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Aza-Henry reaction with nitrones, an under-explored transformation

Gatien Messire,[a] Fabien Massicot,[a] Alexis Vallée,[a] Jean-Luc Vasse,[a] and Jean-Bernard Behr*[a]

Abstract: nitromethylation of nitrones occurred efficiently in CH_3NO_2 in the presence of tetramethylammonium fluoride or triazabicyclodecene as promoters. The obtained adducts might be conveniently transformed into vicinal diamines. The process was extended to nitroethane and nitropropane affording mixtures of *syn* and *anti* stereoisomers with low diastereoselectivity.

Introduction

Synthetic tools to access the 1,2-diamine structural motif are of importance due to its prevalence in biologically active natural products, in medicinal chemistry, as well as in the core structure of catalysts used in asymmetric synthesis.[1] Among the methods giving access to the N-C-C-N sequence,[2] the addition of α-nitrogen *C*-nucleophiles such as nitroalkanes to imines or imine equivalents has been exploited and enantioselective versions were recently developed.[3] However, these transformations are usually restricted to a number of reactive imines or require formation or pre-activation of the imine *in situ*, as exemplified by the cross-dehydrogenative addition of nitromethane to tertiary amines.[4] The direct addition of nitromethane to unactivated imines (aza-Henry or nitro-Mannich type reactions) has been attempted only recently using 3,4-dihydroisoquinoline **1** (Figure 1) as a model substrate.[3c] Enantioselective aza-Henry reaction with the same imine proved possible by using bi-functional thiourea catalysts, which afforded the nitro amine product in optimal 77% *ee*.[3d] Surprisingly, there are few examples reporting the use of nitrones as imine surrogates in aza-Henry reactions. Nitrones such as **2** are conveniently prepared by oxidation of the corresponding amines and are often obtained as easy to handle and stable crystalline compounds.[5] Furthermore, the highly polarized double bond of nitrones is responsible for their high electrophilic character and for their susceptibility to nucleophilic addition of organometallic reagents.[6] Hence, nitrones have been used as key substrates in the synthesis of designingly functionalized iminosugars.[6a-c] But to the best of our knowledge only four examples of aza-Henry reactions with nitrones have been reported over the years and no systematic exploration of such transformation has been attempted.[7] The contrasting results obtained during nitromethylation of nitrones in these early investigations (modest yields or conversion) possibly hampered its wider development. In this study, we explored the scope and limitations of the reaction with a series of achiral and chiral nitrones, providing a basis for future work in this field in view of enantioselective transformations.

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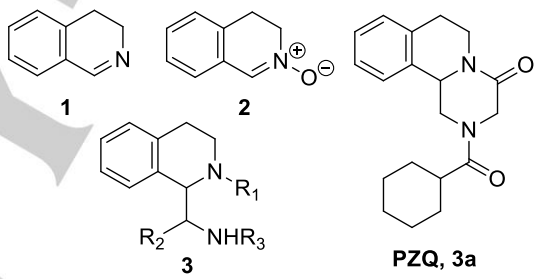

Figure 1. Structures of key compounds 1-3.

Results and Discussion

Optimization, scope of bases. As a prelude of our investigation, nitrone **2** was chosen as the model substrate. Compound **2** is easily prepared from tetrahydroisoquinoline and its derivatives have valuable biological interests especially the 1-(aminomethyl)-1,2,3,4-tetrahydroiso-quinolines **3**.[8,9] (±)-Praziquantel (PZQ) **3a** is the main drug prescribed against all Schistosoma species and, as such, is indicated in the list of essential drugs of WHO.[9] Retrosynthetically, compounds **3** might be obtained from **2** by initial addition of nitroalkanes and subsequent reduction. In most cases the reactive nitronate is generated by a base, among which amines, hydroxides or alcoholates are the most widely used.[10] We began our study with the treatment of nitrone **2** and nitromethane with sodium ethanolate in ethanol, reiterating conditions that have been used in initial assays.[7] After 24 h no addition product could be detected in the reaction mixture and **2** was entirely recovered (Table 1, entry 1).

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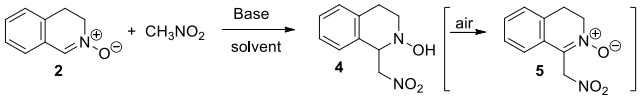


Entry	Base (equiv.)	Solvent	Time (h)	Conversion (%)	Yield (%)[c,d]
1	EtONa (2)	EtOH[a]	24	0[b]	–
2	TMAF (0.25)	CH_3NO_2	24[e]	66	28
3	TMAF (1.0)	CH_3NO_2	6[e]	84	47
4	TMAF (1.3)	CH_3NO_2	2.5[e]	90	57
5	TMAF (1.6)	CH_3NO_2	2.5[e]	96	74
6	TMAF (2.0)	CH_3NO_2	2.5[e]	96	73
7	TMAF (1.6)	MeOH[f]	2.5	27	–
8	TMAF (1.6)	THF[g]	2.5	66	–
9	TMAF.4 H_2O (1.6)[h]	CH_3NO_2	2.5	18	–
10	TBAF.3 H_2O (1.6)	CH_3NO_2	2.5	96	75
11	TBAOH (1.6)[i]	CH_3NO_2	2.5	50	–
12	DBU (1.6)	CH_3NO_2	2.5	92	61
13	TBD (0.3)	CH_3NO_2	2.5	36	–
14	TBD (1.6)	CH_3NO_2	2.5	87	67
15	TBD (1.6)	CH_3NO_2	6[e]	93	68
16	MeONa (1.6)	MeOH[f]	2.5	52	–
17	K_2CO_3 (1.6) + TBABr (0.3)[h]	CH_3NO_2	2.5	13	–
18	CsF (1.6)[h]	CH_3NO_2	2.5	13	–
19	CsF (1.6) + TBABr (0.3)[h]	H_2O / CH_3NO_2	2.5	0[b]	–
20	CsF (1.6) + TBABr (0.3)[h]	CH_3NO_2	2.5	54	–
21	CsF (1.6) + TBABr (0.3)[h]	CH_3NO_2	24	81	52
22	CsF (1.6) + TBABr (1)[f]	CH_3NO_2	16	80	64
23	TBABr (1)	CH_3NO_2	2.5	0[b]	–

[a] In the presence of 2 equiv. of nitromethane. No further evolution of the reaction after this time; maximum conversion reached.
[b] The reaction product was not detected in the ^{1}H NMR spectrum of the crude.
[c] Isolated yield (chromatography on silica gel) of pure **4**.
[d] – means that the yield was not determined, due to low conversion.
[e] No further evolution after this time (maximum conversion reached)
[f] A mixture of MeOH/CH_3NO_2 (1/2) was used as the solvent.
[g] In the presence of 6 equiv. of nitromethane.
[h] Heterogeneous reaction mixture due to insoluble material.
[i] Methanolic solution of TBAOH was used (1M).

Table 1. Optimization of nitromethylation of nitrone **2**.

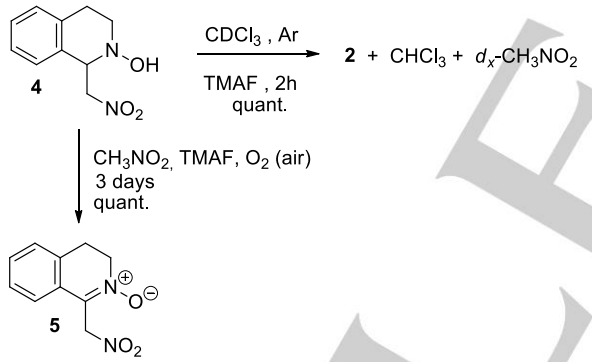
Due to its peculiar basicity in non-aqueous solvents, fluoride anion is a good alternative for the removal of C-H acidic hydrogens in aprotic solvents.[11] Ammonium fluorides have notably been used to initiate Henry reaction with sugar-derived aldehydes and chiral quaternary ammonium fluorides proved their efficiency in enantioselective carbon-carbon bond formation reactions with nitromethane.[12] Hence, when tetramethylammonium fluoride (TMAF) was used as the base (0.25 equivalent) in CH_3NO_2 as the solvent, conversion reached 66% and 2-hydroxy-1-nitromethyl-1,2,3,4-tetrahydroisoquinoline **4** was isolated in 28% yield. The recovery of only a small portion of the formed product was explained by oxidation of **4** into ketonitrone **5** in the presence of air oxygen. Exploration of various reaction conditions (amount of TMAF, reaction time, see Table 1) allowed to increase the yield up to 75% and led to the following conclusions: (a) an excess of TMAF is needed to ensure substantial conversion, 1.6 equivalents appearing as the upper limit (entries 2-6); (b) for a given amount of TMAF, the conversion reached a *plateau* and no further evolution was observed even after prolonged reaction time, maximum conversion being obtained with 1.6 equiv of TMAF after 2.5 h (see in the following section the plots of conversion *vs* time); (c) complete conversion could not be achieved even with 2 molar ratio of TMAF; remaining nitrone was still present in the crude reaction mixture, to a small extent though; (d) the presence of MeOH as a co-solvent significantly impacted the conversion (entry 7), most likely due to a profound depletion of the p*K*a of fluoride in methanol; (e) lowering the amount of nitromethane to 5-6 equivalents reduced conversion (entry 8); (f) tetrabutylammonium fluoride trihydrate (TBAF.3H_2O) was as efficient as anhydrous TMAF but hydrated TMAF (TMAF.4H_2O) gave very low conversion, certainly because of insolubility of this reagent in nitromethane (entries 9,10).

