1,3-Dipolar Cycloaddition of Nitrile Imines with Functionalized Acetylenes: Regiocontrolled $Sc(OTf)_3$-Catalyzed Synthesis of 4- and 5-Substituted Pyrazoles

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Abstract: 1,3-Dipolar cycloaddition of *C*-aryl-*N*-aryl- and *C*-carboxymethyl-*N*-aryl-nitrile imines with functionalized acetylenes have been studied. Regioisomeric mixtures have been obtained with the 5-substituted pyrazole as the major cycloadduct. Under scandium triflate catalysis a reversal in the regiochemistry was observed, especially in the case of *C*-carboxymethyl-*N*-aryl-nitrile imines.

Keywords: dipolar cycloadditions, regiochemistry, nitrile imines, pyrazoles, scandium triflate

Owing to its high synthetic efficiency and high regio- and stereoselectivity, the 1,3-dipolar cycloaddition (1,3-DC) of 1,3-dipoles with π-electronic-deficient systems has emerged as a popular way for obtaining five-membered heterocycles.[1] The synthetic utility of the 1,3-DC reaction stems from the wide scope and from the relevance of numerous targets achievable by this chemistry,[2] since many 1,3-dipolar species are readily available and react with a variety of dipolarophiles. In particular, nitrogen-containing heterocycles have attracted widespread attention in the field of synthetic organic chemistry as well as in medicinal chemistry.[3] Among them, pyrazoles are synthetic targets of utmost importance in the pharmaceutical industry, since such a five-membered heterocyclic moiety represents the core structure of numerous drugs.[4]

Only two routes of general importance for the assembly of 4- and 5-substituted pyrazoles have been reported so far. The first is the ring closure using hydrazines with β-diketones[5a] or a derivative of comparable reactivity and the second is the 1,3-DC of diazoalkanes with unfunctionalised and carboxyalkyl acetylenes.[5b–d]

The 1,3-DC of nitrile imines in situ generated from hydrazonoyl halides and a base to triple-bond derivatives is a potentially powerful method for the synthesis of the pyrazole ring. However, a deep search in the literature revealed a lack of general investigation about this reaction, in contrast with the impressive number of papers related to the use of alkenes as dipolarophiles. Alkynes have a reduced dipolarophilic activity and react more slowly than alkenes by a power of 10.[1] Simple alkynes such as phenyl acetylene react with diphenyl nitrile imine to give in 72% yield the 1,3,5-triphenyl pyrazole[6] but a 90:10 mixture of 5- and 4-phenyl pyrazoles was obtained with *C*-phenyl *N*-methyl nitrile imine.[7] Moreover, alkynes with electron-withdrawing substituents have a higher propensity to form 4-substituted pyrazoles, and methyl propiolate adds to diphenyl nitrile imine to yield mixtures of 5- and 4-substituted pyrazoles in 78:22 ratio.[8] Recent works[9] reported the regioselective synthesis of 5-substituted 3-dimethoxyphosphonopyrazoles[9a] through the 1,3-DC of *C*-dimethoxyphosphono *N*-aryl nitrile imines with monosubstituted acetylenes and methyl propiolate with yields in the range 12–40% and computational study for the cycloaddition of nitrilimines to methyl propiolate.[9b]

With the aim to extend the scope of nitrile imines cycloaddition and following our interest for the [3+2] cycloaddition of 1,3-dipoles for the synthesis of heterocycles of pharmaceutical interest,[10] we report herein the 1,3-DC of *C*-aryl-*N*-aryl- and *C*-carboxymethyl-*N*-aryl-nitrile imines with functionalized acetylenes such as benzyl propiolate and *N*-phenyl-propiolamide, with a particular focus addressed toward the regiochemistry of the final pyrazoles in both the uncatalyzed and the $Sc(OTf)_3$-catalyzed reaction. Even though Lewis acids were found to be effective in controlling the stereoselectivity in 1,3-DC of relatively stable 1,3-dipoles such as nitrones,[11] azomethine ylides,[12] and carbonyl ylides,[13] cycloadditions of nitrile imines with alkenes in the presence of Lewis acids have been scarcely reported.[14] Moreover, Lewis acid catalysts, including rare-earth-metal triflates, have never been used to control the regioselectivity of 1,3-DC of nitrile imines and acetylenes.

