Tosylhydrazone Promoted Diastereoselective Intramolecular 1,3-Dipolar Cycloadditions: Synthesis of Tetrahydropyrrolo[3,4-c]pyrazoles

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A very straightforward diastereoselective synthesis of tetrahydropyrrolo[3,4-c]pyrazoles by intramolecular 1,3-dipolar cycloaddition is described. The starting materials for the synthetic route are *N*-Boc-protected α -amino acids, which are first transformed into *N*-allyl- α -amino ketones through conventional methodologies. Then, a one-pot sequence that involves formation of a tosylhydrazone from the ketone, base induced decomposition of

the hydrazone, and intramolecular 1,3-dipolar cycloaddition of the diazo compound generated, gives rise to the bicyclic systems with total diastereoselectivity and high preservation of the enantiomeric purity. However, the analogous process employing α -amino aldehydes lacks stereoselectivity. DFT computational modeling has been carried out to account for the different behavior of the two types of systems.

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Introduction

The desire for practical and synthetically efficient organic transformations has led to the discovery of many innovative strategies, concepts and methodologies. In this context, tosylhydrazones are versatile synthetic intermediates that have been used for the unconventional transformation of carbonyl compounds through different types of transition-metal-catalyzed as well as metal-free processes.^[1] Over the last few years, we and others have demonstrated that in the presence of a metal catalyst, mainly Pd and Cu, tosylhydrazones can be used as a general source of diazo compounds without any limitation in the structure of the carbonyl precursor. Indeed, several important transformations such as cross-couplings,^[2] oxidative cross-coupling^[3] and cascade reactions^[4] have been devised. The same strategy has been applied in the absence of a metal catalyst to provide for new metal-free carbon-carbon and carbon-heteroatom bond forming reactions.^[5] Thus, tosylhydrazones can be seen as a vehicle to accomplish a variety of unconventional modifications of carbonyl compounds. Importantly, we have also demonstrated that this strategy is very useful for the elaboration of α -chiral carbonyl compounds, even if they are configurationally unstable, without erosion of the enantiomeric purity.^[6]

On the other hand, and in continuing with our interest in metal-free processes employing tosylhydrazones, we have recently reported a new and general procedure for the synthesis of cyclopropanes by *in situ* base-promoted decomposition of tosylhydrazones in the presence of alkenes (Scheme 1, a).^[7] This intermolecular process is postulated to proceed through diastereoselective construction of a pyrazoline ring by 1,3-dipolar cycloaddition followed by a spontaneous extrusion of nitrogen with retention of configuration of the pyrazoline stereocenters.^[8]

Scheme 1. (a) Synthesis of cyclopropanes from tosylhydrazones by 1,3-dipolar cycloaddition/nitrogen extrusion sequence. (b) Synthesis of bicyclic diazenes by intramolecular 1,3-dipolar cycloaddition

The intramolecular version of this type of 1,3-dipolar cycloaddition was reported for the first time by Padwa in 1980 by heating ω -alkenyltosylhydrazones in the presence of NaH to give 1-pyrazolines.^[9] Over the last few years, this methodology has been very useful for the construction of bicyclic and/or tricyclic diazenes (Scheme 1, b).^[10] Recently, Taber modified this procedure to generate the tosylhydrazone *in situ* to deliver carbobicyclopropanes after irradiation of the corresponding bicyclic diazene derivatives.^[11,12]

The construction of heterobicyclic systems is of great importance in the preparation of structurally complex and biologically important natural products.^[13] With this in mind, and continuing with our interest in metal-free processes employing tosylhydrazones, we envisioned the possibility of an asymmetric one-pot synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles **IV** by an intramolecular 1,3-dipolar cycloaddition reaction, starting with α -amino acids derivatives **I** and following the retrosynthetic pathway shown in Scheme 2.

Scheme 2. Retrosynthetic analysis for the synthesis of heterobicyclic compounds.

As usual for intramolecular 1,3-dipolar cycloadditions, the present protocol would allow for the formation of a fused-rings bicyclic core. Furthermore, two novel stereocenters arise from enantiopure and readily accessible starting materials. The carbonyl compounds **II** would be obtained by conventional transformations from the Boc-protected α -amino acids **I**. Pyrrolo[3,4-*c*]pyrazoles are important core structures found in a variety of molecules with a wide range of biological activities, such as anti-inflammatory and anti-tumor drugs as well as protein kinase inhibitors.^[14] Herein we present our results, which have led to the development of a new methodology for the diastereoselective synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles from enantiomerically pure α -amino acids.