Other bases such as tetraethylammonium hydroxide,[13] NEt_3,[14] DABCO,[15] DBU,[16] guanidines,[17] CsOH,[3e] MeONa,[18] K_2CO_3[19] or CsF[20] have been used in the literature as nitronate precursors, in the presence of phase-transfer catalysts when needed. Thus the scope of bases was explored here (entries 11-18) with **2** under the optimal conditions stated above (1.6 equiv of base *vs* nitrone, nitromethane as the solvent, 2.5 h under argon). It was found that only DBU and TBD gave satisfactory results, with almost complete conversion and 61% and 68% isolated yield respectively (entries 12 and 15). Conversely, no reaction occurred in the presence of NEt_3, DABCO, CsOH, MeONa or K_2CO_3 under analogous conditions (results not shown in table 1). With TBD, the reaction occurred at slower rate than with TMAF, reaching maximal conversion after 6 h (see the supporting information). The importance of the amount of base was reinvestigated with TBD showing that sub-molar quantities were insufficient for acceptable conversion (entry 13). Other bases gave unsatisfactory results due either to low solubility in nitromethane (CsOH, MeONa, K_2CO_3, CsF) or to low reactivity (NEt_3, DABCO). However, with the addition of methanol as co-solvent, hydroxide (entry 11) and methoxide (entry 16) proved moderately efficient, giving rise to almost 50% conversion.

Gratifyingly, phase-transfer catalysis (PTC) conditions using tetrabutylammonium bromide (TBABr) as the transfer agent provided a good solution to address the solubility issue of CsF. A traditional liquid–liquid biphasic system (water/nitromethane), in which the reagents partitioned between aqueous (CsF) and organic (TBABr, nitrone) phases, completely disrupted the reactivity of CsF (entry 19). Nevertheless, in the absence of water, fluoride could be smoothly transferred with TBABr from solid CsF in suspension into the organic liquid phase. Catalysis occurred with 0.3 equivalent TBABr but at slower rate in this

heterogeneous system (entries 20-21), 81% conversion being reached after 24h with 52% isolated yield. Here again, formation of nitrone **5** as a by-product, favored by prolonged reaction period, accounted for the unsatisfactory low yield. By increasing the amount of TBABr to 1 equivalent, 80% conversion was obtained in 16 h and the addition product was isolated in 64% yield (entry 22). A control reaction with TBABr alone showed, as expected, that a neutral ammonium species is not able to initiate the reaction by itself (entry 23).

Course of the reaction. In the experiments above with the most convenient bases TMAF or TBD, unsatisfactory yields were observed in situations where conversion stagnated at low ratios or where a significant amount of oxidation product **5** formed. Both trends were addressed by supplementary experiments. Firstly, the ease of oxidation of hydroxylamine **4** was demonstrated by simply mixing it in the standard reaction conditions (TMAF 1.6 equiv, CH_3NO_2 as the solvent), without flushing the system with argon (Scheme 1). After 3 days, complete disappearance of the hydroxylamine occurred with concomitant formation of nitrone **5**. The oxidation of hydroxylamines by air oxygen is usually metal-catalyzed, but the formation of a conjugated system might account here for the ease of such a process in the absence of any metal.[21a] Conversely, compound **4** was not susceptible to oxidation when it was kept under argon, either in solution or neat.



Scheme 1. Stability of nitromethyl isoquinoline **4**.

Secondly, a kinetic study of the reaction course was attempted using various ratios of TMAF (Figure 2). The results show that the transformation is quite rapid, reaching a plateau conversion after 5 h with 0.3 equiv or after 1-2 h with one equivalent or more. However, no further evolution could be noticed even after prolonged reaction period. Having in mind the need for a large excess of CH_3NO_2 to help conversion, these experiments suggest that nitromethylation of nitrones is a reversible process. Reversion of **4** to starting nitrone **2** was monitored by ^{1}H NMR spectroscopy (scheme 1 and supporting information). In the absence of base, nitromethyl adduct **4** was stable in $CDCl_3$ (0.2 mmol/mL) for 24h; no starting nitrone could be detected. But after addition of TMAF, the reaction returned nitrone **2** in several hours, in a very clean manner. The concomitant formation of $CHCl_3$ and partially deuterated CH_3NO_2 was also evidenced in the NMR spectrum, as a result of release of nitromethane and fluoride mediated proton-deuterium exchange with $CDCl_3$.[21b] Such a retroaddition is a problem encountered as well in more classical Henry or aza-Henry transformations.[22]

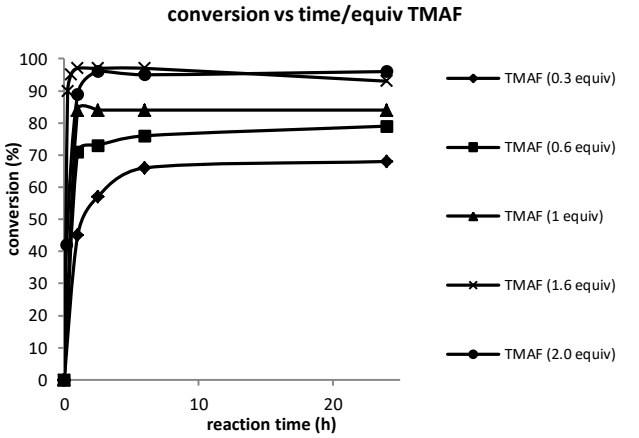
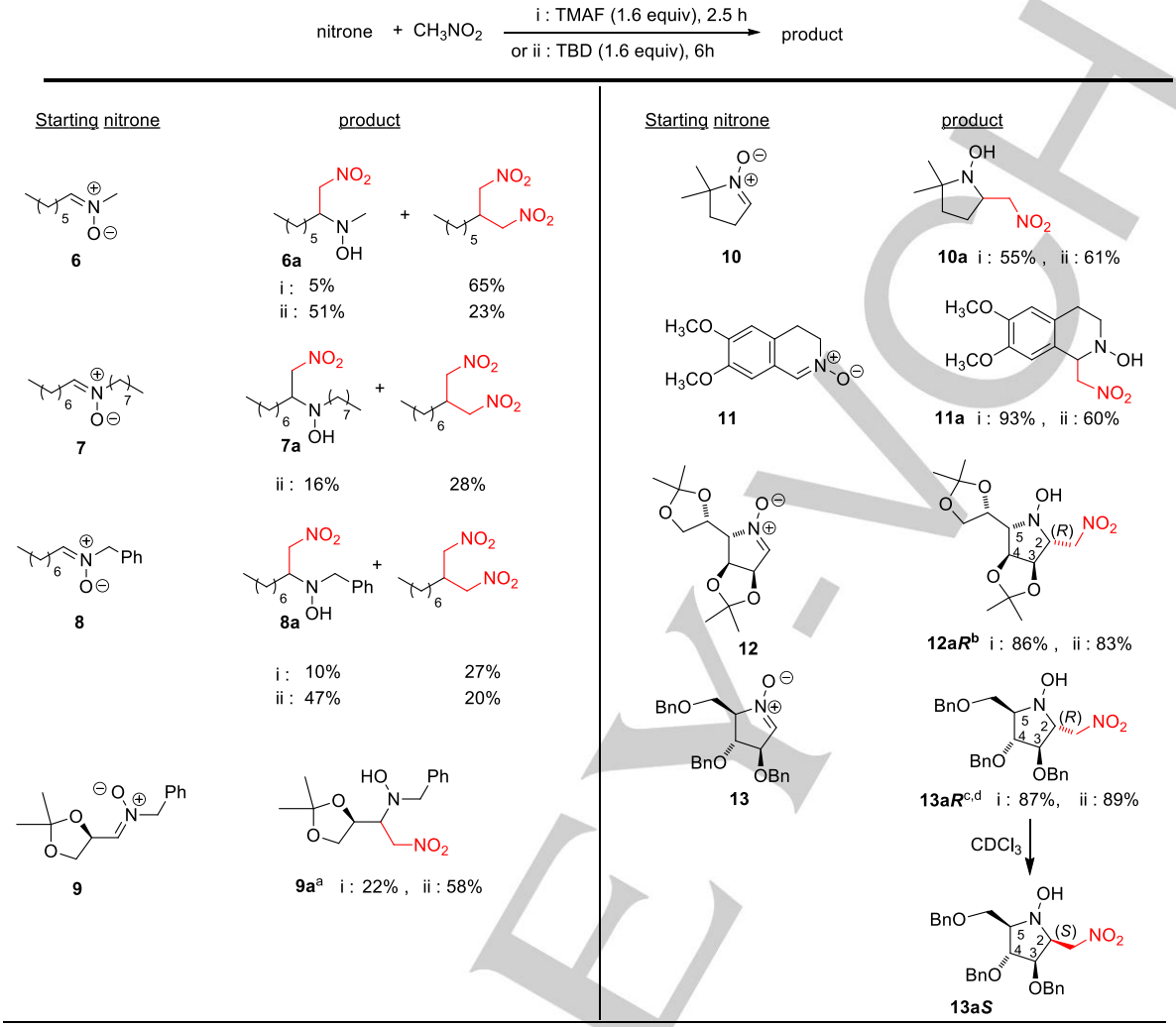