The syntheses of benzylpropiolate[15] (**1**) and of *N*-phenylpropiolamide[16] (**2**, Figure 1) have been performed according to the literature procedure for **1** and with slight modification in the case of **2** (see Supporting Information).

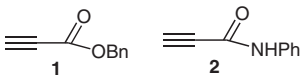

Figure 1 Functionalized acetylenes: benzyl propiolate (**1**) and *N*-phenylpropiolamide (**2**)

The *C*-carboxymethyl-*N*-aryl hydrazonoyl chlorides **3** have been scarcely reported in the literature in contrast with *C*-aryl-*N*-aryl derivatives. 4-Fluoroaniline dissolved in MeOH was first converted to its diazonium salt with

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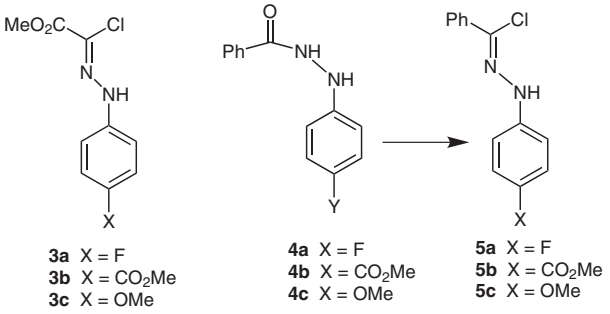
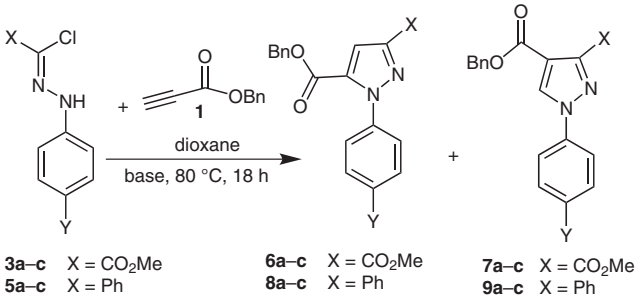
$NaNO_2$/HCl and then by treatment with methyl-2-chloroacetoacetate in MeOH gave **3a** in 96% yield after crystallization.[17] With the same procedure the unknown hydrazonoyl chloride **3b** was obtained starting from methyl-4-aminobenzoate[18] while compound **3c**[19] was obtained from 4-methoxyaniline using as solvent a mixture 1:1 of pyridine and water (Scheme 1).



Scheme 1 *C*-Carboxymethyl-*N*-aryl hydrazonoyl chlorides **3a–c** and *C*-aryl-*N*-aryl hydrazonoyl chlorides **5a–c**

The *C*-aryl-*N*-aryl hydrazonoyl chlorides were obtained starting from the corresponding 4-substituted hydrazines. The reaction with benzoyl chloride in THF in the presence of Et_3N gave the benzoylhydrazines **4a–c**. The subsequent reaction of **4a–c** with triphenylphosphine–CCl_4 in MeCN[20] gave the hydrazonoyl chlorides **5a–c**. (see Supporting Information). Only product **5c**, prepared by reaction of PCl_5 with **4c**, was reported in the literature.[21]

We next examined the conditions required for the cycloaddition of **1** with **3a–c** and **5a–c**. The cycloadditions were carried out in dry dioxane at 80 °C for 18 hours using 2.5 equivalents of Ag_2CO_3 until complete conversion of **1**, which was always used in stoichiometric amount with respect to the dipoles (Scheme 2). The regioisomeric ratio was always calculated by ^{1}H NMR analysis of the crude mixtures using diagnostic signals. The good yields ranging from 58–84% were always referred to the sum of the two isolated regioisomers after column chromatography. The identification of the 5-pyrazoles and the 4-pyrazoles was based on the ^{1}H NMR signals taking advantage from the CH signal on the C5 for the 4-substituted pyrazole which resonates at about δ = 8.0 ppm.