Results and Discussion

The α -allyl amino ketones **5** were prepared following the protocol shown in Scheme 3. Thus, the commercial available *N*-Boc-*L*-amino acids **2** were converted to corresponding Weinreb amide^[15] **3** under standard conditions. Alkylation using NaH as a base gave the derivatives **4** in moderate yields.^[16] Subsequent reaction with several Grignard reagents yielded the α -allyl amino ketones **5**, as the precursors of the bicycles **6**.

We started with the α -allyl amino ketone **5a** to study the intramolecular 1,3-dipolar cycloaddition leading to triazabicycloadduct **6a**. In this case, the putative tosylhydrazone intermediate was not isolated under the reaction conditions. Therefore we decided to develop a one-pot cycloaddition procedure following the reaction conditions previously reported by us for the intermolecular cycloaddition of diazoalkanes generated from the corresponding tosylhydrazones.^[7]

Scheme 3. Synthetic protocol for the preparation of the α -allyl amino ketones **5**.

Thus, **5a** was heated in 1,4-dioxane at 70 °C with tosylhydrazide for 2 h to form the tosylhydrazone, and subsequently, the base (K_2CO_3 , 6 equiv) was added, and the mixture was heated for an additional 12 h. The desired bicycle **6a** was formed as the minor product while major **7a** resulted from the elimination of the starting tosylhydrazone (Bamford-Stevens reaction)^[17] (Table 1, entry 1). Longer reaction time (t_1) for the formation of the *N*-tosylhydrazone did not furnish better results (entry 2).

Table 1. Influence of the reaction conditions in the formation of **6a** by intramolecular 1,3-dipolar cycloaddition.^[a]

Entry	T_1 / T_2 (°C)	t_1 / t_2 (h)	K_2CO_3 (equiv.)	6a : 7a ^[b]
1	70/70	2/12	6	1: 4.6
2	70/70	5/12	6	1: 4.6
3	85/110	12/12	6	1.7: 1
4 ^[c]	85/110	2/12	6	1.9: 1
5	85/110	2/12	10	1.8: 1
6	85	12	6	-
7	110	12	6	-
8	150	1	6	-

(MW)^[d]

[a] Reaction conditions: α -allyl amino ketone **5a** (0.3 mmol), *N*-tosylhydrazide (0.33 mmol), 1,4-dioxane (3.5 mL). [b] Calculated by ^1H NMR on the reaction crude mixture. [c] Optimized reaction conditions. [d] Reaction carried out in the presence of water (10 μL).

On the other hand, increasing temperature in both steps (T_1 and T_2) gave encouraging results, changing the ratio to 2:1 in favor of the

desired bicycle **6a** (entries 3-5). No product was obtained under multi-component conditions (simultaneous addition of the ketone, tosylhydrazide and base), either under heating (entries 6, 7), or at higher temperature under microwave irradiation (entry 8). Therefore, we concluded that it was necessary to form the tosylhydrazone in situ before the generation of the 1,3-dipole, with the optimal conditions being 85 °C and 2 h for the tosylhydrazone formation followed by 110 °C, 12 h in the presence of 6 equiv of K₂CO₃ for the intramolecular 1,3-dipolar cycloaddition (entry 4).

These results prompted us to investigate the scope of this reaction under the optimized conditions, using α -amino ketone derivatives from *L*-Boc-alanine **5a-d** and **5i-k** (entries 1-4 and 9-11), *L*-Boc-valine **5e** (entry 5), *L*-Boc-leucine **5f** and **5l** (entries 6 and 12) and *L*-Boc-phenylalanine **5g**, **5h** and **5m** (entries 7, 8 and 13); and a set of different Grignard reagents bearing Me (entries 1, 5-7, 9, 11 and 13), Et (entries 2 and 8), Ph (entry 3), and Bn (entries 4 and 10) (Table 2). We observed that the transformation proceeds efficiently with the methylketone of *L*-Boc-alanine (entry 1), while bulkier substituents (entries 2-4) provided moderate yields, due probably to increased steric hindrance in the transition state of the dipolar cycloaddition. Similarly, when the reaction was carried out with the methylketone of *L*-Boc-valine (entry 5), the reaction proceeded in moderate yields (50% vs 81%) (entry 5 vs 1) probably as a consequence of the larger steric requirements of the *i*-Pr versus the Me group. From these results we suggest that the TS (transition state) of the reaction is very dependent on the steric hindrance, since variations in R¹ and/or R² can significantly affect the yield of the cycloaddition product.