Figure 2. Time-course of the aza-Henry reaction of **2** with various amounts of TMAF.

The kinetic of the reaction was also studied with TBD and with a heterogeneous (CsF/TBABr) system, affording analogous plots showing dose-dependent maximal conversions (see the supporting information).[23]

Enlarging the scope of nitrones and nitroalkanes. Aza-Henry reaction was applied to a series of nitrones with varied structures (Table 2), by using either TMAF or TBD as the promoter. Acyclic nitrones such as **6**-**8**[24] afforded the expected products in modest yields, due to competing formation of a (bis)nitromethyl alkane. Aldehydes afford such bis(nitromethyl) adducts as well.[25] Here, 1,1-bis(nitromethyl)heptan was obtained in 65% yield from **6** by using TMAF as the base. TBD tuned the ratio in favour of hydroxylamine **6a** (51% isolated yield). Under the same conditions nitrones **7** and **8** gave only 16% and 47% respectively of the expected aza-Henry adduct. Retro-aza-Michael reaction followed by Michael addition to the intermediate nitro alkene might account for the formation of bis(nitromethyl) adducts from targeted hydroxylamines.

Better results were obtained with glyceraldehyde-derived nitrone **9**, which was converted into hydroxylamine **9a** in 58% yield with TBD. The reaction afforded two inseparable diastereoisomers in equal amount (*dr* 55 : 45). Satisfyingly, cyclic nitrones **10**-**13** were converted in good yields into their nitromethyl adducts, either with TMAF or with TBD. Best results were obtained with carbohydrate-derived nitrones **12**-**13**, which afforded **12a*R*** and **13a*R*** in high yield and diastereoselectivity. Addition to nitrone **12** proved completely stereoselective whereas *O*-benzylated **13a*R*** was obtained from **13** as a 10:2.7 inseparable mixture of isomers.



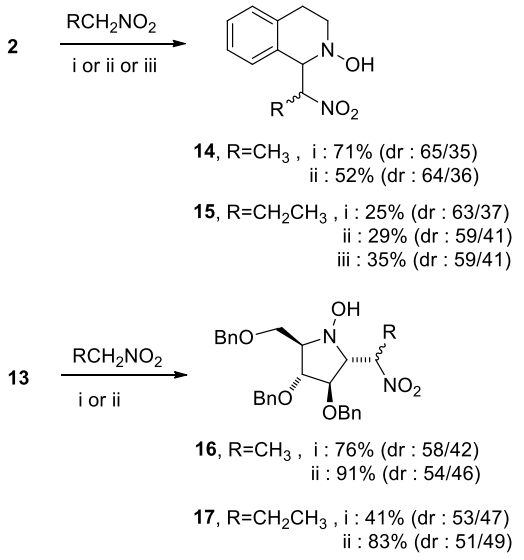
[a] d.r. = 55:45. [b] only one isomer detected by NMR. [c] d.r. = 79:21 in favour of the (2*R*) isomer. [d] epimerization occurs in solution, affording the (2*S*) isomer as the only product after several days

Table 2. Aza-Henry reaction applied to acyclic or cyclic nitrones.

The preferential (2*R*) configuration of the newly formed stereocenter in both structures was assessed by nOe experiments (see Supporting Information) and is consistent with nucleophilic attack from the *Re* side. With such cyclic nitrones, facial approach of the reactant is governed by steric hindrance of the neighboring C-3 substituent, as observed in previous studies with nitrones **12** or **13**.[26] However, whereas **12a*R*** proved configurationally stable, **13a*R*** epimerized after several days in solution ($CDCl_3$) to **13a*S*** (see Supporting Information). Such an isomerization process with iminosugars bearing acidic C-H at C-α to C-2 has already been observed and might result from retro-Michael/Michael equilibration.[27]

Next, nitrones **2** and **13** were used as models to assay nitroethane and nitropropane as nucleophiles (Scheme 2). Due to solubility issues with TMAF in nitropropane, TBAF was engaged as an alternative base. From nitrone **2**, hydroxylamines **14** (71%, TMAF) and **15** (35%, TBAF) were obtained in nitroethane and nitropropane, respectively, as mixtures of the two possible diastereomers. After HPLC separation of *syn*- and *anti*-**14**, each single stereoisomer re-equilibrated in solution to the initial 65/35 composition. The addition of nitroethane and nitropropane to chiral nitrone **13** afforded **16** and **17** respectively as mixtures of *syn*/*anti* (2*R*)-isomers, in good yields (91% for **16** and 83% for **17**, TBD as a base). Stereochemical stability of **16** was studied further. In solution, the 58/42 mixture of epimers remained stable with no emergence of additional stereoisomers, as would happen from a C-2 epimerizing retro-Michael/Michael process. However, as for **14**, a pure sample of HPLC-separated *syn* or

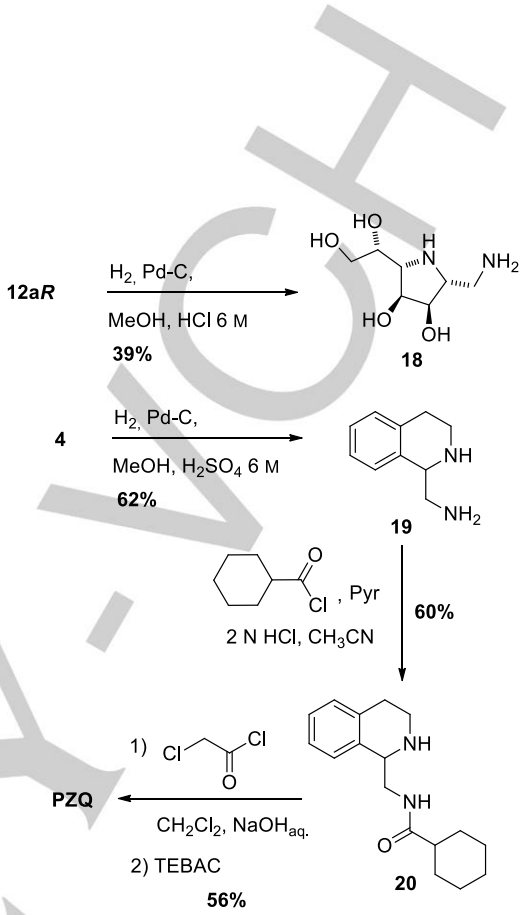
anti-**16** evolved in solution into the original mixture, due to epimerization of the -C(CH_3)(H)-NO_2 stereocenter.[28]



Scheme 2. Reaction of **2** and **13** with nitroethane and nitropropane. Reagents and conditions: i) TMAF, 2.5 h, rt; ii) TBD, 6 h, rt, iii) TBAF.3H_2O, 2.5 h, rt.

Encouraged by these results, we applied the aza-Henry reaction of nitrones to the synthesis of biologically relevant targets (Scheme 3). Thus, iminosugar **18** was prepared in a single step (39% yield) from hydroxylamine **12a*R***. Hydrogenolysis of both nitro and *N*-hydroxy functions was performed concomitantly to hydrolysis of isopropylidenes in the presence of hydrochloric acid. After neutralization of the reaction mixture, diamine **18** was purified by chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH 0.8M, 5/5/1).

