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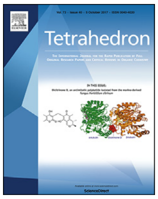

Thermal [3 + 2] cycloaddition of phthalazinium dicyanomethanide with allenoates

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ABSTRACT

The thermal [3 + 2] cycloaddition reaction of phthalazinium dicyanomethanide with various allenoates worked efficiently under mild reaction conditions to give functionalized tetrahydropyrrolo[2,1-*a*] phthalazine derivatives in good to excellent yields and excellent diastereoselectivities.

1. Introduction

1,3-Dipolar cycloaddition reactions represent an important class of synthetic methods for the convergent synthesis of a wide range of heterocycles.[1] Numerous 1,3-dipoles such as nitrone, azomethine ylide, azomethine imine, nitrile oxide, carbonyl ylide, azide, nitrile imine, carbonyl oxide, diazoalkane and diazoacetate have been exploited for research on cycloaddition chemistry.[1] Compared with high-profile dipoles such as nitrone, azomethine ylide, azomethine imine, phthalazinium dicyanomethanide has received little attention although it has several salient features including stability, easy preparation, and high reactivity. In limited examples, it has been used as 1,3-dipole in some thermal, metal-catalyzed and organocatalytic cycloadditions. In 2011, with the use of chiral imidazolidinone as catalyst, the catalytic enantioselective [3 + 2] cycloaddition between enals and phthalazinium dicyanomethanide was achieved to give highly substituted chiral pyrrolophthalazines in high yields and excellent diastereo- and enantioselectivities.[2] In 2015, we reported the Cu(I)-catalyzed highly enantioselective [3 + 3] cycloaddition between phthalazinium dicyanomethanides and iminoester-derived azomethine ylides, providing novel chiral heterocyclic compounds, 2,3,4,11b-tetrahydro-1*H*-pyrazino[2,1-*a*]phthalazine derivatives, in high yields with excellent diastereo- and enantioselectivies.[3] In the same year, we also developed the $Sc(OTf)_3$-catalyzed diastereoselective [3 + 3] cycloaddition of phthalazinium dicyanomethanides with cyclopropane 1,1-diesters, affording a variety of 3,4-dihydro-1*H*-pyrido[2,1-*a*]phthalazine derivatives in high yields with excellent diastereoselectivities.[4] Recently, we developed the phosphine-catalyzed [3 + 2] cycloaddition between phthalazinium dicyanomethanides and allenoates, in which double bond between $C_ß$ and C_γ of allenoates underwent stepwise cycloaddition with dipole to afford a broad range of novel heterocyclic compounds 1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazine derivatives in excellent yields (Scheme 1a).[5] In addition to these catalytic cycloadditions, the thermal [3 + 2] cycloaddition reactions of phthalazinium dicyanomethanide with alkenes,[6] alkynes,[6,7] phosphaalkynes,[8] or thiones[9] have extensively been studied and the [4 + 3] cycloaddition reaction of phthalazinium dicyanomethanide with azoalkenes formed *in situ* was recently reported.[10] However, thermal cycloaddition of phthalazinium dicyanomethanide with allenoates has never been explored although the electron-deficient allenes have similar reaction activity as alkenes and alkynes. In our previous work, we have investigated the thermal [3 + 2] cycloaddition reactions of various azomethine

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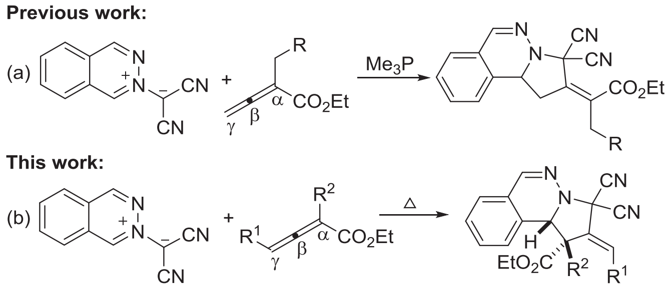


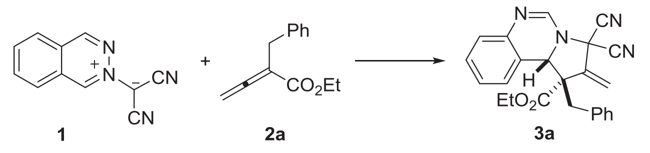
Scheme 1. The [3 + 2] cycloaddition of phthalazinium dicyanomethanide with allenoates.

imines with allenoates, providing a variety of dinitrogen-fused heterocycles in moderate to excellent yields.[11] We also achieved sequential [3 + 2] cycloaddition/rearrangement reaction of imidazolone nitrones with allenoates, affording the methylene imidazolidinone derivatives in high yields.[12] As a continuous interest in cycloaddition reactions,[13] herein, employing phthalazinium dicyanomethanide as 1,3-dipole, we describe thermal [3 + 2] cycloaddition of phthalazinium dicyanomethanide with several types of allenoates, in which double bond between C_{α} and C_{β} of allenoate performed [3 + 2] cycloaddition with dipole to provide functionalized tetrahydropyrrolo[2,1-*a*]phthalazine derivatives (Scheme 1b).