Table 2. General synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles **6a-m** by intramolecular 1,3-dipolar cycloaddition.^[a]

Entry	Product 6
1
2
3
4

5			50
6			52
7			35
8			63
9			61
10			46
11			65
12			31
13			78

[a] Reaction conditions: α -allyl aminoketone **5** (0.3 mmol), *N*-tosylhydrazide (0.33 mmol), 1,4-dioxane (3.5 mL). [b] Isolated yield of **6** as a pure diastereoisomer after flash chromatography.

Moreover, the reaction tolerates substitution on the olefinic double bond with only a slight reduction of the yield, thus when R³=R⁴=Me, (entries 9-10) (Table 2), the adducts **6i-j** were obtained, albeit with lower yields than the adducts obtained with the monosubstituted olefin. Surprisingly, the cycloaddition takes place

also with the sterically encumbered *N*-2-methylallyl derivatives **5k-m** ($R^5 = \text{Me}$) affording the trisubstituted tetrahydropyrrolopyrazoles **6k-m**, that feature two vicinal quaternary centers, with moderate yields.

It is important to point out that the desired tetrahydropyrrolo[3,4-*c*]pyrazoles **6a-m** are obtained as single diastereoisomers, whose structure was confirmed by NOESY experiments on compounds **6b** and **6l** (see supplementary materials for details) (Figure 1). A strong nuclear Overhauser enhancement (NOE) is observed between the two protons **Ha** and **Hb**, with the two diastereotopic protons **Hc** and **Hc'** on the ethyl group, suggesting that the R^1 and R^2 groups (from the α -amino acid and the Grignard reagent, respectively) are in a *trans* arrangement and the group R^2 is *cis* with protons **Ha** and **Hb**.

Figure 1. Relevant NOEs observed in compound **6b**. Some hydrogens have been omitted for clarity.

Moreover, it has been previously demonstrated that tosylhydrazones can be employed to carry out transformations on α -chiral ketones without erosion of the enantiomeric purity, and in particular, in tosylhydrazones derived from *N*-Boc- α -amino acids.^[18,6] To investigate whether this feature is retained also in this transformation, the racemic derivatives were prepared for derivatives **6f** and **6g** and the enantiomeric excesses determined by HPLC. The values obtained, (ee > 99 % for **6f**, and ee > 95 % for **6g**) indicate that again the enantiomeric purity is preserved in these transformations. Therefore, this method allows for the preparation of enantiomerically enriched tetrahydropyrrolo[3,4-*c*]pyrazoles featuring three stereocenters, including one or two quaternary stereogenic centers.

Then, the reaction was extended to the α -allylamino aldehyde **8**^[19] to afford the bicycloadduct **10** (Scheme 4). In this case, the tosylhydrazone **9** was successfully isolated from the reaction, and then subjected to the intramolecular 1,3-dipolar cycloaddition in the presence of K_2CO_3 as a base, to afford the tetrahydropyrrolo[3,4-*c*]pyrazole as a mixture of two diastereoisomers **10a** and **10a'**, together with the Bamford-Stevens side product **11** in a 31:14:55 ratio. In the same manner, the reaction can be performed applying the one-pot protocol from compound **8** with the same result. Unfortunately, for this system, the tetrahydropyrrolopyrazole **10** was obtained as a mixture of diastereoisomers **10a** and **10b** in about 2:1 ratio, and the major isomer could be isolated in a 25 % yield. In this case, nor the yield, neither the diastereoselectivity could be improved by modifying the reaction conditions, and therefore, the reaction was not studied any further.

Scheme 4. Synthesis of tetrahydropyrrolo[3,4-*c*]pyrazole **10** as a mixture of diastereoisomers.

To explain the formation of the heterobicycles **6** and **10** we propose the following mechanism supported by the literature (Scheme 5). First, the condensation of the carbonyl compound with the *N*-tosylhydrazide generates the *N*-tosylhydrazone **A** in situ, which undergoes base promoted decomposition to furnish the diazo compound **B**, which has two alternative pathways: (a) intramolecular 1,3-dipolar cycloaddition reaction with the terminal olefin to afford the desired bicycle **C**; and (b) Bamford-Stevens degradation to give undesired diene **D** after N_2 release.