Recent tension regarding supply of PZQ, the only effective drug to treat schistosomiasis, stimulated a renewed interest in straightforward synthetic accesses. When raised to 500 mg-scale, nitromethylation of **2** afforded **4** in 93% yield, the hydrogenolysis of which gave the known vicinal diamine **19** (62%).[29] Regioselective acylation under conditions from the literature[29] gave **20** in 60% yield. Terminal cyclization with chloroacetyl chloride under phase transfer catalysis using benzyltriethyammonium chloride afforded Praziquantel in 56% overall yield.[4b,30] Concerning the overall reduction/deprotection strategy to aminomethyl derivatives **18** and **19** it should be pointed out that such diamines are also accessible via addition of cyanide ion to nitrones followed by hydrogenolysis, as demonstrated by Goti for related polyhydroxylated cyclic nitrones.[31]



Scheme 3. synthesis of iminosugar **18** and of PZQ **3a**.

Conclusions

Overall, our study comprises an extensive analysis of the aza-Henry reaction applied to nitrones. The results show that the transformation is reversible and requires a large excess of nitromethane to secure high conversion. Ammonium fluorides or strong organic bases such as TBD are convenient promoters. Alternatively, phase-transfer catalysis gave also acceptable yields, which opens the door to various enantioselective strategies of the reaction under kinetic conditions, either with chiral ammonium fluorides,[12b] chiral Brønsted bases[32] or by using cinchona alkaloids as PT catalysts.[33] Nitroethane or nitropropane proved also possible *C*-nucleophiles, affording mixtures of isomerisable ß-alkyl-ß-nitro-hydroxylamines. The reaction was exploited for the synthesis of unprecedented diamino-iminosugar **18** as well as for that of PZQ, the latter requiring four atom-economic steps starting from nitrone **2** and nitromethane. Our synthesis of PZQ affords an alternative to other processes and provides the advantage of chemical diversity through the use of other nitroalkanes.

Experimental Section

General information

Reactants and reagents were purchased from standard suppliers (Sigma-Aldrich, Alfa-Aesar, Fischer Scientific) and were used without further purification. All reactions were conducted under Ar atmosphere using anhydrous solvents, air- or moisture-sensitive reagents and products were stored at -20°C under Ar. Silica gel F254 (0.2 mm) was used for TLC plates, detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid or an aqueous solution of $KMnO_4$ (2%) / Na_2CO_3 (4%), followed by heating. Reactions were monitored either by TLC or by ^{1}H-NMR. Conversion was deduced from the relative amount of nitrone *vs* products (hydroxylamine + oxidation product, if any) in the ^{1}H-NMR spectrum, after analysis of small aliquots of the reaction mixture quenched under the standard conditions. Column chromatography was performed over silica gel M 9385 (40-63 µm) Kieselgel 60. NMR spectra were recorded on Bruker AC 250 (250 MHz for ^{1}H, 62.5 MHz for ^{13}C), 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) or 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C) spectrometers. Chemical shifts are expressed in parts per million (ppm) and were calibrated to the residual solvent peak for ^{1}H and ^{13}C spectra. Coupling constants are in Hz and splitting pattern abbreviations are: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. DEPT 1D NMR experiment, COSY, HSQC, and HMBC 2D NMR experiments were used to confirm the NMR peak assignments for compounds **4, 6−19**. Optical rotations were determined at 20 °C with a Perkin-Elmer Model 241 polarimeter in chloroform. High Resolution Mass Spectra (HRMS) were performed on Q-TOF Micro micromass positive ESI (CV = 30 V). Melting points (mp) were determined on a Tottoli apparatus and were uncorrected.
Nitrone **10** is commercially available. All other nitrones were prepared according to known protocols from either the corresponding amines by using sodium tungstate-H_2O_2 (**2**) or oxone (**7** and **11**) as oxydizing agent,[5a,b] or by condensation of aldehydes with hydroxylamines (**6**,**8**,**9**)[5c] or by intramolecular dispacement from oximes (**12**,**13**).[5d]
Their NMR spectra are given in the Supporting Information

General procedure for the nitroalkylation of nitrones 2, 6–13.

To a solution of nitrone **2**, **6**–**13** (0.35 mmol, 1 equiv) in nitroalkane (380 µL, 20 equiv for nitrones **2, 6-11**; 950 µL, 50 equiv for nitrones **12** and **13**) at room temperature under argon was added the base (0.56 mmol, 1.6 equiv.). The solution was stirred during 2.5 to 6h depending on the base. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted three times with dichloromethane. The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding aza-Henry adducts **4, 6a–13a and 14–17** and eventually the (bis)nitromethyl alkanes **6b** and **7b**.

*1-(Nitromethyl)-3,4-dihydroisoquinolin-2(1H)-ol (**4**).* According to general procedure, obtained after nitromethylation of **2** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 1:1) as a yellow oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.95–3.05 (m, 2H, C$\underline{H_2}$–CH_2–N(OH)), 3.20–3.30 (m, 1H, C$\underline{H_a}H_b$–N(OH)), 3.37–3.47 (m, 1H, $CH_a\underline{H_b}$–N(OH)), 4.76–4.93 (m, 3H, C$\underline{H}$–C$\underline{H_2}$–NO_2), 6.25 (br s, 1H, OH), 7.17–7.27 (m, 4H, 4 CHar); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 26.7 (C$\underline{H_2}$–CH_2–N(OH)), 52.0 (CH_2–N(OH)), 64.9 (CH), 78.0 (CH_2–NO_2), 126.3 (CHar), 126.7 (CHar), 127.7 (CHar), 129.0 (CHar), 131.6 (C_{IV}ar), 134.3 (C_{IV}ar); HRMS (ESI+) m/z calcd for $C_{10}H_{13}N_2O_3$ $[M + H]^+$ 209.0926, found 209.0919.

*N-Methyl-N-(1-nitrooctan-2-yl)hydroxylamine (**6a**).* According to general procedure, obtained after nitromethylation of **6** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 1:1); colorless oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.80 (t, ^3J = 7.5 Hz, 3H, C$\underline{H_3}$–CH_2), 1.25–1.52 (m, 9H, CH_3–(C$\underline{H_2}$)$_4$–C$\underline{H_a}H_b$), 1.65–1.70 (m, 1H, CH_3–$(CH_2)_4$–$CH_a\underline{H_b}$), 2.70 (s, 3H, C$\underline{H_3}$–N(OH)), 3.30–3.45 (m, 1H, CH), 4,38 (dd, ^2J = 12.5 Hz, ^3J = 4.7 Hz, 1H, C$\underline{H_a}H_b$–NO_2), 4,74 (dd, ^2J = 12.5 Hz, ^3J = 7.6 Hz, 1H, $CH_a\underline{H_b}$–NO_2), 6.52 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.0 (C$\underline{H_3}$–CH_2), 22,5 (CH_2), 26.1 (CH_2), 27.4 (CH_2), 29.2 (CH_2), 31.6 (CH_2), 44.3 (CH_3–N(OH)), 65.8 (CH), 75.9 (CH_2–NO_2); HRMS (ESI+) m/z calcd for $C_9H_{21}N_2O_3$ $[M + H]^+$ 205.1552, found 205.1550.

*N-(1-Nitrononan-2-yl)-N-octylhydroxylamine (**7a**).* According to general procedure, obtained after nitromethylation of **7** and purification of the resulting residue by chromatography on silica gel (dichloromethane / diethyl ether / petroleum ether 1:1:8); yellow oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.85–0.90 (m, 6H, 2 CH_3), 1.20–1.35 (m, 21H, 10 CH_2, CH–C$\underline{H_a}H_b$–CH_2), 1.43–1.53 (m, 2H, CH_2), 1.68–1.76 (m, 1H, CH–$CH_a\underline{H_b}$–CH_2), 2.61 (dt, ^2J = 12.5 Hz, ^3J = 7.5 Hz, 1H, C$\underline{H_a}H_b$–N(OH)), 2.79 (dt, ^2J = 12.5 Hz, ^3J = 7.5 Hz, 1H, $CH_a\underline{H_b}$–N(OH)), 3.35–3.45 (m, 1H, CH), 4.37 (dd, ^2J = 12.0 Hz, ^3J = 5.0 Hz, 1H, C$\underline{H_a}H_b$–NO_2), 4.71 (dd, ^2J = 12.0 Hz, ^3J = 8.0 Hz, 1H, $CH_a\underline{H_b}$–NO_2), 4.81 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1 (CH_3), 14.1 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 27.0 (CH_2), 27.6 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.8 (CH_2), 31.9 (CH_2), 56.2 (CH_2–N(OH)), 64.7 (CH), 76.4 (CH_2–NO_2); HRMS (ESI+) m/z calcd for $C_{17}H_{37}N_2O_3$ $[M + H]^+$ 317.2804, found 317.2809.

