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Tandem Reactions of 1,2-Allenic Ketones Leading to Substituted Benzenes and α,β-Unsaturated Nitriles

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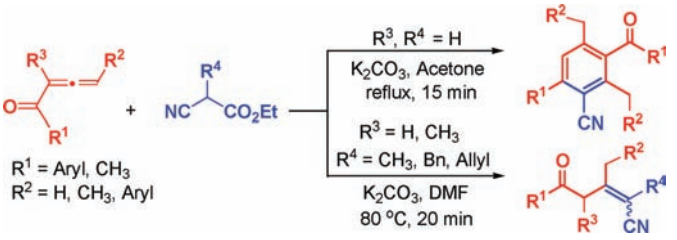
ABSTRACT



One-pot double Michael addition/*intramolecular* aldol reaction/decarboxylation of 1,2-allenic ketones with cyanoacetate offers an efficient and convenient approach to highly functionalized benzenes. With 2-substituted cyanoacetates, the reaction proceeds *via* a different tandem process to afford α,β-unsaturated nitriles effectively.

1,2-Allenic ketones are versatile and useful synthetic intermediates.[1,2] Meanwhile, the Michael addition reaction is among the most powerful methods for the formation of carbon−carbon or carbon−heteroatom bonds.[3] During our studies in utilizing the Michael addition reactions of allenic ketones to prepare compounds with biological and synthetic interest,[4] we serendipitously discovered some unprecedented reactions of 1,2-allenic ketones with cyanoacetate or 2-substituted cyanoacetates. From these reactions, efficient and convenient syntheses of polysubstituted benzenes and α,β-unsaturated nitriles were successfully developed.

Our initial objective was to prepare pyrone−nucleoside hybrids as potential antiviral candidates. The proposed synthesis is based on an elegant strategy toward α-pyrones developed by Ma et al.[5] For this purpose, 1-(4-bromophenyl)-buta-2,3-dien-1-one (**1a**) and diethyl malonate (**2**) were used as model substrates, and they afforded the desired α-pyrone (**3**) smoothly under standard conditions (Scheme 1).[5] When diethyl malonate was replaced by ethyl cyanoacetate (**4**), however, we did not get the expected cyano substituted α-pyrone (**5**). Surprisingly, a biphenyl, 1-(4-bromobenzoyl)-4-(4-bromophenyl)-3-cyano-2,6-dimethyl benzene (**6a**) was obtained. The structure of **6a** was confirmed by its spectroscopic data together with X-ray diffraction analysis (Figure 1).

The unexpected formation of **6a** not only reveals an unprecedented and interesting transformation of allenic ketones but also offers a promising pathway toward

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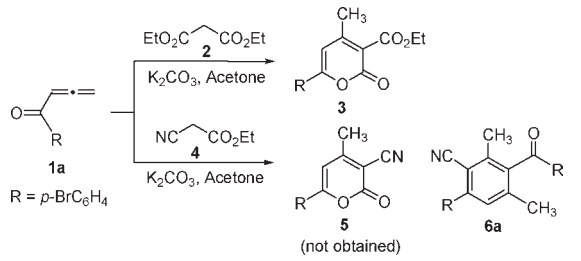
Scheme 1. Reaction of Allenic Ketone **1a** with **2** or **4**



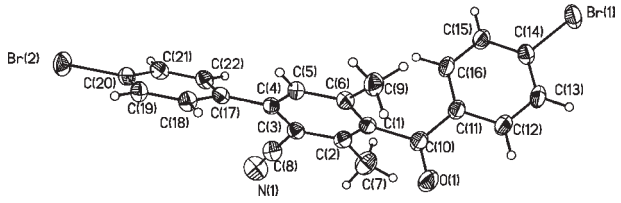
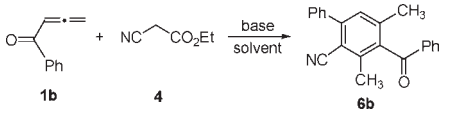


Figure 1. X-ray crystal structure of **6a**.

substituted benzenes. It has been well documented that benzenoid compounds are ubiquitous structural units in a wide variety of naturally occurring compounds and a plethora of pharmaceuticals. While direct functionalization of aromatic precursors is often used to prepare substituted benzenes, selective construction of aromatic rings from simple and readily available acyclic units constitutes another efficient approach for this purpose.[6] Based on the above facts, we were interested in developing the reaction of **1** and **4** into a general and efficient method for the preparation of polysubstituted benzenes.