Scheme 2 1,3-DC of 1 with **3a–c** and **5a–c**

The *C*-carboxymethyl-*N*-aryl-nitrile imines derived from **3a–c** in the absence of any Lewis acid gave balanced mixtures of the cycloadducts **6b/7b** and **6c/7c** (entries 2 and 3) with the exception of the two pyrazoles **6a/7a** derived from the 1,3-dipole **3a** that were obtained in a 74:26 ratio in favor of the 5-isomer (entry 1). In the case of the nitrile imines derived from the *C*-aryl-*N*-aryl hydrazonoyl chlorides **5a–c** a higher preference for the 5-substituted pyrazoles has been observed. In particular **5b** gave the two cycloadducts **8b/9b** in 84:16 ratio (entry 5), while ratios of 65:35 and 55:45 were observed for **5a** and **5c**, respectively (entries 4 and 6).

Upon addition of a catalytic amounts of $Sc(OTf)_3$, a generally good improvement in term of efficiency of these reactions was observed leading to better yields in the case of cycloadducts **6a/7a**, **6b/7b**, and **6c/7c** (entries 1–3), but the most interesting effect was the reversal in the regiochemistry in favor of the 4-substituted pyrazoles. Cycloadducts **6a/7a** were obtained in 21:79 ratio, **6b/7b** in 18:82 ratio while **6c/7c** gave the highest value for the 4-isomer with a 9:91 ratio (entries 1–3). Interestingly, the reaction using **5a–c** did not work with Ag_2CO_3 under scandium catalysis leading to unidentified byproducts, whereas satisfactory yields were obtained by using Et_3N. On the other hand the reversal of regioselectivity was lower starting from **5a–c** under $Sc(OTf)_3$ catalysis (entries 4 and 5), the 4-isomer increased slightly starting from **5a** and **5b**, giving a 54:46 and a 60:40 ratio for **8a/9a** and **8b/9b**, in contrast **5c** gave **8c/9c** in 75:25 ratio thus maintaining the 5-pyrazole as major regioisomer.

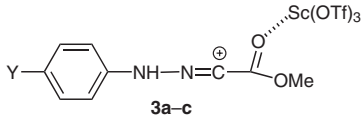
Table 1 1,3-DC of **1** with 1,3-Dipoles Derived from **3a–c** and **5a–c**

Entry	1,3-Dipole	Base	Cycloadducts	Yield (%)[a]	Ratio[a]	Yield (%)[b]	Ratio[b]
1	3a	Ag_2CO_3	**6a/7a**	61	74:26	90	21:79
2	**3b**	Ag_2CO_3	**6b/7b**	58	52:48	88	18:82
3	**3c**	Ag_2CO_3	**6c/7c**	84	53:47	92	9:91
4	**5a**	Et_3N	**8a/9a**	76	65:35	70	54:46
5	**5b**	Et_3N	**8b/9b**	63	84:16	65	60:40
6	**5c**	Et_3N	**8c/9c**	65	55:45	61	75:25

[a] Without $Sc(OTf)_3$.
[b] With 10 mol% $Sc(OTf)_3$.

Under the same reaction conditions, also in the case of the 1,3-DC of **2**, satisfactory yields in the range of 56–90% were achieved (Scheme 3). The ratios 5-pyrazole/4-pyrazole were higher with respect to the reaction with **1** for both the *C*-carboxymethyl-*N*-aryl- and *C*-aryl-*N*-aryl-nitrile-imines in the absence of Lewis acid (entries 1–6, Table 2). Under $Sc(OTf)_3$ catalysis, also in this case a substantial reversal of regioselectivity was observed for the cycloadducts **10a/11a**, **10b/11b**, and **10c/11c** derived from **3a–c** (entries 1–3), with the obtainment of a very good value of 8:92 for cycloadducts **10a/11a**. Starting from dipoles **5a**,**b**, the amount of 4-pyrazoles slightly increased as shown by the variation of the ratios between cycloadducts **12a/13a** and **12b/13b**, from 73:27 to 63:37 and from 68:32 to 51:49, respectively (entries 4 and 5). Also in this case we observed, for the 4-MeO-substituted 1,3-dipole derived from **5c**, the cycloadducts **12c/13c** in 77:23 ratio, very similar to the 75:25 obtained without $Sc(OTf)_3$ catalysis (entry 6).