*N-Benzyl-N-(1-nitrononan-2-yl)hydroxylamine (**8a**).* According to general procedure, obtained after nitromethylation of **8** and purification of the resulting residue by chromatography on silica gel (dichloromethane / diethyl ether / petroleum ether 1:1:8); yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, ^3J = 5 Hz, 3H, CH_3), 1.21–1.44 (m, 10H, CH_3–(C$\underline{H_2}$)$_5$), 1.48–1.57 (m, 1H , CH–C$\underline{H_a}H_b$–CH_2), 1.79–1.89 (m, 1H , CH–$CH_a\underline{H_b}$–CH_2), 3.50–3.55 (m, 1H, CH), 3.82 (d, ^2J = 13.0 Hz, 1H, C$\underline{H_a}H_b$–Ph), 3.98 (^2J = 13.0 Hz, 1H, $CH_a\underline{H_b}$–Ph), 4,42 (dd, ^2J = 12.0 Hz, ^3J = 5.0 Hz, 1H, C$\underline{H_a}H_b$–NO_2), 4.76 (dd, ^2J = 12.0 Hz, ^3J = 8.0 Hz, 1H, $CH_a\underline{H_b}$–NO_2), 4.80 (br s, 1H, OH), 7.27–7.40 (m, 5H, 5 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (CH_3), 22.8 (CH_2), 26.5 (CH_2), 26.9 (CH_2), 29.2 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 60.7 (CH_2–Ph), 64.3 (CH), 76.5 (C$\underline{H_2}$–NO_2), 127.7 (CHar), 128.6 (CHar), 129.2 (CHar), 137.4 (C_{IV}ar); HRMS (ESI+) m/z calcd for $C_{16}H_{27}N_2O_3$ $[M + H]^+$ 295.2022, found 295.2029.

*N-Benzyl-N-(1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-nitro-ethyl-hydroxylamine (**9a,** mixture of two inseparable diastereoisomers)* According to general procedure, obtained after nitromethylation of **9** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); colorless oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.34 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 3.65–3.80 (m, 2H), 3.87–4.08 (m, 7H), 4.12–4.18 (m, 1H), 4.28–4.35 (m, 1H), 4.49–4.57 (m, 2H), 4.64 (dd, ^2J = 13.0 Hz, ^3J = 4.0 Hz, 1H), 4.82 (dd, ^2J = 13.0 Hz, ^3J = 8.5 Hz, 1H), 4.96–5.04 (m, 2H), 5.17 (br s, 1H), 7.28–7.34 (m, 10H, 10 CHar); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 25.1 (CH_3), 25.3 (CH_3), 26.5 (CH_3), 26.6 (CH_3), 61.7 (CH_2), 62.1 (CH_2), 64.1 (CH), 66.2 (CH_2), 66.8 (CH), 68.2 (CH_2), 72.4 (CH_2), 72.8 (CH_2), 73.3 (CH), 74.2 (CH), 108.9 (C_{IV}), 110.1 (C_{IV}), 127.9 (CHar) 127.9 (CHar), 128.7 (CHar), 128.7 (CHar), 129.2 (CHar), 129.3 (CHar), 129.5 (CHar), 136.9 (C_{IV}ar); m/z calcd for $C_{14}H_{20}N_2O_5Na$ $[M + Na]^+$ 319.1270, found 319.1264.

*2,2-Dimethyl-5-(nitromethyl)pyrrolidin-1-ol (**10a**).* According to general procedure, obtained after nitromethylation of **10** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); yellow oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.10 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.50–1.69 (m, 3H, C$\underline{H_2}$–C$\underline{H_a}H_b$–CH), 1.90–2.22 (m, 1H, $CH_a\underline{H_b}$–CH), 3.53–3.75 (m, 1H, CH), 4.49 (dd, ^2J = 13.5 Hz, ^3J = 7.0 Hz, 1H, C$\underline{H_a}H_b$–NO_2), 4.61 (dd, ^2J = 13.5 Hz, ^3J = 7.0 Hz, 1H, $CH_a\underline{H_b}$–NO_2), 4.80 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 18.6 (CH_3), 22.7 (C$\underline{H_2}$– CH_2–CH), 27.0 (CH_3), 34.0 (CH_2–C$\underline{H_2}$–CH), 61.9 (CH), 64.0 (C_{IV}), 79.3 (CH_2NO_2); m/z calcd for $C_7H_{15}N_2O_3$ $[M + H]^+$ 175.1083, found 175.1081.

*6,7-Dimethoxy-1-(nitromethyl)-3,4-dihydroisoquinolin-2(1H)-ol (**11a**).* According to general procedure, obtained after nitromethylation of **11** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 6:4); pale yellow solid; mp 102°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.87–2.90 (m, 2H, C$\underline{H_2}$–CH_2–N(OH)), 3.19–3.24 (m, 1H, C$\underline{H_a}H_b$–N(OH)), 3.32–3.37 (m, 1H, $CH_a\underline{H_b}$–

N(OH)), 3.84 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.71–4.84 (m, 3H, CH–N(OH) and CH_2–NO_2), 6.43 (br s, 1H, OH), 6.56 (s, 1H, CHar), 6.59 (s, 1H, CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.2 (CH_2–CH_2–N(OH)), 51.5 (CH_2–N(OH)), 55.9 (CH_3), 56.1 (CH_3), 64.6 (CH), 78.0 (CH_2–NO_2), 108.9 (CHar), 111.2 (CHar), 122.9 (C_{IV}ar), 126.4 (C_{IV}ar), 147.8 (C_{IV}ar–OMe), 148.5 (C_{IV}ar–OMe); m/z calcd for $C_{12}H_{17}N_2O_5$ $[M + H]^+$ 269.1137, found 269.1134.

*(3aS,4S,6R,6aR)-4-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(nitromethyl)dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrol-5(4H)-ol (**12aR**)*. According to general procedure, obtained after nitromethylation of **12** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); colorless solid; mp 150°C; $[\alpha]_D^{20}$ –17 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.13 (t, 1H, ^{5}CH), 3,59 (q, ^3J = 5.0 Hz, 1H, ^{2}CH), 3.96 (dd, ^2J = 10.0 Hz, ^3J = 5.0 Hz, 1H, $^7CH_aH_b$), 4.08 (dd, ^2J = 10.0 Hz, ^3J = 5.0 Hz, 1H, $^7CH_aH_b$), 4.25–4.31 (m, 2H, ^{4}CH and ^{6}CH), 4.50–4.52 (t, 1H, ^{3}CH), 4.64–4.73 (m, 2H, CH_2–NO_2), 5.5 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3 (CH_3), 25.4 (CH_3), 26.540 (CH_3), 27.3 (CH_3), 66.3 ($^7CH_2$), 70.1 (^{2}CH), 74.4 (^{5}CH), 75.5 (CH_2–NO_2), 76.5 (^{4}CH), 77.5 (^{6}CH), 77.6 (^{3}CH), 110.3 (C_{IV}), 114.5 (C_{IV}); m/z calcd for $C_{13}H_{22}N_2O_7Na$ $[M + Na]^+$ 341.1325, found 341.1336.

*(2R,3R,4R,5R)-3,4-bis(Benzyloxy)-2-((benzyloxy)methyl)-5-(nitromethyl)pyrrolidin-1-ol (**13aR**)*. According to general procedure, obtained as major product after nitromethylation of **13** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.41–3.45 (m, 1H, ^{5}CH), 3.60–3.68 (m, 2H, $^6CH_2$), 3.93–3.95 (m, 1H, ^{3}CH), 3.96–3.98 (m, 1H, ^{4}CH), 4.10–4.14 (m, 1H, ^{2}CH), 4.40–4.58 (m, 7H, CH_aH_b–NO_2 and 3 CH_2–Ph), 4.90 (dd, ^2J = 10.0 Hz, ^3J = 5.0 Hz, CH_aH_b–NO_2), 5.99 (br s, 1H, OH), 7.25–7.34 (m, 15H, 15 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 67.1 (^{2}CH), 68.5($^6CH_2$), 70.7 (^{5}CH), 71.9 (CH_2–Ph), 72.1 (CH_2–Ph), 73.4 (CH_2–NO_2), 73.5 (CH_2–Ph), 83.0 (^{3}CH), 83.3 (^{4}CH), 127,8 (CHar), 127.9 (CHar), 128.0 (CHar), 128.0 (CHar), 128.1 (CHar), 128.1 (CHar), 128.6 (CHar), 128.6 (CHar), 128.6 (CHar), 137.4 (C_{IV}ar), 137.6 (C_{IV}ar) 137.9 (C_{IV}ar); m/z calcd for $C_{27}H_{30}N_2O_6Na$ $[M + Na]^+$ 501.2002, found 501.2011.

