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Calcium Carbide as the Acetylide Source: Transition-Metal-Free Synthesis of Substituted Pyrazoles *via* [1,5]-Sigmatropic Rearrangements†

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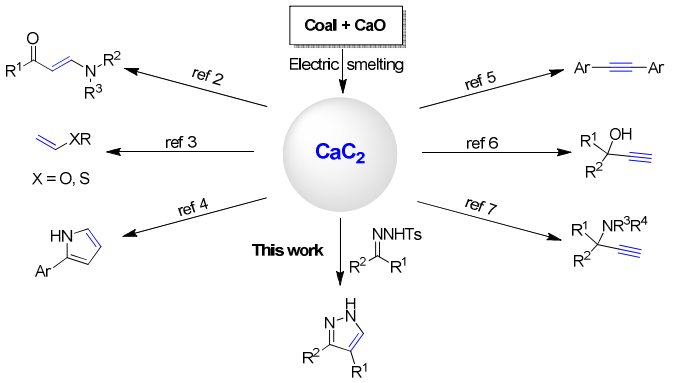
Under transition-metal-free conditions, calcium carbide was used as the acetylide source to react with a wide range of *N*-tosylhydrazones derived from aldehydes or ketones, affording various substituted pyrazoles in good yields with high regioselectivities. The transformations go through [3+2] cycloadditions followed by [1,5]-sigmatropic rearrangements, which are supported by deuterium-labeling experiments.

Introduction

The most suitable type of organic reactions for connecting scientific study to industrial manufacture should be in line with four principles: (i) starting with simple, inexpensive and easy-to-get molecules; (ii) proceeding in mild and safe conditions; (iii) having atom-economy and step-economy; (iv) obtaining valuable products.[1] Taking as an example, calcium carbide (CaC_2) was prepared from an electric smelting furnace of coal and calcium oxide in industrial production, which has become an important basic organic chemical raw material for the manufacture of acetylene and calcium cyanamide. As a main source of the simplest alkyne, solid calcium carbide is a promising candidate for a safer and cheaper alternative to acetylene gas, for the production of acetylene derived chemicals. Up to date, there have been few reports of utilizing CaC_2 directly in organic synthesis due to its insolubility in common organic solvents, which was derived from its highly stable lattice structure.[2-7] Fortunately, polar aprotic solvents such as DMSO were found to be good solvents for CaC_2 with the addition of equivalent amount of base and controlled amounts of water. These few reported methods can be divided into two categories according to the reaction results (Scheme 1). For one of them, the acetylide anion derived from calcium carbide undergoes an electrophilic addition to its triple bond for the synthesis of C=C-containing compounds, such as enaminones[2], vinyl ethers[3] and pyrroles[4]. The other kind of reaction is that the acetylide anion acts as a nucleophile under suitable conditions and attack the electrophilic aryl or carbonyl carbons, leading to the formation of various acetylide molecules, such as diarylethynes,[5] propargyl alcohols[6] and propargyl amines[7]. However, the development of alternative approaches for the direct use of calcium carbide to synthesize other practical acetylene derivatives is still very imperative.



Scheme 1. Synthesis of various commodity chemicals by using calcium carbide as the acetylene source

Pyrazole is one of the most valuable compounds that can be easily obtained from acetylene. As an important class of heterocyclic ring systems, pyrazole derivatives are core frameworks of many biologically active molecules and drug intermediates.[8] Selected pharmaceutical and agromedical examples include Celebrex, Viagra, Acomplia, Fenpyroximate and Tebufenpyrad.[9] The syntheses of pyrazoles have received considerable attention and numerous approaches have been developed in past decades, including the classical condensations of hydrazines with 1,3-dicarbonyl compounds[10], the dipolar [3+2] cycloadditions[11], the

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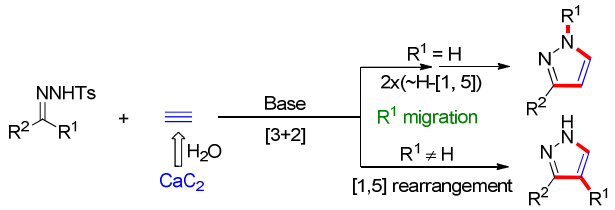
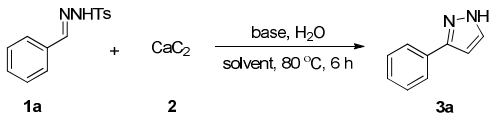
multicomponent reactions of nitrogenous molecules[12], and so on[13]. However, most of the methods are limited to construct 5-substituted pyrazoles while 3-substituted or 3,4-disubstituted pyrazoles act as vital building blocks of many pharmaceuticals and natural products. In order to expand the richness of synthetic methods, we herein report an efficient and highly regioselective strategy for the synthesis of 3-substituted or 3,4-disubstituted pyrazoles *via* transition-metal-free [3+2] cycloaddition/[1,5]-sigmatropic rearrangements (Scheme 2). In this process, calcium carbide was used as the acetylide source to perform with *N*-tosylhydrazones[14,15] derived from aldehydes or ketones.