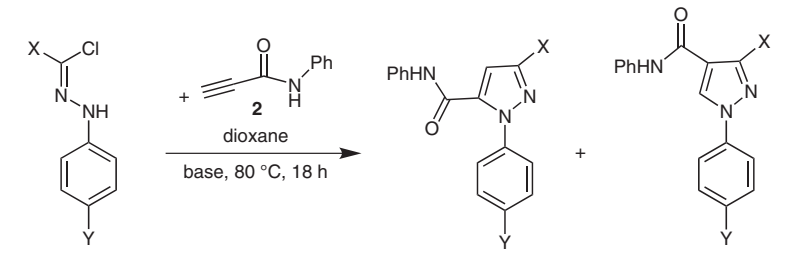
Chemistry for entries 4–6, under scandium catalysis, worked again only in the presence of Et_3N as base. To tentatively explain the failure in the reaction of **5a–c** with both dipolarophiles **1** and **2** under scandium catalysis we could invoke the different mechanism of generation of nitrile imines from hydrazonoyl chlorides in the presence of Et_3N or Ag_2CO_3. In the former case the deprotonation occurs first, quickly followed by the loss of halide ion,[22] leading for both **3a–c** and **5a–c** to the formation of the dipole. With Ag_2CO_3 the first step is a silver ion promoted dehalogenation to give an intermediate nitrilium-like carbocation,[2,23] which, in the case of **5a–c**, led to the formation of several unidentified byproducts arising from the fragmentation of the molecular skeleton. With hydrazonoyl chlorides **3a–c**, the high affinity of scandium triflate for the oxygen of the carbomethoxy group seems to allow the 1,3-DC improving the yield as well, probably due to the enhanced electrophilicity of the carbon (Figure 2).



3a–c

Figure 2 Intermediate nitrilium-like carbocation derived from **3a–c**

As it can be observed from Tables 1 and 2, the regiochemistry of this 1,3-DC shows interesting features and deserves some comments. Domingo[24] recently reported the use of the global electrophilicity index ω proposed by Parr[25] and introduced a unique absolute hierarchy of electrophilicity that is expected to predict the reactivity of a set of dipoles/dipolarophiles for Diels–Alder and for 1,3-DC. In the global electrophilicity scale for common dipoles, the nitrile imines are classified as marginal electrophiles (ω = 0.28), which means that they could act as nucleophiles with strong electrophiles as the dipolarophile **1** (ω = 1.52); therefore they should react with nitrile imines in a normal electron-demand (NED) fashion consistent with a polar mechanism due to the high Δω, leading to 5-substituted cycloadduct mainly. No data are available for **2**, but it is likely that the value of ω would be similar (or higher) to **1**.



3a–c X = CO_2Me
5a–c X = Ph

10a–c X = CO_2Me
12a–c X = Ph

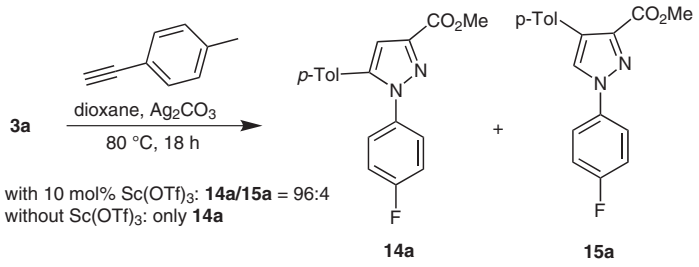
11a–c X = CO_2Me
13a–c X = Ph

Scheme 3 1,3-DC of **2** with **3a–c** and **5a–c**

Table 2 1,3-DC of **2** with 1,3-Dipoles Derived from **3a–c** and **5a–c**

Entry	1,3-Dipole	Base	Cycloadducts	Yield (%)[a]	Ratio[a]	Yield (%)[b]	Ratio[b]
1	3a	Ag_2CO_3	**10a/11a**	66	83:17	94	8:92
2	**3b**	Ag_2CO_3	**10b/11b**	63	72:28	89	39:61
3	**3c**	Ag_2CO_3	**10c/11c**	90	88:12	95	32:68
4	**5a**	Et_3N	**12a/13a**	56	73:27	60	63:37
5	**5b**	Et_3N	**12b/13**b	71	68:32	68	51:49
6	**5c**	Et_3N	**12c/13c**	60	75:25	58	77:23

