Synthesis of chiral pyrazoles through a 1,3-dipolar cycloaddition/[1,5]-sigmatropic rearrangement with stereoretentive migration of a stereogenic group

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Abstract: The reactions between terminal alkyne and α-chiral tosylhydrazones lead to the obtention of chiral pyrazoles with a stereogenic group directly attached at a nitrogen atom, through cascade reactions that include decomposition of the hydrazine into a diazocompound, 1,3-dipolar cycloaddition of the diazo compound with the alkyne and 1,5-sigmatropic rearrangement with migration of the stereogenic group. This strategy has been successfully applied to the synthesis of structurally diverse chiral pyrazoles from α-chiral tosylhydrazones obtained from α-phenylpropionic acid, α-aminoacids and 2-methoxycyclohexanone. Noteworthy, the stereoretentive 1,5-sigmatropic rearrangements represent very rare examples of this stereospecific transformation.

The pyrazole ring is a five-membered heterocycle present in a large number of molecules with biological activity.[1] Compounds containing substituted pyrazoles find widespread as antimicrobials, analgesics, anti-inflammatory agents, CNS and oncology drugs.[2-9] Indeed, pyrazoles are constantly employed as building blocks in drug discovery programs.[6,7] Moreover, structures built around the pyrazole scaffold are also found as key constituents of ligands for transition metals with biological or catalytic activity,[6] receptors in supramolecular chemistry,[5] and functional organic materials.[10] For these reasons, and in spite of the variety of existing methods, the development of new methodologies for the efficient regioselective synthesis of polysubstituted pyrazoles is still an area of very active research.[11,12]

A particularly challenging type of pyrazoles are chiral pyrazoles with a stereogenic carbon attached at N-position. Limited examples of this type of chiral pyrazoles with biological activity have been reported,[13] but their usefulness have been hampered by the lack of general methods for their preparation. Chiral pyrazoles with a stereogenic center attached at the nitrogen have been synthesized from chiral amines,[14] and also by alkylation of the corresponding N-H pyrazole through Mitsunobu reactions of chiral alcohols,[13,15] ring opening of chiral or meso epoxides,[16] and organocatalytic aza-Michael reactions.[17] Nevertheless, these methods are far from general and have been mostly employed on unsubstituted pyrazole.

We have recently reported the regioselective synthesis of 1,3,5-trisubstituted pyrazoles II and 3,4,5-pyrazoles III from the reaction of tosylhydrazones I and terminal alkyne by a 1,3-dipolar cycloaddition/[1,5]-sigmatropic rearrangement sequence (Scheme 1).[18] The mechanism proposed for these cascade processes involves the following steps: 1) decomposition of the tosylhydrazone to produce a diazo compound IV, 2) 1,3-dipolar cycloaddition of the diazo compound with the terminal alkyne to form a 3H-pyrazole V, 3) 1,5-sigmatropic rearrangement which may lead to 1,3,5-substituted 1H-pyrazole II or to a new 4H-pyrazole VI. The latter will undergo additional [1,5]-sigmatropic shifts to provide the aromatic 3,4,5-pyrazole III (Scheme 1).

Scheme 1. Regioselective synthesis of trisubstituted pyrazoles and mechanism proposed.

The step that determines the regioselectivity of the reaction is the [1,5]-sigmatropic rearrangement. For tosylhydrazones derived from acetophenones (X = H, R2 = Ar), the only product obtained is the resultant of the migration of the aryl group to C4 III. In contrast, for 2-substituted acetophenones, in many cases the major or exclusive product obtained is the pyrazole II, derived from the migration of the CH2X group to the nitrogen position. This is indeed a quite intriguing case of double selectivity, i) chemoselectivity on the migrating group, ii) regioselectivity on the sense of the migration.

