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Synthesis of 6-Substituted 6-Nitroperhydro-1,4-diazepines via Novel *Tandem* Retro-Henry and Mannich/Michael Reactions

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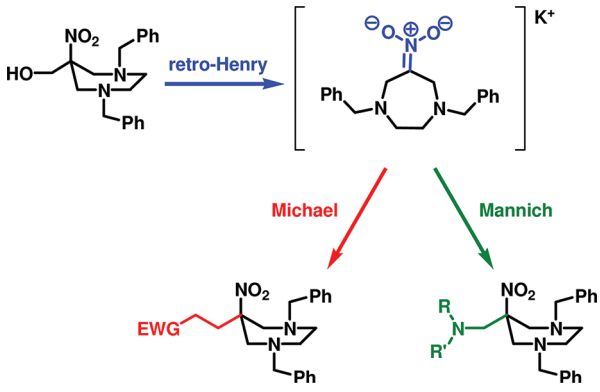
ABSTRACT



***N,N'*-Dibenzyl-6-hydroxymethyl-6-nitroperhydro-1,4-diazepine was converted into a nitronate via retro-Henry reaction, followed by either Michael reaction with several acrylic derivatives or Mannich reaction with different amines, thus leading to 6-substituted 6-nitroperhydro-1,4-diazepines. The *tandem* retro-Henry/Mannich reaction was also carried out using benzylamine as base, solvent, and reagent at the same time. Selective hydrogenation of the nitro group and complete hydrogenolysis were also successfully achieved.**

The optimization and differentiation of the synthesis of variously substituted heterocycles can be considered as a key target in the development of novel drugs, since heterocyclic rings constitute the core of many biologically active compounds. Among them, 1,4-diazepines are of considerable importance due to their wide spectrum of biological and pharmacological activities.[1] In recent years, a variety of 1,4-diazepines have been regarded as peptidomimetic scaffolds with a conformationally constrained core,[2] anti-HIV agents,[3] and inhibitors of protein kinase, caspase and matrix metalloproteinase.[4] Moreover, several functionalized 1,4-diazepines are reported to be under clinical studies for treatment of several pathologies, e.g., overactive bladder or urge urinary incontinence, schizophrenia, obesity, nausea, and vomiting.[5] More particularly, the family of 6-aminoperhydro-1,4-diazepines are well-known serotonin and dopamine receptor antagonists: for example, their benzamides derivatives with alkyl groups at the 1 and 4 ring nitrogen atoms have been proposed as broad

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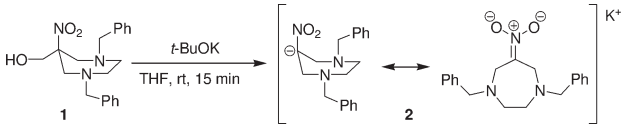
antiemetic agents as they show a potent dopamine D2 and 5-HT3 receptors inhibitory activity.[6] These heterocycles have also been employed as ligands for transition metal ion coordination[7] and used as bleach catalysts or to support cationic group 3 metal alkyl catalysts.[8] Moreover, the gadolinium(III)-complex of the tetraacetic acid derivative of 6-methyl-6-amino-1,4-perhydrodiazepine (AAZTA) was reported as an efficient contrast agent for magnetic resonance imaging.[9] The insertion of various groups at the 6-position would differentiate the biological activity of this versatile heterocycle and would also permit the synthesis of AAZTA derivatives containing various functional groups useful for bioconjugation and relevant for the future development of efficient molecular imaging probes.[10]

In parallel, there is great current interest in the development of new *tandem* and multicomponent domino reactions in order to introduce not only high molecular complexity and diversity but also matched functionalities suitable for further transformations or for the conjugation to biomolecules. Actually, the combination of such reactions with an efficient post-transformation, typically a ring-forming process, has proved to be a powerful tool for the synthesis of highly functionalized heterocyclic compounds.[11]

We have recently reported the fast and easy synthesis of 1,4-dibenzyl-6-hydroxymethyl-6-nitroperhydro-1,4-diazepine (**1**) by double nitro-Mannich reaction between *N*,*N*′-dibenzylethylenediamine, paraformaldehyde, and 2-nitroethanol in nearly quantitative yield.[12] Herein we account for the preparation of a series of derivatives obtained from **1** via novel cascade sequences initiated by a retro-Henry reaction followed by either a Michael or a Mannich reaction. The versatility of these approaches was tested with several acrylic derivatives and with different primary and secondary amines.

The retro-Henry reaction is well-known although rarely employed in organic synthesis;[13] it normally involves a base-mediated process to obtain, in first instance, a carbonyl compound and a stabilized carbanion. This reaction can be applied to β-nitro alcohols[14] and, as shown by Harada et al.,[15] to 6-hydroxymethyl-6-nitroperhydrodiazepines in order to replace the hydroxymethyl group with a hydrogen atom. The stable carbanion/nitronate **2** (Scheme 1) was formed in a few minutes by reaction of **1** with a slight excess of *t*-BuOK in THF. Owing to the resonance stabilization, **2** can be isolated and characterized by spectroscopic techniques (see the Supporting Information for details). In particular, the ^{13}C NMR spectrum in CD_3OD clearly shows that **2** exists as a nitronate with the C=N carbon resonating at 121.7 ppm. This was also confirmed by IR spectroscopy, which shows a strong peak at 1597 cm^{-1} assigned to the C=N stretching of the nitronate, whereas the tertiary aliphatic nitro group in **1** is observed at around 1535 cm^{-1}.