To explore suitable conditions, the reaction of **1b** and **4** mediated by different solvents under the promotion of various bases was investigated and the results are listed in Table 1. First, it was found that increasing the amount of K_2CO_3 from 0.1 to 0.5 equiv improved the reaction remarkably. A further increase from 0.5 equiv did not give an obvious improvement (Table 1, entries 1−4). With 0.5 equiv of K_2CO_3, the reaction was tried in several solvents other than acetone. It was found that while THF, CH_3CN, and ethanol gave similar results as that of acetone (entries 6−8), CH_2Cl_2, DMF, and H_2O had a deleterious effect on this reaction (entries 5 and 9−10). The reaction was then tried with various bases. Inorganic bases Na_2CO_3 and NaOH exhibited similar efficiency as K_2CO_3 (entries 11−12). On the other hand, organic bases such as TBAF, piperidine, DBU, DABCO, and TEA were much less effective. In summary of the optimization, treatment of **1b** and **4** with 0.5 equiv of K_2CO_3 in refluxing acetone for 15 min gave **6b** in an optimum yield of 75% (entry 3).

Table 1. Opimization of the Reaction Leading to **6b**[a]



entry	base (equiv)	solvent	T (°C)	t (min)	yield (%)[b]
1	K_2CO_3 (0.1)	acetone	reflux	60	32
2	K_2CO_3 (0.2)	acetone	reflux	60	41
3	**K_2CO_3 (0.5)**	**acetone**	**reflux**	**15**	**75**
4	K_2CO_3 (1.0)	acetone	reflux	15	76
5	K_2CO_3 (0.5)	CH_2Cl_2	reflux	30	trace
6	K_2CO_3 (0.5)	THF	reflux	30	65
7	K_2CO_3 (0.5)	CH_3CN	reflux	30	66
8	K_2CO_3 (0.5)	EtOH	reflux	30	70
9	K_2CO_3 (0.5)	DMF	80	30	48
10	K_2CO_3 (0.5)	H_2O	80	30	29
11	Na_2CO_3 (0.5)	acetone	reflux	30	72
12	NaOH (0.5)	acetone	reflux	30	72
13	TBAF (1.0)	acetone	reflux	30	18
14	piperidine (1.0)	acetone	reflux	30	49
15	DBU (1.0)	acetone	reflux	30	28
16	DABCO (1.0)	acetone	reflux	30	45
17	TEA (1.0)	acetone	reflux	30	trace

[a] Reaction conditions: **1b** (1.0 mmol), **4** (0.5 mmol). [b] Isolated yields.

With the optimized reaction conditions, the scope of 1,2-allenic ketones was studied. 1-Aryl substituted 1,2-allenic ketones with various substituents on the aryl ring underwent this reaction smoothly with good yields (Table 2, entries 1−12). The reaction was found to be also compatible with 1-alkyl-4-aryl, 1,4-diaryl, or 1-aryl-4-alkyl substituted allenic ketones (entries 13−22). It was noted that various functional groups such as methyl, methoxyl, halides, and cyano are well tolerated.

A tentative pathway for the formation of **6** is depicted in Scheme 2. First, base triggers the cascade process by deprotonating **4** to give anion **A**, which undergoes a Michael addition to **1** to afford the second anion **B**. The Michael addition occurs again with **B** and **1** to give the third anion **C**. Tautomerization of **C** affords the fourth anion **D**, which undergoes an *intramolecular* aldol type reaction to give the fifth anion **E**. Aromatization through cleavage of an ethyl carbonate from intermediate **F** yields the polysubstituted benzene to conclude the process.[7]

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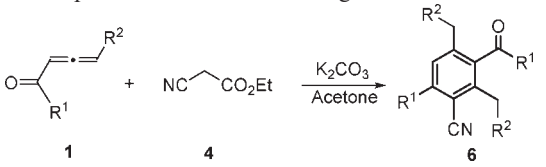
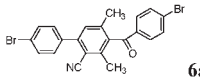
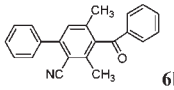
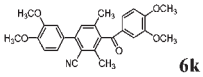
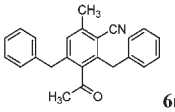
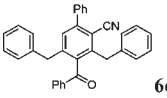
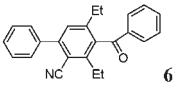
Table 2. Scope of the Reaction Leading to **6**[a]