According to our experimental results and DFT-computational modeling studies, these 1,5-migrations on 3H-pyrazoles A (Scheme 2) proceed through [1s, 5s] concerted mechanisms.[21,22]
Thus, the migration of stereogenic groups should take place with retention of configuration in the migrating group. Noteworthy, 1,5-sigmatropic rearrangements with retention of configuration in the migrating group, although theoretically predicted by the Woodward-Hoffmann rules, are very rare. To the best of our knowledge, the classic example of the stereospecific rearrangement of a methyl-substituted spiro[4.4]nona-1,3-diene stands as the unique example of a 1,5-rearrangement stereoretentive on the migrating group.\[23\-25\] Additionally, no synthetic application oriented to the preparation of enantiomerically enriched materials has been developed based on this principle.

We have previously shown that tosylhydrazones can be employed to achieve transformations of \(\alpha\)-chiral ketones with preservation of the configuration of the \(\alpha\)-carbon, in both Pd-catalyzed processes and intramolecular [3+2]-cycloadditions.\[26\] Taking all this expertise together, we decided to investigate the employment of tosylhydrazones derived from \(\alpha\)-chiral ketones in the cycloaddition/rearrangement cascade as a model to study the [1,5]-sigmatropic shift with migration of a stereogenic center. Additionally, we also anticipated that it might represent a novel way to prepare enantiomerically enriched chiral pyrazoles with appealing structures for medicinal chemistry (Scheme 2).

We initiated our study with \(\alpha\)-chiral ketones 2, which can be obtained in enantiomerically pure form from commercially available carboxylic acid 1 (see supplementary material for details and experimental procedures). Preliminary experiments from the racemic ketone 2a (R\(^1\) = Ph) showed that the cascade sequence proceeded with good yield and moderate regioselectivity (Scheme 3). An array of reactions were carried out on the model system to establish proper experimental conditions, by modifying solvent, temperature and base. Nevertheless, the conditions developed in our previous work (K\(_2\)CO\(_3\), 1,4-dioxane, 110 \(^\circ\)C) turned out to be appropriate again. As expected, the 1,3,5-trisubstituted pyrazole 4a turned out to be the major isomer (6: 1, 4a: 5a) ratio as determined by \(^1\)H NMR on the reaction crude and GC/MS), which could be very easily obtained in pure form after chromatography, due to the very different eluting properties of both regioisomers.

The same reaction was then conducted with the tosylhydrazone obtained from the enantiomerically pure carboxylic acid (\(R\))-\(\alpha\)-2-phenylpropionic acid. Delightfully, a 99 \% ee was obtained, as determined by chiral phase HPLC analysis of the enantiomeric purity. Remarkably, the complete process from the chiral ketone (\(R\))-2a, which involves i) formation of the tosylhydrazone 3, ii) decomposition of 3 to give a diazo compound, iii) 1,3-dipolar cycloaddition, iv) 1,5-sigmatropic rearrangement, had taken place with preservation of the enantiomeric purity (Table 1, entry 1). To determine the absolute configuration of the chiral pyrazole (\(R\))-4a (\([\alpha]_D^{24} = -149.3^\circ\)), the same compound was synthesized by Mitsunobu reaction of the corresponding NH-pyrazole with (\(R\))-1-phenylethanol.\[25\,27\] The opposite enantiomer (\(S\))-4a was obtained (\([\alpha]_D^{26} = +151.3^\circ\)) as determined by the opposite sign of the optical rotation. This observation establishes the \(R\) configuration for the stereogenic center of (\(R\))-4a and confirms that the cascade reaction has indeed taken place with retention of configuration.

