Příloha 6.

Program rektora MU na podporu tvůrčí činnosti studentů

Podpora výzkumné činnosti studentů
(kategorie E,F)

Závěrečná zpráva o výsledcích projektu

Identifikační kód projektu

2	0	0	7	1	4	3	1	E	0	0	1	6

Základní údaje	
Kategorie projektu (čl. 2 odst. 1)	Podpora výzkumné činnosti studentů v oborech lékařství, zdravotnictví, přírodovědy a informatiky
Navrhovatel (jméno, příjmení, UČO)	Marian Buchlovič (106328)
Kontakt (adresa, telefon, e-mail)	Vajanského 2, 93401 Levice, SR; 549 49 5692; buchlo@mail.muni.cz
Fakulta	Přírodovědecká
Studijní program – obor	N-CH ORGA
Název projektu	Využití nových synthonů pro syntézu heterocyklických sloučenin s očekávanou biologickou aktivitou.
Akronym	HETEROBIO
Odborný garant – spoluředitel (+UČO)	prof. RNDr. Milan Potáček, CSc. (638)
VŠ – fakulta – pracoviště	MU-PřF-Ústav chemie
Kontakt (adresa, telefon, e-mail)	Kotlářská 2, 611 37 Brno, 6615, potacek@chemi.muni.cz
Další spolupracovníci	studenti-počet : 0 zaměstnanci-počet: 1

Výstupy projektu

Publikace:

BUCHLOVIČ, Marian - MAN, Stanislav - POTÁČEK, Milan.
Allenyloxime – new source of heterocyclizations to stable cyclic nitrones, *Tetrahedron* **2008** (publikace je přijatá do tisku).

Účast na konferencích formou posteru:

BUCHLOVIČ, Marian - MAN, Stanislav - POTÁČEK, Milan.
Novel application of substituted allenyloximes in synthesis of heterocyclic compounds. In *ChemZi* 3/1 2007. Bratislava : Slovenská chemiská spoločnosť, 2007. ISBN 1336-7242, s. 99-99. 2.9.**2007**, Vysoké Tatry, Tatranské Matliare.

MAN, Stanislav - **BUCHLOVIČ, Marian** - POTÁČEK, Milan.
New way to cyclic nitrones by cyclization of allenyloximes. In *Book of Abstracts - XII. Blue Danube Symposium on Heteroyclic Chemistry*. Budapest : Chemical Research Center, Hungarian Academy of Sciences and Eotvos Lorand University, 2007. ISBN 978-963-7067-15-0, 54 PO-1 s. 10.6.**2007**, Tihani, Maďarsko.

POTÁČEK, Milan - MAN, Stanislav - ZACHOVÁ, Hana - **BUCHLOVIČ, Marian** - GALETA, Juraj.
Allenyl synthon - source of various heterocyclizations and transformations. In *XXVIII th Conference of Organic Chemists Advances in Organic Chemistry - Book of Abstracts*. Vyd. 1. Bratislava : Department of Organic Chemistry, Faculty of Science, Comenius University, 2007. s. 86-86. 16.9.**2007**, Smolenice.

Uvedené výstupy projektu plně zodpovídají předkládanému návrhu.

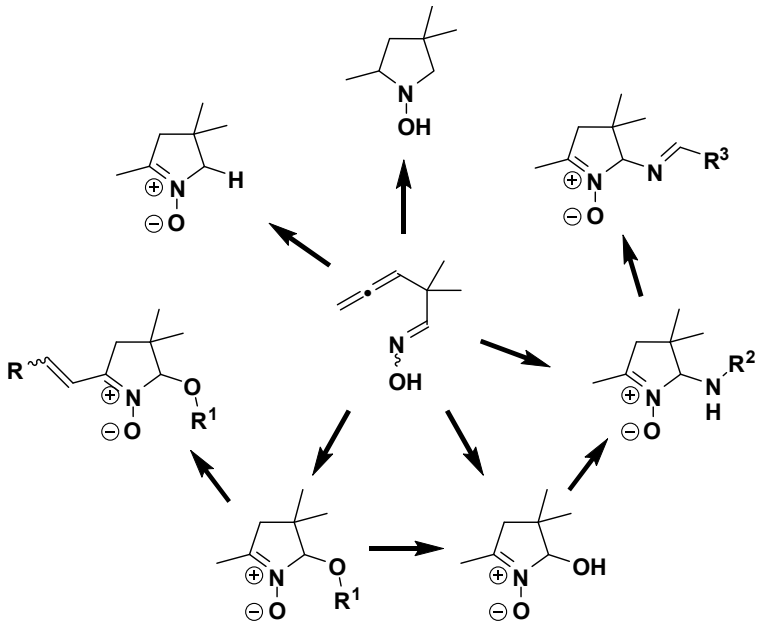
Odborná charakteristika dosažených výsledků

Projekt navazuje na podrobnější studium chemie allenů v rámci Ústavu chemie na Přírodovědecké fakultě. Práce konkrétně popisuje nové možnosti aplikace allenyoxímů v syntéze cyklických nitronů. Zpracované reakční postupy nabízejí novou cestu k strukturně novým stabilním dipolárním sloučeninám, které jsou dále modifikovatelné a použitelné do další syntézy jako substráty pro 1,3-dipolární cykloadice. Podrobně byly výsledky zpracovány ve formě obsáhlé publikace v mezinárodním odborném periodiku z oblasti organické chemie – Tetrahedron.

Charakteristika dosažených výsledků z hlediska projektu

Optimalizovaná syntéza nového derivátu allenyloxímu (2,2-dimethylpenta-3,4-dienaloxim) umožnila studium cyklizačních reakcí prostřednictvím aplikace rozličných reakčních podmínek. Jako produkty studovaných reakcí byly pozorovány 5-členné cyklické nitrony, které byly modifikovány ve druhém kroku syntézy za vzniku derivatizovaných struktur (viz. obrázek níže). Všechny produkty cyklizace byly izolovány a plně charakterizovány moderními metodami organické syntézy (NMR, FTIR, MS, RTG-strukturní analýza). Proces byl studován i z hlediska reakčního mechanizmu a byly navrženy reakční intermediáty pro jednotlivé typy cyklizací. Cyklizace byly rozděleny do dvou kategorií, bazicky iniciované (v přítomnosti KOH, nebo vhodného amínu) a cyklizace v přítomnosti redukčního činidla ($NaBH_4$, $NaBH_3CN$). V prvním případě byl popsán tandemový adičně-cyklizační proces, při kterém dochází, v jednom kroku, k uzavírání kruhu a zavedení funkční skupiny (stereogenního centra) do polohy 2 cílové molekuly.

Produkty cyklizací 2,2-dimethylpenta-3,4-dienaloximu byly testovány i ve smyslu jejich dipolární struktury jako substráty v 1,3-dipolárních cykloadicích s vybranými dipolarofily. Reakce sloužily i jako metody k potvrzení struktury cyklizačních produktů prostřednictvím RTG-analýzy vzniklých dobře krystalických látek. Byl pozorován vznik vždy jen jediného diastereomeru z čehož plyne, že ve všech případech se jednalo o diastereoselektivní průběh cykloadice.



Účast na odborných akcích v porovnání s plánem

1. 59. Zjazd chemikov, Vysoké Tatry, Slovenská republika, 2-6. září, 2007.
2. Účast formou posteru.
3. plánovaná akce ano X ne □

Všechny plánované akce byly uskutočneny.

Čerpání finančních prostředků (uvádět v tisících Kč na jedno desetinné místo)

	položka	**přiděleno**	**čerpání**
1	Odměna řešitele	13,0	13,0
2	Odměna garanta	0	0
3	Odměny pro spolupracovníky	0	0
4	Zákonné odvody	0	0
5	Sociální fond	0	0
6	Dohody o provedení práce	5,0	5,0
7	Stipendium pro spolupracovníky	0	0
8	Cestovné	10,0	11,4
9	Studijní literatura	14,0	11,7
10	Drobný hmotný a nehmotný majetek	9,0	4,8
11	Materiál	55,0	58,7
12	Služby	11,0	12,4
13	**Celkem**	117,0	117,0

Zdůvodnění rozdílů v plánovaném čerpání finančních prostředků

Cestovné:

Návrh projektu počítal s jiným výměnným kurzem pro slovenskou korunu, který se v čase konání konference a sepisování návrhu výrazně měnil.

Drobný hmotný majetek:

Uvažovaný produkt překračoval předpokládané náklady, proto byl zakoupen materiál za nižší cenu jako náhrada.

Literatura:

Navrhovaná publikace nebyla v čase obdržení grantu již dostupná, a proto bylo zakoupeno několik levnějších učebnic.

Služby:

Elementární analýza všech připravených sloučenin, která byla nutná pro přípravu publikace, mírně překročila předpokládané náklady. Bylo vsak nezbytně nutné provést tuto analýzu u všech syntetizovaných produktů.