Scheme 1. Formation of the Carbanion/Nitronate Intermediate



We thought to use such a species as a nucleophile with the aim to further functionalize the heterocycle ring and to obtain precursors of 6-aminoperhydro-1,4-diazepines variously substituted at the 6-position. First, simple halo and pseudohalo compounds (e.g., short aliphatic chlorides and bromides, mesylates, tosylates) were used as substrates for common substitution reactions. However, no formation of the desired products or any other byproduct was observed. The attempts of using carbonyl or carboxyl derivatives (including acetone, acetonitrile, ethyl acetate) for carbonyl addition reactions were also unsuccessful.

Instead, a Michael addition followed the retro-Henry reaction when two molar equivalents of an acrylic compound were added along with *t*-BuOK in THF. The corresponding products were formed within a few hours in good yields and relatively pure. The results obtained with several commercial acrylic compounds as well as acrylic derivatives synthesized ad hoc are reported in Table 1 (see the Supporting Information for details).

Adamantyl derivatives **6** and **9** were synthesized with the aim at preparing molecules able to form inclusion compounds with β-cyclodextrin with high affinity and selectivity.[16] The other compounds have been prepared in order to get a series of 6-nitro-1,4-diazepines substituted at the 6-position with protected or pseudoprotected functional groups.

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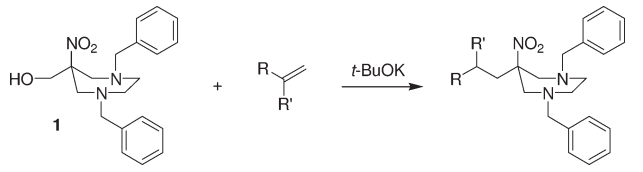
Table 1. *Tandem* Retro-Henry/Michael Reaction

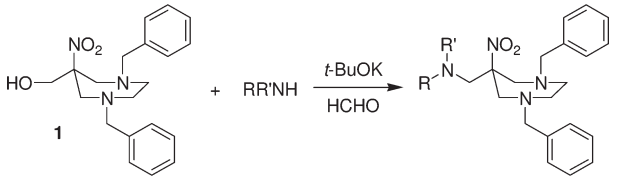


entry	R	R′	product	yield (%)
1	COOMe	H	**3**	90
2	COOMe	Me	**4**	92
3	COO*t*Bu	H	**5**	74
4	$COOCH_2Ad$	H	**6**	44
5	$CONH_2$	H	**7**	81
6	CN	H	**8**	77
7	CONHAd	H	**9**	31

It must be noted that Michael addition does not take place with α,β-usaturated aldehydes or ketones: indeed, when acrolein, 1-penten-3-one, 4-hexen-3-one or 2-cyclohexenone were used, the nitronate was recovered completely unreacted.

The retro-Henry reaction was successfully followed by a Mannich reaction when nitrodiazepine **1** was mixed with a primary or secondary amine and paraformaldehyde in the presence of a strong base. Also for this *tandem* reaction, yields and purities of the products obtained from most amines were satisfactory (Table 2).

Table 2. *Tandem* Retro-Henry/Mannich Reaction



entry	R	R′	product	yield (%)
1	$C_{12}H_{25}$	H	**10**	68
3	CH_2COOEt	H	**11**	51
3	CH_2CH_2NHBOC	H	**12**	42
4	$PhCH_2$	H	**13**	29
5	$-(CH_2)_5-$		**14**	73
6	$-CH_2CH_2OCH_2CH_2-$		**15**	71

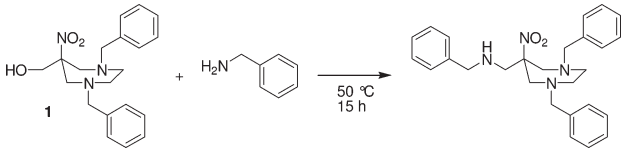
When considering the reactivity of the nitronate obtained after retro-Henry reaction with **1**, it can be envisaged that the succeeding reaction occurs only with acrylates or with imine intermediates obtained during the Mannich reaction between the amines and paraformaldehyde. Simple substitution with halo- or pseudohalocompounds or addition to carbonyl derivatives do not take place probably due to steric hindrance. To confirm this hypothesis, the *tandem* retro-Henry/Michael reaction with ethyl *trans*-2-butenoate was attempted. Analogously, the reaction between **2** and *N*-ethylidenebenzylamine (a substituted imine prepared from benzylamine and acetaldehyde) was carried out. In both cases the reaction did not occur, confirming our hypothesis of steric hindrance on the reactive site. Thus, it can be concluded that the carbanion needs a nonsubstituted sp^2 carbon to react further.

