Synthetic Methods

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Regioselective One-Step Synthesis of Pyrazoles from Alkynes and N-Tosylhydrazones: [3+2] Dipolar Cycloaddition/[1,5] Sigmatropic Rearrangement Cascade**

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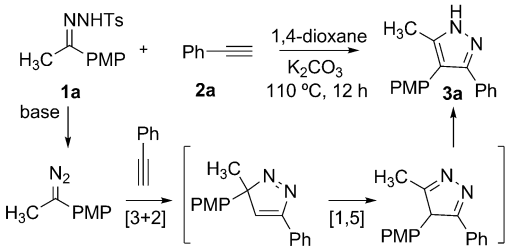
The pyrazole is a very important heterocycle in pharmaceutical and agrochemical industries.[1] Compounds containing the pyrazole substructure find application in a wide variety of therapeutical areas, which includes antimicrobials, analgesics, anti-inflammatory agents, CNS and oncology drugs.[2] Examples of leading commercial drugs based on the pyrazole scaffold include celecoxib,[3] lonazolac,[4] and rimonabant.[5] Currently, pyrazoles are constantly employed as building blocks in drug discovery programs,[6] and are also found as key constituents of ligands for transition metals,[7] receptors in supramolecular chemistry,[8] liquid crystals,[9] and polymers.[10] For these reasons, the development of new methodologies for the regioselective synthesis of polysubstituted pyrazoles continues to be an active area of research of high impact in fine chemistry.[11]

The most popular approaches to the synthesis of trisubstituted pyrazoles consist of: 1) condensation of hydrazines with 1,3-dicarbonyl compounds or synthetic equivalents;[12] 2) [3+2] cycloadditions of diazo compounds or other N=N-containing dipoles with alkynes[13–15] or alkenes;[16] 3) transition-metal-catalyzed cross-coupling reactions.[17] Nevertheless, the efficient preparation of 3,4,5-trisubstituted pyrazoles in a regioselective manner is still a challenging task which involves several synthetic steps.[18] Methodologies based on condensation reactions require multistep routes to synthesize the pyrazole precursors, while routes based on dipolar cycloaddition reactions usually feature regioselectivity problems, and are limited to the availability of the diazo compounds.

In the recent years, we have been interested in the development of new synthetic applications of tosylhydrazones. Indeed, we and others, have shown that tosylhydrazones can be employed as a general source of diazo compounds from carbonyl compounds with almost no restriction regarding the structure of the hydrazone.[19] Taking advantage of this powerful transformation, a remarkable number of novel transition metal catalyzed[20] and transition-metal-free[21] reactions have been reported. In this context, we report herein a new method for the regioselective preparation of 3,4,5- and 1,3,5-trisubstituted pyrazoles from readily available N-tosylhydrazones and terminal acetylenes through a [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence.

In an initial experiment, we conducted the reaction between the tosylhydrazone **1a** and phenylacetylene (**2a**) in 1,4-dioxane and in the presence of K_2CO_3 at 110 °C (Scheme 1). The reaction afforded the pyrazole **3a** as a single regioisomer. Formation of **3a** could be explained through a process which involves a [3+2] dipolar cycloaddition of the diazo compound, generated by decomposition of the hydrazone,[22] with the terminal alkyne to give a 3*H*-pyrazole and subsequent [1,5] sigmatropic rearrangement and aromatization.



Scheme 1. Formation of the pyrazole **3a** from the tosylhydrazone **1a** and phenylacetylene (**2a**) through the [3+2] cycloaddition/[1,5] rearrangement sequence. The identity of the regioisomer **3a** was deduced by NOESY experiments. PMP = *p*-MeOC$_6$H$_4$, Ts = 4-toluenesulfonyl.

Notably, the synthesis of pyrazoles from tosylhydrazones and terminal acetylenes had been previously reported by Aggarwal et al., but it was restricted to hydrazones derived from aromatic aldehydes, and therefore, to the preparation of monosubstituted and 3,5-disubstituted pyrazoles.[13] Moreover, the [3+2] cycloaddition/[1,5] sigmatropic rearrangement sequence has been previously described in reactions of α-diazocarbonyl compounds with alkynes,[14] but the examples with nonstabilized diazo compounds are very limited in scope and synthetic interest.[24] Furthermore, the reactions of tosylhydrazones with terminal alkynes in the presence of a Cu^I catalyst proceed in a completely different manner, thus giving rise to allenes by formation of a Cu carbene intermediate.[24]

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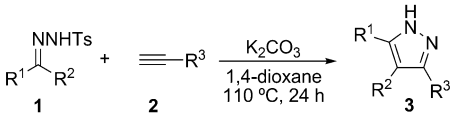
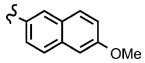
This initial result prompted us to investigate the scope of this transformation, oriented to develop a novel method for the generation of 3,4,5-trisubstituted pyrazoles which are not easily available from other methodologies. After some optimization work in the model reaction, we found that the best yields were achieved by employing a 1:2 hydrazone/alkyne ratio and 2 equivalents of K_2CO_3, in 1,4-dioxane as solvent at 110 °C. These reaction conditions were applied to a set of hydrazones (**1**) and terminal alkynes (**2**), and the results are summarized in Table 1.