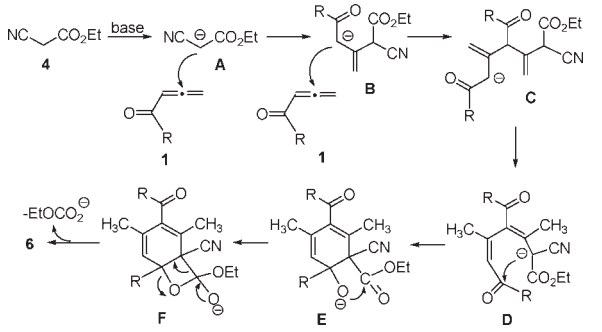


entry	R^1	R^2	6	yield (%)[b]
1	*p*-BrC_6H_4	H	 **6a**	81
2	C_6H_5	H	 **6b**	75
3	*m*-FC_6H_4	H	**6c**	70
4	*m*-BrC_6H_4	H	**6d**	71
5	*o*-FC_6H_4	H	**6e**	67
6	*o*-ClC_6H_4	H	**6f**	71
7	*p*-ClC_6H_4	H	**6g**	80
8	*m*-$CH_3C_6H_4$	H	**6h**	72
9	*p*-$CH_3C_6H_4$	H	**6i**	76
10	*p*-$CH_3OC_6H_4$	H	**6j**	70
11	*3,4*-di-$CH_3OC_6H_3$	H	 **6k**	77
12	*p*-NCC_6H_4	H	**6l**	76
13	CH_3	C_6H_5	 **6m**	61
14	CH_3	*p*-FC_6H_4	**6n**	50
15	C_6H_5	C_6H_5	 **6o**	68
16	C_6H_5	*p*-FC_6H_4	**6p**	58
17	*p*-$CH_3C_6H_4$	C_6H_5	**6q**	66
18	*p*-$CH_3C_6H_4$	*p*-FC_6H_4	**6r**	54
19	*p*-ClC_6H_4	C_6H_5	**6s**	68
20	*p*-ClC_6H_4	*p*-FC_6H_4	**6t**	57
21	C_6H_5	CH_3	 **6u**	45
22	*p*-ClC_6H_4	CH_3	**6v**	42

[a] Reaction conditions: **1** (1.0 mmol), **4** (0.5 mmol), K_2CO_3 (0.5 equiv), acetone (5 mL), reflux, 15 min. [b] Isolated yields.

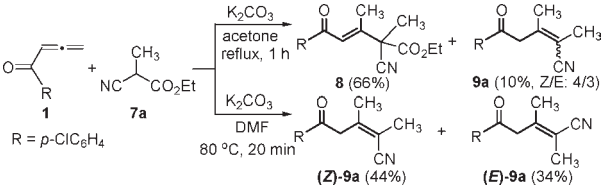
Based on the proposed mechanism, we noticed that 2-substituted cyanoacetates (**7**) would not be possible substrates for the formation of **6**. It was then of interest to determine what kind of products would be formed from the reaction of **1** with **7**, which, to the best of our knowledge, has not been studied yet.[8] Thus, 1-(4-chlorophenyl)-buta-2,3-dien-1-one (**1**) and ethyl 2-methyl cyanoacetate (**7a**) were treated with K_2CO_3 in refluxing acetone for 1 h (Scheme 3). Separation of the resulting mixture gave a β,

Scheme 2. Plausible Pathway for the Formation of **6**



γ-unsaturated nitrile (**8**, 66%) together with an α,β-unsaturated nitrile (**9a**, 10%). Further efforts were then made to improve its selectivity and yield. During the optimization, we found that the nature of solvents had remarkable effects on the selectivity of this reaction. While the reaction run in acetone mainly afforded **8**, **9a** was obtained as a dominating product (78%) by treating **1** and **7a** with K_2CO_3 in DMF at 80 °C for 20 min. **9a** was obtained as a mixture of stereoisomers (Z/E = 4:3, which are separable by column chromatography). The configuration of the carbon−carbon double bond of the more polar *E*-isomer was determined on the basis of the X-ray diffraction analysis (Figure 2).

Scheme 3. Reactions of α-Substituted Cyanoacetate with Allenic Ketone in Different Solvents



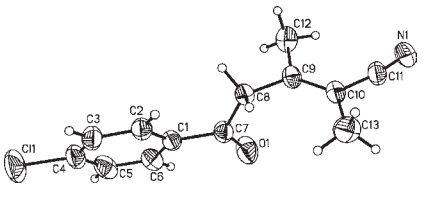
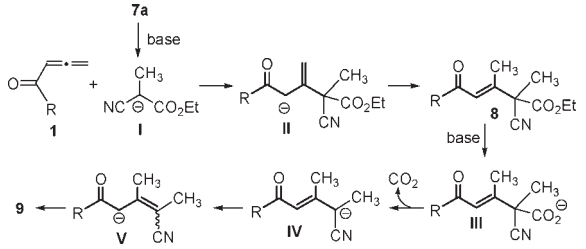


Figure 2. X-ray crystal structure of **(*E*)-9a**.