Materiál:

Rozdíl v jednotlivých kapitolách byl využitý v spotřebě vhodného materiálu.

Datum: 28. 5. 2008

Príloha

Elsevier Editorial System(tm) for Tetrahedron
Manuscript Draft

Manuscript Number: TET-D-08-00456

Title: Allenyloxime - a new source of heterocyclizations to stable cyclic nitrones

Article Type: Full Length Article

Corresponding Author: Prof. Dr. Milan Potacek, PhD

Corresponding Author's Institution: Masaryk University

First Author: Marian Buchlovic, MSc

Order of Authors: Marian Buchlovic, MSc; Stanislav Man, Ph.D.; Milan Potacek, Professor

Graphical Abstract

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Fonts or abstract dimensions should not be changed or altered.

Allenyloxime – a new source of heterocyclizations to stable cyclic nitrones

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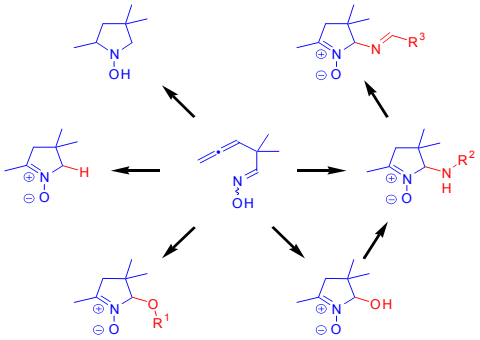
Marian Buchlovič, Stanislav Man, Marek Nečas and Milan Potáček*



Pergamon

TETRAHEDRON

Allenyloxime - a new source of heterocyclizations to stable cyclic nitrones

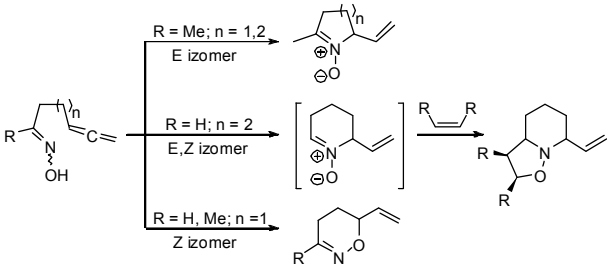
Marian Buchlovič, Stanislav Man and Milan Potáček*

Department of Chemistry, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic

Abstract—A variety of conditions including reductive and/or basic agents in aqueous or alcoholic solution was applied to 2,2-dimethylpenta-3,4-dienal oxime. Formation of a various 5-membered heterocycles with excellent chemical selectivity was observed. Most of the reactions yielded cyclic nitrones with stable dipolar structure and unique functionalities present. All products of cyclization were isolated and fully characterized.

1. Introduction

Although there is remarkable great development in the field of allene chemistry, [1] allenyloximes have not attracted a lot of attention among chemists during the last decade. There are only several papers dealing with the allenyloxime cyclizations,[2,3] which were discussed in our previous report.[4] Distinct advance in allenyloxime chemistry was made by Gallagher et al., who for the first time presented an idea of approaching nitrone-type compounds by allenyloxime cyclization using $AgBF_4$ (as electrophilic catalyst) in dichloromethane (Scheme 1).[5]



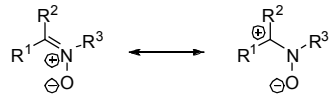
Scheme 1. Cyclization of allenyloximes.

Methodology is based on cyclization allenyloximes with minimally substituted alkyl chain leading to 5 or 6-membered cyclic nitrones bearing vinyl substitution.

However, the dipolar compounds could be effectively isolated only in the case of ketoximes. Due to their lower reactivity in dipolar cycloadditions, they afforded reasonable yields of nitrones. Aldoximes providing more reactive and unstable nitrones were trapped *in situ* by adding a dipolarophile.

Procedure is also complicated by a different reactivity dependent on the presence of *E*/*Z* oxime isomers, where particular Z-isomers showed considerable yields of cyclization *via* oxygen (Scheme 1). Nevertheless this method has got a very good application in preparation of some synthetically interesting targets.[5,6]

On the other hand nitrones (azomethine oxides) were first prepared in 1890 by Beckman.[7] Application and new methods in preparation of nitrones, as important building blocks in organic synthesis, still maintains in the center of the general interest more than a century after their discovery. Most of the studied chemistry is based on their dipolar properties (Scheme 2).



Scheme 2.

Keywords: allenyloximes; nitrones;.cyclization reaction; heterocyclization.
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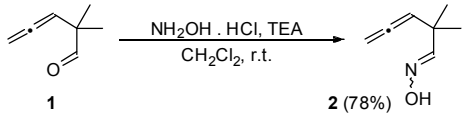
This behavior is opening a relatively easy access to different heterocyclic structures *via* 1,3-dipolar cycloadditions. Depending on the type of dipolarophile used, isoxazole with alkene, alkyne and allene dipolarophiles or more complex rings with isocyanates, nitriles and thiocarbonyles could be obtained. Efficiency of such reactions is documented by a wide application not only in heterocyclic but also in the natural products chemistry.[8]

Our interest shown in this paper is the ability of the prepared allenyloximes to undergo heterocyclizations. We present several methods based on simple conditions without any metallic catalyst involved. The procedure provides suitable way to construct 5-membered stable cyclic nitrones together with introduction of various functional groups in one step process.

2. **Results and discussion**

We have selected 2,2-dimethylpenta-3,4-dienal oxime **2** as a principal building block for our experiments. Unsubstituted allenyl moiety with no additional steric demands and the presence of geminal methyl groups[9] makes this compound ideal for investigation aimed on the allenyloxime cyclization potential. Good avalibility[10] of allenylaldehyde **1** and its easy transformation to desired oxime **2** (Scheme 3), supported our proposal even more.

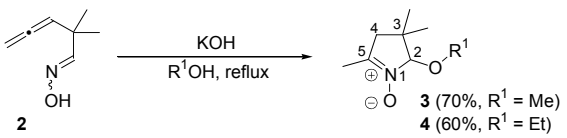


Scheme 3. Preparation of starting material.

The work, for the most parts, deals with examination of this particular derivative and through a methodical approach points out possible applications in the synthetic field.

2.1. Base catalyzed cyclizations

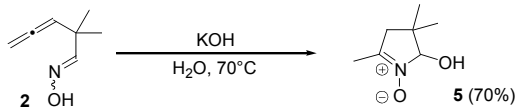
One of the first successful attempts on cyclization was based on application of a base catalysis. Oxime **2** undergoes ring-closure in alcoholic solution of potassium hydroxide yielding alkoxy-substituted nitrones **3** and **4** (Scheme 4). The base present in 0.1 equivalent to starting compound seems to be the most efficient choice. At this concentration the reactions still proceed within 4 hours and the separated crude product possesses a high level of purity (suitable for another reactions) and yield (>90% for **3**, >80% for **4**).



Scheme 4. Cyclization of oxime **2** in alcohols

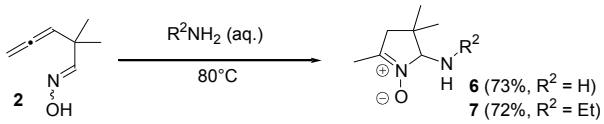
To obtain nitrones as colourless oils, high vacuum distillation was used as the only working method. However, thermal instability of concentrated products above 80°C makes this procedure less efficient and notably lowers the yields (70% and 60% respectively).

Based on the very good stability of oxime **2** in alkaline aqueous solution, we were able to switch from organic solvents to water as a medium and implement the same methodology. Compound **2** showed a rapid cyclization in alkaline water leading to hydroxy-substituted nitrone **5** (Scheme 5). Since very low solubility of the starting compound in water, higher concentration of base (2 equivalents) had to be used to gain homogeneity of the reaction mixture and speed up the process. Otherwise partial decomposition was observed.



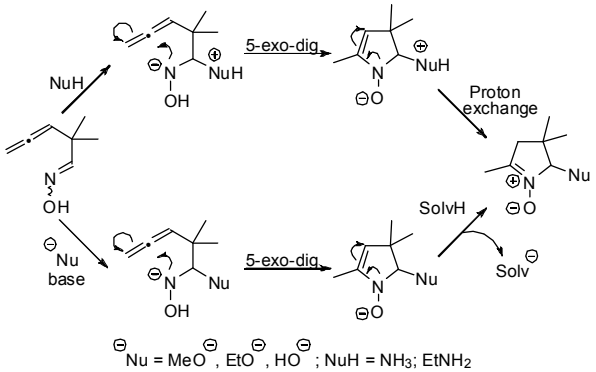
Scheme 5. Cyclization of oxime **2** in alkaline aqueous solution

When oxime **2** was heated in concentrated aqueous ammonia or ethylamine (with no other base present), cyclization led exclusively to nitrones **6** and **7,** respectively. Both products, like in the previous cases, involved addition of nucleophile on C=N bond (Scheme 6).