The validity of the *tandem* protocol herein reported is further confirmed in view of the alternative pathway to prepare the same type of compounds, i.e., via the formation of a suitable γ-nitroester or β-nitroamine, followed by cyclization in the presence of paraformaldehyde and *N,N*′-dibenzylethylenediamine.[12] In fact, besides adding a synthetic step, this procedure results disadvantageous because the increased sterical hindrance of the nitro-derivative favors the formation of the byproduct 1,3-dibenzylimidazolidine thus lowering the final yield, as observed previously for the synthesis of similar compounds (e.g., 1,4,6-tribenzyl-6-nitroperhydro-1,4-diazepine from 1-(2-nitroethyl)benzene).[17]

The synthesis of **5** in one step by double-Mannich/Michael reaction was also attempted using *N,N*′-dibenzylethylendiamine, paraformaldehyde, nitromethane, and *tert*-butyl acrylate to allow the cyclization and then the Michael addition to the nitronate. A one-step reaction was in fact successfully exploited for the synthesis of **1** by double nitro-Mannich/Henry reactions with nitromethane and excess of paraformaldehyde.[12] However, in this case, the desired 6-substituted nitrodiazepine formed only in negligible amount, whereas the main products were **1,** 1,4-dibenzyl-6-nitroperhydro-1,4-diazepine and 1,3-dibenzylimidazolidine.

In order to investigate whether an amine could act at the same time as reagent, base and solvent in the *tandem* retro-Henry/Mannich reaction, nitrodiazepine **1** was reacted with benzylamine. In Table 3, the result obtained using benzylamine only (entry 3) is compared with the yields of the reactions carried out under other conditions (entries 1 and 2).

Table 3. *Tandem* Retro-Henry/Mannich Reaction with Benzylamine



entry	base	HCHO	solvent	product	yield (%)
1	*t*-BuOK	yes	THF	**13**	29
2	$PhCH_2NH_2$	yes	THF	**13**	16
3	$PhCH_2NH_2$	no	$PhCH_2NH_2$	**13**	27

According to these results, the *tandem* retro-Henry/Mannich reaction can indeed be run using an amine which

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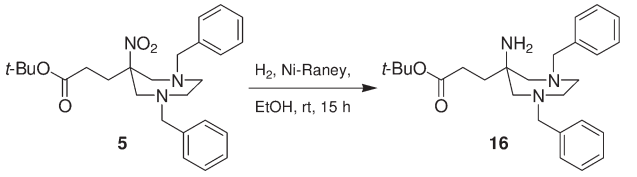
acts contemporaneously as base, reagent, and solvent, leading to the desired product with a yield comparable to those achieved through the other synthetic patways. Thus, it can be summarized that (1) the OH proton of **1** is acidic enough to be removed by a base weaker than *t*-BuO$^-$ (this confirms our previous hypothesis that, during hydrogenolysis of the nitrodiazepine **1**, the retro-Henry reaction may occur and thus acetic acid has to be used in order to avoid this side reaction)[12] and (2) formaldehyde is formed in situ as a consequence of the initial retro-Henry reaction.

As an example of continuation toward the preparation of applicable multifunctional compounds, the nitro group of the *tert*-butyl ester derivative **5** was selectively reduced by hydrogenation in the presence of Raney-nickel (Scheme 2): the reaction leads to 6-aminodiazepine **16** protected with benzyl groups at the ring nitrogen atoms and with a *tert*-butyl ester on the pendant arm. Such a reaction would allow to achieve a variety of 6-aminoperhydro-1,4-diazepines further functionalized at the 6-position.

Scheme 2. Selective Reduction of the Nitro Group of **5**



Finally, as demonstrated by the synthesis of AAZTA and other similar derivatives,[9,12] the complete hydrogenolysis of these 6-substituted-6-nitro-1,4-dibenzylperhydro-1,4-diazepines leads to the free amines that can be further alkylated with *tert*-butyl bromoacetate in order to obtain a series of bifunctional chelating agents useful for bioconjugation reactions. Although such a protocol is currently under investigation and optimization, the complete hydrogenation of **5** was carried out with 10% Pd/C catalyst in MeOH and 3 molar equiv of acetic acid leading to the aminodiazepine **17** (Scheme 3).

Scheme 3. Hydrogenolysis of Nitrodiazepine **5**

In summary, a novel synthetic access to 6-substituted 6-nitroperhydro-1,4-diazepines, relying on a simple procedure involving the formation of a stable carbanion via retro-Henry reaction, followed by either Michael or Mannich reactions, has been reported. The versatility of the approaches was tested with several acrylic derivatives and with different primary or secondary amines. The *tandem* retro-Henry/Mannich reaction of *N*,*N*′-dibenzyl-6-hydroxymethyl-6-nitroperhydro-1,4-diazepine with only benzylamine further simplifies this procedure. Moreover, the selective hydrogenation of the nitro group demonstrates the versatility of this class of compounds: the primary amine obtained can be further functionalized in the presence of other orthogonally protected functional groups. Analogously, exhaustive hydrogenation allowed to obtain an unprotected aminodiazepine suitable for further modification.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.