Scheme 5. Possible mechanistic pathways for the 1,3-dipolar cycloaddition from tosylhydrazone derivatives of α -aminoketones and/or α -aminoaldehydes.

The intramolecular 1,3-dipolar cycloaddition to form the tetrahydropyrrolo[3,4-*c*]pyrazoles **6** proceeds with complete diastereoselectivity, whereas the formation of compounds **10** takes place with very poor diastereoselectivity. To understand the different behaviors of the diazo compounds generated from the ketones **5** and the aldehyde **8** respectively, DFT based computations of the possible transition states (TS) for the dipolar cycloadditions were performed on model structures **I** and **II** at the B3LYP/6-311++G** level (Scheme 6).^[20]

Scheme 6. Energy calculations of the transition states from the model diazo compounds **I** and **II** at the B3LYP/6-311++G** level of theory.

We started our studies with the diazo compound **I** (R = Me) (Scheme 6) which derives from methyl ketone **5a**. Four competing transition states (**TSA-I** – **TSD-I**) lead to the corresponding diastereomeric tetrahydropyrrolopyrazoles (**12A-D**) (Scheme 6). The transition states corresponding to the bicyclic systems with a *cis*-fusion (**TSB-I** and **TSD-I**) are clearly favored, whereas those that would furnish *trans*-fused bicycles **12A** and **12C**, feature very distorted transition states and are energetically very disfavoured (**TSA-I** and **TSC-I**). The results of the computations indicated that **TSB-I**, that leads to the bicycle **12B**, is more stable by 2.10 Kcal/mol than **TSD-I**, which would lead to diastereoisomer **12D**. In **TSD-I**, the methyl substituents at C1 and C2 are in a *syn*-periplanar disposition, and therefore, significant steric interactions are present, whereas in **TSB-I**, the methyl substituents are in a nearly *anti*-periplanar arrangement (Figure 2). Therefore, the minimized steric interactions in **TSB-I** are responsible for the diastereoselectivity of the cycloaddition.

Figure 2. Molecular models obtained for **TSB-I** and **TSD-I** (b3lyp/6-311++G**).

Lastly, we studied the cycloaddition with the diazocompound **II** derived from aldehyde **8** (R = H) (Scheme 6). Taking into consideration the results presented above, we decided to consider only the transition states **TSB-II** and **TSD-II**, that lead to *cis*-fused bicycles **13B** and **13D** respectively (Scheme 6). In this case, both TS featured very similar energy values, $\Delta G_{act} = 18.7$ and 19.0 Kcal/mol for **TSB-II** and **TSD-II** respectively, which is in agreement with the lack of stereoselectivity observed in the reaction. The small energy difference between **TSB-II** and **TSD-II** (0.3 Kcal/mol) could be explained considering that now, since R = H, there is no significant steric interaction between the substituents at C1 and C2 in **TSD-II**, and therefore, the energy of both transition states is very close.

Conclusions

In summary, we have described a new metal-free procedure for the diastereoselective synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles by base-promoted intramolecular 1,3-dipolar cycloaddition of tosylhydrazones of α -allylaminoketones. Notably, the starting materials are readily available from α -amino acids. Interestingly, the stereogenic center in the α -amino acid is not affected during the synthetic sequence. The stereochemistry of the final products was assigned by two-dimensional NMR studies and also by computational analysis of the competing transition states. From these results we conclude that the TS of the reaction, and thus the yield of product, is highly sensitive to the steric hindrance. The major advantages of this procedure is the operational simplicity, in that it is not essential to use an inert atmosphere or ultra-dry solvents. Moreover, the reaction can be conducted in a one-pot manner directly from the carbonyl compound, and the tosylhydrazone intermediate does not have to be isolated. Finally, this approach allows the construction of more than one heterocyclic ring at a time with control of new stereogenic centers. For these reasons, we believe that this short, metal-free protocol may become a useful tool for the construction of biologically important scaffolds in both organic synthesis and medicinal chemistry.

Acknowledgments

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Two for one. A straightforward diastereoselective synthesis of tetrahydropyrrolo[3,4-*c*]pyrazoles by intramolecular 1,3-dipolar cycloaddition from enantiomerically pure α -amino acids is described. This is a metal-free procedure with the advantages of an operational simplicity.

The reaction can be conducted in one-pot directly from the carbonyl compound without isolation of the tosylhydrazone intermediate, allowing the construction of more than one heterocyclic ring at a time with control of new stereogenic centers.

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