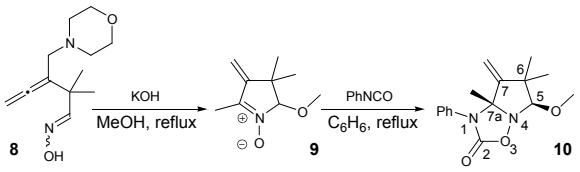
Scheme 6. Cyclization of oxime **2** in aqueous amine solutions.

Nitrones **5**-**7** are characterized by a very good solubility in water (**6** is strongly hygroscopic), which necessarily makes any extraction to organic solvents difficult. Nitrone **5** is practically insoluble in diethylether. But we found extraction to dichloromethane to be the most effective. Anyway, extraction procedures have to be done from brine (by addition of NaCl solubility of nitrones was decreased). In the case of compound **5**, setting pH to neutral values was necessary, due to its ability of salt formation in the presence both base and acid (for complete procedures see experimental section).



Scheme 7. Proposed mechanism for nitrones **3**-**7** formation

We assume that the mechanism of all the mentioned cyclizations is initiated by the addition of a nucleophile on carbon atom of C=N bond of the oxime moiety. Then after formation of a negatively charged nitrogen atom of the former oxime, its nucleophile addition favours the attack upon central allenylic atom described as 5-exo-digonal ring closure.[11] The process ends probably at the more stable tautomer containing endocyclic double bond (Scheme 7). This intermediate, substituted cyclic enamine, could be stabilized by protonation on β-nonsaturated carbon, forming observed nitrone product. Such a pathway correlates well with behaviour of alkynylhydroxylamine systems published earlier[12] and differs from electrophile catalyzed procedure discussed above.[5] The nucleophile itself could react as an anion, which we believe occurs in the case of nitrones **3**-**5** formation, where alkoxide and hydroxide ion, respectively, is present in the reaction mixture (shown as lower path in scheme 7). That means enamine intermediate is protonated probably with a participation of the used solvent. It is supported by experiments in dry aprotic solvents where usage of pure alkoxides as nuclephiles did not cause any cyclization. Alternatively, nitrones **6** and **7** are most probably products of ammonia/amine molecule addition, followed by consequent deprotonation of amino moiety in a proton exchange process (shown as higher path in Scheme 7). Moreover, the role of the base seems to be crucial for all cyclizations. First, in alcohol or water as a medium, presence of the base determines the concentration of alkoxide and hydroxide ions, respectively, considered as cyclization initiators. It should be mentioned here, that without adding any base, no cyclic products were detected. Second, base (including ammonia) could take part in acid-base reactions with starting material,[13] which is documented by increased solubility of oxime **2** in water, resulting in a notable influence on reaction times and purity of the isolated products as was mentioned above.



Scheme 8. Cyclization of oxime **8**

To support the proposed mechanism on a more general basis, we have done several experiments on substituted oxime **8** that showed interesting behaviour under conditions of base catalyzed cyclization. As products of the reaction in methanol unusual nitrone **9** containing exocyclic double bond and morpholine were observed (Scheme 8). Since the difficulties with purification process, the structure of compound **9** was determined by 1,3-dipolar cycloaddition with phenylisocyanate and subsequent X-ray analysis[14] of cycloadduct **10** (Figure 1) . Interestingly the cycloaddition, according to NMR analysis of the crude reaction mixture, proceeds with complete diastereoselectivity, yielding exclusively one diastereomer **10** (racemate) only.

Nevertheless, the same mechanism as shown in Scheme 7 assuming enamine intermediate as a key step could be fully expected in this case and so perfectly explaining the cleavage of C-N bond in oxime **8** (Scheme 9).

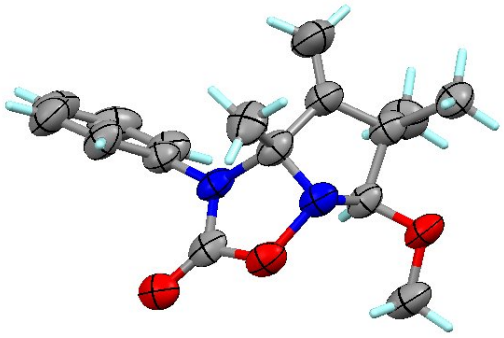
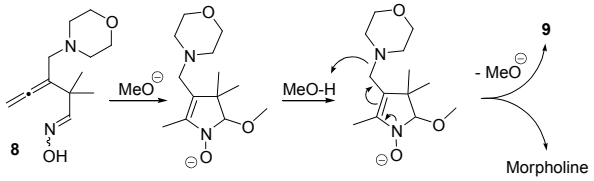


Figure 1. ORTEP structure representation of compound **10**



Scheme 9. Cyclization mechanism of nitrone **9** formation

Both solvents (alcohol and water) used in the reactions with starting compound **2** listed above afforded products with full characterization and determination of their structure by X-ray diffraction.[14] Structure of nitrone **3** was confirmed by the analysis of its corresponding picrate.[4] Compound **5** containing hydroxy group was identified indirectly by the structure analysis of its cycloadduct **11** with dimethyl acetylenedikarboxylate (Figure 2) as a single diastereomer. Cycloaddition had to be used here again for a structure elucidation because by the direct X-ray analysis of **5** we were not able to fully assign the structure. The hydroxy group on the stereogenic carbon atom appeared like flipping from one position above to below of the pyrroline ring plane and this way exchanging its position with hydrogen atom. Later we have found that our knowledge is matching with already published information[15] where nitrone **5** was prepared by oxidation of **16** by a peracid.

The observed interesting and exceptional properties of atoms in compound **5** that at first caused some problems in the product identification inspired us to perform additional experiments. Figure 3 shows that the differentiation in chemical shifts of the diastereotopic hydrogen atoms of CH_2 (~2.4 ppm) and methyl groups (~1.15 ppm) in ^{1}H NMR of **5** was lost when the sample was measured between 30-35°C. Repeated measurements at different temperatures showed that methyl signal coalescence temperature is 30°C. It could be assumed that it is a consequence of configuration inversion at the stereogenic centre (hydroxy substituted carbon), which necessarily means that a bond cleavage takes place.

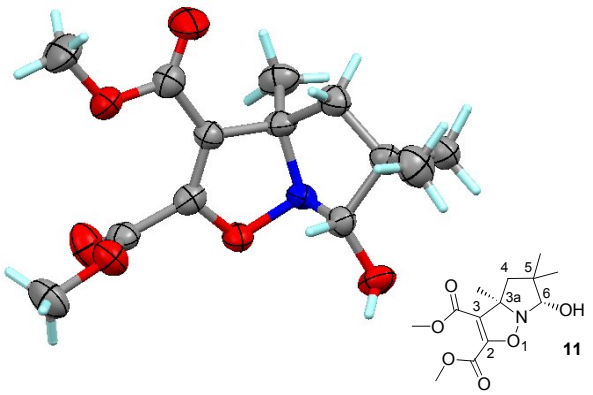


Figure 2. ORTEP structure representation of compound **11**

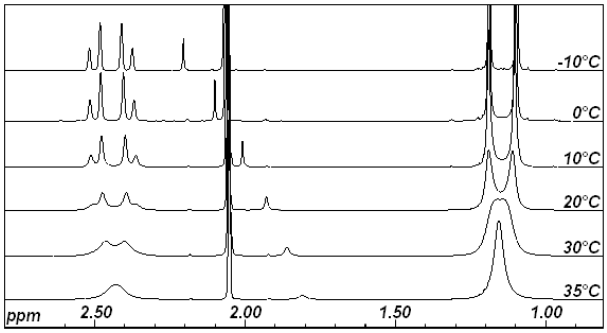
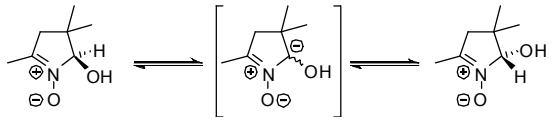


Figure 3. Influence of the temperature upon ^{1}H-NMR signals of compound **5** (500 MHz, $CDCl_3$).

If we exclude the possibility of carbon-carbon or carbon-heteroatom bond breaking under such mild conditions, there is only a carbon-hydrogen atom dissociation left as an option (a simple proton exchange between the two oxygen atoms would not affect chemical shifts that way as it is observed), which may explain the described behaviour. If you take into consideration the neighbouring electron atracting nitrogen atom, such a transformation could be expected. Proposed mechanism is shown in Scheme 10.



Scheme 10. Mechanism of configuration inversion in compound **5**

Such a process should be strongly influenced by the acidity of the solution. Based on the experimentally proved ability of nitrone **3** to form picrates,[4] we have simulated the same conditions for compound **5** by addition of picric acid to the measured solution.