Scheme 2. R^1 migration in this transformation.

Results and discussion

Table 1. Optimization of the reaction conditions.[a]



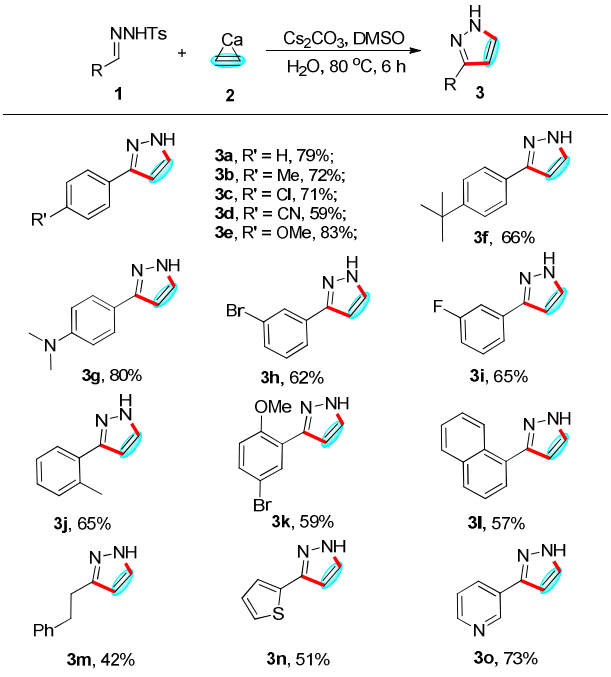
Entry	Base	Solvent	T (°C)	Yield of **3a**[b] (%)
1	Cs_2CO_3	THF	80	58
2	KOH	THF	80	32
3	K_2CO_3	THF	80	22
4	*t*-BuOLi	THF	80	18
5	Et_3N	THF	80	trace
6	Cs_2CO_3	Dioxane	80	29
7	Cs_2CO_3	DMF	80	18
8	Cs_2CO_3	CH_3CN	80	trace
9	Cs_2CO_3	Toluene	80	n.d.
10	**Cs_2CO_3**	**DMSO**	**80**	**86 (79)**
11	Cs_2CO_3	DMSO	60	66
12	Cs_2CO_3	DMSO	100	80
13[c]	Cs_2CO_3	DMSO	80	52

[a] Reaction conditions: All reactions were performed with **1a** (0.5 mmol), **2a** (2 mmol), base (0.5 mmol), H_2O (2.5 mmol) and 2.0 mL solvent at 80 °C for 6 h unless otherwise noted. [b] Yields were analyzed by GC-MS using *n*-dodecane as an internal standard. The number in the parentheses is isolated yield. [c] **2a** (1 mmol), H_2O (1.25 mmol).

At the outset of this transformation, we treated *N*-tosylhydrazone (**1a**) with calcium carbide (**2**) as the model substrates for reaction development (Table 1). Initially, the desired product **3a** was obtained in 58% yield under simple conditions that Cs_2CO_3 was used as base and 5 equiv H_2O (see Supporting Information for details) were added to THF in a Schlenk tube at 80 °C for 6 h (entry 1). Screening of various bases, such as KOH, K_2CO_3, *t*-BuOLi and Et_3N, did not improve the yield of **3a** (entries 2-5). A series of solvents were then tested and DMSO was found to be the best choice for this transformation, elevating the yield to 86% (entry 6-10). Besides, the yield dropped to 66% or 80% when the temperature was changed to 60 °C or 100 °C, respectively (entries 11 and 12). Finally, we tried to halve the amount of calcium carbide and H_2O, while it led to a lower yield of 52% (entry 13).