Table 1: Regioselective synthesis of 3,4,5-trisubstituted pyrazoles.[a]



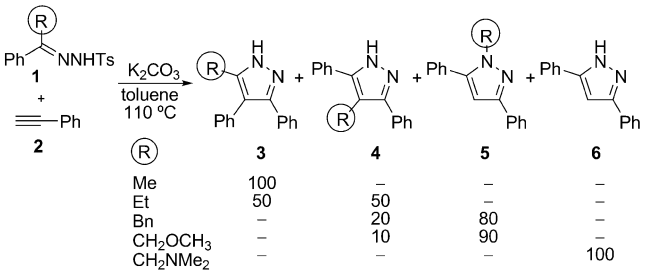
Entry	R^1	R^2[c]	R^3[c]	Yield [%][b,d]	
1	Me	PMP	Ph	**3a**	74(56)
2	Me	PMP	*p*-$MeOC_6H_4$	**3b**	82(55)
3	Me	PMP	*p*-tol	**3c**	63
4	Me	PMP	*p*-NCC_6H_4	**3d**	77(63)
5	Me	PMP	*p*-$CF_3C_6H_4$	**3e**	80
6	Me	PMP	*m*-$MeOC_6H_4$	**3f**	82
7	Me	PMP		**3g**	70
8	Me	PMP	2-naphtyl	**3h**	81
9	Me	PMP		**3i**	77(75)
10	Me	PMP	2-pyridyl	**3j**	63
11	Me	PMP	$SiiPr_3$	**3k**	76(62)
12	Me	PMP	Bn	**3l**	53(27)
13[c]	Me	PMP	1-cyclohexenyl	**3m**	53(52)
14	Me	PMP	Cy	**3n**	28
15	Me	*p*-ClC_6H_4	Ph	**3o**	75(63)
16	Me	*p*-NCC_6H_4	Ph	**3p**	58
17	Me	*p*-$EtO_2CC_6H_4$	*p*-tol	**3q**	63
18	Me	*p*-$EtO_2CC_6H_4$	*p*-NCC_6H_4	**3r**	72(62)
19	Me	$Ph_2CH{=}CH$	*p*-NCC_6H_4	**3s**	(46)
20	*n*Pr	Ph	Ph	**3t**	77(50)[e]
21	Et	Ph	Ph	**3u**	60[f]
22	Et	Et	*p*-NCC_6H_4	**3v**	53(32)

[a] See the Supporting Information for reaction conditions. [b] Yield of isolated product. [c] Carried out with 4 equiv of alkyne. [d] Yields for one-pot reactions from the ketone and tosylhydrazide[26] are indicated in brackets. [e] 2:1 mixture of the regioisomers **3** and **4** (Scheme 2). [f] 1:1 mixture of regioisomers.

First, the scope of the reaction was evaluated with regard to the structure of the alkyne employing the hydrazone **1a** as a substrate (Table 1, entries 1–14). The reaction is general for all types of aromatic-substituted terminal alkynes, bearing electron-donating or electron-withdrawing substituents (Table 1, entries 1–8), as well as π-exceeding (entry 9) and π-deficient heterocycles (entry 10). The reaction with benzyl acetylene, as an example of a primary alkyl substituent, also led to the pyrazole **3l** with moderate yield (entry 12). However, a substantial drop in the yield was observed with alkenyl and secondary alkyl substituents (entries 13 and 14, respectively). Remarkably, the reaction with triisopropylsilylacetylene led to the straightforward synthesis of the silylsubstituted pyrazole **3k** in high yield (entry 11).

Regarding the structure of the tosylhydrazone, the process takes place efficiently with hydrazones derived from acetophenones featuring all types of substituents in the aromatic ring (Table 1, entries 15–18). Moreover, the hydrazone of 4,4-diphenyl-3-buten-2-one provided the trisubstituted pyrazole **3s**, with migration of the alkenyl group (entry 19). The replacement of the methyl group by a longer alkyl chain led to a decrease in the regioselectivity, thus giving rise to a mixture of the isomeric NH-pyrazoles **3** and **4** (entries 20 and 21), and can be understood by considering the higher migration ability of the *n*-alkyl groups, relative to the methyl group, in the [1,5] sigmatropic rearrangement. Finally, the reaction with the tosylhydrazone of 3-pentanone led to the desired pyrazole **3v** (entry 22).[25,26] These results show that the cascade reaction is an excellent method for the preparation of 3,4-diarylpyrazoles, a scaffold present in several compounds with interesting biological activity.[27]