The resulted spectra (Figure 4) demonstrate a notable suppression of the configuration inversion. On the other hand presence of a base in D_2O solution enhanced the process (not shown). Therefore both experiments support our proposed mechanism.

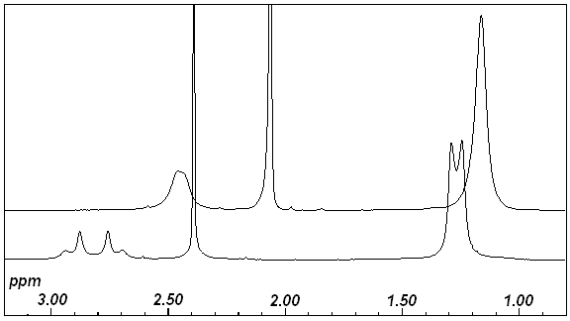
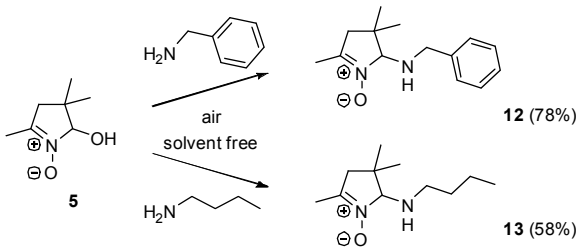


Figure 4: ^{1}H-NMR spectra (300 MHz, $CDCl_3$, 30°C) of compound **5** (upper spectrum) and mixture of compound **5** and 1.5 ekv. of picric acid .

After solving the structure of compound **5**, we have focused on its chemical reactivity. Most curious transformation of the structure was observed in the presence of amines. As the most demonstrative behaviour of compound **5** is a reaction where simple mixing of nitrone **5** at room temperature with a small excess of benzylamine without any solvent leads to the product of substitution **12** (Scheme 11). The exact structure of **12** was confirmed by X-ray structure analysis (Figure 5).[14]



Scheme 11. Reaction of nitrone **5** with amines

Analogous conditions, except higher temperature, were used for the reaction with aliphatic amine. We have chosen butylamine with higher boiling temperature to avoid application of high pressure arrangement. The reaction afforded expected product **13** (Scheme 11) and in combination with method described above (Scheme 6) represent a second route to amino substituted nitrones.

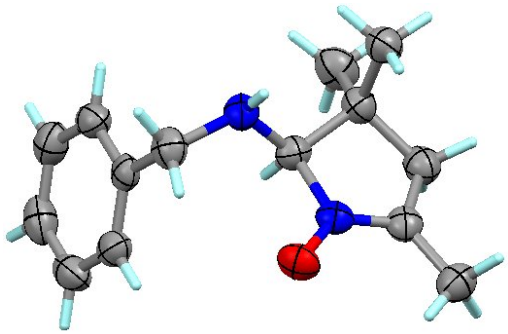
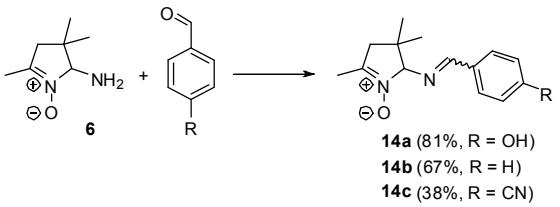


Figure 5. ORTEP representation of compound **12**

The mechanism, however, surely cannot be considered within the polar substitutions. As the most simple and

convincing argument is the fact that the reaction is oxygen dependent and under protective argon atmosphere there are only traces of products detectable (process studied on the reaction with benzylamine). Secondly, we were neither able to carry out the procedure in a solvent nor in the solvent bubbled with air during the reaction. The oxygen presence requirement could indicate a possible hidden oxidation step in the reaction mechanism. Oxidation or any other involvement of oxygen in reaction with nitrone moiety producing radical species is probably the process trigger. It is supported by the well known ability of these compounds to act as spin traps and affords relatively stable radical abducts, e.g. with singlet oxygen[16] or superoxide anion radical.[17] Since the absence of solvent makes the study of the mechanism difficult, we have not been able to come out with any experimentally supported suggestions yet. Despite the unsolved course of the reaction, method is very simple, effective and offers a new type of stable nitrones in good yields.

The second object of our further experimental study, nitrone **6**, is constitutionally a completely new compound represented by amino functionality located right next to the nitrone moiety. We were interested in its applications in chemical transformations. As demonstrative experiment, the treatment with several *para*-substituded benzaldehydes was chosen. The reactions led clearly to expected condensation products **14a-c** (Scheme 11).

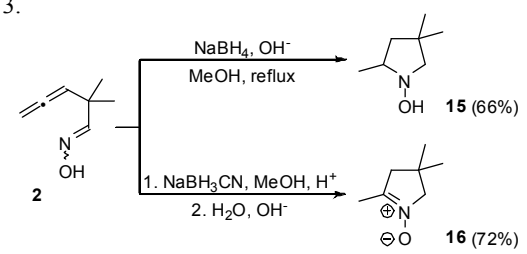


Scheme 11. Condensation of nitrone **6** with benzaldehydes

The nitrone group seems to be unaffected by this procedure or by the purification process. Furthermore no side products were detected, indicating that any involvement of other molecular parts in the reaction does not occur. Such a knowledge greatly increases the synthetic potential of compound **6** and indicates a lot of other possible transformations based on amino group.

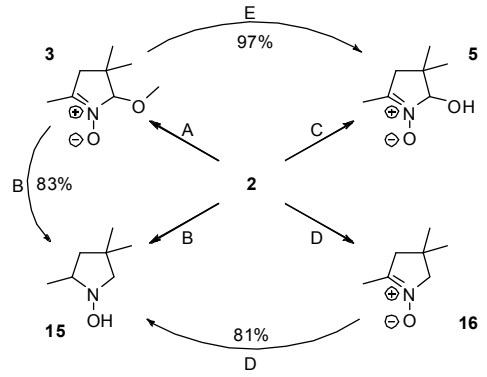
2.2. Cyclizations under reductive conditions

A presence of reducing agents could also initiate the ring closure of allenyloxime **2**. We have observed a great difference in product character depending on the property of the reduction agent used. Treatment with sodium borohydride under basic conditions leads to substituted pyrrolidine-1-ol **15**, as we have already reported earlier.[4] On the other hand, cyanoborohydride reduction, implicates a formation of cyclic nitrone **16** exclusively (Scheme 12). Surprisingly no acyclic product of oxime reduction (amine or hydroxylamine) was detected. To come out with any reaction mechanism proposal, we have done several experiments to gain any evidence for reaction intermediates. The selected results are shown in Scheme 13.

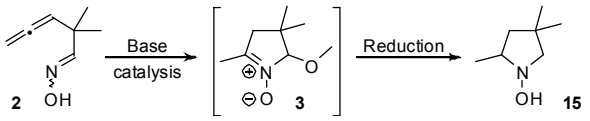


Scheme 12. Cyclization of oxime **2** under reductive conditions

First, mechanism of pyrrolidine **15** formation was considered. Based on the experimental proof that conversion **3** to **15** is possible under the same conditions as **2** to **15** (Scheme 13), we assumed that mechanism of reductive cyclization with sodium borohydride is stepwise including the base catalyzed cyclization to nitrone **3** as the first step, followed by the reduction of nitrone moiety together with C-O bond cleavage (Scheme 14).



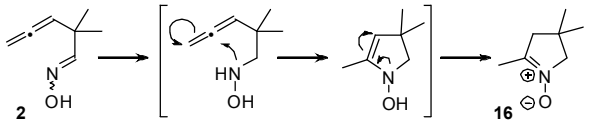
Scheme 13. Interconversion of cyclization products **3**, **5**, **15**, **16**. ***A***: KOH, MeOH, refl.; ***B***: $NaBH_4$, OH^-, MeOH, refl,; ***C***: KOH, H_2O, 80°C; ***D***: $NaBH_3CN$, H^+, MeOH, then OH^-/H_2O; ***E***: H_2SO_4 (1.5 ekv.), H_2O. Yields represent isolated crude products.



Scheme 14. Proposed mechanism of compound **15** formation

Nitrone **16** formation[18] is probably the result of oxime reduction to hydroxylamine, followed by cyclization to the observed product (Scheme 15). This proposal is based on the published procedure,[19] where set of oxime derivatives was transformed to corresponding hydroxylamines under similar conditions. Moreover, we have experimentally proved instability of the isolated nitrone **16** under same reductive conditions (Scheme 13, conversion **16** to **15**). Thus, we can anticipate that the cyclization takes place during the separation process caused probably by concentrating of hydroxylamine in aqueous solution in the

presence of the base and brief heating. Similar observations were made by House et al. on alkene analogues.[20]



Scheme 15. Proposed mechanism of nitrone **16** formation

Another interesting transformation was observed when nitrone **3** was acidified by the treatment with hydrochloric acid in water. Instead of expected chloride, immediate conversion to hydroxy substituted nitrone **5** proceeded. (Scheme 13, conditions *E*).