*(2R,3R,4R,5S)-3,4-bis(Benzyloxy)-2-((benzyloxy)methyl)-5-(nitromethyl)pyrrolidin-1-ol (**13aS**)*. Present in the reaction mixture as a minor product after nitromethylation of **13** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.18–3.22 (m, 1H, ^{5}CH), 3.65–3.68 (m, 2H, $^6CH_2$), 3.76–3.78 (m, 1H, ^{4}CH), 3.82–3.85 (m, 1H, ^{2}CH), 4.06–4.08 (m, 1H, ^{3}CH), 4.38–4.57 (m, 6H, 3 CH_2–Ph), 4.65 (dd, ^2J = 10.0 Hz, ^3J = 5.0 Hz, CH_aH_b–NO_2), 4.77 (dd, ^2J = 10.0 Hz, ^3J = 8.0 Hz, CH_aH_b–NO_2), 5.81 (br s, 1H, OH), 7.24–7.31 (m, 15H, 15 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 67.4 (^{2}CH), 69.3 ($^6CH_2$), 71.8 (CH_2–Ph), 71.9 (CH_2–Ph), 72.8 (CH_2–NO_2), 72.9 (^{5}CH), 73.5 (CH_2–Ph), 80.1 (^{3}CH), 81.3 (^{4}CH), 127,8 (CHar), 127.9 (CHar), 127.9 (CHar), 128.0 (CHar), 128.1 (CHar), 128.2 (CHar), 128.4 (CHar), 128.5 (CHar), 128.5 (CHar), 128.6 (CHar), 128.6 (CHar), 128.7 (CHar), 128.8 (CHar),137.2 (C_{IV}ar), 137.6 (C_{IV}ar) 137.8 (C_{IV}ar); m/z calcd for $C_{27}H_{30}N_2O_6Na$ $[M + Na]^+$ 501.2002, found 501.2008.

*1-(1-Nitroethyl)-3,4-dihydroisoquinolin-2(1H)-ol (**14A, minor diastereoisomer**)*. According to general procedure, obtained as minor product after nitroethylation of **2** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 3:7); yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.37 (d, ^3J = 6.6 Hz, 3H, CH_3), 2.72–2.81 (m, 1H, CH_aH_b–N(OH)), 3.02–3.10 (m, 2H, CH_2–CH_2–N(OH)), 3.35–3.43 (m, 1H, CH_aH_b–N(OH)), 4.87–4.91 (m, 2H, CH–NO_2 and CH–N(OH)), 6.10 (br s, 1H, OH), 7.12–7.25 (m, 4H, 4 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.9 (CH_3), 28.8 (CH_2–CH_2–N(OH)), 54.5 (CH_2–N(OH)), 70.9 (CH–N(OH)), 86.3 (CH–NO_2), 126.2 (CHar), 126.9 (CHar), 127.5 (CHar), 128.9 (CHar), 132.7 (C_{IV}ar), 135.7 (C_{IV}ar); m/z calcd for $C_{11}H_{15}N_2O_3$ $[M + H]^+$ 223.1083, found 223.1078.

*1-(1-Nitroethyl)-3,4-dihydroisoquinolin-2(1H)-ol (**14B, major diastereoisomer**)*. According to general procedure, obtained as major product after nitroethylation of **2** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 3:7); yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48 (d, ^3J = 6.8 Hz, 3H, CH_3), 2.80 (dt, ^2J = 17.2 Hz , ^3J= 5.5 Hz, 1H, CH_aH_b–CH_2–N(OH)), 2.99–3.05 (m, 1H, CH_aH_b–CH_2–N(OH)), 3.27 (dt, ^2J = 12.6 Hz, ^3J = 5.7 Hz, 1H, CH_aH_b–N(OH)), 3.43–3.49 (m, 1H, CH_aH_b–N(OH)), 4.70 (d, ^3J = 7.1 Hz, 1H, CH–N(OH)), 4.83–4.91 (m, 1 H, CH–NO_2), 6.68 (br s, 1H, OH), 7.03 (d, ^3J = 7.5 Hz, 1H, CHar), 7.12–7.24 (m, 3H, 3 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.4 (CH_3), 25.4 (CH_2–CH_2–N(OH)), 50.4 (CH_2–N(OH)), 69.2 (CH–N(OH)), 84.8 (CH–NO_2), 126.1 (CHar), 127.8 (CHar), 128.3 (CHar), 128.9 (CHar), 130.7 (C_{IV}ar), 134.7 (C_{IV}ar); m/z calcd for $C_{11}H_{15}N_2O_3$ $[M + H]^+$ 223.1083, found 223.1089.

*1-(1-Nitropropyl)-3,4-dihydroisoquinolin-2(1H)-ol (**15A, minor diastereoisomer**)*. According to general procedure, obtained as minor product after nitropropylation of **2** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 3:7); yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, ^{3}J = 7.3 Hz, 3H, CH_3), 1.48–1.55 (m, 1H, CH_aH_b–CH_3), 2.32–2.41 (m, 1H, CH_aH_b–CH_3), 2.75–2.84 (m, 1H, CH_aH_b–CH_2–N(OH)), 2.95–3.09 (m, 1H, CH_aH_b–CH_2–N(OH)), 3.08–3.15 (m, 1H, CH_aH_b–N(OH)), 3.44–3.50 (m, 1H_b, CH_aH_b–N(OH)), 4.67 (dt, ^3J = 10.6 Hz, ^3J = 3.0 Hz, 1H, CH–NO_2), 4.77 (d, ^3J = 3.0 Hz, 1H, CH–N(OH)), 5.96 (br s, 1H, OH), 7.09–7.24 (m, 4H, 4 CHar). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.3 (CH_3), 20.8 (CH_2–CH_3), 28.1 (CH_2– CH_2–N(OH)), 53.7 (CH_2–N(OH)), 70.6 (CH–N(OH)), 93.6 (CH–NO_2), 126.4 (CHar), 126.7 (CHar), 127.4 (CHar), 128.8 (CHar), 132.6 (C_{IV}ar), 135.0 (C_{IV}ar); m/z calcd for $C_{12}H_{17}N_2O_3$ $[M + H]^+$ 237.1239, found 237.1235.

*1-(1-Nitropropyl)-3,4-dihydroisoquinolin-2(1H)-ol (**15B, major diastereoisomer**)*. According to general procedure, obtained as major product after nitropropylation of **2** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 3:7); yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.74–1.81 (m, 1H, CH_aH_b–CH_3), 2.02–2.13 (m, 1H, CH_aH_b–CH_3), 2.74 (dt, ^2J = 17.0 Hz, ^3J = 5.0 Hz, 1H, CH_aH_b–CH_2–N(OH), 2.81 (dt, ^2J = 17.0 Hz, ^3J = 3.5 Hz, 1H, CH_aH_b–CH_2–N(OH), 3.29–3.40 (m, 1H, CH_aH_b–N(OH)), 3.43–3.52 (m, 1H, CH_aH_b–N(OH)), 4.52 (td, ^3J = 11.1 Hz, ^3J = 3.0 Hz, 1H, CH–NO_2), 4.59 (d, ^3J = 8.7 Hz, 1H, CH–N(OH)), 6.33 (br s, 1H, OH), 7.09–7.27 (m, 4H, 4 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.7 (CH_3), 24.2 (CH_2–CH_3), 24.7 (CH_2–CH_2–N(OH)), 49.1 (CH_2–N(OH)), 68.5 (CH–N(OH)), 92.6 (CH–NO_2), 126.0 (CHar), 127.9 (CHar), 129.0 (CHar), 129.1 (CHar), 130.7 (C_{IV}ar), 134.6 (C_{IV}ar); m/z calcd for $C_{12}H_{17}N_2O_3$ $[M + H]^+$ 237.1239, found 237.1235.

