, 32.3, 37.6, 52.0, 55.6, 125.8, 128.3, 128.4, 141.9, 155.7 ppm; elemental analysis calcd (%) for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00; found: C 71.78, H 8.21, N 6.11.

Methyl ester of (*S*)-(1-cyclopropyl-4-phenylbutyl)carbamic acid (20) and 1-cyclopropyl-4-phenylbutan-1-one (22): From **18** (0.5 mmol), flash chromatography (10:1 hexane/AcOEt) gave 61 mg (65%) of **22** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.7$–0.9 (m, 2H), 0.9–1.0 (m, 2H), 1.8–2.0 (m, 3H), 2.55 (t, $J=8.5$ Hz, 2H), 2.65 (t, $J=8.2$ Hz, 2H), 7.1–7.4 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=10.9$, 11.1, 20.7, 25.7, 35.4, 42.9, 126.1, 128.6, 128.7, 142.0, 211.0 ppm; HRMS calcd for $C_{13}H_{16}O$: 188.1201; found: 188.1196.

Eluted second crystalline **20** (19 mg, 15%). M.p. 73–75°C; $[\alpha]_D^{23}=-44.7$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.15$–0.55 (m, 4H), 0.7–0.8 (m, 1H), 1.5–1.7 (m, 4H), 2.5–2.7 (m, 2H), 2.99 (brs, 1H), 3.63 (s, 3H), 4.51 (brs, 1H), 7.0–7.4 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=2.8$, 4.1, 16.8, 28.0, 35.8, 36.1, 52.2, 55.9, 126.0, 128.5, 128.6, 142.5, 157.0 ppm; HRMS calcd for $C_{15}H_{22}NO_2$: 248.1650; found: 248.1648.

Dimethyl ester of (4*R*,6*R*,7*R*,8*R*)-1-oxo-5-oxy-4,6-diphenyltetrahydropyrazolo[1,2-*c*][1,3,4]oxadiazine-7,8-dicarboxylic acid (29): From **27** (0.1 mmol), flash chromatography (4:1 toluene/AcOEt) afforded 40 mg (94%) of **29**. $[\alpha]_D^{25}=-82.2$ ($c=0.96$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.42$ (t, 3H, $J=7.2$ Hz), 0.6–1.4 (m, 6H), 3.71 (s, 3H), 3.74 (s, 3H), 3.87 (dd, $J=10.8$, 9.4 Hz, 1H), 4.18 (ddd, $J=10.8$, 9.2, 2.6 Hz, 1H), 4.36 (dd, $J=11.7$, 3.5 Hz, 1H), 4.93 (d, $J=9.4$ Hz, 1H), 5.13 (dd, $J=3.5$, 11.8 Hz, 1H) 5.58 (t, $J=11.8$, 1H), 7.8–7.3 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=48.4$, 51.9, 52.3, 58.2, 67.5, 79.0, 84.4, 129.1, 129.4, 130.1, 130.4, 131.3, 132.0, 132.4, 133.3, 151.9, 171.3, 172.1 ppm; MS (CI): *m/z* (%): 427 (88) [M^++1], 411 (100), 397 (62); elemental analysis calcd (%) for $C_{22}H_{22}N_2O_7$: C 61.97, H 5.20, N 6.57; found: C 61.88, H 5.32, N 6.47.

Dimethyl ester of (4*R*,6*S*,7*R*,8*R*)-(1-oxo-5-oxy-4-phenyl-6-propyltetrahydropyrazolo[1,2-*c*][1,3,4]oxadiazine-7,8-dicarboxylic acid (30): From **28** (0.1 mmol), flash chromatography (6:1 toluene/AcOEt) afforded 35 mg (90%) of **30**. $[\alpha]_D^{25}=-32.6$ ($c=0.6$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.49$ (t, $J=7.3$ Hz, 3H), 0.5–1.0 (m, 4H), 3.71 (s, 3H), 3.75 (s, 3H), 3.87 (dd, $J=9.4$, 10.8 Hz, 1H), 4.18 (ddd, $J=2.6$, 9.2, 10.8 Hz, 1H), 4.36 (dd, $J=3.5$, 11.7 Hz, 1H), 4.93 (d, $J=9.4$ Hz, 1H), 5.13 (dd, $J=3.5$, 11.8 Hz, 1H), 5.58 (t, $J=11.8$ Hz, 1H), 7.3–8.0 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=13.7$, 18.6, 29.5, 31.0, 49.3, 52.9, 23.0, 59.1, 66.9, 78.8, 81.3, 128.1, 128.4, 128.9, 131.0, 149.1, 168.2, 168.7 ppm; MS (CI): *m/z* (%): 393 (16) [M^++1], 375 (20), 216 (100); elemental analysis calcd (%) for: $C_{19}H_{24}N_2O_7$ C 58,16, H 6,16, N 7,14; found: C 57.94, H 6.22, N 7.00.

Acknowledgments

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