Products **15** and **16** were determined by X-ray analysis.[14] Compound **15** was analysed as a corresponding picrate.[4] Structure of nitrone **16** (a liquid) was confirmed in the form of the cycloaddition product with phenylisocyanate (Figure 6, structure **17**).

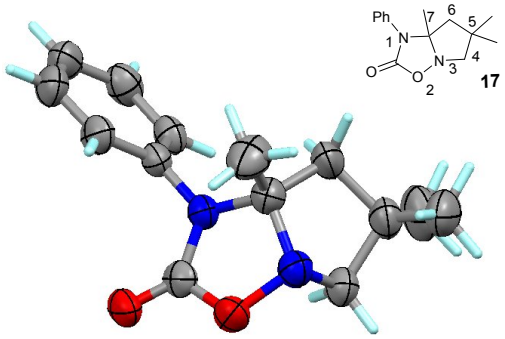


Figure 6. ORTEP representation of compound **17**

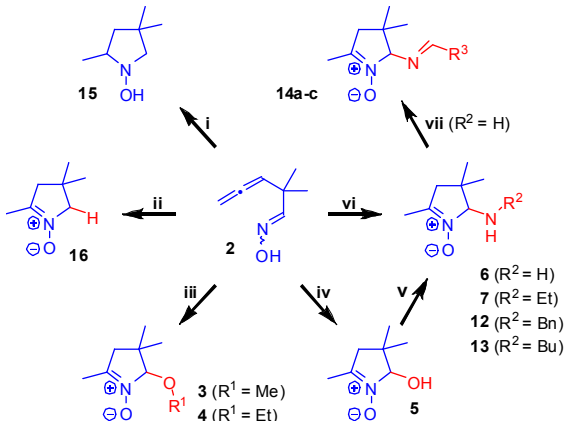
3. Summary and conclusion

We have established an effective method for newly functionalized stable 5-membered cyclic nitrones synthesis by a tandem addition-cyclization one step process (Scheme 17). This way allenyloxime **2** was transformed into twelve cyclic products (11 classified as nitrones, Table 1) differing in functionality and/or reaction pathway used. All cyclizations were performed in alcoholic or aqueous solutions. Reactions offered exclusive products with no side reactions involved. Additionally, the chemistry of selected products in relation to their reaction mechanism and possible synthetic applications were studied. Some of the new unusual reactions were described and qualified as potentially very helpful in possible consequent research.

In conclusion, our study demonstrated that chosen allenyloxime **2** is a suitable substrate for heterocyclizations. Presented work highlights the chemistry of allenyloximes and shows that just one simple starting compound may be a source of plenty of different products as presented in Table 1.

Starting compound	Nitrone	Substitution in position 2	Number of steps	Overall yield [%]
2	16	H	1	72
2	5	OH	1	70
2	3	O	1	70
2	4	O	1	60
2	6	NH_2	1	73
2	7	N H	1	72
2	13	N H	2	42
2	12	N H	2	57
2	14a-c	N R	2	28-59

Table 1. Summarized yields of cyclic nitrones.



Scheme 17. Heterocyclizations of allenyloxime **2** and transformations of products; (***i***) $NaBH_4$, OH^-, MeOH, refl.; (***ii***) $NaBH_3CN$, H^+, MeOH, then OH^-/H_2O; (***iii***) KOH, R^1OH, refl.; (***iv***) KOH, H_2O, 80°C; (***v***) R^2NH_2, no solvent, air; (***vi***) R^2NH_2, H_2O, 80°C; (***vii***) aldehyde, C_6H_6 or Et_2O, refl.

4. Experimental section

4.1. Instrumentation and materials

All chemicals were used as purchased. Solvents (benzene, diethyl ether) were dried over sodium/benzophenone and distilled before use. Column chromatography was performed on Horizon HPFC System (Biotage), with FLASH Si 25+M cartridge. All distillations were carried out using BÜCHI Glass Oven B-580 "Kugelrohr" apparatus. Melting points are uncorrected. FTIR spectra were recorded with Genesis ATI (Unicam) apparatus. NMR spectra were collected on a Bruker AC-300 (all experimental section data) and Bruker AC-500 (low temperature measurements, see figure 3). TMS (δ = 0.00 ppm) and $CHCl_3$ (δ = 7.27 ppm) for ^1H and $CDCl_3$ (δ = 77.23) for ^{13}C NMR were used as internal standards, interaction constants are in [Hz]. MS data were obtained with MS TRIO 1000 (Fisons) apparatus at 30 eV in the EI mode. Diffraction data were collected on a Kuma KM-4 four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined using the **SHELXTL** program package.[22] The hydrogen atoms were placed in calculated idealized positions and refined as riding.

*4.2. 2,2-Dimethylpenta-3,4-dienal oxime (**2**)*

Improved reported[4] procedure: A solution of hydroxylamine hydrochloride (13.9 g, 0.200 mol), triethylamine (20.6 g, 0.204 mol) and 3Å molecular sieves (6g) in dichloromethane (150 ml) were cooled down to 0°C, then allenylaldehyde[10] **1** (20.0 g, 0.182 mol) was added slowly. The mixture was stirred at room temperature for 5 hours. After filtration (to remove mol. sieves), solution was washed with water (3x100ml) and brine (1x100ml) and dried over $MgSO_4$. Residual solvent was removed under reduced pressure and subsequent oil was purified by distillation on Kugelrohr apparatus (121°C, 8 mbar) to give **2** (colorless oil, 17.73 g, 78%). For spectral data see reference.[4]

*4.3. 2-Methoxy-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**3**)*

Improved reported[4] procedure: Potassium hydroxide (645 mg, 11.5 mmol) was dissolved in methanol (100ml) and then oxime **2** (14.4 g, 0.115 mol) was added. The mixture was refluxed for 4 hours under argon atmosphere. Afterwards, solution was concentrated under reduced pressure to remove most of the solvent. Then 30 ml of water was added, followed by extraction with dichloromethane (5x30 ml). Combined extracts were dried over $MgSO_4$ and evaporated. Obtained oil was purified by distillation using a Kugelrohr apparatus (65°C, $2.5x10^{-2}$ mbar) to give nitrone **3** as colorless oil (12.66 g, 70%). For spectral data see reference.[4] Calcd. for $C_8H_{15}NO_2$ (157.21): C, 61.12; H, 9.62; N, 8.91. Found: C, 60.86; H, 9.62; N, 8.97.

*4.4. 2-Ethoxy-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**4**)*

Same procedure as for **3**, 6.00 g (47.9 mmol) of oxime **2**, KOH (269 mg, 4.79 mmol), EtOH (60 ml), water (10 ml) and extraction with dichloromethane (5x15 ml) was used to get nitrone **7** (4.92 g, 60%) as colorless oil after same distillation method (70°C, $2.0x10^{-2}$ mbar). δ_H ($CDCl_3$): 1.08 (s, 3H, H_3C-C-CH_3), 1.17 (s, 3H, H_3C-C-CH_3), 1.24 (t, $^3J_{H,H}$ = 6.9, 3H, O-CH_2-CH_3), 2.03 (s, 3H, N=C-CH_3), 2.31 (d, $^2J_{H,H}$ = 17.5, 1H, N=C-CH_2), 2.54 (d, $^2J_{H,H}$ = 17.5, 1H, N=C-CH_2), 3.83-3.94 (m, 1H, O-CH_2), 4.35-4.45 (m, 1H, O-CH_2), 4.55 (s, 1H, CH); δ_C ($CDCl_3$): 12.9 (N=C-CH_3), 15.3 (O-CH_2-CH_3), 22.1 (H_3C-C-CH_3), 27.4 (H_3C-C-CH_3), 36.5 (H_3C-C-CH_3), 45.6 (N=C-CH_2), 68.9 (O-CH_2), 106.2 (CH), 143.8 (C=N); IR (film): 1038, 1111, 1178, 1243,1344, 1387, 1446, 1468, 1610, 2872, 2929, 2972; MS m/z (%): 172 (M^+, 33), 127 (65), 112 (100), 100 (20), 72 (39), 56 (50), 41 (65). Anal. Calcd. for $C_9H_{17}NO_2$ (171.24): C, 63.13; H, 10.01; N, 8.18. Found: C, 62.92; H, 10.10; N, 7.93.