With the optimized reaction conditions in hand (Table 1, entry 10), we turned our attention to the scope and limitations of this [3+2] annulation between *N*-tosylhydrazones derived from aldehydes and calcium carbide (Table 2). To our delight, a wide range of *N*-tosylhydrazones with different substitution patterns could be used as the substrates, generating the corresponding products in moderate to good yields under the standard reaction conditions. For R' = H, Me, Cl, CN, OMe, *t*-Bu or NMe_2, the starting materials smoothly transferred to the corresponding products in 59-83% yields (**3a-3g**). The substrate with a substituent on the *meta*- or *ortho*-position of the phenyl ring could also transform to the desired products in good yields (**3h-3j**). In general, *N*-tosylhydrazones with electron-neutral or electron-donating substituents furnished the desired products (**3a-3b**, **3e-3g**, **3j**) in higher yields than those with electron-withdrawing groups (**3c-3d**, **3h-3i**). Furthermore, 5-bromo-2-methoxyphenyl-, 1-naphthyl-, 2-furanyl- and 3-pyridyl-bearing *N*-tosylhydrazones were also found to be good substrates, delivering the products (**3k-3l**, **3n-3o**) in 51-73% yields. Remarkably, *N*-tosylhydrazone derived from aliphatic aldehyde was compatible with the reaction conditions to afford the corresponding product **3m**, albeit with lower efficiency.

Table 2. Substrate scope of *N*-tosylhydrazones derived from aldehydes.[a]



[a] Reaction conditions: All reactions were performed with **1** (0.5 mmol), **2** (2 mmol), base (0.5 mmol), H_2O (2.5 mmol) and 2.0 mL solvent at 80 °C for 6 h unless otherwise noted.

To further define the scope of our method, the substrate scope was extended to different types of *N*-tosylhydrazones derived from ketones, as shown in Table 3. Initially, we conducted the reaction between *N*-tosylhydrazones derived from acetophenone (**4a**) and calcium carbide (**2**) under the standard conditions (Scheme 1). The

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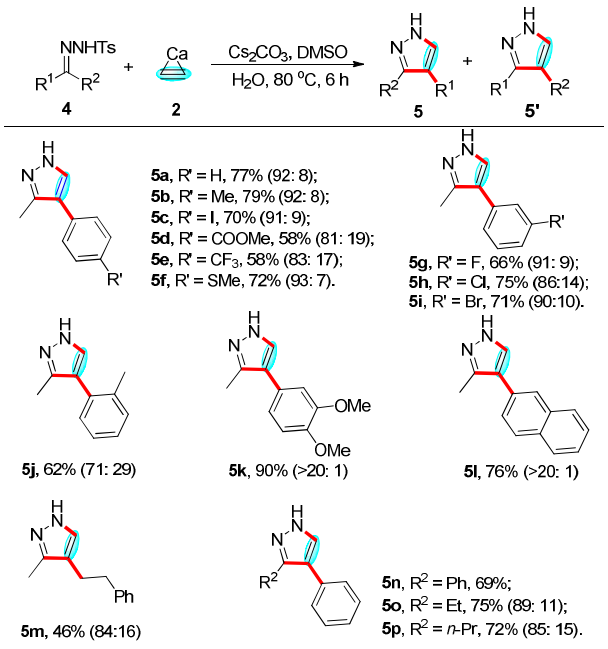
reaction afforded the pyrazole **5a** and **5a'** with high regioselectivity, and **5a** was isolated in 77% yield. These two regioisomers could be explained through a process that involves [3+2] dipolar cycloaddition, subsequent [1,5] sigmatropic rearrangements and aromatization. The aryl group has a higher electron density than the alkyl group, so that it showed higher migration ability in the [1,5] rearrangement, making **5a** as the major isomer.[11a,11b] The observation of two regioisomers prompted us to investigate the influence of the substituents R^1 and R^2 in the outcome of the reactions. Notably, the reaction system tolerates a variety of valuable functional groups on the aryl ring of the *N*-tosylhydrazones, including Me, I, COOMe, CF_3, SMe, F, Cl and Br substituents (**5b-5j**). In these cases, target products were obtained in good yields with regioselectivities of more than 5: 1, providing ample potential for further synthetic elaborations. Both disubstituted and 2-naphthyl-substituted *N*-tosylhydrazones smoothly underwent the annulation to afford the desired products **5k**, and **5l** in 90% and 76% yields respectively, with excellent regioselectivities. Pleasingly, when *N*-tosylhydrazone derived from aliphatic ketones was examined, **5m** was obtained in 46% yield as the major isomer. The scope of R^2 groups was then investigated. For R^2 = Ph, Et or *n*-Pr, the corresponding products could be afforded in 69-75% yields (**5n-5p**). Inspired by the results above in Table 2, we tried to use *N*-tosylhydrazones derived from heterocyclic ketones as substrates but failed.