The cascade sequence was then extended to various systems featuring different substituents at \(R^1\) and \(R^2\) (Table 1). In all cases, moderate to high regioselectivities and very high enantiomeric excesses for the major isomer were obtained.\[28\,29\] The reaction was compatible with an array of substituents on the terminal position of the alkyne, including aromatics with different electronic properties, heteroaromatics, a benzyl substituent, and even a trialkylsilyl group. Regarding the non migrating substituent on the hydrazone \(R^1\), aryl and primary alkyl groups were tolerated. Importantly, chiral pyrazoles with a stereogenic center attached at the nitrogen and with different substituents at \(R^1\) and \(R^2\), such as compounds 4b-k, would be difficult to prepare in a regioselective...
manner through alternative methodologies. Approaches involving the alkylation of the N-H pyrazole, such as the Mitsunobu reaction used in the synthesis of (S,)(+)-4a, would give a mixture of the two possible regioisomers derived from the alkylation of each nitrogen.

Table 1: Synthesis of chiral pyrazoles R(·)-4 from α-chiral tosylhydrazones 3 and terminal alkynes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>4: 5 %</th>
<th>e.e. (%)</th>
<th>Yield 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>86: 14</td>
<td>99</td>
<td>48: 51</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>4-Tol</td>
<td>85: 15</td>
<td>99</td>
<td>48: 54</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>93: 7</td>
<td>93</td>
<td>48: 65</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>4-NC₆H₄</td>
<td>82: 18</td>
<td>98</td>
<td>48: 71</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Si(Pr)₂</td>
<td>73: 27</td>
<td>85</td>
<td>48: 57</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>3-Thiophen</td>
<td>88: 12</td>
<td>98</td>
<td>48: 57</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Bn</td>
<td>85: 15</td>
<td>97</td>
<td>48: 33</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>Ph</td>
<td>68: 32</td>
<td>92</td>
<td>48: 45</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>4-F-C₆H₄</td>
<td>64: 36</td>
<td>99</td>
<td>48: 58</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>4-NC₆H₄</td>
<td>70: 30</td>
<td>97</td>
<td>48: 43</td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>4-MeOC₆H₄</td>
<td>100: 0</td>
<td>90</td>
<td>48: 40</td>
</tr>
</tbody>
</table>

[a] Determined by ¹H NMR on the reaction crude. [b] Determined by chiral phase HPLC by comparison with a sample prepared from the racemic tosylhydrazone. [c] Isolated yield of the major isomer 4 after column chromatography. [d] e.e. not determined due to the decomposition of the material under the HPLC conditions.

To expand the scope of the synthesis of N-chiral pyrazoles to different classes of chiral ketones, we decided to explore the reaction with the tosylhydrazones of α-aminoketones derived from α-amino acids. Indeed, the reactions of L-proline derived chiral tosylhydrazones 6 were extended to the NH-pyrazole derived from the migration to C4 was not even detected. Again, the cascade process proceeded with nearly perfect retention of configuration in most cases, furnishing the pyrazoles 7 with very high enantiomeric ratio. Similarly, starting from N-Bn-N-Boc-(L)-phenylalanine, the tosylhydrazone 8 was prepared. The cycloaddition/rearrangement sequence led to the N-chiral pyrazole 9 as unique regioisomer, and importantly with 99 % ee (Scheme 5).

In our previous communication,[13] we had reported that tosylhydrazones derived from α-N-pyrrole substituted ketones, instead of the 1,3,5-trisubstituted pyrazoles with high yields and total regioselectivity. Therefore, we decided to explore the same reaction with the analogous chiral derivatives. To this aim, chiral tosylhydrazone 10 was prepared from L-Leucine in enantiomerically pure form (Scheme 5). As expected, the 1,3-dipolar cycloaddition/1,5-rearrangement occurred with total regioselectivity, leading to the chiral 1-(1H-1-pyrrolyl)ethyl-1H-pyrazole 11 with complete retention of configuration (99 % ee).

Finally, we turned our attention into tosylhydrazones derived from cyclic ketones. The hydrazone of 2-methoxycyclohexanone 12 was chosen for this study. After some experimentation, it was found that the cycloaddition/rearrangement sequence proceeded successfully by performing the reaction in CH₂CN and employing Cs₂CO₃ as base, leading to the pyrazole 13. Interestingly, treatment of the reaction mixture with BF₃·OEt₂ led quantitatively to the new pyrazole 14 with loss of methanol (Scheme 6).