*4.5. 2-Hydroxy-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**5**)*

Potassium hydroxide (269 mg, 4.79 mmol) was dissolved in water (2.5 ml) and then oxime **2** (0.300 mg, 2.40 mmol) was added. The mixture was then heated to 70°C under argon atmosphere for 3 hours. After cooling to room temperature, solution was neutralized to pH = 7-8 (lacmus) and 0.5 g of NaCl was added to saturate the solution. Then mixture was extracted with dichloromethane (7x5 ml). Combined extracts were dried over $MgSO_4$ and evaporated. Crude solid product was crystallized from Et_2O/CH_2Cl_2 = 5/1 to give nitrone **5** as white solid (240 mg, 70%), mp 142-144°C. δ_H ($CDCl_3$): 1.16 (br, 6H, H_3C-C-CH_3), 2.06 (s, 3H, H_3C-C=N), 2.45 (br, 2H, CH_2), 5.08 (s, 1H, CH); δ_C ($CDCl_3$): 13.4 (N=C-CH_3), 22.2[23] (br, H_3C-C-CH_3), 27.1[23] (br, H_3C-C-CH_3), 36.9 (H_3C-C-CH_3), 45.7 (CH_2), 99.7 (CH), 145.6 (C=N); IR (KBr): 821, 1120, 1153, 1174, 1190, 1228, 1330, 1386, 1450, 1468, 1633, 2744, 2844, 2933, 2964. MS m/z (%): 144 (M^+, 68), 97 (40), 82 (40), 73 (100), 56 (60), 41 (90). Calcd. for $C_7H_{13}NO_2$ (143.18): C, 58.72; H, 9.15; N, 9.78. Found: C, 58.98; H, 9.27; N, 9.65.

*4.6. 2-Amino-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**6**)*

Oxime **2** (0.500 g, 3.99 mmol) was mixed with concentrated (8 ml, 26%) aqueous ammonia solution in a closed apparatus fitted with a balloon to avoid over pressuring. After 24 hour of vigorous stirring at 80°C homogenous pale yellow solution was concentrated under reduced pressure to remove the rest of ammonia, followed by adding NaCl (1.5g) and extraction with dichloromethane (8x10ml). Combined extracts were dried over $MgSO_4$ and evaporated. Resulting oil was purified by

column chromatography (EtOAc/MeOH = 1/1) to give white solid (403 mg, 71%), mp (unstable). δ_H ($CDCl_3$): 1.00 (s, 3H, H_3C-C-CH_3), 1.26 (s, 3H, H_3C-C-CH_3), 2.03 (s, 3H, N=C-CH_3), 2.07 (br, 2H, NH_2), 2.31 (dm, $^2J_{H,H}$ = 17.5, 1H, CH_2), 2.47 (dm, $^2J_{H,H}$ = 17.5, 1H, CH_2), 4.27 (t, $^3J_{H,H}$ = 8.4, 1H, CH); δ_C ($CDCl_3$): 13.2 (N=C-CH_3), 21.7 (H_3C-C-CH_3), 26.8 (H_3C-C-CH_3), 36.5 (H_3C-C-CH_3), 45.2 (CH_2), 87.6 (CH), 140.6 (C=N). IR (KBr): 924, 1188, 1217, 1387, 1470, 1631, 2872, 2937, 2958; MS m/z (%): 143 (M^+, 40), 110 (20), 71 (50), 56 (100), 41 (35); Calcd. for $C_7H_{14}N_2O$: 142.20.

4.7. 2-(Ethylamino)-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (7)

Oxime **2** (0.350 g, 2.80 mmol) was added into aqueous ethylamine (4 ml, 70%) in a closed apparatus fitted with a balloon to avoid over pressuring. After 11 hour heating at 80°C, reaction mixture was concentrated under reduced pressure to remove the unreacted amine, then 350 mg of NaCl added and extracted with of dichloromethane (7x5 ml). Combined extracts were dried over $MgSO_4$ and evaporated. Resulting oil was purified by column chromatography (Et_2O/MeOH = 6/1) to give yellowish oil (343 mg, 72%). δ_H ($CDCl_3$): 1.01 (s, 3H, H_3C-C-CH_3), 1.12 (t, $^3J_{H,H}$ = 7.1, 3H, N-CH_2-CH_3), 1.18 (s, 3H, H_3C-C-CH_3), 1.18 (s, 3H, H_3C-C-CH_3), 1.84 (br, 1H, NH), 2.03 (dd, $^4J_{H,H}$ = 3.1, $^4J_{H,H}$ = 1.5, 3H, N=C-CH_3), 2.35 (dm, $^2J_{H,H}$ = 17.5, 1H, N=C-CH_2), 2.42 (dm, $^2J_{H,H}$ = 17.5, 1H, N=C-CH_2), 2.73-2.86 (m, 1H, N-CH_2-CH_3), 3.16-3.28 (m, 1H, N-CH_2-CH_3), 4.28 (d, $^3J_{H,H}$ = 8.3, 1H, CH); δ_C ($CDCl_3$): 12.8 (N=C-CH_3), 15.6 (N-CH_2-CH_3), 22.0 (H_3C-C-CH_3), 27.6 (H_3C-C-CH_3), 36.4 (H_3C-C-CH_3), 41.7 (N-CH_2-CH_3), 45.5 (N=C-CH_2), 92.9 (CH), 141.1 (C=N); IR (film): 1142, 1178, 1207, 1240, 1369, 1389, 1470, 1614, 1666, 2871, 2927, 2964; MS m/z (%): 171 (M^+, 50), 153 (95), 110 (80), 98 (70), 84 (100), 56 (85), 41 (95)); Calcd. for $C_9H_{18}N_2O$: 170.25.

4.8. 2,2-Dimethyl-3-(morpholinomethyl)penta-3,4-dienal oxime (8)

2,2-Dimethyl-3-(morholinomethyl)penta-3,4-dienal (4.15 g, 19.8 mmol), prepared according with the published method,[10] was slowly added to a mixture of hydroxylamine hydrochloride (1.52 g, 21,9 mmol) and 3Å molecular sieves (3g) in 40 ml of dichloromethane and then stirred under argon atmosphere for 4 hours. Afterwards, sodium hydroxide (1.5g in 20ml of water) was added to the mixture. After disolving the solid, molecular sieves were filtered off. Organic phase was separated and residual water phase was extracted with diethylether (6x25 ml). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give **8** (3.56 g, 80%) as white solid, mp 77-79 °C. δ_H ($CDCl_3$): 1.27 (s, 6H, H_3C–C–CH_3), 2.44 (t, $^3J_{H,H}$ = 4.6, 2H, O–CH_2–CH_2–N), 2.93 (t, $^5J_{H,H}$ = 2.4, 2H, N–CH_2–C=), 3.69 (t, $^3J_{H,H}$ = 4.6, 4H, O–CH_2–CH_2–N), 4.83 (t, $^5J_{H,H}$ = 2.4, 2H, H_2C=C), 7.43 (s, 1H, CH), 7.67 (br, 1H, OH); δ_C ($CDCl_3$): 25.3 (H_3C–C–CH_3), 38.6 (H_3C–C–CH_3), 53.7, 58.5, 67.2, 77.6 (C=C=CH_2), 105.3 (C=C=CH_2), 157.5 (N=C), 207.2 (C=C=CH_2); IR (KBr): 875, 945, 1007, 1117, 1303, 1454, 1954 (=C=), 2858, 2966, 3074, 3163; MS m/z (%): 225 (M^+, 10), 207 (90), 122 (30), 100 (100), 56 (25). Calcd. for $C_{12}H_{20}N_2O_2$ (224.30): C, 64.26; H, 8.99; N, 12.49. Found: C, 64.04; H, 8.87; N, 12,38.

4.9. 2-Methoxy-3,3,5-trimethyl-4-methylene-3,4-dihydro-2H-pyrrole 1-oxide (9)

Potassium hydroxide (75 mg, 1.34 mmol) was dissolved in methanol (30 ml) and then allenyloxime **8** (3.00 g, 13.4 mmol) was added. The mixture was refluxed for 11 hours. After cooling to room temperature solution was concentrated under vacuum. Then water (10 ml) was added and mixture extracted with dichloromethane (4x15ml). The combined extracts were then washed with water (2x20 ml) and brine (1x20 ml), dried over $MgSO_4$ and evaporated. The obtained oil was purified by column chromatography (EtAc/MeOH = 18/1) to give ~70% of yellow brown oil. δ_H ($CDCl_3$): 1.15 (s, 3H, H_3C-C-CH_3), 1.26 (s, 3H, H_3C-C-CH_3), 2.06 (s, 3H, H_3C-C=N), 3.90 (s, 3H, O-CH_3), 4.57 (s, 1H, CH), 4.99 (s, 1H, CH_2), 5.13 (s, 1H, CH_2); δ_C ($CDCl_3$): 8.9 (N=C-CH_3), 22.0 (H_3C-C-CH_3), 27.7 (H_3C-C-CH_3), 41.1 (H_3C-C-CH_3), 61.6 (O-CH_3), 105.3 (CH_2), 106.4 (CH), 143.3, 151.7.