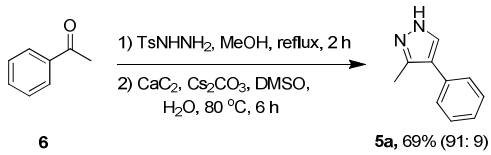
Table 3. Substrate scope of *N*-tosylhydrazones derived from ketones.[a, b]



[a] Reaction conditions: All reactions were performed with **4** (0.5 mmol), **2** (2 mmol), base (0.5 mmol), H_2O (2.5 mmol) and 2.0 mL solvent at 80 °C for 6 h unless otherwise noted.

[b] Only the major isomer **5** was shown in Table 3, yield of **5** was isolated yield, the ratio of **5** and **5**' was detected by GC/MS using *n*-dodecane as an internal standard.

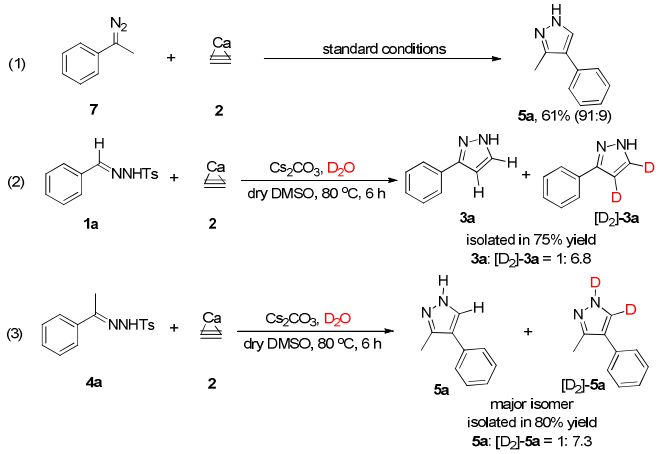
Considering that the *N*-tosylhydrazones are easily obtained by condensation reactions between tosylhydrazides and aldehydes or ketones, we then developed a one-pot synthesis of 3,4-substituted pyrazoles through the use of *N*-tosylhydrazones generated *in situ* (Scheme 3). Therefore, a mixture of acetophenone **6** and tosylhydrazide was stirred at 70 °C for 2 h in methanol, followed by removal of the solvent. The remaining crude mixture was then treated with CaC_2, Cs_2CO_3, H_2O, and DMSO under the standard reaction conditions. Gratifyingly, the desired product **5a** could also be obtained in similar yield and regioselectivity compared to those described in Table 3. This reaction demonstrates the potential of this method for the convenient synthesis of various pyrazoles directly from widely available aldehydes or ketones.



Scheme 3. One-pot synthesis of **5a** and **5a'** from acetophenone. Reaction conditions: 1) **6** (0.5 mmol), tosylhydrazide (0.5 mmol), reflux, 2 h; 2) CaC_2 (2 mmol), Cs_2CO_3 (0.5 mmol), H_2O (2.5 mmol), DMSO (2 mL), 80 °C, 6 h.

In order to demonstrate the potential practical applications of this protocol, we conducted the reaction on a gram scale (see Supporting Information for details), using 2.74 g (10 mmol) *N*-tosylhydrazone **1a** to produce 0.92 g of 1*H*-pyrazole **3a** with a yield of 64%.

To gain more insights into these two transformations, several control experiments were conducted. First, diazo compound **7** was used to take the place of *N*-tosylhydrazone in the [3+2] cycloaddition under the standard conditions.[16] The corresponding pyrazole product **5a** was generated in 61% yield, which means the diazo compound may be an intermediate in this transformation (Scheme 4, eq 1). Deuterium-labeling experiments were next carried out. The reaction of **1a** and **2** was performed in dry DMSO at 80 °C for 6 h in the presence of Cs_2CO_3 and D_2O. It was found that the reaction afforded a mixture of **3a** and [D_2]-**3a** (1: 6.8 ratio) in 75%



Scheme 4. Control experiments.