*(2R,3R,4R,5R)-3,4-bis(Benzyloxy)-2-((benzyloxy)methyl)-5-((R)-1-nitroethyl)pyrrolidin-1-ol (**16A, minor diastereoisomer**)*. According to general procedure, obtained as minor product after nitroethylation of **13** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6);TLC : diethyl ether / petroleum ether 4:6; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59 (d, ^3J = 6.8 Hz, 3 H, CH_3), 3.49–3.54 (m, 1H, $^6CH_aH_b$), 3.62–3.67 (m, 2H, ^{5}CH and ^{2}CH), 3.72–3.79 (m, 1H, $^6CH_aH_b$), 4.04–4.08 (m, 2H, ^{3}CH and ^{4}CH), 4.42–4.65 (m, 6H, 3 CH_2–Ph), 4.81–4.87 (m, 1H, CH–NO_2), 5.63 (br s, 1H, OH), 7.30–7.37 (m, 15H, 15 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.2 (CH_3), 67.4 ($^6CH_2$), 70.5 (^{5}CH), 71.6 (^{2}CH), 71.7 (CH_2–Ph), 72.0 (CH_2–Ph), 73.4 (CH_2–Ph), 82.4 (CH–NO_2), 82.6 (^{3}CH), 83.8 (^{4}CH), 127.8–128.5 (15 CHar), 137.6 (C_{IV}ar), 137.7 (C_{IV}ar), 138.0(C_{IV}ar); m/z calcd for $C_{28}H_{32}N_2O_6$ $[M + H]^+$ 493.2339, found 493.2333.

*(2R,3R,4R,5R)-3,4-bis(Benzyloxy)-2-((benzyloxy)methyl)-5-((R)-1-nitroethyl)pyrrolidin-1-ol (**16B, major diastereoisomer**)*. According to general procedure, obtained as major product after nitroethylation of **13** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.54 (d, ^3J = 6.8 Hz, 3H, CH_3), 3.61–3.67 (m, 2H, $^6CH_aH_b$ and ^{5}CH), 3.72–3.79 (m, 2H, $^6CH_aH_b$ and ^{2}CH), 3.97 (dd, ^3J = 7.0 Hz, ^3J = 2.5 Hz, 1H, ^{4}CH), 4.08–4.12 (m, 1H, ^{3}CH); 4.42–4.65 (m, 6H, 3 CH_2–Ph), 4.95–5.01 (m, 1H, CH–NO_2), 5.98 (br s, 1H, OH), 7.30–7.37 (m, 15H, 15 CHar). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.7 (CH_3), 66,7 ($^6CH_2$), 69.5 (^{5}CH), 71.5 (^{2}CH), 71.6 (CH_2–Ph), 71.8 (CH_2–Ph) and 73.4 (CH_2–Ph), 83.2 (^{3}CH), 83.3 (CH–NO_2), 83.7 (^{4}CH), 127.77–128.51 (15 CHar), 137.3 (C_{IV}ar), 137.6 (C_{IV}ar) and 137.98 (C_{IV}ar); m/z calcd for $C_{28}H_{32}N_2O_6$ $[M + H]^+$ 493.2339, found 493.2333.

(2R,3R,4R,5R)-3,4-bis(Benzyloxy)-2-((benzyloxy)methyl)-5-((R)-1-nitropropyl)pyrrolidin-1-ol ***(17A, minor diastereoisomer).*** According to general procedure, obtained as minor product after nitropropylation of **13** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.76–1.83 (m, 1H, C$\underline{H}_a$H$_b$–CH$_3$), 1.95–2.02 (m, 1H, CH$_a\underline{H}_b$–CH$_3$), 3.54–3.58 (m, 1H, ^{6}C$\underline{H}_a$H$_b$), 3.63–3.78 (m, 3H, ^{6}CH$_a\underline{H}_b$, ^{2}CH and ^{5}CH), 4.02–4.04 (m, 1H, ^{3}CH), 4.06–4.07 (m, 1H, ^{4}CH), 4.40–4.63 (m, 6H, 3 C$\underline{H}_2$–Ph), 4.75–4.81 (m, 1H, CH–NO$_2$), 5.39 (br s, 1H, OH), 7.21–7.35 (m, 15H, 15 CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.4 (CH_3), 24.1 ($\underline{C}H_2$–CH$_3$), 67.6 ($^6CH_2$), 70.8 (^{5}CH), 71.5 (^{2}CH), 71.8 ($\underline{C}H_2$–Ph), 71.9 ($\underline{C}H_2$–Ph), 73.5 ($\underline{C}H_2$–Ph), 82.6 (^{3}CH), 84.3 (^{4}CH), 90.7 (CH–NO$_2$), 127.8–128.6 (15 CHar), 137.4 (C_{IV}ar), 137.7 (C_{IV}ar), 138.0 (C_{IV}ar); m/z calcd for $C_{29}H_{34}N_2O_6Na$ [M + Na]$^+$ 529.2315, found 529.2321.

(2R,3R,4R,5R)-3,4-bis(Benzyloxy)-2-((benzyloxy)methyl)-5-((R)-1-nitropropyl)pyrrolidin-1-ol ***(17B, major diastereoisomer).*** According to general procedure, obtained as major product after nitropropylation of **13** and purification of the resulting residue by chromatography on silica gel (diethyl ether / petroleum ether 4:6); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.89–1.95 (m, 1H, C$\underline{H}_a$H$_b$–CH$_3$), 2.08–2.17 (m, 1H, CH$_a\underline{H}_b$–CH$_3$), 3.54–3.57 (m, 1H, ^{2}CH), 3.63–3.78 (m, 3H, $^6CH_2$ and ^{5}CH), 3.97 (dd, ^3J = 7.1 Hz, ^3J = 2.5 Hz, 1H, ^{4}CH), 4.19 (dd, ^3J = 7.1 Hz, ^3J = 2.5 Hz, 1H, ^{3}CH), 4.40–4.63 (m, 6H, 3 C$\underline{H}_2$–Ph), 4.75–4.81 (m, 1H, CH–NO$_2$), 5.22 (br s, 1H, OH), 7.21–7.35 (m, 15H, CHar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.8 (CH_3), 23.7 ($\underline{C}H_2$–CH$_3$), 66.7 ($^6CH_2$), 69.4 (^{5}CH), 71.1 (^{2}CH), 71.6 ($\underline{C}H_2$–Ph), 72.1 ($\underline{C}H_2$–Ph), 73.5 ($\underline{C}H_2$–Ph), 83.3 (^{3}CH), 84.5 (^{4}CH), 89.6 (CH–NO$_2$), 127.8–128.5 (C_{AR}), 137.7 (C_{IV}ar), 137.8 (C_{IV}ar), 138.1 (C_{IV}ar); m/z calcd for $C_{29}H_{34}N_2O_6Na$ [M + Na]$^+$ 529.2315, found 529.2321.

(2R,3R,4S,5S)-2-(Aminomethyl)-5-((R)-1,2-dihydroxyethyl)pyrrolidine-3,4-diol ***(18).*** To a solution of **12aR** (106 mg, 0.333 mmol, 1 equiv) in dry methanol (5 mL) under argon was added 10 wt. % Pd/C (35 mg, 0.033 mmol, 0.1 equiv) and 6 N HCl (1 mL). The suspension was stirred 48 h under hydrogen (1 bar) then filtered over Celite. The Celite was rinsed with methanol and the filtrate was concentrated under reduced pressure to eliminate HCl. Amberlyst A-26 resin (OH^-) was added to the residue in solution in methanol (5 mL) until reaching basic conditions, then the crude was filtered and evaporated under reduced pressure. Purification of the resulting residue on silica gel ($CHCl_3$ / MeOH / NH_4OH 0.8M 5:5:1) afforded **18** as a yellow oil (25 mg, 39%). $[\alpha]_D^{20}$ +3.6 (c 0.56, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 2.65 (dd, ^2J = 12.8 Hz, ^3J = 7.0 Hz, 1H, C$\underline{H}_a$H$_b$–NH$_2$), 2.81 (dd, ^2J = 12.8 Hz , ^3J = 5.0 Hz, 1H, CH$_a\underline{H}_b$–NH$_2$), 2.88–3.04 (m, 1H, ^{2}CH), 3.08 (dd, ^3J = 5.2 Hz, ^3J = 4.0 Hz, 1H, ^{5}CH), 3.53–3.63 (m, 2H, $^7CH_2$), 3.65–3.71 (m, 2H, ^{3}CH and ^{6}CH), 3.87 (m, 1H, ^{4}CH); ^{13}C NMR (CD_3OD, 125 MHz) δ 45.3 (CH_2–NH$_2$), 65.5 (^{2}CH), 65.6 (^{5}CH), 65.7 (^{7}CH), 72.8 (^{6}CH), 74.3 (^{4}CH), 75.1 (^{3}CH); m/z calcd for $C_7H_{17}N_2O_4$ [M + H]$^+$ 193.1188, found 193.1189.