4.10. (5R,7aS)-5-Methoxy-6,6,7a-trimethyl-7-methylene-1-phenyltetrahydropyrrolo[1,2-b][1,2,4]oxadiazol-2(1H)-one (10)

Phenylisocyanate (289 mg, 2.42 mmol) was added to a solution of nitrone **9** (410 mg, 2.42 mmol) in dry benzene (8 ml) and heated under reflux for 4 hours. Solvent was removed under vacuum and crude product was crystallized from Et_2O to give 356 mg (51%) of white solid, mp 120-122 °C. δ_H ($CDCl_3$): 1.10 (s, 3H, H_3C-C-CH_3), 1.32 (s, 3H, H_3C-C-CH_3), 1.62 (s, 3H, N-C-CH_3), 3.67 (s, 3H, O-CH_3), 4.43 (s, 1H), 4.63 (s, 1H), 5.14 (s, 1H), 7.15-7.42 (m, 5H, CH_{Ar}); δ_C ($CDCl_3$): 24.7 (CH_3), 25.3 (CH_3), 26.2 (CH_3), 42.9 (H_3C-C-CH_3), 59.0 (O-CH_3), 86.1 (N-C-CH_3), 106.2 (O-CH), 112.7 (C=CH$_2$), 129.1 (CH_{Ar}), 129.5 (CH_{Ar}), 129.9 (CH_{Ar}), 133.8 (C_{Ar}), 153.8 (C=CH_2), 156.1 (C=O); IR (KBr): 704, 746, 910, 1041, 1101, 1124, 1161, 1209, 1365, 1496, 1763, 2939, 2983; MS m/z (%): 169 (45), 139 (80), 119 (100), 91 (80), 67 (35), 64 (35)); Calcd. for $C_{16}H_{20}N_2O_3$: 288.34.(MS spectrum does not contain M^+)

4.11. (3aR,6S)-Dimethyl-6-hydroxy-3a,5,5-trimethyl-3a,4,5,6-tetrahydropyrrolo[1,2-b]isoxazole-2,3-dicarboxylate (11)

Nitrone 5 (200 mg, 1.40 mmol) was suspended in dry benzene (5ml) and dimetyl acetylenedikarboxylate (218 mg, 1.54 mmol) was added. The mixture was stirred at room temperature for 5 hours. Then the solvent was removed under vacuum and solid product was crystallized from Et_2O to give 11 (white solid, 303 mg, 76 %), mp 149-151 °C. δ_H ($CDCl_3$): 1.07 (s, 3H, H_3C-C-CH_3), 1.11 (s, 3H, H_3C-C-CH_3), 1.51 (s, 3H, N-C-CH_3), 1.96 (d, $^2J_{H,H}$ = 13.9, 1H, CH_2), 2.28 (d, $^2J_{H,H}$ = 13.9, 1H, CH_2), 2.50 (d, $^3J_{H,H}$ = 8.1, 1H, OH), 3.75 (s, 3H, O-CH_3), 3.89 (s, 3H, O-CH_3),

4.44 (d, $^3J_{H,H}$ = 8.1, 1H, CH); δ_C ($CDCl_3$): 21.6 (CH_3), 26.5 (CH_3), 28.1 (CH_3), 37.6 (H_3C-*C*-CH_3), 49.0 (CH_2), 52.0 (O-CH_3), 53.4 (O-CH_3), 70.0 (N-*C*-CH_3), 99.3 (CH), 115.0 (O-C=*C*), 151.2, 159.9, 162.7; IR (KBr): 1072, 1109, 1167, 1306, 1350, 1433, 1456, 1649, 1720, 1741, 2968, 2983, 3228 (br, OH); MS m/z (%): 286 (M^+, 30), 268 (20), 238 (20), 200 (100), 168 (35), 71 (55), 42 (50)); Calcd. for $C_{13}H_{21}NO_6$: 287.31.

*4.12. 2-(Benzylamino)-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**12**)*

Nitrone **5** (200 mg, 1.40 mmol) was rubbed with benzylamine (154 mg, 1.44 mmol) and left standing at room temperature with an access of air for 9 hours. The obtained solid product was then crystallized from Et_2O to give **12** (white solid, 253 mg, 78%), mp 91-93 °C. δ_H ($CDCl_3$): 1.04 (s, 3H, H_3C-C-CH_3), 1.15 (s, 3H, H_3C-C-CH_3), 2.02 (dd, $^4J_{H,H}$ = 3.0, $^4J_{H,H}$ = 1.5, 3H, N=C-CH_3), 2.08-2.19 (m, 1H, NH), 2.32 (dm, $^2J_{H,H}$ = 17.4, 1H, N=C-CH_2), 2.40 (dm, $^2J_{H,H}$ = 17.4, 1H, N=C-CH_2), 4.21 (dd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 6.3, 1H, N-CH_2), 4.33 (dm, $^3J_{H,H}$ = 10.9, 1H, CH), 4.48 (dd, $^2J_{H,H}$ = 13.5, $^3J_{H,H}$ = 5.0, 1H, N-CH_2), 7.21-7.43 (m, 5H, CH_{Ar}); δ_C ($CDCl_3$): 13.1 (N=C-CH_3), 22.3 (H_3C-C-CH_3), 27.2 (H_3C-C-*C*H_3), 37.0 (H_3C-*C*-CH_3), 45.3 (N=C-*C*H_2), 51.7 (N-CH_2), 92.1 (CH), 127.1 (CH_{Ar}), 128.4 (CH_{Ar}), 140.6, 140.9; IR (KBr): 706, 758, 1174, 1188, 1389, 1450, 1468, 1493, 1514, 1604, 2867, 2922, 2960, 3253; MS m/z (%): 233 (M^+, 5), 215 (50), 91 (100), 65 (30), 56 (30), 41 (70). Calcd for $C_{14}H_{20}N_2O$ (232.32): C, 72.38; H, 8.68; N, 12.06. Found: C, 72.60; H, 8.47; N, 12.11.

*4.13. 2-(Butylamino)-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**13**)*

Nitrone **5** (200 mg, 1.40 mmol) was mixed with butylamine (1.00g, 13.7 mmol) and heated at 80 °C for 7 hours with an access of air. Then remaining amine was removed under vacuum. Crude product was purified by column chromatography (Et_2O/MeOH = 9/1) to give colorless oil (161 mg, 58%). δ_H ($CDCl_3$): 0.91 (t, $^3J_{H,H}$ = 7.2, 3H, CH_2-CH_3), 1.00 (s, 3H, H_3C-C-CH_3), 1.17 (s, 3H, H_3C-C-CH_3), 1.31-1.51 (m, 4H, CH_2-CH_2-CH_3), 1.81 (br, 1H, NH), 2.01 (dd, $^4J_{H,H}$ = 3.1, $^4J_{H,H}$ = 1.5, 3H, N=C-CH_3), 2.32 (dm, $^2J_{H,H}$ = 17.4, 1H, N=C-CH_2), 2.39 (dm, $^2J_{H,H}$ = 17.4, 1H, N=C-CH_2), 2.70-2.78 (m, 1H, N-CH_2), 3.14-3.22 (m, 1H, N-CH_2), 4.25 (s, 1H, CH); δ_C ($CDCl_3$): 12.9 (N=C-*C*H_3), 14.1 (CH_2-*C*H_3), 20.3 (*C*H_2-CH_3), 22.2 (H_3*C*-C-CH_3), 27.7 (H_3C-C-*C*H_3), 33.0 (N-CH_2-*C*H_2), 36.6 (H_3C-*C*-CH_3), 45.5 (N=C-*C*H_2), 47.2 (N-CH_2), 93.3 (CH), 141.0 (N=*C*-CH_3); IR (KBr): 788, 1141, 1192, 1228, 1367, 1389, 1468, 1612, 1668, 2869, 2927, 2956, 3284; MS m/z (%): 199 (M^+, 100), 181 (30), 110 (55), 84 (55), 57 (35), 42 (40). Calcd. for $C_{11}H_{22}N_2O$ (198.31): C, 66.62; H, 11.18; N, 14.13. Found: C, 66.60; H, 11.27; N, 13.94.

*4.14. General procedure for nitrones **14a,b** preparation*

Nitrone **6** (150 mg, 1.05 mmol) was dissolved in dry Et_2O (10ml) and then aldehyde (1.07 mmol) was added. The mixture was heated under reflux for 5 hours (**14a**) or 7 hours (**14b**). After solvent evaportion crude nitrones were purified by column chromatography (Et_2O/MeOH).