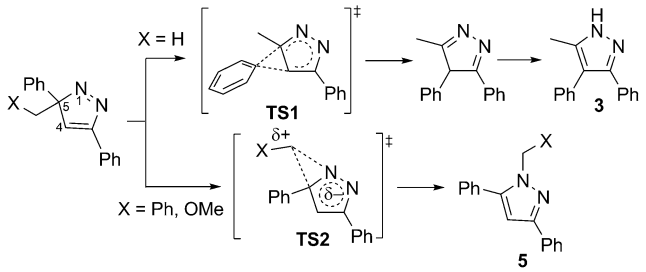
The observation of two regioisomers (Table 1, entries 20 and 21) prompted us to investigate of the influence of the substituents R^1 and R^2 in the outcome of the reactions. Indeed, the introduction of substituents different from methyl and aryl led to a change not only in the selectivity but also in the sense of the [1,5] rearrangement (Scheme 2). While in the case of a primary alkyl group (R = Et) both isomers **3** and **4**



Scheme 2. Influence of the structure of the hydrazone **1** on the regioselective formation of 1*H*-pyrazoles. Ratio of products determined by ^1H NMR spectroscopy.

are obtained in a similar ratio, formation of the 1,3,5-pyrazole **5** through a clockwise migration is clearly preferred when R = Bn and R = CH_2OMe. Finally, the reaction of the hydrazone derived from α-dimethylaminoacetophenone (R = CH_2NMe_2) exclusively provided the disubstituted pyrazole **6** with loss of the R group.

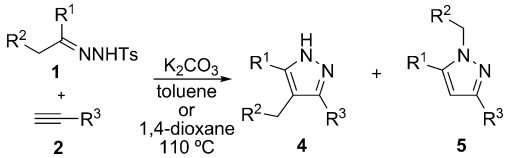
The existing mechanistic studies relative to the regioselectivity of [1,5] shifts on 3*H*-pyrazoles (van Alphen–Hüttel rearrangement)[23,28–30] suggest that the migration of the R group to N1 to give the pyrazole **5** occurs through the transition state **TS2** with partial charge separation (Scheme 3). This pathway must be favored for substituents which stabilize the partial positive charge developed in the transition state (X = Ph, OMe). Moreover, the higher electron density on N1 versus C4, justifies the regioselectivity of the [1,5] shift. In the absence of this effect (X = H), migration

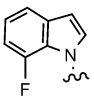


Scheme 3. Proposed transition states for the [1,5] shift.

of the aryl group to C4 through **TS1** must be favored. Finally, excessive stabilization of the carbocation (Scheme 2; R = CH_2NMe_2) leads to a different reaction pathway with dissociation of the R group through a retro-Mannich-type reaction.

Table 2: Regioselective synthesis of the 1,3,5-trisubstituted pyrazoles **5**.[a]



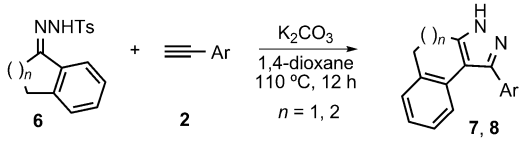
Entry	R^1	R^2	R^3	**4/5**[b]	Yield [%][c,d]	
1	Ph	Ph	Ph	1:4	**5a**	44
2	Ph	Ph	Bn	1:2	**5b**	35
3	Ph	Ph	*p*-NCC_6H_4	1:3	**5c**	67
4	Ph	Ph	*p*-$CF_3C_6H_4$	1:4	**5d**	56
5	Ph	Ph	PMP	0:1	**5e**	53
6	Ph	Ph	*m*-$MeOC_6H_4$	1:5	**5f**	47
7	Ph	Ph		0:1	**5g**	76(63)
8	Me	Ph		0:1	**5h**	56
9[d]	Ph	PMP	*p*-$CF_3C_6H_4$	0:1	**5i**	70
10[e,f]	Ph	MeO	*p*-NCC_6H_4	1:7	**5j**	42
11[e,f]	Me	BnO	*p*-NCC_6H_4	0:1	**5k**	56
12[f,g]	Ph		*p*-$CF_3C_6H_4$	0:1	**5l**	74
13[f]	Ph			0:1	**5m**	45
14[f]	Ph		*p*-$CF_3C_6H_4$	0:1	**5n**	57(23)
15[d,f]	PMP		*p*-$CF_3C_6H_4$	0:1	**5o**	57(51)

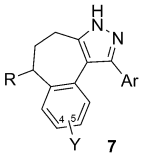
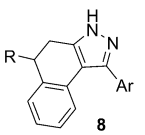
[a] See the Supporting Information for reaction conditions. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated pure regioisomer **5**. [d] Yields for one-pot reactions from the ketone and tosylhydrazide[26] are indicated in brackets. [e] NaOH was employed as base. [f] 1,4-Dioxane as solvent. [g] Carried out with 4 equiv of alkyne.