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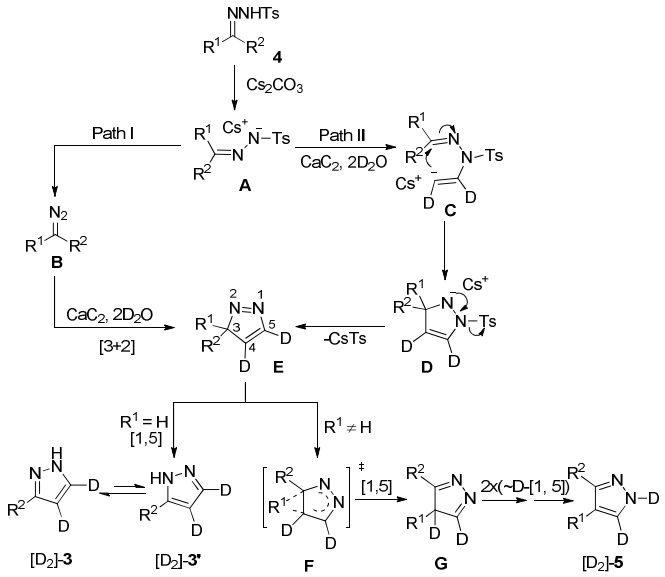
total yield (Scheme 4, eq 2). Moreover, the treatment of **4a** under the same conditions gave a mixture of **5a** and [D_2]-**5a** (1: 7.3 ratio) in 80% total yield (Scheme 4, eq 3). The structures of [D_2]-**3a** and [D_2]-**5a** showed that the hydrogen or deuterium atom on N1 was shifted from C3 or C4 of the pyrazole ring, respectively. In addition, [1,3] sigmatropic shift is orbital-symmetry forbidden that should be solvent-participating process during aromatization, while [D_1]- or [D_3]-**3a** were not observed. Therefore, we deduced that the transformation ended up with multiple [1,5]-H shifts but not a [1,3]-H shift during the process of aromatic isomerization.[17]

Taking into account of the experimental results, we proposed the mechanism for the synthesis of substituted pyrazoles **3** and **5** outlined in Scheme 5. Initially, the deprotonation of *N*-tosylhydrazone **4** in the presence of Cs_2CO_3 gives the cesium salt **A**. In one possible way, the reactive diazo compound **B** is rapidly generated *in situ*, followed by a [3+2] cycloaddition with [D_2]-acetylene gas to afford 3*H*-pyrazole compound **E** (Path I). Another possibility is that nucleophilic addition of the counter *N*-anion of intermediate **A** to [D_2]-acetylene gas affords the carbonic anion intermediate **C**. Subsequent intramolecular nucleophilic attack of the carbonic anion species of **C** leads to the generation of intermediate **D**. Then, the Ts anion and cesium ion eliminate from intermediate **D** to deliver the 3*H*-pyrazole compound **E** (Path II). The result of Eq. 1 in Scheme 4 appears to be strong evidence for possible involvement of the diazo intermediate, although Path II cannot be ruled out. The nonaromatic 3*H*-pyrazole has a trend to isomerize to an aromatic 1*H*-pyrazole. Therefore, when R^1 is H, [D_2]-**3** is formed *via* a [1,5-H] shift and a tautomerism. When R^1 is an electron-rich group that has higher migration ability, relative to the alkyl group, a migration of R^1 to C4 through the transition state **F** must be favored. The subsequent multiple [1,5]-sigmatropic rearrangements lead to the formation of [D_2]-**5**.



Scheme 5. Proposed mechanism.

Conclusions

In summary, we have successfully developed a facile transition-metal-free method for the preparation of substituted pyrazoles via [3+2] cycloaddition of *N*-tosylhydrazones derived from aldehydes or ketones with calcium carbide. Deuterium-labeling experiments have been conducted to clarify the reaction pathways that [1,5] sigmatropic rearrangements are involved in the transformation. Moreover, the one-pot synthesis of pyrazoles from readily available aldehydes or ketone is also successfully developed. In addition, the available starting material (CaC_2), the superbasic catalytic conditions (Cs_2CO_3/DMSO), and the valuable reaction products make this protocol attractive for both academia and industry. Further applications of this reaction are currently underway in our laboratory.

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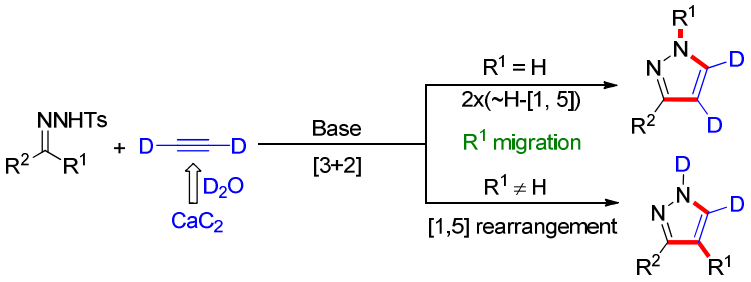

Calcium carbide was used as the acetylide source to synthesize substituted pyrazoles via [3+2] cycloaddition/[1,5] sigmatropic rearrangements.