Scheme 4. Plausible Pathway for the Formation of **9**



A plausible pathway for the formation of **9** is shown in Scheme 4. In the first phase of the tandem process, the Michael addition of anion **I** with allenic ketone **1** and subsequent isomerization and protonation yield a β,γ-unsaturated nitrile **8**. In the second stage, a base catalyzed decarboxylation of **8** and the subsequent isomerization and protonation afford **9**. The much improved selectivity toward **9** by using DMF as the reaction medium may be explained by the enhanced basicity of the carbonate in DMF compared with that in acetone, which is essential for the decarboxylation process.

Various allenic ketones and different α-substituted cyanoacetates were then studied to determine the scope of the above process leading to the synthetically and biologically important α,β-unsaturated nitriles.[9] Table 3 lists the successful results of this reaction with a variety of substrates under the optimized conditions.

Finally, the cyano group, which had played a key role as a reactivity controlling element during the above processes, could be used as a convenient chemical handle for the preparation of other useful compounds. It is well-known that biphenyl tetrazole is an important and powerful pharmacophore.[10] Compounds with this framework have shown various pharmacological and biological activities.[11,12] We noticed that most of the products included in Table 1 are ready substrates toward biphenyl tetrazole derivatives. As an example, **6b** was treated with Me_3SiN_3 and a catalytic amount of *n*-Bu_2SnO for 50 h at 90 °C in *o*-xylene.[10a] The corresponding biphenyl tetrazole (**10**) was obtained in 75% yield (Scheme 5). This results in a convenient and efficient sequence of reactions toward biphenyl tetrazoles from the readily accessible allenic ketones without using any transition metal catalysts.

In conclusion, we have developed an efficient and novel protocol for the preparation of polysubstituted benzenes and an effective synthetic method toward α,β-unsaturated nitriles *via* tandem reactions of 1,2-allenic ketones with cyanoacetate or 2-substituted cyanoacetates. Remarkable advantages of these new strategies include high efficiency, readily available starting materials, and mild reaction conditions. In addition, the resulting cyano substituted biphenyls can be smoothly functionalized to the pharmaceutically interesting biphenyl tetrazole. Further exploration of the reaction scope and elaboration of the resulting products are currently underway.

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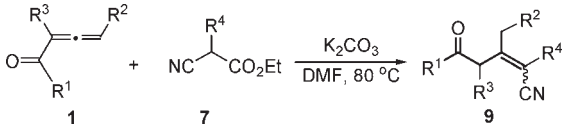
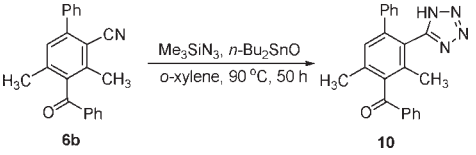
Table 3. Synthesis of α,β-Unsaturated Nitriles[a]



						yield (%)[b]	
entry	R^1	R^2	R^3	R^4	**9**	*Z*	*E*
1	*p*-ClC_6H_4	H	H	CH_3	**9a**	44	34
2	*p*-BrC_6H_4	H	H	CH_3	**9b**	45	34
3	*o*-FC_6H_4	H	H	CH_3	**9c**	35	31
4	*p*-$CH_3C_6H_4$	H	H	CH_3	**9d**	49	35
5	*p*-$CH_3OC_6H_4$	H	H	CH_3	**9e**	47	38
6	C_6H_5	H	H	CH_3	**9f**	41	30
7	*p*-BrC_6H_4	H	H	Bn	**9g**	44	32
8	*p*-$CH_3C_6H_4$	H	H	Bn	**9h**	43	32
9	*p*-$CH_3OC_6H_4$	H	H	Bn	**9i**	41	32
10	*p*-$CH_3OC_6H_4$	H	H	Allyl	**9j**	43	36
11	C_6H_5	C_6H_5	H	CH_3	**9k**	36	26
12	C_6H_5	H	CH_3	CH_3	**9l**	48	32
13	*p*-ClC_6H_4	H	CH_3	CH_3	**9m**	44	30

[a] Reaction conditions: **1** and **7** (1.0 mmol), K_2CO_3 (1 equiv), DMF (5 mL), 80 °C, 20 min. [b] Isolated yields.

Scheme 5. Synthesis of Biphenyl Tetrazole from **6b**



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Supporting Information Available. Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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