Noteworthy, previous examples of the cycloaddition/rearrangement cascade on cyclic tosylhydrazones furnished 3,4,5-trisubstituted pyrazoles with counterclockwise migration to C4.[14,15] Thus, in the examples above, the presence of the methoxy group is essential to drive the reaction towards the formation of the pyrazoles 13. Importantly, determination of the...
Scheme 6. Synthesis of chiral fused pyrazoles 13. [a] Isolated yield of the major isomer 13 after column chromatography. [b] ee determined by chiral phase HPLC by comparison with a sample prepared from the racemic tosylhydrazone. [c] Formed upon addition of BF₃·OEt₂ to the reaction mixture.

As summary, we have presented herein a straightforward synthesis of unprecedented chiral pyrazoles from terminal alkynes and α-chiral-N-tosylhydrazones, through a cascade process that involves a 1,3-dipolar cycloaddition followed by a 1,5-sigmatropic rearrangement. It is important to note that the adequate selection of substituents in the starting tosylhydrazones leads to reactions that are highly selective in three different levels: i) chemoselectivity: one of the two possible groups undergoes migration; ii) regioselectivity: the migration takes place preferentially to one of the two possible positions; iii) stereospecificity: the migration of stereogenic groups occurs with retention of configuration. From a mechanistic point of view, to the best of our knowledge, we have provided here the first 1,5-sigmatropic rearrangements with retention of configuration on the migration group that do not involve spirocyclic systems, and also that employ enantiomerically pure materials. Therefore, these are unique examples of a largely anticipated stereospecific transformation. Finally, and taking into account the ready availability of the starting materials required for these reactions, these results open the possibility of developing applications of these new classes of pyrazoles in medicinal chemistry and as chiral ligands for transition metals.

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Keywords: pyrazole • tosylhydrazone • [1,5]-sigmatropic rearrangement • diazo compound • stereospecific

[19] In a very recent publication employing terminal alkynes and cycloalkyltosylhydrazones, under very similar reaction conditions, the 3Hpyrazoles could be isolated in some cases: R. R. Merchant, D. M. Allwood, D. C. Blakemore, S. V. Ley, J. Org. Chem. 2014, 79, 8800.
[21] See supporting information for details on computational studies.
For the $[1,5]$-sigmatropic rearrangements on 3H-pyrazole-5-carboxylates and 3H-pyrazoles-4,5-dicarboxylates, depending on the nature of the migrating substituent, mechanisms that span from concerted $[1,5]$-sigmatropic rearrangements to ionic stepwise processes involving the presence of ion pairs have been proposed:


The description of the synthesis of (±)-4a through the Mitsunobu reaction is included in the supporting information.

The employment of a freshly prepared tosylhydrazone is of outmost importance to obtain the pyrazole with high and reproducible enantiomeric ratio. Tosylhydrazones 3 that had been stored for some time provided pyrazoles with lower enantiomeric purity.

Partial epimerization over the time have been observed for some pyrazoles 4 and 7. To obtain reliable values of the enantiomeric ratio it is important to conduct the HPLC analysis readily after the isolation.
Retention of configuration in [1,5]-sigmatropic shifts, predicted by the Woodward-Hoffmann rules but very poorly documented experimentally, is observed in the reactions of $\alpha$-chiral tosylhydrazones with terminal alkynes. The chiral pyrazoles obtained are formed through a cascade involving a 1,3-dipolar cycloaddition followed by a site-regio- and stereospecific [1s,5s]-sigmatropic rearrangement.

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Synthesis of chiral pyrazoles through a 1,3-dipolar cycloaddition/[1,5]-sigmatropic rearrangement with stereoretention migration of a stereogenic group.