*4.14.1. 2-(4-Hydroxybenzylideneamino)-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**14a**)*

Et_2O/MeOH = 4/1, white solid (210mg, 81%), mp 174-176 °C. δ_H ($CDCl_3$): 1.00 (s, 3H, H_3C-C-CH_3), 1.20 (s, 3H, H_3C-C-CH_3), 2.18 (s, 3H, N=C-CH_3), 2.47 (d, $^2J_{H,H}$ = 18.0, 1H, N=C-CH_2), 2.83 (d, $^2J_{H,H}$ = 18.0, 1H, N=C-CH_2), 4.59 (s, 1H, N-CH), 6.66 (d, $^3J_{H,H}$ = 8.6, 1H, CH_{Ar}), 7.17 (d, $^3J_{H,H}$ = 8.6, 1H, CH_{Ar}), 7.97 (s, 1H, N=CH), 10.62 (s, 1H, OH); δ_C ($CDCl_3$): 13.6 (N=C-*C*H_3), 23.0 (H_3*C*-C-CH_3), 28.5 (H_3C-C-*C*H_3), 38.1 (H_3C-*C*-CH_3), 47.0 (CH_2), 103.3 (N-CH), 116.5 (CH_{Ar}), 126.1 (C_{Ar}-C=N), 130.8 (CH_{Ar}), 149.2 (N=*C*-CH_3), 161.3 (C-OH), 166.1 (N=CH); IR (KBr): 837, 1076, 1163, 1172, 1238, 1286, 1518, 1583, 1606, 1641, 2478, 2569, 2671, 2798, 2873, 2929, 2962; MS m/z (%): 247 (M^+, 5), 127 (80), 120 (30), 112 (100), 41 (55). Calcd. for $C_{14}H_{18}N_2O_2$ (246.30): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.12; H, 7.37; N, 11.26.

*4.14.2. 2-(Benzylideneamino)-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**14b**)*

Et_2O/MeOH = 3/1, white solid (162 mg, 67%), mp 88-90 °C. δ_H ($CDCl_3$): 1.09 (s, 3H, H_3C-C-CH_3), 1.24 (s, 3H, H_3C-C-CH_3), 2.11 (s, 3H, N=C-CH_3), 2.44 (d, $^2J_{H,H}$ = 17.5, 1H, N=C-CH_2), 2.79 (d, $^2J_{H,H}$ = 17.5, 1H, N=C-CH_2), 4.63 (s, 1H, N-CH), 7.37-7.47 (m, 3H, CH_{Ar}), 7.80-7.84 (m, 2H, CH_{Ar}), 8.42 (s, 1H, N=CH); δ_C ($CDCl_3$): 13.2 (N=C-*C*H_3), 23.1 (H_3*C*-C-CH_3), 28.5 (H_3C-C-*C*H_3), 38.0 (H_3C-*C*-CH_3), 46.7 (CH_2), 102.1 (N-CH), 128.6 (CH_{Ar}), 129.2 (CH_{Ar}), 131.6 (CH_{Ar}), 135.3 (C_{Ar}-C=N), 144.9 (N=*C*-CH_3), 165.0 (N=CH); IR (KBr): 1178, 1240, 1450, 1610, 1643, 2958; MS m/z (%): 231 (M^+,5), 127 (85), 112 (100), 41 (50) ; Calcd. for $C_{14}H_{18}N_2O$: 230.31.

*4.14.3. 2-(4-Cyanobenzylideneamino)-3,3,5-trimethyl-3,4-dihydro-2H-pyrrole 1-oxide (**14c**)*

Nitrone **6** (150 mg, 1.05 mmol) was dissolved in dry benzene (10ml) then 3Å molecular sieves (1.5g) and cyanobenzaldehyde (159 mg, 1.21 mmol) were added. The mixture was heated under reflux for 9 hours and then solvent evaporated. Crude product was purified by column chromatography (Et_2O/MeOH = 4/1) to give **14c** (yellowish oil, 102 mg, 38%). δ_H ($CDCl_3$): 1.10 (s, 3H, H_3C-C-CH_3), 1.27 (s, 3H, H_3C-C-CH_3), 2.12 (s, 3H, N=C-CH_3), 2.50 (d, $^2J_{H,H}$ = 17.7, 1H, N=C-CH_2), 2.80 (d, $^2J_{H,H}$ = 17.7, 1H, N=C-CH_2), 4.70 (s, 1H, N-CH), 7.71 (d, $^3J_{H,H}$ = 8.1, 1H, CH_{Ar}), 7.94 (d, $^3J_{H,H}$ = 8.1, 1H, CH_{Ar}), 8.49 (s, 1H, N=CH); δ_C ($CDCl_3$): 13.1 (N=C-*C*H_3), 23.0 (H_3*C*-C-CH_3), 28.4 (H_3C-C-*C*H_3), 37.9 (H_3C-*C*-CH_3), 46.5 (CH_2), 101.3 (N-CH), 114.7 (*C*-CN), 118.3 (C-*C*N), 129.3 (CH_{Ar}), 132.3

(CH_{Ar}), 138.9 (C_{Ar}-C=N), 145.5 (N=*C*-CH_3), 163.1 (N=CH); IR (KBr): 1178, 1176, 1244, 1385, 1465, 1610, 1643, 2227, 2872, 2906, 2927, 2962; MS m/z (%): decomposition.

4.15. 2,4,4-Trimethylpyrrolidin-1-ol[4] ***(15)***

4.16. 3,3,5-Trimethyl-3,4-dihydro-2H-pyrrole 1-oxide ***16***

Allenyloxime **2** (2.00 g, 16.0 mmol) was added to solution of $NaBH_3CN$ (1 g, 16.0 mmol) in methanol (30g). Solution was cooled down to 0°C and concentrated HCl was dropwise added to set pH ≈ 3 (lacmus). The mixture was then stirred at room temperature for 3 hours (pH was checked every 30 min. and kept in acidic region). Solvent was removed under vacuum then water (8ml) was added and finally NaOH pellets were supplied to make mixture alkaline. Then solution was stirred for 5 minutes. After extraction with dichloromethane (5x10 ml), combined extracts were dried over $MgSO_4$ and evaporated. The crude product was distilled at Kugelrohr apparatus (70 °C, $3x10^{-2}$ mbar) to give **16** (colorless oil, 1.46 g, 72%). δ_H ($CDCl_3$): 1.14 (s, 6H, H_3C-C-CH_3), 1.96 (s, 3H, N=C-CH_3), 2.45 (s, 2H, N=C-CH_2), 3.68 (s, 2H, N-CH_2); δ_C ($CDCl_3$): 12.7 (N=C-*C*H_3), 28.3 (H_3C-C-*C*H_3), 32.3 (H_3C-*C*-CH_3), 48.2 (N=C-CH_2), 74.5 (N-CH_2), 144.5 (N=*C*-CH_3); IR (film): 1171, 1240, 1254, 1389, 1458, 1622, 2872, 2958; MS m/z (%): 255 (50), 128 (M^+, 100). Calcd. for $C_7H_{13}NO$ (127.18): C, 66.10; H, 10.30; N, 11.01. Found: C, 66.16; H, 10.30; N, 10.83.

4.17. 6,6,7a-Trimethyl-1-phenyltetrahydropyrrolo[1,2-b][1,2,4]oxadiazol-2(1H)-one (**17**)

Phenylisocyanate (187 mg, 1.57 mmol) was added to a solution of nitrone **16** (200 mg, 1.57 mmol) in dry benzene (4 ml) and stirred at room temperature under argon atmosphere for 5 hours. Solvent was removed under vacuum and crude product was crystallized from Et_2O to give **17** (white solid, 309 mg, 80%), mp 111-113 °C. δ_H ($CDCl_3$): 1.17 (s, 3H, *H*$_3$C-C-CH_3), 1.21 (s, 3H, H_3C-C-C*H*$_3$), 1.71 (s, 3H, N=C-*C*H_3), 1.75 (d, $^2J_{H,H}$ = 14.2, 1H, N-C-CH_2), 2.24 (d, $^2J_{H,H}$ = 14.2, 1H, N-C-CH_2), 3.08 (d, $^2J_{H,H}$ = 9.4, 1H, N-CH_2), 3.48 (d, $^2J_{H,H}$ = 9.4, 1H, N-CH_2), 7.30-7.47 (m, 5H, CH_{Ar}); δ_H ($CDCl_3$): 27.3 (CH_3), 28.2 (CH_3), 28.9 (CH_3), 35.8 (H_3C-*C*-CH_3), 49.1 (N-C-*C*H_2), 69.1 (N-CH_2), 88.9 (N-*C*-CH_2), 125.5 (CH_{Ar}), 127.3 (CH_{Ar}), 129.7 (CH_{Ar}), 135.4 (C_{Ar}), 155.9 (C=O); IR (KBr): 705, 1092, 1211, 1244, 1377, 1495, 1753, 2868, 2958, 2970; MS m/z (%): 248 (M^+, 20), 127 (100). Calcd. for $C_{14}H_{18}N_2O_2$ (246.30): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.37; H, 7.32; N, 11.10.

Acknowledgments

The present work has been supported by Masaryk University Rector's Program for Students' Creative Activity Support.

Authors thank to Marek Nečas for X-ray analyses and Lubomír Prokeš for Mass spectra measurement.

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