(1,2,3,4-Tetrahydroisoquinolin-1-yl)methanamine ***(19).*** To a solution of **4** (289 mg, 1.39 mmol, 1 equiv) in dry methanol (8 mL) under argon was added 10 wt. % Pd/C (148 mg, 0.139 mmol, 0.1 equiv) and 6 N HCl (2 mL). The suspension was stirred 24 h under hydrogen (1 bar) then filtered over Celite. The Celite was rinsed with methanol and the filtrate was concentrated under reduced pressure to eliminate HCl. Amberlyst A-26 resin (OH^-) was added to the residue in solution in methanol (5 mL) until reaching basic conditions; filtration and evaporation under reduced pressure afforded **19**[29] as a brown oil (139 mg, 62%), which was used without further purification; ^{1}H NMR (CD_3OD, 250 MHz) δ 2.84 (t, ^3J = 5.6 Hz, 2H, C$\underline{H}_2$–CH$_2$–NH), 3.07–3.28 (m, 4H, C$\underline{H}_2$–NH, C$\underline{H}_2$–NH$_2$), 4.20 (dd, ^3J = 9.5 Hz, ^3J = 4 Hz, 1H, CH–NH), 7.15–7.26 (m, 4H, 4 CHar). ^{13}C NMR (CD_3OD, 125 MHz) δ 29.7 ($\underline{C}H_2$–CH$_2$–NH), 39.6 (CH$_2$–NH), 44.3 (CH$_2$–NH$_2$), 54.5 (CH–NH), 127.5 (CHar), 127.5 (CHar), 128.3 (CHar), 130.7 (CHar), 135.2 (C_{IV}ar), 136.8 (C_{IV}ar). m/z calcd for $C_{10}H_{15}N_2$ [M + H]$^+$ 163.1235, found 163.1237.

N-((1,2,3,4-Tetrahydroisoquinolin-1-yl)methyl)cyclohexane-carboxamide ***(20).*** **20** was prepared according to the literature[29] from **19** (0.181 g, 1.12 mmol, 1 equiv), pyridine (0.121 mL, 1.51 mmol, 1.35 equiv), 2 N HCl (0.560 mL, 1.12 mmol, 1 equiv) and cyclohexanecarbonyl chloride (0.224 mL, 1.68 mmol, 1.5 equiv) and was obtained as a pale yellow solid (183 mg, 60%); mp 104–106 °C (lit.[29] 111–113°C); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.03–1.24 (m, 5H), 1.57–1.87 (m, 5H), 2.05–2.15 (m, 1H), 2.79–2.88 (m, 2H), 3.05–3.09 (m, 1H, C$\underline{H}_a$H$_b$–NH), 3.19–3.23 (m, 1H, CH$_a\underline{H}_b$–NH), 3.37 (ddd, ^2J = 14 Hz, ^3J = 9.1 Hz, ^3J = 4.5 Hz, 1H, C$\underline{H}_a$H$_b$–NH–CO), 3.84 (ddd, ^2J = 14.0 Hz, ^3J = 6.4 Hz, ^3J = 3.3 Hz, 1H, CH$_a\underline{H}_b$–NH–CO), 4.19 (dd, ^3J = 9 Hz, ^3J = 2.7 Hz, 1H, C$\underline{H}$–NH), 5.75 (br s, 2H), 6.83 (br s, 1H, NH–CO), 7.09–7.10 (m, 1H, CHar), 7.16–7.19 (m, 2H, 2 CHar), 7.22–7.24 (m, 1H, 1 CHar); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.83 (CH_2), 25.85 (CH_2), 26.04 (CH_2), 28.7 (CH_2), 29.64 (CH_2), 29.69 (CH_2), 39.54 (CH$_2$–NH), 43.16 ($\underline{C}H_2$–NH–CO), 45.49 ($\underline{C}H$–CO), 55.3 (CH–NH), 126.6 (CHar), 126.84 (CHar), 127.1 (CHar), 129.3 (CHar), 134.4 (C_{IV}ar), 134.6 (C_{IV}ar), 176.90 (CO).

(±)-Praziquantel (PZQ) ***(3a).*** PZQ was prepared according to the literature[30,4b] from **20** (55 mg, 0.202 mmol, 1 equiv), sodium hydroxide (50% in water, 0.097 mL, 1.21 mmol, 6.0 eq), chloroacetyl chloride (25 mg, 0.017 mL, 0.222 mmol, 1.1 eq) and Benzyltriethylammonium chloride (4.6 mg, 0.020 mmol, 0.1 eq) and was obtained as a pale yellow solid (35 mg, 56%); mp 133°C (lit.[31] 132–134°C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24–1.34 (m, 3H), 1.48–1.60 (m, 2H), 1.72–1.85 (m, 5H), 2.47 (tt, ^3J = 11.5 Hz, ^3J = 3.1 Hz, 1H), 2.77–2.84 (m, 2H), 2.87–3.02 (m, 2H), 4.08 (d, ^2J = 17.5 Hz, 1H), 4.48 (d, ^2J = 17.5 Hz, 1H), 4.79–4.87 (m, 2H), 5.17 (dd, ^2J = 13.1 Hz, ^3J = 2.5 Hz, 1H), 7.18–7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.7, 28.7, 29., 29.2, 39.1, 40.8, 45.1, 49.0, 55.0, 125.5 CHar, 127.0 CHar, 127.5 CHar, 129.3 CHar, 132.8 (C_{IV}ar), 134.7 (C_{IV}ar), 164.4 (CO), 174.8 (CO).

Supporting Information (see footnote on the first page of this article) plots representing time-course of the aza-Henry reaction with TBD or under PTC conditions, NMR monitoring of retro-aza-Henry of **4** and isomerization of **13a*R***, NOESY spectra for **12a*R***,**13a*R***,**13a*S***, copies of ^{1}H- and ^{13}C-NMR spectra of nitrones **2**, **5-9**, **11-13**, of products **3a**, **4**, **6a-13a**, **14-20** and of dinitromethyl adducts.

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Keywords: nitrones • reactivity • aza-Henry • nitromethylation • vicinal diamines

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(23) With TBD, the retro-aza-Henry process was favored after prolonged reaction time, which was evidenced by an increase in the relative amount of nitrone in the reaction mixture. The reaction under PTC was more sluggish, as observed on kinetic plots (see SI). Surprisingly, similar conversions were obtained either with an excess of CsF (1.6 equiv.) *vs* TBABr (0.3 equiv) or the reverse (0.3 equiv CsF, 1.6 equiv TBABr), with ca 70% conversion after 6h. Lowering the amount of both reagents to 0.3 equiv. afforded an unsatisfactory conversion of 35% after 24h. When used as the phase transfer catalyst, TBAI proved less efficient than TBABr.
(24) Nitrone **10** is commercially available. All other nitrones were prepared according to known protocols from either the corresponding amines by using sodium tungstate-H_2O_2 (**2**) or oxone (**7** and **11**) as oxydizing agent (reference 5a and 5b for experimental procedure), or by condensation of aldehydes with hydroxylamines (**6**,**8**,**9**, reference 5c), or by intramolecular dispacement from oximes (**12**,**13**, reference 5d). Their NMR spectra are given in the Supporting Information.
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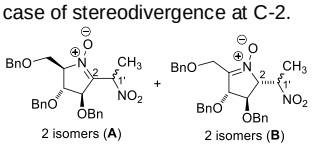
(28) Additionally, air-oxidation of hydroxylamine **16** in the presence of Pd afforded two diastereomeric sets of constitutionally isomeric nitrones (structures below), which confirms a conserved configuration at C-2 in **16**. Only one regioisomer **A** would have been obtained in the case of stereodivergence at C-2.



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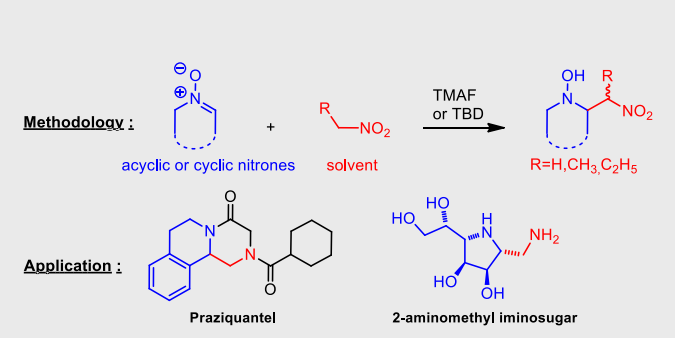

Comprehensive study of the addition of nitroalkanes to nitrones was conducted. The reaction proved efficient with TMAF or TBD as bases, in the presence of a large excess of RCH_2NO_2. Phase-transfer catalysis gave also acceptable yields. Nitroethane or nitropropane afforded mixtures of isomerisable diastereomers. The reaction was applied to the synthesis of biologically relevant compounds.

Key topic : nitrone reactivity