At this point, the scope of this reaction as a new way to synthesize 1,3,5-trisubstituted pyrazoles (**5**) was evaluated. As presented in Table 2, the reactions with the benzyl containing hydrazones (entries 1–8) led to the pyrazoles **5** as the major or unique isomers in all cases, and could be isolated as pure regioisomers with synthetically acceptable yields. The incorporation of a more electron-rich aromatic ring such as the *p*-methoxyphenyl group in the migrating fragment led to the exclusive formation of the pyrazole **5i** (entry 9). Very high regioselectivities were also achieved for the rearrangement of alkoxymethyl groups (entries 10 and 11). Then we examined α-*N*-azole-substituted tosylhydrazones (entries 12–15), with the expectation that the N-azole substituent might also exert a weak stabilization of the incipient carbocation in the transition state. To our delight, these systems provided the corresponding 1,3,5-substituted pyrazoles **5** with complete regioselectivity, in reactions suitable for the high-throughput generation of druglike molecules. For instance, the results in entry 13 show the assembly of **5m**, containing three different heterocycles, in one single synthetic operation.

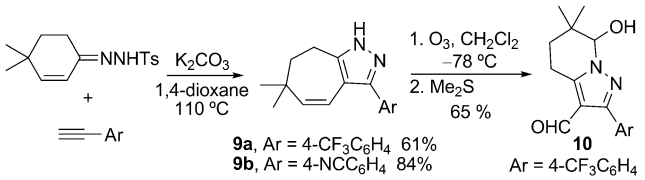
We next explored the reactions with the tosylhydrazones **6** derived from cyclic ketones. We anticipated that the [3+2] cycloaddition/[1,5] rearrangement sequence would give rise to the trisubstituted pyrazoles **7**–**8** with expansion of the carbocyclic ring (Table 3). Indeed, the reactions with hydrazones derived from tetralones and indanones led to the corresponding pyrazoles fused to a seven-membered ring (**7**) and to a six-membered ring (**8**), respectively. The [1,5] rearrangement takes place again in a regioselective manner, thus giving rise exclusively to the pyrazole in which migration of the aryl group has occurred. Moreover, variations on the aromatic rings of both coupling partners and also in the scaffold are tolerated. This transformation could be also accomplished with the tosylhydrazone of cyclohexenone

Table 3: Synthesis of the benzofused pyrazoles **7** and **8** from cyclic tosylhydrazones **6**.



	Ar	Y	R		Yield [%][a]
	Ph	H	H	**7a**	45
	p-$CF_3C_6H_4$	H	H	**7b**	80
	p-NCC_6H_4	H	H	**7c**	82
	p-$CF_3C_6H_4$	5-F	H	**7d**	64
	Ph	4-MeO	H	**7e**	(78)
	p-$CF_3C_6H_4$	4-MeO	H	**7f**	60
	p-$CF_3C_6H_4$	H	Me	**7g**	65
	2-pyridyl	H	H	**7h**	67
	Ph	–	H	**8a**	42
	p-$CF_3C_6H_4$	–	H	**8b**	57
	2-pyridyl	–	H	**8c**	51 (43)
	p-$CF_3C_6H_4$	–	Me	**8d**	45

[a] Yields for the one-pot reactions from the ketone and tosylhydrazide[26] are given within parentheses.



Scheme 4. Synthesis of the benzocycloheptapyrazoles **9** and ozonolysis to the tetrahydropyridopyrazole **10**.

(Scheme 4), thus giving rise to the benzocycloheptapyrazoles **9**, which correspond to the rearrangement of the sp^2-carbon atom to C4. Benzocycloheptapyrazoles (**9**) are interesting intermediates which could be further elaborated through functionalization or oxidation of the double bond. For instance, the ozonolysis of **9a** led to the densely functionalized tetrahydropyridinopyrazole **10** in quantitative yield.

In summary, we have presented a novel and general approach for the regioselective synthesis of substituted pyrazoles through a catalyst-free [3+2] cycloaddition/[1,5] rearrangement cascade. We have shown that the nature of the substituents controls the sense of the rearrangement, and may lead to either 3,4,5- or 1,3,5-trisubstituted pyrazoles in a very straightforward manner. Moreover, the employ of cyclic tosylhydrazones leads to benzofused pyrazoles, which are not easily accessible from other routes. From a synthetic point of view, and taking into consideration the ready availability of the starting materials, the experimental simplicity of the reactions, and the importance of pyrazoles, especially in agro- and medicinal chemistry, this methodology may become a very useful tool for the synthetic chemists.

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