[a] Without $Sc(OTf)_3$.
[b] With 10 mol% $Sc(OTf)_3$



Scheme 4 1,3-DC of **3a** with *p*-tolylacetylene

The observation for the regioselectivity in favor of 4-substituted pyrazoles with nitrile imines derived from **3a–c** with respect of nitrile imines from **5a–c** might be represented as in Figure 3, in which the presence of the CO_2Me group can form a chelate transition state **B**, where the carboxymethyl and the carbonyl groups of the dipolarophiles coordinate in a bidentate fashion the $Sc(OTf)_3$.

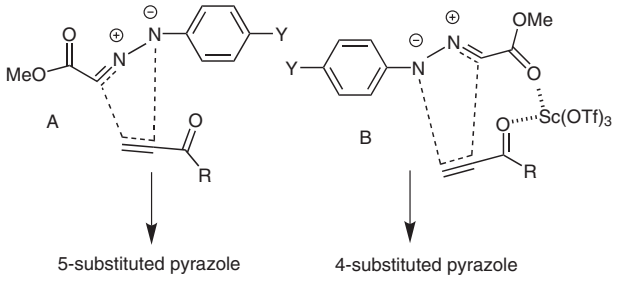


Figure 3 Proposed transition state between generic dipolarophiles and nitrile imines derived from *C*-carboxymethyl-*N*-aryl hydrazonoyl chlorides.

Moreover, when a dipolarophile is activated by coordination to a Lewis acid catalyst a reversal in the regioselectivity can occur which has been already observed for 1,3-DC of nitrones with α,β-unsaturated compounds.[26]

The results obtained from **5c** (entries 6 in Table 1 and Table 2) have to be compared with those derived from **5a**,**b**: according to Domingo, the strongly electron-donating 4-MeO group of **5c** must decrease the value of ω thus rendering the Δω with **1** (or **2**) higher, and this might be the explanation for the persistency of 5-pyrazole as the major regioisomer with or without scandium catalysis.

These hypotheses seem to be strengthened through observing the results of the reaction of **3a** with *p*-tolylacetylene, in which the possibility of a bidentate chelation with the catalyst is unlikely (Scheme 4). We carried out this reaction without catalytic $Sc(OTf)_3$ and have found only the 5-pyrazole **14a** in 30% yield, while the same reaction run with 10 mol% of the $Sc(OTf)_3$ gave in 69% yield a 96:4 ratio of 5-pyrazole/4-pyrazole (**14a**/**15a**).

In conclusion, we have developed a method for the regiocontrolled synthesis of pyrazoles based on the 1,3-DC of nitrile imines with functionalized acetylenes.[27] Our investigations revealed that the *N*-phenylpropiolamide **2** are better substrates than benzyl propiolate **1** for the obtainment of the 5-pyrazoles. The 4-substituted regioisomers can be obtained with the use of $Sc(OTf)_3$ as a catalyst using *C*-carboxymethyl-*N*-aryl nitrile imines both with **1** and **2**. The methodology appears to be suitable for the control of the regiochemistry of this 1,3-DC and could be potentially useful for applications in medicinal chemistry.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(27) **General Procedure for the 1,3-DC of 1 and 2 with with 3a–c and 5a–c**
To a solution of **1** or **2** (1 mmol) and the precursor of the 1,3-dipoles (1 mmol) in 1,4-dioxane (4.4 mL) was added Ag_2CO_3 (0.69 g, 2.5 mmol) and catalytic $Sc(OTf)_3$ (0.1 mmol) as specified in Tables 1 and 2. The reaction mixture was stirred at 80 °C for 18 h. The reaction was then filtered on Celite and the solvent was removed under vacuum. Purification was carried out as reported in the Supporting Information. Characterization for all the compounds is available as Supporting Information.