2. Results and discussions

Initially, the [3 + 2] cycloaddition was investigated with phthalazinium-2-dicyanomethanide (**1**) and allenoate (**2a**) as model substrates (Table 1). The reaction was performed at the room temperature. Several solvents were first screened. Treatment of the phthalazinium-2-dicyanomethanide (**1**) with the allenoate (**2a**) in THF for 48 h afforded the cycloadduct **3a** in 68% yield with excellent diastereoselectivity (entry 1). With the use of dichloromethane as the solvent, the yield was remarkably increased to 76% yield (entry 2). Protic solvents such as H_2O and MeOH could not help improve the yields (entries 3, 4). To our delight, the polar solvent acetonitrile demonstrated excellent compatibility, leading to the product **3a** in 89% yield (entry 5). When the reaction temperature was increased to 40 °C, the reaction time was shortened to 24 h and the yield was still excellent 90% (entry 6). Higher reaction temperature such as 60 °C did not further improve the result, on the contrary, resulted in the deterioration of the yield. Based on the above results, the [3 + 2] cycloaddition reactions were next performed in MeCN at 40 °C for 24 h.

Table 1
Screening of the reaction conditions[a].



1 **2a** **3a**

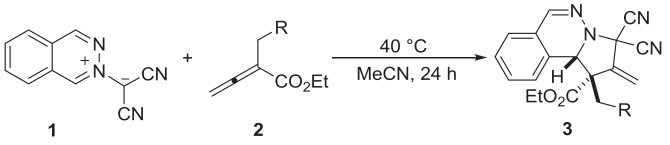
Entry	Solvent	Temp. (°C)	t (h)	Yield[b] (%)
1	THF	25	48	68
2	CH_2Cl_2	25	48	76
3	MeOH	25	48	74
4	H_2O	25	48	56
5	MeCN	25	48	89
6	MeCN	40	24	90
7	MeCN	60	24	85

[a] The reaction was carried out with 0.1 mmol of **1** and 0.15 mmol of **2a** in 2 mL of solvent.
[b] Isolated yield; > 20: 1 dr, determined by ^1H NMR data.

With the optimized conditions in hand, the scope of α-substituted allenoates were next evaluated. As shown in Table 2, the [3 + 2] cycloaddition reaction of phthalazinium-2-dicyanomethanide (**1**) with various α-arylmethyl-substituted allenoates (**2**) proceeded smoothly to provide the cycloadducts in good to excellent yields (80–94%) with excellent diastereoselectivities (entries 1–13). The allenoates bearing both electron-donating and electron-withdrawing substituents on the benzene ring could perform the reaction to give the corresponding product (entries 1–12). Moreover, the substitution pattern had no remarkable influence on the reactivity and stereoselectivity, probably due to the long distance between the aryl group and the reactive center. Particularly, allenoates containing electron-withdrawing groups seemed to produce the corresponding products in higher yields, compared with those allenoates with electron-donating group (entries 2–9 vs 10–12). Additionally, 2-naphthyl substituted allenaote **2m** also worked well to afford the cycloadduct **3m** in 88% yield (entry 13). The α-methyl-substituted allenoate **2n** was also a compatible substrate, performing the [3 + 2] cycloaddition reaction with phthalazinium-2-dicyanomethanide (**1**) to afford the corresponding product **3n** in 82% yield (entry 14). The ethoxycarbonyl substituted allenoate **2o** underwent the reaction to afford the cycloadduct **3o** in 90% yield (entry 15). The relative configuration of these products has been determined through X-ray crystallographic data of the product **3h**.[14] The regioselectivity that the double bond between C_{α} and C_{β} of allenoate performs cycloaddition with dipole might be the consequence of thermodynamic control.

As shown in Table 3, ethyl buta-2,3-dienoate and γ-substituted allenoates have also been investigated in this thermal [3 + 2] cycloaddition reaction with phthalazinium-2-dicyanome-thanide, providing the cycloadducts in good to excellent yields and excellent diastereoselectivities. Ethyl buta-2,3-dienoate performed the reaction to produce the product **3p** in 88% yield (entry 1). The reactions of several γ-alkyl substituted allenoates (**2q**–**2t**) with phthalazinium-2-dicyanome-thanide (**1**) proceeded smoothly in

Table 2
[3 + 2] cycloaddition of phthalazinium-2-dicyanome-thanide with α-substituted allenoates[a].



1 **2** **3**

Entry	R	3	Yield[b] (%)
1	Ph (**2a**)	**3a**	90
2	2-FC_6H_4 (**2b**)	**3b**	92
3	3-FC_6H_4 (**2c**)	**3c**	86
4	4-FC_6H_4 (**2d**)	**3d**	93
5	3-ClC_6H_4 (**2e**)	**3e**	89
6	4-ClC_6H_4 (**2f**)	**3f**	94
7	3-BrC_6H_4 (**2g**)	**3g**	88
8	4-BrC_6H_4 (**2h**)	**3h**	91
9	3-$CF_3C_6H_4$ (**2i**)	**3i**	86
10	3-MeC_6H_4 (**2j**)	**3j**	85
11	4-MeC_6H_4 (**2k**)	**3k**	83
12	3,5-$(OMe)_2C_6H_3$ (**2l**)	**3l**	80
13	2-naphthyl (**2m**)	**3m**	88
14	H (**2n**)	**3n**	82
15	CO_2Et (**2o**)	**3o**	90

[a] The reaction was carried out with 0.1 mmol of **1** and 0.15 mmol of **2** in 2 mL of MeCN.
[b] Isolated yield; > 20: 1 dr, determined by ^1H NMR data.